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COMPUTERIZED ANALYSIS OF ELECTRICAL AND MECHANICAL COORDINATION IN THE ANTRODUODENAL REGION. L.M.A.Akkermans, J.M.M. Roelofs, J.M. de Ridder, M. Breedijk, A.J.P.M. Smout, J.M. van Nueten, J.A.J. Schuurkes, P. Wittebol. Dept. of Surgery University Hospital Utrecht, the Netherlands and Janssen Pharmaceutica, Beerse, Belgium.

In the isolated guinea pig stomach cisapride lengthened the interval between successive antral contractions and enhanced the extent of antroduodenal mechanical coordination. The mechanism of this coordination is still unknown. The aim of this study was to develop a computerized method of analysis of mechanical and electrical events involved in antroduodenal coordination. Antroduodenal contractile and myoelectric signals obtained from 7 dogs with implanted strain gages and electrodes were analyzed. After digitalization data reduction was performed, ECA, ERA and phasic contractions were detected. Times of event and amplitude were filed. Time intervals between antral and duodenal events were calculated. After administration of cisapride 84% of the duodenal contractions occured within 3.5–6.5 s after the antral contraction, which is within 22% of the antral cycle. In the control the ratio between the duration of antral and duodenal ECA intervals was 3.43 ± 0.15 (mean ± SEM). After cisapride this ratio increased to 3.84 ± 0.16 and was frequently found to be 4.0 during periods of several min. In this case antral and duodenal cycles were phase-locked. This provides an optimal condition for a coordinated mechanical activity between antrum and proximal duodenum. A significant positive correlation ($p < 0.001$) was found between the amplitudes of the duodenal contraction and the preceeding antral contraction.
Conclusions: Computerized analysis offers the possibility to analyse data obtained from the gastroduodenal area. Apart from the preferential occurence of duodenal contractions in a short part of the antral cycle two other phenomena seem to play a role in establishing antroduodenal coordination. One is the modulation of gastric ECE frequencies toward 4 times the duodenal frequency. Another is the positive correlation between the amplitude of the duodenal contractions and the amplitude of the preceeding antral contractions.

RELATIONS BETWEEN GASTRIC EMPTYING AND SYMPTOMS AFTER BILLROTH II RESECTION. L.M.A. Akkermans, A.J.P.M. Smout, J.M.M. Roelofs, F.G. Pasma, P. Wittebol. Dept. of Surgery, University Hospital, Utrecht, the Netherlands.

The objective of this study was to investigate the relations between the postprandial symptoms that may develop after distal gastric resection and the patterns of emptying of the gastric remnant. Emptying studies were performed in 19 symptomatic (S+) and in 16 asymptomatic (S-) patients, 2 - 10 years after BII resection without vagotomy. Semisolid (porridge) and solid (pancake) meals of identical composition, labeled with ^{99m}Tc tin colloid, were used. Normal emptying rates of these semisolid and solid meals are 64 ± 7 %/h and 57 ± 6 %/h, respectively, and normal lag phase durations are 4.8 ± 1.4 and 22.2 ± 4.4 min.
RESULTS: SEMISOLID MEAL: In both patient groups the lag phase was absent and emptying in the first few min after the meal was accelerated. Initial emptying was significantly faster in S+ than in S- patients (activity present in the stomach after 5 min: 45 ± 4.3 % and 80 ± 2.9 %, respectively). At 60 min after the meal the remaining activities were not significantly different. SOLID MEAL: Both in S+ and in S- patients the lag phase was shorter than in controls, but the two patient groups were not different in this respect. S+ patients emptied solids significantly slower than S- patients (emptying rates: 49 ± 4.6 %/h (S+) and 64 ± 8.7 %/h (S-)). In the S+ patients significant correlations were found between the severity of the symptoms, the delay in solid emptying and the initial acceleration of semisolid emptying. Preliminary results indicate that the emptying pattern is disturbed least in patients exhibiting phasic contractile activity in their gastric remnant.
CONCLUSIONS: In both S+ and S- BII patients gastric emptying starts earlier and the initial emptying of semisolids is faster than in controls. S+ patients differ from S- patients by a more precipitous initial emptying of semisolids and by a slower emptying of solids. The severity of the symptoms is related to these abnormalities.

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THREE MECHANISMS OF VOMITING INDUCED BY CENTRAL STRESSFUL STIMULATION. I. Altaparmakov and *O. Kolev. University Hospitals Bergmannsheil, Dept. of Gastroenterology and Hepatology, 4630 Bochum 1/FRG; *University of Sofia, Dept. of Oto-Neurology, Bulgaria.

The purpose of the study was to determine the central pathways of gut motility response to labyrinthine stimulation and the role of stomach (S) and duodenum (D) in vertigo, nausea and vomiting. Vestibular irritation by a water at 3° C, 7° C and 10° C was induced 6 times at 15 min intervals on 19 healthy volunteers. The interdigestive migrating complexes (IMC) and the pressure were registered by a probe with 4 electrodes and 4 microballons placed in gastric antrum and upper duodenum. Blood pressure and pulse rate were monitored for autonomic response. A computer analysis of electronistagmogramm and of direction, velocity of propagation and of spike power-spectrum was performed. The labyrinthine stimulation decreased the duration of ph I in S. by 10,7% and by 15,3% in D., increased the duration ph II by 18,1% in S. and decreased it by 10,8% in D., do not change the ph III duration and its freqeuency in S., but increased the frequency of ph III in D. by 26,2% and its frequency from 0,8 to 2,7 c/h. No correlation between nistagmus, vertigo, nausea and motility patterns in S. and D. were presented. An inhibition of stomach and a stimulation of duodenal activity were observed in a pre-vomiting period in all tests. The vomiting results as consequence of 3 types pertubances in IMC: I - aborally migrating burst of spike activity in S. during previously started orally migrating ph III-like activity in D (50% of the cases); II - aborally migrating burst of spike activity in S. during previously started non-propulsive ph III-like activity in D. (37,5%); III - antiperistalsis of duodenal ph III activity into stomach (12,%). Conclusions: 1. Three types of G.I. motor activity induce a vomiting by central acting stressful stimuli; 2. A gastro-duodenal discoordination plays a major role in vomiting; 3. A vertigo & nausea are not equivalent to G.I. motility disorders; 4. The results suggest thalamic, limbic and cortical pathways for G.I. motility disturbances by labyrinthine stimulation.

PATCH CLAMP ANALYSIS OF SINGLE IONIC CHANNELS OF CIRCULAR AND LONGITUDINAL SMOOTH MUSCLE OF THE CANINE COLON. T.E. Ary and K.M. Sanders. Univ. Nevada School of Medicine, Reno, NV 89557 USA.

Excitability mechanisms and the ionic mechanisms of neurotransmitters and drugs have been difficult to study in syncytial smooth muscles because of the difficulties in voltage clamping these tissues. Therefore, we have employed the patch clamp technique (Hamill et al. Pflug. Arch 391:85-100, 1981) to examine single ionic channels in the membranes of freshly dispersed smooth muscle cells from the canine proximal colon. Dogs were anesthetized with pentobarbital and strips of proximal colon were removed and dissected to separate circular from longitudinal layers. These were treated with trypsin and collagenasé to disperse single cells from the syncytium. Only healthy, relaxed cells that stuck to the floor of the dispersion vessel were used for these studies. Patch pipets formed gigaseals readily with the muscle membranes, and inside-out membrane patches could be excised from longitudinal and circular cells. Longitudinal cells exhibited multiple channel activity. When the patch pipet was filled with 140 mM K^+ (bath $[K^+]$=6 mM), voltage-dependent channels were apparent with slope conductances of 67 pS. When the potassium ion gradient was altered (patch pipet filled with 50 mM K^+ and 90 mM $Choline^+$) no apparent change in conductance of the channels was observed. A significant increase in open-time probability, including opening of multiple channels in the patch was observed at depolarized command potentials. In contrast, when patch seals were obtained from cells dispersed from the circular layer a voltage dependent channel was observed with a slope conductance of 20 pS. The results of this study suggest that the circular and longitudinal layers of colonic smooth muscle differ in ionic channel populations which may produce the differences in the electrical events observed in these two muscles by traditional intracellular recordings. (Supported by NIAAA Grant AA 05883).

ELECTRICAL ACTIVITY OF MUSCULARIS MUCOSAE AND EXTERNAL MUSCLE LAYERS IN THE CANINE PROXIMAL COLON IN VIVO. F. Angel, F. Crenner, G. Chalkiadakis and J.F. Grenier. Inserm U 61, Pavillon Chirurgical B, Hôpital Civil, 67091 Strasbourg cedex, France.

We studied the electrical activity of the muscularis mucosae compared to the activity of the external muscle in vivo by means of extracellular electrodes. Two squares(1x1cm) of external muscle were carefully dissected on a proximal colonic loop at two different sites in 4 anesthetized dogs. Two sets of electrodes were implanted very close together at the level of the two dissected sites : one electrode on the muscularis mucosae and the other one on the external muscle at each site. Because the muscularis mucosae is an extremely thin muscle, the electrical signals coming from this layer present a high global source impedance. Therefore we developed special electrodes, which consist of a monopolar contact silver electrode surrounded by a guard ring. The electrical activity of each layer was recorded using a pseudo-differential mode between the electrode and the ring. A very rigorous chloruration of the electrodes allowed D.C recordings to be performed during 3 hours after surgery. We also developed filtering devices characterized by a fast attenuation (-24dB/octave) to visualize spike potentials. Using that particular type of electrodes our results showed that : 1. the two muscle layers exhibited slow potential variations (mean amplitude : 0.4mV), at a frequency of 3 to 5 slows waves per minute in the muscularis mucosae and 2 to 14 waves per minute in the external muscle. 2. Spiking activity showed two distinct types : the first one consisted of bursts of multiples fast oscillations (amplitude ranging from 0.1 to 0.7mV) ; the second one consisted of single slower oscillations (amplitude renging from 0.3 to 0.9mV). These two types of activity were seen alternatively or superposed on the external muscle layers whereas the muscularis mucosae showed more frequently the single oscillations. 3. Finally spiking activities did not seem to be correlated at a same site between the muscularis mucosae and the external muscle layers. In conclusion this study shows for the first time myoelectrical activities in the muscularis mucosae in vivo.

RELATIONSHIP BETWEEN THE SPIKE ACTIVITIES OF THE SMALL AND LARGE INTESTINES. E. Atanassova, A. Noeva, S. Gachilova. Institute of Physiology Bulgarian Academy of Sciences. Sofia, Bulgaria

In vivo experiments were performed on dogs with chronically implanted electrodes on the muscle wall of the stomach, small and large intestines. The electrical activity of the muscle wall of the gastrointestinal tract was recorded in starved dogs and after feeding.

When the spike activity of the myoelectrical complex (MEC) reached the end of the ileum, continuous spike activity was observed in the terminal part of the ileum which spread in the ascending colon. After disappearance of the spike activity in the small intestines, the terminal ileum exhibited independent spike activity. The number of the spike potentials in a group and the spike potential frequency increased. This spike activity spread in the colon too.

Immediately after feeding the spike activity spread along the length of the stomach, small intestines to the colon (gastro-colic response). On the background of the continuous spike activity of the stomach and small intestnes after feeding we observed an increase in the spike activity of the terminal ileum and of the colon at the end of the second, during the third hour, as well as the fifth - sixth hour after feeding

Relationship between the spike activities of the small and large intestines was established during the spike activity of the MEC, outside it and after feeding. Of importance to this relationship is the most terminal part of the ileum, which behaves as a region increasing the colonic activity.

TACHYKININ INDUCED REGIONAL GASTRIC MOTILITY CHANGES: PERIPHERAL AND CENTRAL EFFECTS. W.D. Barber and T.F. Burks. Departments of Anatomy and Pharmacology, College of Medicine, University of Arizona, Tucson, AZ 85724.

This study was conducted on anesthetized cats to evaluate regional gastric responses following the local intraarterial administration of selected tachykinins during various distending pressures. The tachykinins, including substance P, physalaemin and substance K, were administered locally via the splenic artery while changes in wall tension and intragastric pressure in the antrum and corpus-fundic regions were recorded. Wall tension was monitored by strain gauges attached transversely midway along the greater curvature of the corpus and along the inferior border of the antrum. Intragastric pressure was altered and monitored by balloons in the corpus-fundic region and antrum. The responses of the corpus-fundic region and antrum during the local intraarterial injection of the tachykinins were evaluated at nondistended and systolic levels. At nondistended volumes the response of the corpus-fundic region to the tachykinin was characterized by a brief initial relaxation followed by sustained contraction. In contrast, large phasic contractions with a periodicity of 3-5/minute occurred in the antrum. The onset of these activity patterns occurred 10-20 seconds after injection of the peptide. These peptide-induced gastric changes were dose dependent. Sustained distention of the corpus-fundic region at systolic levels prior to local intraarterial administration of the tachykinins significantly reduced the amplitude of the phasic contractions of the antrum. The peptide induced sustained contractions of the corpus-fundic region and phasic activity pattern of the antrum were inhibited by atropine. Single unit extracellular recordings from neurons in the region of nucleus and tractus solitarius in the brainstem showed changes in activity which reflected the peptide induced gastric changes. These brain-gastric interactions were vagally mediated. The results of this study have shown that regulatory mechanisms which underlie the varying activity patterns of the stomach may be linked to peptides such as substance P which are endogenous to the stomach. (Supported by USPHS grant AM31804.)

TACHYGASTRIA: NEUROGENIC AND MYOGENIC CAUSES. B.L. Bardakjian, S.A. Chung, D.T. Valdez, and N.E. Diamant. University of Toronto, Ontario, Canada.

Tachygastria has been attributed to increased levels of catecholamines, endogenous opiates and prostaglandins, and to ectopic antral pacemakers. In human gastric circular muscle, acetylcholine was shown to increase the depolarization plateau of the electrical control activity (ECA) in normal muscle, whereas it increased the ECA frequency and nearly abolished the depolarization plateau in muscle from a patient with tachygastria. This study investigates neurogenic and myogenic causes of tachygastria using both animal and computer models. Methods: I. Chronic Studies: In five dogs, the vagosympathetic nerve trunks were isolated in bilateral cervical skin loops for vagal blockade by cooling. Bipolar electrodes and strain gauges were implanted on the stomach serosa to monitor the electrical and contractile activities. II. Acute Studies: In four dogs, the gastroepiploic artery was cannulated for drug injection. Bipolar electrodes were implanted along the greater curvature on stomach serosa for stimulation and recording of the ECA. III. Computer Studies: A multiportal relaxation oscillator was used to model the ECA of gastric circular muscle. It was stimulated when either one or two input portals were activated. Results: I. Chronic Studies: Vagal blockade caused an increase in ECA frequency and it abolished the contractile activity in both fasting and fed states. II. Acute Studies: Intra-arterial injection of norepinephrine increased the ECA frequency distally but not proximally and abolished the electrical spiking activity. Electrical DC stimulation of the proximal antrum increased the ECA frequency in the distal antrum. III. Computer Studies: Stimulation increased the frequency of oscillator output when only one input portal was activated. It prolonged the depolarization plateau and decreased the frequency of oscillator output when two input portals were activated simultaneously. Conclusion: Tachygastria may be attributed to: (1) Neurogenic defects possibly causing sympathetic dominance. (2) Myogenic defects possibly causing resting memebrane potential changes and failure of some membrane channels to activate.

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EFFECTS OF PLATELET ACTIVATING FACTOR (PAF) ON THE DIGESTIVE MOTILITY IN THE CONSCIOUS RAT. T. Bardon and J. Derégnaucourt. Rhône-Poulenc Santé, Centre de Recherches, B.P. 14, 94403 Vitry-sur-Seine - FRANCE

Platelet Activating Factor is now recognised as a potential mediator in inflammatory, painful and/or allergic reactions as prostaglandins and leukotrienes are. Since such reactions may be accompanied by disorders of the digestive motility and transit, and since an *in vitro* receptor mediated spasmogenic effect of PAF on ileal smooth muscle has been demonstrated (1,2,3) it was of interest to evaluate the action of PAF on the digestive motor function in conscious animals.

The intraperitoneal administration of PAF-acether (1,5, 25 $\mu g.kg^{-1}$) to rats chronically fitted with intraparietal electrods implanted all along the digestive tract induced an immediate decrease of the antrum and duodeno-jejunum activity for 5-20 minutes in both fed and fasted states.

A striking feature of our observations is the PAF-induced disruption of the Migrating Motor Complexes (MMC) in fasted rats, for a dose related period (1-3 hours), whereas spiking activity was only slightly increased (20 %) in the caeco-colonic segment for 5 to 10 minutes. Preliminary results we obtained with PAF-acether given intracerebroventricularly in fed rats indicated a possible immediate restauration of the MMC pattern for 30-60 minutes, as already shown with PGE_2 and calcitonin (4).

In conclusion, the apparent dissociation between the responses obtained on small and large intestine may reflect a different susceptibility of the two portions to PAF effects. Overall, these results suggested a possible role for PAF in the digestive motor function changes observed during gastrointestinal or general inflammatory and allergic states probably associated with circulatory disturbances.

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SPINAL CORD AS THE MAJOR SITE OF ACTION OF SUBSTANCE P ON COLONIC MOTILITY. Th. Bardon, J.P. Ferré and Y. Ruckebusch. Rhône-Poulenc Santé, C.R. de Vitry, 13 quai Jules-Guesde, 94407 Vitry-sur-Seine, and Dept. of Physiology, Ecole Nationale Vétérinaire, 31076 Toulouse Cédex (France).

The localization of substance P (SP) in the myenteric neurons, the submucosal plexuses and the mucosal cells along the digestive tract is consistent with a role in the modulation of gut motility and/or secretion. Immunoreactive SP is also found in the brain and spinal cord, where its release is considered as functionally-related to pain and analgesia. Since the spinal cord is the site of action for other modulators of gastrointestinal motility, we tested the effect of SP administered intrathecally (IT), before and after SP depletion by capsaicin, on the motor function of both small and large intestine and compared it to the effect of SP administered intracerebroventricularly (ICV).

Rats were fitted with intraparietal electrodes implanted on the duodenojejunum and the cecocolonic segment. A motility index was automatically obtained at 10-min intervals from continuous EMG recordings. Twelve rats received SP (5-10 µg, i.e. a range of 3-6 nmol) or saline (5 µl) ICV. Twelve other rats received SP (20-80 ng) IT 2 days before and 2 days after capsaicin (15 µg) or saline (5 µl) IT. After an inconstant period of excitation (5 min), SP given IT caused a dose-related 30-50 % decrease in the spiking activity of the transverse and the distal colon for 30-50 min, without major changes in duodenojejunal activity. The colonic myoelectric activity was depressed transiently (less than 30 min) and then permanently increased by 50-100 % after capsaicin treatment without changes in activity of the duodenojejunum. This effect persisted and was no longer depressed by SP at doses of 20-80 ng IT. In contrast, SP by ICV route did not modify the colonic motor activity but did reduce the spiking activity of the duodenum by 20-30 % and induced a fasted pattern.

The results indicate that substance P in the spinal cord may play a role in the inhibition of the motility of the distal part of the digestive tract, a phenomenon possibly associated with noxious stimuli.

MECHANISMS OF SUBSTANCE P (SP)- AND ACETYLCHOLINE (ACh)-INDUCED COLONIC CONTRACTIONS IN VITRO AND IN VIVO.
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Isolated circular muscle strips from the canine proximal colon contracted to ACh (EC_{50} = 29.8 μM, maximum = 34.2 ± 1.6 g) and SP (EC_{50} = 1.1 μM, maximum = 15.5 ± 1.6 g). D-Pro^2-D-$Trp^{7,9}$-SP (K_B = 5.1 μM) and D-Arg^1-D-$Trp^{7,9}$-Leu^{11}-SP (K_B = 3.7 μM) antagonized SP-induced contractions. Atropine (0.1 μM) antagonized ACh-, but not SP-induced contractions. ACh and SP responses were resistant to tetrodotoxin (TTX, 1μM). Reducing the extracellular calcium concentration (2.5 mM to 1.0 μM) eliminated neuronal responses and reduced ACh (28.4 ± 4.6%) and SP (59.5 ± 3.1%) contractions. In anesthetized dogs circular muscle motor activity was recorded from the proximal colon using force transducers. A motility index (MI) was calculated to quantify contractions to intraarterial (i.a.) injections of ACh (ED_{50} = 73.2 ng/kg, maximum MI = 6347 ± 715) and SP (ED_{50} = 75.9 ng/kg, maximum MI = 12850 ± 2071). Intravenous (i.v.) SP injections at similar doses did not significantly increase colonic motility. D-Pro^2-D-$Trp^{7,9}$-SP (10 μg/kg, i.a.) antagonized maximum SP-induced contractions by 59.0 ± 5.8% without altering maximum ACh-induced responses. Atropine (0.1 mg/kg, i.v.) reduced both ACh (92.6 ± 1.9%)- and SP (88.6 ± 3.4%)-induced contractions. TTX did not alter ACh- but reduced SP-induced responses by 76.7 ± 6.1%. Hexamethonium (20 mg/kg, i.v.) did not alter ACh but reduced SP responses (57.8 ± 7.4%) in 5 of 6 dogs tested. These results indicate that ACh and SP contractions in vitro and ACh contractions in vivo are mediated primarily by the stimulation of receptors located on circular smooth muscle. However, SP effects in vivo appear to be mediated by neuronal ACh release and to a lesser extent by direct stimulation of circular smooth muscle. The neuronal mechanism of action may be direct or, more likely, involves a reflex pathway.

THE ACCUMULATION AND RELEASE OF [^{3}H]-ADENINE NUCLEOTIDES BY NERVES IN THE GUINEA-PIG INTERNAL ANAL SPHINCTER.
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The responses of the guinea-pig internal anal sphincter to ATP resemble, sufficiently, those to stimulation of inhibitory non-adrenergic non-cholinergic (NANC) nerves to suggest that this, or a related adenine nucleotide may have a transmitter function in this preparation (Lim & Muir, 1983). The ability of these inhibitory nerves to accumulate and release adenine nucleotides has now been examined.

Sphincteric strips (2mm x 5mm, unstretched) were incubated in [^{3}H]-adenosine (50 μCi/ml, 37°C, 1 hr) and superfused with Krebs containing atropine, phentolamine and guanethidine (each 10^{-6}M). Changes in tension were recorded isometrically and the [^{3}H] overflow measured by liquid scintillation counting.

Field stimulation (200-900 pulses, 2-20 Hz, 0.5 ms) relaxed the sphincter and increased [^{3}H] overflow. Tetrodotoxin (TTX, 10^{-6}M), calcium withdrawal but not 6-OHDA pretreatment (150 mg/kg day 1, 250 mg/kg day 2, animal sacrificed day 3) which destroys adrenergic nerve terminals as shown histochemically, inhibited the [^{3}H] overflow. Verapamil at a dose (10^{-6}M) which blocks mechanical but not electrical responses to field stimulation (Lim & Muir, unpublished), had no effect on evoked [^{3}H] overflow. Sodium nitroprusside (10^{-6}M), a guanylate cyclase inhibitor which relaxed the sphincter independently of NANC nerves, failed to enhance [^{3}H] overflow. NANC nerves in this sphincter can clearly accumulate and release adenine nucleotides, a view consistent with these compounds having a transmitter role in this preparation.

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MEMBRANE PROPERTIES OF GASTRIC CIRCULAR MUSCLES NEAR MYENTERIC PLEXUS AND SUBMUCOSA.
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Electrical slow waves linearly decrease in amplitude as they propagate from the myenteric to the submucosal borders of antral circular muscle. Since contractile force depends upon slow wave amplitude in the antrum, the mechanisms responsible for the diminished slow waves were investigated. Canine antral muscle strips (25 x 1mm), cut parallel to the circular fibers, were pinned in cross-section in a partitioned chamber (Abe and Tomita, J.Phys.1968). Circular muscle cells at several distances (0.2 - 3 mm) from the stimulating plates and near either the myenteric (MY) plexus or the submucosa (SM) were impaled, and the amplitudes of steady-state voltage responses to depolarizing and hyperpolarizing currents were plotted as functions of current strength and distance from the stimulating plate. Hyperpolarizations were linearly dependent upon current intensity in both muscles. Depolarizations revealed rectification as current intensity increased. This effect was more significant in SM muscles. Length constants averaged 2.4 ± 0.4 mm and 1.7 ± 0.9 mm (n=5) for MY and SM muscles, respectively and were significantly different ($p < 0.05$). Membrane time constants were determined by fitting voltage responses to exponentials. Time constants averaged 81 ± 38 and 76 ± 29 msec (n=5), respectively, and were not significantly different. These data suggest that the electrical coupling between cells of MY and SM differs, but passive membrane conductance may not differ. During hyperpolarization of MY muscles, active depolarizations were observed before anode break which often reached threshold. These responses were a function of i) magnitude of the hyperpolarization; ii) time after preceding slow wave. These events were not observed in submucosal muscles. These data suggest that either hyperpolarizing or depolarizing stimuli increase the probability of generating slow waves in myenteric muscles, and may help to explain how either "inhibitory" or "excitatory" chemical stimulation can increase slow wave frequency. (Funded by NIH Grant AM32176)

APPLIED POTENTIAL TOMOGRAPHY, A SIMPLE, NON-INVASIVE METHOD FOR MEASURING LIQUID GASTRIC EMPTYING IN MAN.
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Applied Potential Tomography (APT) is a means by which changes in resistivity may be used to obtain data in the form of a tomographic image (1) Sutton et al (2) have demonstrated changes in epigastric impedance following a liquid meal. We have utilised these changes to produce sequences of images which show the time course and origin of the impedance changes.

The apparatus consists of a ring of 16 electrodes, placed around the area to be studied, connected to an electronic switching system. Information from this is relayed to a microprocessor which produces both a visual display and a digital readout.

In vitro experiments showed that for solid objects and inflated balloons, immersed in a tank of saline, the changes in resistivity were directly proportional to the volume of the object ($r = 0.9961$).

In vivo experiments showed that the APT recorded changes in resistivity in an area around the epigastrium in subjects drinking water. Therefore APT and scintography were performed simultaneously in 10 healthy volunteers. There was no significant difference between the ½-emptying times by both methods in all 10 ($p>0.05$, Student's t-test) and in 7 of the subjects the slope of the emptying curve showed good correlation ($r = 0.91$). In the remaining 3 subjects, two late electrode failures were experienced and one subject failed to empty during the second half of the study period.

In conclusion, APT is a non-invasive method which may be used to study liquid gastric emptying in man. It is easy to perform and may be repeated several times with the same subject without discomfort or exposure to ionising radiations.

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VAGAL EFFERENT RESPONSES TO MECHANICAL AND CHEMICAL STIMULATION IN THE UPPER GASTROINTESTINAL TRACT.
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Feedback regulation of gastric emptying is suggested to involve vagal reflexes activated as chyme, entering the duodenum, stimulates a wide range of mechanical and chemical receptor endings. Evidence for such reflexes stems from the reduced effect of luminal stimuli after vagotomy. However, after vagotomy, gastric emptying is disturbed and the sensitivity of the stomach to non-vagal influences could well be reduced. To circumvent such problems we have attempted to study such reflexes by recording the activity of pre-ganglionic vagal efferent fibres during mechanical and chemical stimulation of the upper GI tract.

Unitary recordings were made from the right cervical vagus of the urethane anaesthetized ferret. 55 efferent units were recorded which showed a low frequency, irregular spontaneous discharge with no cardiovascular or respiratory modulation. Mechanical inputs were tested with gastric and duodenal distension with 0.9% NaCl. Chemical inputs were examined with duodenal perfusions of HCl, glucose, tryptophan, hypotonic and hypertonic solutions. Gastric distension evoked a short latency, slowly adapting response (excitation or inhibition) in 91% of units tested. Duodenal distension was also an effective stimulus resulting in either excitation or inhibition (mainly the latter) of 89% of units. In contrast, chemical stimulation resulted in either no effect (48% of units) or weak effects (<20% change in frequency) following a long and often variable latency. A degree of chemical specificity was evident with units responding to 1 or occasionally 2 of the perfusions. HCl was the most effective and in this respect the only unit showing chemospecificity was strongly excited by this acid. 10 units failed to respond to either mechanical or chemical stimulation. No non-spontaneous efferents were recruited during chemical stimulation.

These results indicate a weak chemoreceptive input to the dorsomotor vagal nucleus. Since the vagi are predominantly sensory with a wide range of chemical sensitivities, one might conclude that such afferent fibres are concerned mainly with behavioural effects, for example, satiety.

ACTION OF HISTAMINE H_2-RECEPTOR ANTAGONISTS ON DOG INTESTINAL MOTILITY: A NEW COMPUTERIZED METHOD FOR THE EVALUATION OF MIGRATING MYOELECTRIC COMPLEXES.
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The effects of three histamine H_2-receptor antagonists, Cimetidine (3-30 mg/Kg i.v.), Ranitidine (0.3-3 mg/Kg i.v.) and Famotidine (0.1-1 mg/Kg i.v.), on intestinal motility were evaluated in conscious fasted dogs. The animals had intramural electrodes permanently fitted at different levels along the small intestine. The electromyographic signal on bipolar leads was recorded on paper and on magnetic tape using a multiband frequency modulation recorder. The tracing was subsequently computer-processed in order to illustrate for each lead the various phases of the MMCs on the basis of time intervals with spikes. Differences among the H_2-blockers used were seen in their effects on frequency of MMC and duration of the examined phases.

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GASTROESOPHAGEAL REFLUX VARIES ACCORDING TO A CIRCADIAN RHYTHM.
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Occurrence of gastroesophageal reflux (GER) may vary over time,being more frequently detected postprandially and during daytime (1,2).Aim of this study was to evaluate whether GER variation shows the rhythmic characteristics of a bioperiodic phenomenon along the 24-h span.Duplicate 24-hour esophageal pH recording tests (24 h-pHT) were performed,within a period of 5 days,in non consecutive days,in a group of 20 subjects (F:18,M:2; mean age 49 years,range 27-74 years) with symptoms of GER but without endoscopic and histologic evidence of esophagitis.During the investigation diet and schedules of physical activities were standardised.Intraesophageal pH was sampled every 0.25 sec,averaged over 5 sec and continuously recorded for 24-hours by means of a combined Ingold pH glass electrode on a portable solid state memory recorder (Autronicord CM 18). Location of the glass electrode above the gastroesophageal junction (5 cm) was identical in the two studies.GER episode was defined as intraesophageal pH <3 U for at least 5 sec.GER, expressed as episodes/hour, was analysed by means of the cosinor procedure (3) to validate the occurrence of a significant circadian rhythm (CR) and,thus,to quantify the rhythmometric parameters as:mesor (24-h mean), double amplitude (total extent of variability) and acrophase (timing of circadian crest). RESULTS. A statistically significant circadian rhythm of GER ($p<0.03$) was identified in the first study and confirmed in the second investigation; on the average the acrophase timing (hour:min) was localised at 14:49 in the first study,and at 14:24 in the second study.The mean number of GER/h over the 24-h span differed significantly between the two studies: 1.3 ± 0.3 ($\pm$SE) and 1.8 ± 0.3 ($p<0.05$),respectively.The total variability of GER from mesor (double amplitude) differed significantly between the two studies: 0.7 ± 0.2 and 1.4 ± 0.3 ($p<0.01$),respectively.Analysis of data, subtracting prandial and two postprandial hours,confirmed the occurrence of a significant circadian rhythm for GER ($p<0.002$ and $p<0.02$,first and second study,respectively).

CONCLUSIONS. Results of the present study suggest that, at least in patients with symptoms of GER,the gastroesophageal reflux occurs in a circadian rhythmic fashion with a phasic crest in the early afternoon. The CR of GER seems to be not determined by meal timing. The extent of variability of the CR may vary in repeated observation.

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CHANGES IN MECHANICAL PROPERTIES OF CIRCULAR MUSCLE ASSOCIATED WITH INTESTINAL BYPASS.
A. Bortoff, L. Sillin, A. Ziegler, A. Sterns and K. Snyder. Upstate Medical Center, Syracuse, NY, 13210.

The purpose of these studies was to determine what changes occur in the mechanical response to acetylcholine (ACh) of intestinal muscle which has undergone either atrophy or hypertrophy. In an attempt to produce disuse atrophy and work hypertrophy one-half of the jejuno-ileum was bypassed in 6 cats by the Roux-en-Y procedure. At the time of surgery a 6 cm segment of jejunum was removed from the anastomotic region for use as controls. Three months later similar segments were removed from the proximal end of the bypassed segment and from the jejunum proximal to the anastomosis. These segments will be referred to as control (C), bypassed (BP) and functional (F), respectively. Rings of circular muscle were removed by blunt dissection after inverting 1-2 cm segments and stripping away the mucosa-submucosa. Five rings were placed in a 10 ml chamber which was perfused at 5 ml/min with Krebs solution (32°C) containing tetrodotoxin (2×10^{-7} g/ml) and physostigmine (10^{-6} M). The lower end of each ring was fixed by means of a stainless steel rod and the upper end was attached to a strain gauge transducer with pre-stretched silk thread. Optimal length (L_o) was determined by stimulating with electric current (60 Hz, 20 V/cm) passed between two Pt plates at either end of the chamber. L_o, (circumference in mm $\pm$ SD) was: C, 31.7 ± 2.9; BP, 26.8 ± 3.5; F, 33.3 ± 4.4. Maximal tension in response to ACh occurred at a concentration of 10^{-5} M. Tension values, ($N\times10^{-5}/m^2\pm$SD) were: C, $2.84\pm.6$; BP, 2.10 ± 1.10; F, 3.19 ± 1.15. BP values were less than F in all 6 cats ($p<.05$). C values were greater than BP in 5 of 6 cats, and less than F in 5 of 6 cats. It is concluded that Roux-en-Y bypass tends to result in atrophy and a decreased contractile response to ACh in the BP segment, and hypertrophy with an increased contractile response to ACh in the F segment.
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(A-5)

INTERDIGESTIVE GASTRIC MOTILITY AND SERUM MOTILIN IN ELDERLY SUBJECTS WITH AND WITHOUT CHRONIC ATROPHIC GASTRITIS. M.Bortolotti, P.Vezzadini, G.Fradà, G.Bonora, G.Bersani, G.Barbagallo Sangiorgi, G.Labò.
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The study was carried out in 6 normal subjects with a mean age of 76 yrs, range 70–84 yrs (group A) and in 6 patients with chronic atrophic gastritis with a mean age of 75 yrs, range 67–81 yrs (group B) using a manometric probe positioned in the stomach (S) and proximal duodenum (D), perfused with a pneumohydraulic low-compliance pump and connected to pressure transducers and a polygraph. Blood samples for motilin assay were drawn every 15 min during a recording period of about 300 min. Six non-aged controls (mean age 34 yrs, range 18–60 yrs) were also studied (group C). Results :

Group	No.of cases with phase III		Motilin (pmol/l)° during motor recording		
	S	D	motor quiescence	irregular motility	peak value
A	0	1	202±116*	228±134*	257±143*
B	1	2	293±261*	295±257*	335±280*
C	6	6	42±22	93±43	123±38

° mean ± SD ; * significantly different from controls.

The serum motilin fluctuations were also expressed as the integrated motilin output (IMO). The mean IMO in the 2 elderly groups was significantly lower than controls, but no significant difference was found between the 2 groups. The pressure waves showed a normal amplitude and frequently were grouped in clusters propagated from the stomach to the proximal duodenum. Conclusion. In both elderly groups, the incidence of phase III's is significantly lower than in controls and the serum motilin is steadily and markedly high without the normal cyclic fluctuations. The presence or absence of acid secretion does not seem to influence the abnormal pattern of interdigestive gastric motility and motilin release in aged subjects.

INTRACELLULAR RECORDINGS OF CELLS IN THE MYENTERIC PLEXUS OF RAT DUODENUM. SJH Brookes, WR Ewart, and DL Wingate. GI Science Research Unit and Dept of Physiology, London Hospital Medical College, London E1 2AJ, England.

To date, intracellular recordings of myenteric neurones have almost exclusively been made in the guinea pig; in order to test the generality of these results we have recorded from cells in the rat duodenum. Using standard techniques, stable recordings have been made of 63 cells in 30 rats. Probable glial cells (n=27) had large resting potentials (70±5 mV), a relatively low input impedance (43±12 MegOhms) and were completely inexcitable even when strongly depolarised. Neurones, however, produced impulses of 40-80 mV in response to strong depolarisation. They did not fit into the Type 1 (S Cell) and Type 2 (AH Cell) classification used in guinea pigs (J Physiol 1973, 231:471), they could however be classified as single- or multiple-spiking according to their response to depolarising current. Most neurones (27/36) only gave one impulse to any size of depolarisation, these cells had a relatively large resting potential (59±9 mV) and an average input impedance of 95±32 MegOhms. In comparison, multiple-spiking cells (9/36) fired repeatedly to strong depolarisation though they quickly adapted; they had a lower resting potential (55±6 mV) and a higher input impedance (133±61 MegOhms). Both types of cell could show long after-hyperpolarisations following impulses. Both fast and slow excitatory synaptic events were recorded from single-spiking cells although no evidence for inhibitory synaptic potentials has yet been found. Slow EPSPs lasted from 5-30 seconds, caused an increase in cell resistance, a depolarisation (2-10 mV) and a marked increase in excitability; often temporarily converting single spiking into multiple spiking neurones. Preliminary results indicate that, as in the guinea pig, some slow EPSPs are mimicked by applied exogenous Substance P.

These results indicate that although rat myenteric plexus neurones share many features with those of guinea pigs, they do not easily fit into the classification conventionally used for guinea pig myenteric neurones.

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SUCCINATE DEHYDROGENASE (SDH) ACTIVITY IN OPOSSUM ESOPHAGEAL MUSCLE. R.L. Bowers, N.W. Weisbrodt, and W.P. Dubinsky, Dept. of Physiology and Cell Biology, Univ. Texas Medical School, Houston, TX 77225 U.S.A.

Muscles from different regions of the esophagus differ in their dependence on oxygen and in their resistance to fatigue upon repetitive electrical stimulation. Circularly-oriented striated muscle strips (ST) fatigue readily whether in a hypoxic or normoxic environment. Circularly-oriented smooth muscle strips (SM) resist fatigue in a normoxic environment but readily fatigue if made hypoxic. Lower esophageal sphincter muscle (LES) depends upon oxygen to maintain tone. These results suggest that these muscles may differ in their oxidative capacity. Therefore, the present study was designed to further characterize the oxidative capacity of these muscles using the activity of SDH as an index of respiratory capacity. Muscle strips were homogenized in nine volumes of 0.175 M KCl, pH=7.5, frozen and thawed three times, and spun at 700 xg for 15 min. The supernatant was assayed by the method of Hochstadt et al (1975). When this procedure was used on opossum gastrocnemius muscle our result (5.79±0.36 µmol/min·gram wet weight) was similar to values reported for other skeletal muscles. The values for the esophageal muscle were:

SDH Activity (mean±SEM) (µmol/min·gram)		
ST	SM	LES
4.50±0.27	7.22±0.61	4.80±0.47

The relatively lower oxidative capacity of ST may reflect its easy fatigueability even in the presence of O_2. The higher SDH activity of SM may account for its ability to resist fatigue only in the presence of O_2. Like SM, LES is sensitive to hypoxia, but has a significantly lower SDH activity. However, since LES can maintain tone at very low levels of myosin phosphorylation, it therefore exhibits lower energy consumption. (Supported by NIH Grant AM19886)

INFLUENCE OF CORTICOTROPHIN RELEASING FACTOR, CORTICOTROPHIN AND CORTISOL ON NORMAL AND MOTILIN INDUCED GASTROINTESTINAL MOTILITY IN DOGS. L. Buéno, J. Fioramonti and M.P. Primi. Department of Pharmacology INRA, 180 chemin de Tournefeuille, 31300 Toulouse, France.

The gastrointestinal motor effects of intracerebroventricular (ICV) vs intravenous (IV) administration of corticotrophin releasing factor (CRF), corticotrophin (ACTH) and cortisol as well as their antagonistic action against motilin-induced gastric motor response were investigated in fasted dog chronically prepared with strain-gauge transducers on the antrum and proximal jejunum.

Administered ICV at doses of 20 to 100 ng/kg in fasted dog, CRF rapidly suppressed during 3 and 6 hours respectively the gastric cyclic migrating motor complex (MMC) without affecting that of the jejunum while a 5 times higher dose IV administered was inactive. Similar disruptive effects on gastric MMC were observed after ICV administration of ACTH (0.5 U/kg) or cortisol (0.1 µg/kg), these effects being also observed for IV administration of 10 times higher dose of ACTH but not cortisol and after a 2-3 h time lag.

The motilin induced gastrointestinal MMC following an IV administration of 0.25 µg/kg of synthetic 13 Nleu-motilin was abolished when performed 2 hours after the intravenous injection of CRF (100 ng/kg) while a similar dose of CRF, ICV administered, only partially reduced the motor response to motilin. Both ICV and IV administration of ACTH and cortisol were unable to block the gastric motor effects of IV motilin.

It is concluded that in dog (i) CRF may be involved in the central control of the interdigestive gastric motility, the other hormones of the pituitary adrenocortical system changing the gastric motility through feed-back mechanism affecting brain CRF level, (ii) circulating CRF is able to affect the gastric motor response to motilin through a peripheral or hormonal pathway mechanisms independently of its effects on pituitary adrenocorticotrophic function.

JEJUNAL MOTOR RESPONSE TO GASTRIC DISTENSION IN THE DOG. J.S. Bull, D. Grundy and T. Scratcherd. Department of Physiology, The University, Sheffield, S10 2TN, England.

The conversion from fasted to fed motor patterns is suggested to involve stimuli acting in a sequential manner at different sites, i.e. cephalic, gastric and intestinal phases. In the present study the jejunal motor response to gastric distension was quantified and compared with that of feeding in order to assess the contribution of the former to the disruptive effect on the migrating motor complex (MMC) of a normal meal.

Five dogs were prepared with Thomas-type cannulae in the stomach and duodenum. After full recovery, jejunal motility was recorded manometrically from 2 sites, 35 and 50 cm from the pylorus, before, during and after a 200-500 ml gastric balloon distension started early in phase I and maintained for 1-3 h. Gastric distension and feeding disrupted the MMC with a mean latency of 18.4 ± 2 min and 7.2 ± 1 min respectively (mean ± S.E., n=25, P<0.001). The motility evoked under both conditions consisted of irregular bursts of contraction interspersed with variable periods of quiescence. The mean data for computer analysis confirms this similarity. However there were quantitative differences in the time course of the response revealed when motility was analysed in 10 min blocks. Postprandial motility was most intense in the first period following the onset of activity and then decreased to a lower maintained level. In contrast, the contractile activity evoked by gastric distension increased steadily and peaked in the third 10 min period. Contractile activity in subsequent periods was of lower amplitude and was less regular than the corresponding periods of fed activity. On deflation MMC activity returned but the appearance of phase III could not be predicted from the previous MMCs.

Gastric distension contributes significantly to the postprandial motor pattern. However, the shorter latency response to feeding could be of cephalic origin while dietary components reinforce the later stages of the response. Similar experiments during corpus distension in dogs with a separated antrum and gastroenterostomy would appear to eliminate both release of gastrin and intramural reflexes in the genesis of this motor response.

ELECTRICAL ACTIVITY IN THE LONGITUDINAL MUSCLE OF HUMAN COLON. M.M. Chambers, Y.J. Kingma and K.L.Bowes. University of Alberta, Edmonton, Alberta, Canada T6G 2G3.

Having observed that slow-wave electrical activity does not exist in human circular colon muscle, in the same way as in canine circular muscle, it is necessary to investigate the electrical activity of longitudinal muscle in order to understand the overall control system in this organ. Intracellular electrode recordings are extremely difficult to obtain from human colonic longitudinal muscle. Therefore, we have applied the sucrose-gap technique to the measurement of signals from this tissue.

Specimens from all parts of the colon were obtained from patients undergoing surgery to the large bowel: they were immediately immersed in oxygenated Krebs' In the laboratory, after removal of the mucasa, taenial strips were cut to be approximately 1 x 15mm. It was essential that strips were cut parallel to the longitudinal muscle fibers; circular muscle was not removed. Tissues were mounted in an organ bath designed for single sucrose-gap measurements: a strain gauge was attached to that end of the sample which was in Krebs' solution.

The taenial strips contracted in a typical manner; large amplitude contractions (up to 4g), often with ripples (20-30cpm) superimposed upon them. Electrical recordings showed bursts of oscillatory activity which preceded the contractile activity. The rate of electrical oscillations corresponded to the ripple frequency of the contractions; the duration of the electrical bursts corresponded to the duration of the concomitant contractile activity. These observations do not coincide with results obtained by others, using in-vivo techniques.

We conclude that slow-wave activity as seen in, for instance, human stomach tissue, is not present in human longitudinal colonic muscle. Electrical activity does, however, probably control contractile activity in this layer, in that it always precedes it. It is likely that, given the lack of correlation between electrical and contractile activity in the circular muscle layer, that the contractile activity of the whole organ may well be controlled by the electrical activity in the longitudinal muscle.

EFFECT OF LOW RESIDUE DIET AND VAGOTOMY ON RABBIT COLON. B.N. Catchpole. University of Western Australia, Nedlands, Australia 6009.

Low residue diet (LRD) is said to raise human (1) and rabbit (2) colonic pressures. Whether pressure rises on both sides of the gut is unknown, nor if the effects are mediated by a parasympathetic neural arc. Of four groups of rabbits (40 in all) two groups were weaned onto LRD of soya chips (2% fibre), milk and vitamins, and two onto normal rabbit diet (ND). All animals had laparotomy, one LRD and one ND group having truncal vagotomy and pyloromyotomy additionally. After three months, rectal and caecal pressures during anaesthesia were recorded for 30 minutes before and 30 minutes after a bolus of i.v. neostigmine (0.05 mg/kg^{-1}). Motility indices, maximum pressures attained and duration of pressures over 25 mm Hg were studied in every time period.

Neither LRD nor vagotomy affected any parameter of caecal contractility. Faeces, however, became soft, glutinous and adherent with intermittent periods of diarrhoea in both groups of LRD.

In the rectum LRD raised motility indices ($p < 0.01$), maximum pressures attained ($p < 0.05$) and duration of pressures > 25 mm Hg ($p < 0.01$). Vagotomy had no effect. Rectal motility indices were significantly higher ($p < 0.01$) than those in the ascending colon, average differences varying with diet but not with operation.

Data indicate LRD raises left bowel but not right colon contractility and explains predominance of left-sided diverticulosis if motility changes are similar in man. Mechanism is unexplained. Truncal vagotomy does not seem to affect caecal contractile behaviour.

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TRIMEBUTINE INDUCES ACTIVITY FRONTS OF THE INTERDIGESTIVE MIGRATING MOTOR COMPLEX IN HUMAN JEJUNUM. MECHANISM OF ACTION S.Chaussade, S.Grandjouan, D.Couturier, D.Thierman-Duffaud* Hopital Cochin, 75674 Paris cedex 14, France.

Trimebutine (TMB)*(2-dimethylamino 2-phenylbutyl 3.4.5-trimetoxybenzoate hydrogen maleate) increases spiking activity and duodenal transit in man and dog. TMB is therefore used in the treatment of various gastrointestinal motility disorders. Material and method : Manometric recording of proximal jejunum was provided by a 4 lumen probe (distal openings were 10 cm apart). Spontaneous motility patterns have been recorded until the end of the first activity front (P3). 25 mn after it, either placebo (n=5), TMB 50 mg (n=4), or TMB 100 mg (n=5) were intravenously injected to healthy volonteers according to a prospective randomized double-blind protocol. In 5 other subjects, TMB 100 mg was injected 40 mn after a 500 Kcal liquid meal. Manometric recordings always lasted until a post-injection P3 occurred. The search for humoral or neuronal mediation of TMB effects was provided 1) by plasma concentrations of motilin and somatostatin measured** 2 mn before, 5, 10, and 35 mn after TMB 100 mg. 2) in 4 volonteers by IV injection of Naloxone (NLX 0.8 mg), an opioid receptor antagonist, 2 mn before TMB 100 mg. Results : 1) the period between injection and next P3 was not different after TMB 50 mg or placebo. 2) TMB 100 mg constantly induced a premature P3 in fasted state (0.81 mn ±0.39 after injection) and also in fed state (1.18 mn ±0.45 after injection). 3) patterns of TMB-induced P3 (velocity, frequency of contractions) were not different from spontaneous P3 except for slightly enhanced duration in fasted state, reduced duration in fed state. 4) plasma concentrations of motilin and somatostatin were not modified by TMB 100 mg compared with placebo. 5) the occurrence of TMB-induced P3 was constantly inhibited by previous IV injection of NLX. Conclusions : Premature P3 was constantly induced by TMB 100 mg in fasted and also in fed states. This effect should be related to a stimulation of endogenous opiate receptors.

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(A-7)

IDENTIFICATION AND CHARACTERIZATION OF THE ADENOSINE RECEPTOR ON MYENTERIC NERVE ENDINGS. F.L. Christofi and M.A. Cook. Department of Pharmacology and Toxicology, University of Western Ontario, London, Ontario, Canada. N6A 5C1.

Receptors which mediate the actions of adenosine and related nucleosides have been classified as A_1 or A_2 subtype at the CNS. Similar classification at the myenteric plexus, where adenine nucleosides function as presynaptic inhibitors of acetylcholine release, is lacking. Experiments carried out using the stimulated guinea-pig ileum preparation have revealed similar efficacies for the A_1 agonists R-Phenylisopropyladenosine (R-PIA) and cyclohexyladenosine (CHA), as well as for the A_2 agonist 5'-N-ethylcarboxamidoadenosine (NECA), as inhibitors of the twitch response.

These agonists were sensitive to competitive antagonism by methylxanthines, such as theophylline and 8-(4-Sulfophenyl)-1,3-dipropylxanthine, and Schild analysis for theophylline has revealed similar pA_2 values (4.9 - 5.1) with each of the agonists. These findings suggest that the agonists are acting at the same adenosine receptor and do not support the involvement of more than one receptor mediating the inhibitory response. However, the possibility that the myenteric adenosine receptor may display some of the characteristics of central A_1 receptors is supported by the finding of stereospecific agonism using R and S diastereoisomers of PIA and related compounds.

Parallel experiments using purified myenteric varicosities derived from guinea-pig myenteric plexus have revealed a binding site for R-PIA and NECA which displays stereospecificity for the A_1 agonist and at which the methylxanthines act as competitors. Clear structural specificity obtained in these studies suggests that this binding site is comparable with the functional adenosine receptor in the myenteric plexus.

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VAGAL CONTROL OF POSTPRANDIAL CANINE PLASMA MOTILIN AND GASTRIN LEVELS. S.A. Chung, K.E. Hall, G.R. Greenberg, and N.E. Diamant. University of Toronto, Ontario, Canada.

The relationship between postprandial vagal integrity, plasma motilin and gastrin concentrations was investigated in 4 conscious dogs. Bipolar recording electrodes were implanted serosally along the entire small bowel and the vagosympathetic trunks, previously isolated in skin loops, were blocked by cooling. A meat-based liquid food was infused by tube into the gastric fundus and hormone concentrations determined (mean ± SE pM). Fasting values of motilin (68±4) and gastrin (5±1) rose to peaks of 81±8 and 8±1 respectively, which correlated with Phases III and II of the upper migrating motor complex (MMC). Feeding produced a postprandial electrical pattern and a significant decline in motilin to a plateau of 28±3 in an hour. With blockade, the fed pattern was replaced by bursts of spikes (postprandial vagally independent complex or PVIC) that cycled with the same periodicity as the fasting MMC. During Phase III of the PVIC, motilin rose to a peak of 70±9. The motilin peak and pattern were equivalent to that observed with the MMC. Following termination of blockade, postprandial activity reappeared coinciding with a fall in motilin to 34±4. In contrast, postprandial, gastrin levels peaked at 22±3 and levelled off at 18±2 by 40 minutes. Vagal blockade significantly decreased gastrin to a nadir of 11±1. Upon termination of blockade, gastrin recovered to 18±3. In conclusion, the postprandial fall in motilin and rise in gastrin are primarily mediated by vagal excitatory pathways. Conversely, the PVIC Phase III motilin peaks are vagally independent, a situation comparable to the control of the fasting motilin peaks observed with the MMC. Moreover, the findings associated with blockade were not due to a premature end of the fed pattern since the electrical activity and hormonal levels returned to their postprandial status upon termination of blockade.

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VAGAL CONTROL OF SMALL INTESTINAL MOTILITY IN THE FASTED AND POSTPRANDIAL STATES. S.A. Chung, K.E. Hall, and N.E. Diamant. Departments of Physiology and Medicine, University of Toronto, Toronto, Ontario, Canada, M5S 1A8.

We investigated the hypothesis that vagal control of the fasting migrating motor complex (MMC) and the feeding pattern differs in the proximal and distal small intestine. Mechanical and electrical activity were monitored by strain gauges and recording electrodes implanted on the stomach and small intestine of six dogs. The vagosympathetic nerve trunks of each dog were isolated in bilateral cervical skin loops and blocked by cooling. The dogs were studied awake and unrestrained. For feeding, a meat-based liquid food was infused by tube into the gastric fundus. MMC Phases I, II and III were observed in all fasting dogs. Feeding produced an immediate postprandial pattern in the proximal 50% of the small bowel, but the distal onset was delayed. Vagal blockade abolished gastric contractions and spiking activity in both fasting and fed states as well as the feeding pattern over the entire small bowel. However, in the small bowel, migrating bursts of spikes termed vagally independent complexes (VICs) and postprandial vagally independent complexes (PVICs) were observed passing from the duodenum to terminal ileum. The cycle periods and migration times of the VIC and PVIC were not significaty different from each other or that of the MMC. In the distal 25% of the small bowel, Phases I, II and III of the MMC, VIC and PVIC were not significantly different. However, in the proximal 50%, the length of Phase III remained unchanged, while Phase II was absent in the jejunum and either absent or replaced by a very different highly variable low level spiking activity in the duodenum. On termination of vagal blockade, normal fasting or fed activity appeared in the small bowel, however reappearance of the feeding pattern was delayed distally. We conclude: 1) the duodenum, jejunum and ileum respond differently to the removal of vagal influences, the ileum being the least sensitive, 2) the fasting vagal influence is exerted primarily on Phases I and II of the duodenal and jejunal MMC, 3) vagal integrity plays a role in control of the feeding pattern over the entire small bowel, and 4) the VIC and PVIC are the vagally independent correlates of the small bowel MMC .

GI MOTILITY PATTERN OF INDIGESTION, NAUSEA AND VOMITING. C.F. Code, J.H. Steinbach, J.F. Schlegel, G.A. Hallenbeck and J.R. Amberg. VA Medical Center and University of California, San Diego, CA 92161 U.S.A.

The objective was to determine the changes in distribution of barium in stomach and small bowel and the nature of the contractions producing them, during indigestion associated with nausea and vomiting. Healthy, conscious, well trained, fasted dogs were used. Motor action of the stomach and small bowel was observed fluroscopically using a Siemens X-ray image intensifier and was recorded on video tape. After a control period of observation, apomorphine, usually in increasing doses of 0.5,1.0 or 2.0 mg/hr, was given continously intravenously.

Increased duodenogastric reflux regularly occurred during the nauseous, pre-vomiting period. This was always due to duodenogastric incoordination, during which segmental contractions, usually in the bulb or orad 1/3 of the duodenum, occurred while the pylorus was open and drove duodenal contents into the stomach.

Just prior to vomiting, an anti-perstaltic contraction, the emetic contraction, arising in the orad jejunum or duodenum forced all the contents before it into the stomach through a wide open pylorus. The barium, refluxed into the stomach by duodenal segmental or by anti-perstaltic emetic contractions, was sometimes carried by an anti-perstaltic gastric contraction from the antrum to the fundus.

Before and after vomiting, the character of the contractions in the small bowel, particularly distal to the site of origin of the emetic contraction, changed from segmental to bursts or sequences of peristaltic contractions passing over long distances of bowel (50-100 cm or more, pseudofronts). Sometimes two or three bands of such activity were present simultaneously.

The net effect of the pattern was to quickly clean out the contents of the stomach and entire small bowel, ejecting, by vomiting, that of the orad jejunum, duodenum and stomach and forcing the remainder into the large bowel.

MIGRATING AND NON-MIGRATING POSTOPERATIVE ELECTRICAL RESPONSE ACTIVITY IN HUMAN COLON. R.E. Condon, C.T. Frantzides, V. Cowles. Dept of Surgery, Medical College of Wisconsin, Milwaukee, WI.

Sets of teflon-coated stainless steel bipolar electrodes were placed in ascending and descending colon in 8 patients during laparotomy; leads were brought through needle punctures in the abdominal wall. Signals were recorded simultaneously by a polygraph for visual analysis and on magnetic tape for computer analysis. Recordings began on postoperative (PO) day 1 and continued (4 hr/day) for 8 consecutive days.

Eight ERA patterns were observed: Type 1: random action potentials singly and in bursts in both right and left colon present on the 1st (3/7 patients) or 2nd PO day. Type 2: ERA in clusters covering <50% of each slow wave (ECA) but occurring on each successive ECA in both right and left colon. Type 2M: Type 2 ERA migrating aborally or orally (velocity 2.2 +0.2 cm/min) and ocurring only in left colon. Type 2 and 2M ERA appeared on the 2nd (2/7 patients) or 3rd PO day. Type 3: ERA in clusters covering >50% of each ECA, and occurring on each successive ECA, in both right and left colon. Type 3M: Type 3 ERA migrating orad or aborad (velocity 1.9 +0.2 cm/min), seen only in left colon. Type 3 and 3M ERA appeared after the 3rd PO day. Type 4: Clusters of 3 or more non-migrating long ERA bursts (12.2+1.0 sec); observed in right and left colon after the 2nd PO day. Type 4M: Type 4 ERA migrating (velocity 1.2 +0.1 cm/sec) aborally or orally, in right and left colon after the 3rd PO day. This activity was frequently associated with complaints of "gas pains" and with defecation. Type 5: Individual long ERA bursts (duration 12.8+1.0 sec) always migrating aborally (velocity 1.7+0.2 cm/sec) in right and left colon from the 4th PO day. Most often this activity was associated with passage of flatus or defecation.

The appearance of ERA types 3M, 4M and 5 was associated with progressive clinical recovery from postoperative ileus. The time frame of resolution of postoperative ileus in man is consistent with that of subhuman primates as previously reported from this laboratory.

EFFECT OF CISAPRIDE ON ESOPHAGEAL MOTOR ACTIVITY BEFORE AND AFTER ATROPINE ADMINISTRATION.

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I.v. Cisapride (C) administration stimulates LES pressure and esophageal primary peristalsis (1), and its effect has been proposed to be mediated by an increased acetylcholine release within the gut wall (2). The aim of this study was to evaluate whether the effect of i.v. C on distal esophageal motor activity varies in the presence of i.v. Atropine (A) administration. Patients complaining of heartburn and/or regurgitation with endoscopic evidence of grade I esophagitis and/or pH-metric evidence of gastroesophageal reflux were investigated. Intraluminal pressures were recorded by means of a three-lumen silicon rubber catheter with a lumen ending into a sleeve sensor interposed between side-holes located 7 cm apart. Throughout the study period the continuously perfused manometric probe was positioned with the sleeve sensor straddling the LES. In 8 patients (M:5, F:3; age range 24-58 yrs) pressures were recorded for a 20 min period after placebo i.v. administration followed by C (8 mg in 2 min) i.v. injection and a continuous i.v. C infusion (25 µg/min) for 40 min; A (1.0 mg in 1 min) i.v. was injected 20 min after i.v. C administration. In 7 patients (M:5, F:2; age range 36-58 yrs) pressures were recorded for a 20 min period after placebo i.v. administration followed by A (0.5 mg in 1 min) i.v. injection and a continuous i.v. A infusion (1.25 µg/min) for 40 min; C (8 mg in 2 min) i.v. was injected 20 min after i.v. A administration.

RESULTS. During C administration LES pressure and amplitude of primary peristaltic contractions increased significantly from 13.1±2.6 to 23.8±4.0 (M±SE, cm H_2O) ($p < 0.01$) and from 115.0±25.7 to 155.1±35.1 ($p < 0.05$) respectively. The following A administration did not affect LES pressure response and, conversely, did totally revert the C effect on primary peristalsis. During A administration LES pressure was not significantly affected (from 15.1±2.9 to 12.1±2.1 cm H_2O), while amplitude of primary peristaltic contractions decreased significantly (from 83.8±13.4 to 46.1±9.6 cm H_2O; $p < 0.01$). The following C administration did not affect both LES and peristaltic response to A.

CONCLUSIONS. The effect of Cisapride on distal esophageal motor activity in the presence of Atropine administration appears to be, at least partly, mediated by muscarinic receptors. The different motor response of the distal esophageal body and LES to the C-A or A-C administration suggests that the two drugs interact differently at the two esophageal sites.

1. Corazziari et al. Ital.J.Gastroenterol. 15:185; 1983.
2. Pfeuffer-Friederich et al. Gastrointestinal Motility.Ed. Roman 527; 1983.

SMOOTH MUSCLE BETA-ADRENEERGIC RECEPTOR: CORRELATING OCCUPANCY WITH PHYSIOLOGIC RESPONSE OF INTACT CELLS. J.L. Conklin and F.S. Fay, University of Massachusetts Medical School, Worcester, MA 01605.

Despite the elucidation of biochemical, ionic and electrophysiologic events translating ß-adrenergic receptor activation into inhibition of smooth muscle cell (SMC) contraction, little progress has been made in understanding the receptor-ligand interactions initiating them. In previous studies we have explored the kinetics of SMC responses to ß-ligands. To further investigate the interaction of SMC ß-receptor with its activators and correlate our physiologically derived kinetic data with these interactions, we have characterized the binding of the ß-antagonist, (±) [^{3}H] CGP-12177 (CGP), to ß-receptors on freshly isolated, intact SMCs. SMCs are obtained by enzymatic disaggregation of the gastric muscularis of Bufo marinus. Carbachol-induced SMC contraction is inhibited by (-)isoproterenol (ISO), (K_{act} = 0.1µM), and this inhibition is blocked by (-)pindolol (PIN) (K_d = 560 pM). At equilibrium binding SMCs had 10,000 specific and saturable CGP binding sites/cell, (K_D = 550 pM). The K_d determined from k_{-1} and k_{+1} is 350 pM. Binding is stereoselective since (-)ISO is nearly 50 times more potent than (+)ISO in inhibiting CGP binding. CGP binding sites correspond to functional ß-receptors since PIN blocks CGP binding (K_d = 760 pM) and ß-stimulation of SMCs (K_d = 560 pM) with essentially the same potency. Unexpectedly, (-)ISO is nearly 100 times more potent an inhibitor of contraction than of CGP binding. Computer assisted analysis of the (-)ISO binding inhibition curve demonstrates high (10 nM) and low (2.2 µM) affinity sites for ISO binding. This disparity between ISO K_{act} and K_d may be explained by an agonist-induced decrease in receptor affinity, which commonly accompanies desensitization. The use of intact smooth muscle cells allows the identification of physiologically relevant receptor sites.

COMMON BILE DUCT FLOW MEASUREMENT AND SPHINCTER OF ODDI (SO) MANOMETRY.

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Sphincter of Oddi (SO) function is sometimes assessed intraoperatively by measuring the flow through the sphincter area. The aim of the present study was to comparatively evaluate flow measurements and residual pressure within the common bile duct (CBD) with SO resting and phasic activity recorded during surgery in a close time sequence. Twelve patients (M:4; F:8; age range from 28 to 70 years) with stones in the gallbladder and no stones in CBD were investigated. Manometric recordings were performed by means of a three-lumen catheter (length: 200cm; E.D.: 1.7mm) continuously perfused with sterilized distilled water by a minimally compliant hydraulic capillary infusion system. To obtain intraoperative manometry of the common bile duct SO the catheter was passed through the cystic duct and the choledochus into the duodenum and then withdrawn to localize the recording orifices within the SO high pressure zone. Flow and residual pressure have been measured according to the method described by Von Brücke.

Results. No correlation was found between maximal and mean SO resting pressure or amplitude of SO phasic contractions and either the flow of contrast fluid through the SO or the intrabiliary residual pressure. A statistically significant direct correlation ($r=0.63; p < 0.05$) was found between frequency of SO phasic contractions and intrabiliary residual pressure. Identification of SO function as normal or abnormal, according to previous data derived from control populations, diverged in the two methods in 5 of the 12 patients.

Conclusions. The resistance to the passage of fluid from the CBD into the duodenum, as measured by the method used in this study, was not predictable by measurements of SO resting and phasic pressure, but appeared to be directly related to the frequency of SO phasic contractions. These data suggest that resistance to flow into the duodenum reflect both abnormalities of SO pressures and elevated frequencies of SO phasic contractions.

MIGRATING ACTION-POTENTIAL COMPLEXES (MAPC), A MOTILITY PATTERN ASSOCIATED WITH DIARRHEA IN MAN. G. Coremans, S. Chaussade, J. Janssens, G. Vantrappen. Center for G.I. Research, University of Leuven, Belgium.

Some diarrheogenic bacteria and ricinoleic acid induce in the rabbit ileum a specific myoelectrical pattern, called MAPC. These myoelectric complexes probably represent peristaltic contractions that propel fluid over a considerable distance in the small bowel. A similar myoelectrical pattern has not yet been demonstrated in man. We studied slow wave- and spike activity in the human jejunum by means of a novel intraluminal electromyographic technique allowing the simultaneous recording from 8 bipolar electrodes built in a 5 mm polyvinyl tube at 10 cm intervals. The tube was positioned under fluoroscopic control with the proximal electrode at the angle of Treitz. Continuous uninterrupted recordings of electrical activity were obtained in each subject for periods lasting between 1.5 and 3.5 hours. Eleven healthy subjects served as controls. Diarrheogenic patterns were studied in one patient with secretory diarrhea and in 8 normal subjects after administration of ricinoleic acid (100 ml by mouth or via jejunal tube). In the control group, during a total recording period of 20 h, one MAPC, similar to that induced in rabbit ileum, was recorded (4.5 sec. in duration, migrating over a distance of 40 cm at a speed of 2.2 cm/sec). In the patient, 10 such spike bursts were observed during a 150 min recording period. Administration of ricinoleic acid to 8 normal subjects induced 9 typical MAPC's in a recording period of 26.5 hours. The duration of these MAPC's was 8.4 ± 1.7 sec (mean ± SE), the migrating distance 44.4 ± 6.7 cm (mean ± SE) and the propagation velocity 1.9 ± 0.2 cm/sec (mean ± SE). This is the first description of MAPC activity in the human small intestine. This motility pattern is observed with markedly increased frequency in secretory and laxative induced diarrhea, and may be an important factor in the pathogenesis in diarrhea.

STIMULATION OF PROPULSIVE MOTILITY PATTERNS BY CISAPRIDE IN THE UPPER GUT OF MAN. G. Coremans, S. Chaussade, J. Janssens, G. Vantrappen, P. Ceccatelli. Center for G.I. Research, University of Leuven, Belgium.

The effect of Cisapride (C.) on the electrical activity of the human upper gut has not been studied thus far. We investigated this effect in 7 volunteers by means of a novel intraluminal electromyographic technique allowing the simultaneous recording from 8 bipolar electrodes built in a 5 mm polyvinyl tube at 10 cm intervals. The proximal electrode was located at the level of Treitz. Prolonged uninterrupted recording of slow waves and spikes allowed to study the basal electrical rhythm, its phase locking or unlocking and the contractile activity. Cisapride 10 mg, injected IV during early phase 1, dramatically increased the motor activity at all levels of recording for at least 30 min, as shown by the highly significant increase in number of spike bursts ($F=86.8$; $p = 0.0001$). The most obvious effect was observed during the first 5 min period when a non-migrating phase 3-like activity that lasted for 2.6 ± 0.4 min occurred almost simultaneously at all levels. Apart from its non-migration and its shorter duration, the pattern differed from a normal phase 3 by the absence of spikes on some slow waves and by the absence of a strong phase-locking between different electrode sites. The initial phase-3 like pattern was followed by a 25 min period during which two different motility patterns were observed with increased frequency. In 3 subjects there was a marked increase in minute rhythm (from 4 bursts in the control period to 44 in the corresponding 25 min treatment period); 23% of these minute rhythm contractions travelled distally over a distance of 36.4 ± 4.5 cm (mean ± SE) at a propagation velocity of 4.1 ± 1.8 cm/sec. The second pattern, observed in 3 other patients, consisted of ultra rapid peristaltic rushes (single spike bursts progressing distally at a speed of 19.2 ± 1.2 cm/sec). Their incidence increased from 3 in the control period to 18 during the treatment period. Conclusion: Cisapride induces in the human upper gut an unique pattern of contractile activity which seems to be highly propulsive. This motor pattern is probably responsible for the accelerated small bowel transit which has been observed after cisapride.

THE SLOW WAVE FREQUENCY PLATEAUS OF THE HUMAN SMALL INTESTINE. G. Coremans, J. Janssens, G. Vantrappen, S. Cucchiara, P. Ceccatelli. Center for G.I. Research, Laboratory of G.I. Motility, University of Leuven, Belgium.

The characteristics of the slow wave (S.W.) frequency gradient of the human small intestine are largely unknown, apart from the S.W. frequency plateau in the duodenum. This is due mainly to the lack of a valid technique allowing to record in man the S.W. activity simultaneously at several levels of the small bowel. The aim of this study was to determine whether the S.W. frequency in the human small intestine decreases gradually or step-wise (with frequency plateaus). Therefore, the electrical activity of the small intestine was studied in 21 normal volunteers by means of intraluminal bipolar electrodes built in the rim of a series of suction holes arranged along a 5 mm polyvinyl tube at 10 cm intervals. Slow waves were recorded simultaneously at 6 levels over a 50 cm bowel length. The jejunum was examined in three 30 min. recordings with the proximal electrode located successively at 10 cm, 60 cm and 110 cm below Treitz (T10;T60;T110). S.W. coupling between electrodes was determined during 5 min. periods of uninterrupted S.W. recording. A plateau was defined as the zone in which S.W.'s were phase-locked (phase lag less than 360°). All subjects exhibited a step-wise decrease in S.W. frequency from 11.51 ± 0.12 cycles(c)/min at T 10, to 9.99 ± 0.16 c/min at T 160, giving rise to several frequency plateaus. The number of steps (phase-unlocking between two adjacent electrodes) per 50 cm bowel length increased from 1.24 ± 0.14 in the proximal jejunum (T10-60) to 2.0 ± 0.31 one meter more distally (T110-160), indicating that the length of the plateaus decreased along the small bowel. The fall in S.W. frequency between two plateaus was greater in the proximal than in the distal jejunum (0.91 ± 0.19 c/min and 0.55 ± 0.06 c/min resp.; $p < 0.05$). The location of the steps was not fixed but moved over a distance of 26.7 ± 3.3 cm in the proximal jejunum and of 16 ± 2.4 cm in the distal jejunum. It is concluded that the S.W. frequency gradient of the human small intestine decreases stepwise giving rise to several frequency plateaus of decreasing length. The location of the plateaus varies in time in each subject.

CHOLEDOCHODUODENAL JUNCTION (CDJ) DYSMOTILITY ASSOCIATED WITH CHOLELITHIASIS AND HYDROPS OF THE GALLBLADDER. K.L. Cox, A.T.W. Cheung, C.L. Lohse, E.M. Walsh and C.K. Iwahashi-Hosoda. Univ. of California, Davis, CA 95616, U.S.A.

Since biliary calculi tend to occur in the gallbladder rather than in the extrahepatic ducts, it is speculated that stasis in the gallbladder may play a role in the pathogenesis of stones. LaMorte et al reported that before developing gallstones guinea pigs fed a high-cholesterol diet had enlarged gallbladders which responded normally to cholecystokinin (1). Using intravital microscopy, we have documented abnormal CDJ motility in 5 male Hartley guinea pigs in which 2 had stones in the gallbladder and all 5 had enlarged, irregularly shaped gallbladders. These guinea pigs weighed from 130 to 350 gms and had been fed regular Purina guinea pig chow. They were products of 2 litters suggesting a genetic predisposition to their biliary tract disease. These animals and 10 weight-matched male controls were fasted overnight before being anesthetized and having a laparotomy exposing the biliary tract. After injecting fluorescein into the gallbladder, intravital microscopy documented bile duct and CDJ motility. The 10 normal controls had contractions of the sphincter ducts choledochi (SDC) at 6±1/min and of the ampulla at 1.2±.2/min. Their bile ducts were the same diameter as the relaxed SDC. All 5 guinea pigs with abnormal gallbladders had SDCs which did not contract and the 2 with gallstones had dilated bile ducts above the SDC. Dissection of the ducts demonstrated no stones within the lumen of the ducts.

In conclusion, altered CDJ motility was associated with stones and enlargement of the gallbladder. We postulate stasis in the gallbladder may be due to CDJ dysmotility leading to enlargement of the gallbladder and gallstone formation. This dysmotility may have a genetic predisposition.

(1) LaMorte, W.W. et. al.: Hepatology 5:21-27, 1985.

INTRAVITAL MICROSCOPY: A NEW IN VIVO METHOD FOR QUANTITATING BILIARY MOTILITY. K.L. Cox, A.T.W. Cheung, E.M. Walsh, C.K. Iwahashi-Hosoda and C.L. Lohse. University of Californit, Davis, CA 95616 U.S.A.

The purpose of this study was to use intravital microscopy, a sensitive in vivo technique which has not been previously used to study biliary motility, to document and quantitate biliary motility and flow rates in guinea pigs.

Male guinea pigs weighing 250-350 gm were fasted overnight before being anesthetized and having a laparotomy exposing the biliary tract. Bile flow rates for 6 animals were quantitated by collecting bile for 30 min from the papilla and a bile duct cannula. The volume of bile collected from the papilla, 177±16 ul/min/kg, was significantly ($P < 0.01$) greater than the volume collected from the bile duct cannula, 117±9 ul/min/kg. With the utilization of epivioiet irradiation and 40-80 x magnification, the intravital microscope documented movement of fluorescent tracers with the assistance of low-light-level Dage S.I.T. videocamera. Fasting bile flow rates (F) of 170±9 ul/min/kg for 4 guinea pigs, comparable to flow rates measured by collecting bile from the papilla, was determined by using intravital microscopy to measure internal radius (r) of the duct and distance (d) 10 um diam. fluorescent beads traveled over time (t). $F=\pi r^2 d/t$. The phenomena of biliary motility was viewed on a television screen and documented on videotape. After injecting fluorescein into the gallbladder in 10 guinea pigs, we observed rhythmic, asymmetrical contractions of the sphincter ductus cholecochi (SDC) at 6±1/min milked bile into the ampulla nad prevented reflux of bile during ampullary contractions. The ampulla at 1.2±.2/min propelled bile into the duodenum through the papilla. The bile duct narrowed in diam. as it was stretched towards the duodenum during SDC contractions and was without peristalsis. Following injection of (Ensure) into the duodenum, the frequency of SDC contractions decreased, the duration of SDC and ampullary contractions increased, and the interval between SDC contractions increased.

In conclusion, intravital microscopy proved to be a sensitive, in vivo technique in which to quantitate bile flow rates and document biliary motility.

EFFECT OF PROENKEPHALIN A AND PROOPIOMELANOCORTIN PROCESSING FRAGMENTS ON MOTILITY IN THE SMALL INTESTINE. T. P. Davis and G. Hoyer. University of Arizona, Department of Pharmacology, Health Sciences Center, Tucson, AZ 85724 U.S.A.

Opioid peptides are derived from three precursor proteins proopiomelanocortin (POMC), preproenkephalin A and preproenkephalin B. POMC contains the sequence of β-endorphin (β-E), α-endorphin and γ-endorphin. Preproenkephalin A contains the sequence of peptide E, met-enkephalin, and other biologically active peptides. Our laboratory has been studying the functional significance of (1) proteolytic processing of the POMC related fragment β-E and the preproenkephalin A fragment, peptide E in the wall of the small intestine and (2) the effects of processing fragments on phasic and tonic pressure changes in the isolated, vascularly perfused canine small intestine (Burks and Long, A.J.P. 211:619, 1966). We reported previously (Davis et al, JPET 227:499, 1983) that β-E is metabolized by regions of the canine small intestine to met-enkephalin, α-endorphin, γ-endorphin, and des-enkephalin-γ-endorphin. Each of these β-E fragments was vascularly perfused (1 μg/ml) while measuring contractions with an intraluminal balloon. β-E perfusion showed an initial tonic followed by a series of phasic pressure changes. The sequential processing fragments α-and γ-endorphin showed phasic pressure changes with a slight amount of superimposed tonic activity. The parent peptide, β-E elicited the highest pressure (44.5 mmHg) increase above baseline and the shortest fragments met-enkephalin and des-enkephalin-γ-endorphin were the lowest (2-9 mmHg). Incubation of peptide E with the small intestine also yielded several biologically active fragments which showed increases in phasic and tonic pressure. The contractile response to peptide E perfusion consisted of phasic superimposed upon tonic pressure changes which lasted throughout the duration of peptide perfusion (5 min), whereas, the processing fragments BAM12 and met-enkephalin both showed an initial tonic pressure change of short duration (20 sec) followed by a long phasic response with no superimposed tonic activity. The rank order of phasic pressure increase was peptide E > BAM 22P > BAM 12P > met-enkephalin. This supports our earlier finding on β-E that a correlation exists between fragment length and the specific type of contractile response.

PRE-GANGLIONIC TRANSMISSION OF SEROTONINERGIC ACTIVITY IN THE DIGESTIVE TRACT. HI Davidson, G-P Zara, M-A Pilot, HH Thompson. GI Science and Surgical Research Units, The London Hospital Medical College, 26 Ashfield Street, London E1 2AJ, UK

We have studied the effects of serotonin (5-HT) and its precursor 5-hydroxytryptophan (5-HTP) on canine small intestinal myoelectric activity and used the ganglionic blocker hexamethonium to investigate their mode of action.

Serotonin was given as an intravenous infusion at 3 different rates, 5, 10 and 20 ug/kg/min. 5-HTP was given iv either as an infusion (20 ug/kg/min) or as a single injection (5 mg/kg). Hexamethonium (2 and 48 mg/kg/hr) was infused iv for 30 minutes during the 5-HT or 5-HTP infusion, or after the single injection of 5-HTP.

Both serotonin and 5-HTP significantly increased spiking activity during the infusion. Whereas the effect of serotonin was confined to the period of infusion, increased spiking activity was present for at least 2 hours following 5-HTP. The single iv injection of 5-HTP caused a large initial increase in spiking activity, followed by irregular activity. High doses of hexamethonium abolished all activity induced by 5-HT and 5-HTP for one hour, after which a motility pattern comparable to control was resumed. At a low dose, hexamethonium inhibited the increase in spiking activity caused by 5-HTP, but only partially inhibited the serotonin-induced activity. A regular fasting pattern with MMCs was observed when the infusion of 5-HT or 5-HTP was discontinued.

These experiments show that both serotonin (5-HT) and its precursor have an excitatory effect on small intestinal motility. The results with hexamethonium also suggest that both 5-HT and 5-HTP may be acting via the ganglion, but that 5-HT also has another mode of action, probably a direct effect on smooth muscle.

THE USE OF ELECTRICAL FIELD SIMULATION TO STUDY ELECTRICAL COUPLING IN THE CANINE COLON. N.G. Durdle, Z. Sawicki, Y.J. Kingma, and K.L. Bowes. University of Alberta, Edmonton, Alberta, T6G 2G7, Canada.

Electrical slow wave activity in the stomach and small intestine has been effectively modelled using coupled relaxation oscillators. Such modelling has been useful in providing information regarding the role of the slow wave in controlling contractions in these organs.

The low degree of coupling in the canine colon results in randomly varying relative phase angles between regions. This has prevented measurement of the degree of coupling and the construction of a coupled oscillator model.

The objective of this study was to use electrical field stimulation to entrain the slow wave and to study coupling characteristics using variations in relative phase angles as a function of entrainment frequency.

Circularly and longitudinally oriented in vitro stips of canine colon were superfused with Krebs-Ringer solution and stimulated with a muscle stimulator using pulses of 200 millisecond duration and frequency ranging from 100% to 150% of the basel frequency. Slow wave frequencies and relative phase angles were plotted as a function of stimulation frequency.

The results confirm that coupling is very small in both the longitudinal and circular directions and that it is very difficult to entrain slow waves at frequencies more than 10% higher than the basel frequency. The results indicate that coupling in the circular direction is not greater than in the longitudinal direction. Stimulation frequencies 10% greater than the basel frequency result in an increase in slow wave frequency without entrainment.

It is concluded that field stimulation does not yield sufficient data to create the required coupled oscillator model.

VENTROMEDIAL HYPOTHALAMUS (VMH) STIMULATION ALTERS FASTING AND FED MYOELECTRIC ACTIVITY OF THE RAT SMALL INTESTINE. C. Eeckhout and C. Reyes-Vazquez. Department of Physiology Universidad Nacional Autonoma de Mexico,04510 Mexico.

Stimulation of the ventromedial hypothalamus (satiety center) stops feeding in rats. The question arises whether the VMH besides being involved in the regulation of feeding is also involved in the regulation of fasting and fed myoelectric activity of the small intestine. In 7 rats bipolar stimulating electrodes made of insulated Nichrome wire of 60um diameter were positioned stereotaxically and bilaterally in the VMH and 4 bipolar silver electrodes were placed on the small intestine. Experiments were performed after animals had recovered from surgery and while they were conscious and unrestrained. Stimuli to the VMH were delivered by means of an optical stimulus isolation unit for periods of various duration at a frequency of 60 Hz, a pulse width of .1 msec and intensities varying from 0.1 to 5 mA. Before starting stimulation, myoelectric activity was recorded for a 1 h period as a control. In the fasting state regular migrating complexes were observed. Stimulation for a short period during phase III in the duodenum caused only a transient disruption of the MMC, whereas stimulation at higher intensities caused disruption of the MMC pattern for the entire stimulation period (up to 1 h). During stimulation the intensity of spiking activity decreased. Stimulation of the VMH in rats fed at libitum caused a prompt decrease in the amount of spiking activity. Spiking activity increased immediately when the stimulation ceased. The rapidity of these effects suggests a nervous mechanism. In conclusion the present experiments indicate that the VMH can influence fasting and fed myoelectric activity of the small intestine. The mechanism of the decrease in activity is unknown. (Supported by PCSACNA-222333 of the Consejo Nacional de Ciencia y Technologia (Conacyt) de Mexico and by the National Fund for Research (NFWO) of Belgium.)

MOTOR PATTERNS OF THE CANINE SMALL INTESTINE. H.J. Ehrlein, M. Schemann and M.L. Siegle. Institute of Zoophysiology, University of Hohenheim, Stuttgart, Fed. Rep. of Germany.

The motor patterns of the small intestine are unsufficiently investigated and documented. Therefore, we studied the canine duodenal, jejunal and ileal motility by means of closely spaced strain gage transducers. The analysis of the temporal and spatial distribution of contractions and the fluoroscopically observed transit of chyme enabled the recognition of different motor patterns. Two patterns of segmenting activity and four patterns of propulsive activity were found. The segmenting activity consisted of (1) stationary individual contractions, and (2) stationary clusters of contractions. Patterns of propulsive activity were: (1) the migrating motor complex, (2) migrating clusters of contractions, (3) propagative waves, and (4) migrating power contractions. The rate of the aboral migration differed markedly between the propulsive motor patterns; it increased in the order: migrating motor complex, migrating clusters of contractions, migrating power contractions, propagative waves. The propagation velocity generally decreased from the proximal to the distal part of the small intestine. Only the migrating power contractions moved along the small intestine with slightly increasing velocity. The transit rate of digesta depended (1) on the propagation velocity of the motor patterns, and (2) on their length of spread. A retrograde transport of chyme was produced by two different motor patterns: (1) retrograde propagative waves, and (2) retrograde power contractions. The patterns of retrograde moving activity occurred only during intestinal disorders, after strong intestinal stimuli, or after the administration of hormones and drugs. Conclusion: The small intestine produces several patterns of segmenting, propulsive and retrograde moving activity.

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INTERDIGESTIVE SMALL BOWEL MOTILITY IN ACHALASIA. J.F. Erckenbrecht, P. Nemes, T. Peeters, W. Berges, M. Wienbeck. Dept. of Internal Medicine D, University Hospitals, Düsseldorf, F.R. Germany and Katholieke Universität, Leuven, Belgium.

This study examines the question whether the motor disorder in achalasia is limited to the esophagus or includes other organs such as the small bowel. The occurence of phase III and the number and propagation of single contractions during phase II of the migrating motor complex (MMC) in the upper small bowel of 6 patients with achalasia (4 men, 2 women; age 41 ± 14 yrs) and 6 healthy controls were studied manometrically at 6 closely spaced recording sites. Basal recordings lasted for 4 h, followed by the i.v. application of somatostatin (125 ug as a bolus, followed by an infusion of 1.5 ug/kg bw/h) for 1 h. Results ($\bar{x}$ ± SEM): The characteristics of phase III of the MMC and the total number of contractions of phase II were not different in achalasic patients and healthy controls. However, simultaneous contractions of phase II of the MMC expressed as percentage of the total number of phase II contractions were increased in the achalasic patients as compared to the healthy controls (27% ± 2 vs 8% ± 1; $p < 0.01$), while propagated single contractions were reduced (13% ± 2 vs 41% ± 5; $p < 0.01$). After application of somatostatin the number of phase II contractions expressed as percentage of the total number of contractions of the MMC cycle was reduced from 66% ± 9 to 11% ± 1 ($p < 0.001$) both in achalasic patients and healthy volunteers. Summary: In achalasia upper small bowel motility shows pronounced disturbances of phase II of the MMC. The number of simultaneous contractions is increased, while propagated contractions are reduced. It is concluded that the motor disorder in achalasia is not confined solely to the esophagus.

MOTILITY RECORDINGS IN THE UPPER SMALL BOWEL STRESS HEALTHY VOLUNTEERS. J.F. Erckenbrecht, S. Rehm, A. Schoepe-Stiller, H.J. Lübke, M. Wienbeck. Dept. of Internal Medicine D and Occupational Medicine, University Hospitals, Düsseldorf, F.R. Germany.

This study aimed to quantitate mental stress in healthy volunteers during motility recordings in the upper small bowel. Eight males (age 22-30 yrs) were studied during two 5 hour periods one with and one without intestinal intubation. The tube was a standard 6 lumen motility probe. Stress was assessed by a number of objective and subjective indicators. The first encompassed measurements of blood pressure, breath rate, heart rate, levels of serum adrenaline and noradrenaline, and the finger pulse amplitude before and during an additional stress application (100 dB broad frequency noise). The subjective response to the tube was evaluated by a standardized interview allowing to quantitate 8 different stress symptoms. Results ($\bar{x}$ ± SD): Blood pressure, heart rate, and the levels of serum adrenaline and noradrenaline remained unchanged. The intubation had only minor effects on breath rate (12/min ± 2 ⟶ 14/min ± 2; $p < 0.05$) and finger pulse amplitude recovery (25% ± 10 ⟶ -7% ± 2; $p < 0.05$). However, during intubation the stress symptoms increased markedly (score 0.46 ± 0.17 intubated vs 0.31 ± 0.21 not intubated; $p < 0.01$). There was no correlation between the objective and subjective indicators of mental stress. It is concluded that motility recordings in the human upper small intestine via an oro-intestinal tube expose normal persons to pronounced mental stress which is only incompletely reflected by objective variables.

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THE EFFECT OF MENTAL STRESS BY NOISE ON MOTILITY AND FLUID ABSORPTION IN THE HUMAN UPPER SMALL BOWEL. J.F. Erckenbrecht, A. Schoepe-Stiller, J. Borgos, S. Rehm, M. Wienbeck. Dept. of Internal Medicine D, University Hospitals, Düsseldorf, F.R. Germany.

Mental stress by noise accelerates small bowel transit and increases stool weight and stool frequency (Gut 25 (1984) 1311). We hypothesized that alterations of transmural fluid transport may be responsible for these changes. To answer this question motility and transmural fluid transport in the upper small bowel of 16 male healthy volunteers (age 22-30 yrs) were investigated with and without mental stress in a randomized cross-over study. Mental stress was exerted by a 100 dB noise applied intermittently for 5 hours. Blood pressure, heart rate, breath rate, and serum adrenaline levels served as indicators of mental stress. Motility and transmural fluid transport in the duodenum and jejunum were measured by means of a perfused 5 lumen tube. Results ($\bar{x}$+SD): Noise increased heart rate (62/min ± 9 ⟶ 67/min ± 9; $p < 0.05$) and breath rate (14/min ± 2 ⟶ 15/min ± 3; $p < 0.05$). Blood pressure and serum adrenaline levels remained unchanged. Noise did not alter the number, duration, and propagation velocity of phase III or the cycle length of the migrating motor complex (MMC). Also, transmural transport of water and electrolytes were not changed by mental stress. Summary: Alterations of the MMC and transmural fluid transport in the upper small bowel are not responsible for the increase of stool weight and stool frequency under mental stress by noise. It is concluded that the changes of bowel habits under mental stress are due to an altered function of the colon rather than the small intestine.

Supported by Der Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen , F.R. Germany.

ABNORMAL MOTILITY PATTERNS IN THYROTOXICOSIS. D.F.Evans K.C.Ballantyne, C.A.Pegg, J.D.Hardcastle, Dept. of Surgery University Hospital, Nottingham, UK.

Diarrhoea and increased bowel frequency are symptoms often associated with thyrotoxicosis and this has been shown to be characterised by increased small bowel transit (1). Other factors important in motility of the GI tract have not been examined.

In this study gastrointestinal motility and transit have been measured for 24 hours in 15 patients with untreated thyrotoxicosis (mean T_3=6.99 ± 3.9mmol) and 20 age-matched normal controls. Fasting small bowel migrating motor complexes (MMC) and motility after a 500kcal meal were recorded using two tethered radiotelemetry capsules. Mouth to caecal and whole gut transit times were measured by breath hydrogen excretion and radio-opaque marker methods

There was a significant increase in the frequency of the MMC, more rapid mouth to caecal transit time and an increased whole gut transit in the thrtoxic patients when compared to the normals. Disruption of the MMC by the meal was shorter in the thrtoxic group but this failed to reach significance.

	Patients n=15	Normals n=20	t or u
MMC intervals (mean)	75.4min	105.4min	t=4.8
sem	(± 4.34)	(± 4.2)	p=0.001
Median mouth to caecal	335 min	450 min	u=57
transit (range)	(195-460)	(300-595)	p=0.003
Median whole gut	26 hours	36 hours	u=45
transit (range)	(12-56)	24-100)	p=0.02
Median disruption of	334min	432min	
MMC by meal (range)	(220-504)	(186-564)	p=ns

In this study abnormalities have been seen in small bowel motility and transit in thyrotoxic patients although only 33% complained of diarrhoea or increased bowel frequency at the time of the study. Thyrotoxicosis does therefore cause objective changes in GI motility

(1) Shafer RB, Prentiss RA, Bond JH. Gastrointestinal transit in thyroid disease. Gastroenterology 1984 86: 852-855

NONINVASIVE MEASUREMENTS OF GASTRIC ELECTRICAL AND CONTRACTILE ACTIVITY. B.O. Familoni, Y.J. Kingma, I. Rachev, K.L. Bowes. University of Alberta, Edmonton, Alberta, CANADA, T6G 2G3.

Electrogastrography on patients has been reported by various authors. With suitable electrode placement reliable recordings of gastric electrical activity can be made. This method yields only information regarding existence and frequency of gastric electrical signals. The method would be more suitable as a diagnostic tool if the occurrence of actual contractions and the direction of propagation could be registered. We have developed a method to obtain this information from skin-electrodes placed on the torso. A four electrode method is used to measure the impedance of the torso in the region of the gastric antrum. Two of these electrodes serve to inject a 1.0 mA,100 kHz current into the body, and two other electrodes are used to measure the voltage drop at this frequency over the gastric region. Changes in the shape of the stomach can thus be detected. The two measuring electrodes can simultaneously be used to register the myographic activity of the stomach. The antral contraction waves, if they exist, can occur only synchronous with the ECA; thus cross-correlation of the impedance signal and the gastrogram will reveal the occurrence of contraction waves. To obtain information about the propagation direction of the contractions is more difficult with this method. Since the signal propagation along the antrum shows similarity with that of the cardiac atria and since the P-wave polarity (with given electrode locations) is determined by the propagation direction we have made the assumption that a similar relationship holds for the antrum. To predict the features to look for in the measured signals we have developed a mathematical model. A distinct difference between initial and terminal slope of the measured signals should indeed indicate the direction of propagation. Measurements on 10 subjects confirmed that this non-invasive method yields electrical (in all 10 cases) as well as contractile (in 8 cases) information on the stomach, making it a potentially useful diagnostic tool.

NALOXONE RESISTANT EFFECTS OF CENTRAL ADMINISTRATION OF OPIATES ON DIGESTIVE MOTILITY IN DOGS. J. Fioramonti, L. Buéno and M.J. Fargeas. Department of Pharmacology INRA, 180 chemin de Tournefeuille, 31300 Toulouse, France

Intracerebroventricular (ICV) administration of morphine or some endogenous opioid peptides has been found to inhibit intestinal transit time and to modify gastrointestinal and colonic motility. In most of these studies attempts to block these effects have been rarely performed. We report here three examples of effects of centrally administered opiates which are not blocked by naloxone.

Experiments were performed in six dogs chronically fitted with strain gage transducers sutured to the serosa of the antrum, the proximal jejunum and the proximal colon.

In fasted dogs the colonic motility index was nearly tripled during the hour following ICV administration of morphine (10 µg/kg). This effect was not blocked by previous ICV admnistration of naloxone at a dose of 100 µg/kg. A similar increase of the colonic motility index was observed after IV administration of morphine (100 µg/kg). This effect was blocked by naloxone given IV or ICV at respective doses of 1 and 0.1 µg/kg.

($D\text{-}Ala^2$, Met^5) enkephalinamide (DALAMIDE) ICV administered 30 min after a meal (20 ng/kg) restored a fasted pattern of MMC on the jejunum. DALAMIDE ICV given (50 ng/kg), 10 min before a meal, significantly ($P < 0.01$) increased the postprandial colonic motility index. These effects were not blocked by previous ICV administration of naloxone (100 µg/kg) or a selective δ antagonist, ICI 174864 (0.5 µg/kg) and were not reproduced by IV administration of DALAMIDE at a 10 times higher dose.

These results suggest that in dogs, the effects of central administration of opioid peptides on digestive motility do not involve µ or δ opiate receptors and that the receptors involved in the effects of central administration of morphine on colonic motility are different from those involved in the central effects of morphine intravenously administered.

CHANGES IN CHOLINE ACETYLTRANSFERASE ACTIVITY IN MYENTERIC DENERVATED RAT JEJUNUM. D.A. Fox, P. Bass, M.L. Epstein, and J.L. Dahl. University of Wisconsin, Madison, WI U.S.A.

Serosal application of the cationic surfactant benzalkonium chloride (BAC) to the rat jejunum destroys over 90% of myenteric neurons without altering the number of submucosal neurons. In order to determine the relative distribution of cholinergic nerves in the myenteric and submucosal plexuses, we have measured the activity of the enzyme choline acetyltransferase (ChAT), a specific marker for cholinergic neurons, in both normal and BAC-treated jejunum. A 0.062% solution of BAC was applied to the serosal surface of a 3 cm segment of rat jejunum as previously described (J. Pharmacol. Exp. Ther. 227:538-543, 1983). BAC-treated and contiguous untreated (control) segments of jejunum were removed 2, 5, 15, 22, and 45 days after BAC-treatment, frozen in liquid nitrogen, and stored at -80°C until the time of assay. The tissue segments were homogenized in 25 mM phosphate buffer, pH 7.4 containing 0.1 mM mercaptoethanol, 1 mM EDTA, and 20 mM phenylmethylsulfonylfluoride. The homogenates were centrifuged at 27,000 x g for 30 minutes. ChAT activity in the resultant supernatant solutions was measured essentially as described by Fonnum (J. Neurochem. 24:407-409, 1975). Total ChAT activity per unit length of jejunum was 60%, 70%, 125%, 122%, and 178% of that found in control segments at 2, 5, 15, 22, and 45 days, respectively, after BAC-treatment. These results, together with our previous data which demonstrated a significant reduction in the total number of ganglion cells in the myenteric plexus after BAC-treatment, suggest that: (1) a substantial portion of intestinal ChAT is located in the submucosal plexus and (2) a decrease in cholinergic neurons in the myenteric plexus elicits a compensatory increase in ChAT activity in the submucosal plexus. (Supported by NIH grants AM32594 to PB and AM32978 to MLE and funds provided by the Research Committee of the UW Graduate School to JLD).

EXPRESSION OF PEPTIDE RESPONSES DEPENDS UPON STUDY ENVIRONMENT. J.E.T. Fox, S.M. Collins, and E.E. Daniel. Program for Study of Control of Smooth Muscle Function, McMaster University, Hamilton, Ontario, Canada, L8N 3Z5.

To determine the effects of structural complexity on peptide action, we compared the actions of peptides on circular muscle of the canine gastric corpus and small intestine: (a) in vivo using anaesthetized dogs receiving peptide by close intraarterial injection; (b) in vitro using circular muscle strips suspended in tissue baths; and (c) on single circular muscle cells isolated by collagenase. Tetrodotoxin was used as a neural blocking agent and 48/80 as a mast cell degranulating agent. Results are illustrated below:

PEPTIDES	IN VIVO		IN VITRO STRIPS		
	Nerve	Muscle	Nerve	Muscle	Mast Cell
Gastrin (G)/Bombesin (B)	↑1,↓2	0	0	↑1	
Motilin (M)	↑1,2	0	0	0	
Substance P (SP)	↓2*,↑1*,2	↑1,2	0	↑1,2	
Met enkephalin (MET)	↑2*,↑1,2	↑2	↓2	0	
Dynorphin (D)	↑1,2	0	↓2	0	
Neurotensin (N)	↑1*,2*	↑1,2	0	↑2*,↑1*,2	↑1,2
Galanin (Gal)	0	↑1,2	0	↓2	

*excitation; ↓inhibition; 0 no response; 1 stomach; 2 small intestine; *occurs at lowest concentration

In addition G, B, M, and SP contracted the isolated cell at 100-fold (10^{-13} M), less than that required for the strip studies. Thus for G, B, and M, neural responses were present only in vivo; whereas myogenic, excitatory responses absent in vivo were found in vitro. SP neural actions were only present in vivo, but muscle responses occurred in all situations. In contrast, MET myogenic excitatory actions were seen only in vivo. N and Gal inhibited the muscle both in vivo and in vitro, but N stimulated nerves only in vivo and excited via muscle and mast cells only in vitro. Thus, expression of occupation of peptide receptors on muscles, nerves, and mast cells appears to be determined by the local environment. Furthermore, since peptides may act at more than one site to produce the same or opposite effects, caution must be used in attempting to define the physiological mechanism on the basis of data obtained exclusively in vivo or in vitro. Also, the single isolated cell may not be a simple unit of the tissue strip. MRC supported.

EFFECT OF PUTATIVE ENTERIC NEUROTRANSMITTERS ON NORMAL AND MYENTERIC NEURON-ABLATED RAT JEJUNUM. D.A. Fox, J.R. Herman, M.L. Epstein, and P. Bass. University of Wisconsin, Madison, WI 53706 U.S.A.

The site of action of several putative enteric neurotransmitters was evaluated by comparing their responses on isolated control and myenteric neuron-ablated rat jejunum. The myenteric plexus was destroyed by serosal application of the cationic surfactant benzalkonium chloride (BAC) (J. Pharmacol. Exp. Ther. 227:538-543, 1983). Fifteen days after 0.062% BAC treatment, both the treated and an orad control jejunal segment (~ 2.0 cm) were removed and suspended in isolated tissue baths for the measurement of isometric tension of the longitudinal muscle. Contractile responses were expressed as a percentage of the maximum tissue contraction produced by barium chloride, whereas relaxant responses were expressed as a percentage of papavarine-induced maximum relaxation. The BAC-treated jejunal segments were previously shown to be unresponsive to ganglionic stimulants and nerve-selective electrical stimulation but fully responsive to carbachol (Fed. Proc. 44:824, 1985). Substance P caused a dose-dependent contraction in both control and BAC-treated tissues. Norepinephrine caused a dose-dependent relaxation in both control and BAC-treated jejunum. In the case of both substance P and norepinephrine, there was not a significant difference in the ED_{50} values and maximum responses between control and BAC-treated jejunum. In contrast, 5-HT elicited a dose-dependent contraction in control jejunum (max. response:80.3±3.5%) which was markedly greater than the BAC-treated jejunum (max. response:13.6±7.1%). CCK-8 contracted the control (30.0±4.0% max. contraction) but not the BAC-treated tissue. VIP relaxed control jejunum (max. response:42.9±5.1%) to a much greater extent than the BAC-treated tissue (max. response:7.5±4.8%). It is concluded that substance P and norepinephrine act predominantly on the longitudinal smooth muscle, whereas 5-HT, CCK-8, and VIP probably act indirectly through the myenteric plexus. (Supp. by NIH grant AM32594 to PB and AM32978 to MLE.)

GALANIN, A PEPTIDE WITH POTENT SMOOTH MUSCLE INHIBITORY ACTIONS IN THE CANINE SMALL INTESTINE. J.E.T. Fox[1] and T.J. McDonald.[2] Program for Study of Control of Smooth Muscle Function, McMaster University,[1] Hamilton, Ontario, University of Western Ontario,[2] London, Ontario, Canada.

The 29 amino acid peptide galanin was recently isolated from porcine upper small intestine by Tatemoto et al (FEB LET, 1983, 164, 124). At least for the rat gastrointestinal tract it is located in nerves (Rokaeus et al, Neurosci, 1984, 47, 1661) and excites isolated rat stomach, duodenum, ileum, and colon strips. We investigated its action on circular muscle contractility (as monitored by serosoal strain gauges) of the canine small intestine by close intraarterial injection during Na pentobarbital anaesthesia. Neither synthetic nor purified natural galanin (a gift of Dr. Tatemoto) produced any responses in the quiescent gut. However, when phasic activity (spontaneous, field-stimulated, or motilin-induced) was present, either synthetic or natural galanin produced inhibition of both phasic and toxic activity at $\simeq 10^{-10}$ mols ia. The inhibition was not reduced by atropine, hexamethonium, naloxone, or yohimbine treatment suggesting that inhibitory muscarinic, nicotinic, opiate or adrenergic receptors on nerves were not involved. Sufficient tetrodotoxin to eliminate field-stimulated responses and produce spontaneous phasic activity increased the duration of the galanin inhibition. Both synthetic and natural galanin at 9×10^{-10} mols eliminated the excitatory response to intraarterial acetylcholine for the duration of the galanin inhibitory response. These results suggest that galanin produces inhibition by a direct action on the smooth muscle alone. It is more effective following tetrodotoxin because field-stimulated neural excitatory input has been eliminated. Thus galanin would appear to be a putative neural peptide which in the canine small intestine acts directly on the smooth muscle to produce inhibition as a non-adrenergic, non-cholinergic inhibitory neurotransmitter. Supported by the MRC of Canada.

MORPHINE EFFECT ON MONKEY COLONIC MOTILITY. C.T. Frantzides, R.E. Condon, W.J. Schulte, T. Matsumoto, V.Cowles. Dept. of Surgery, Medical College of Wisconsin, Milwaukee, WI.

We investigated the effect of morphine on colonic myoelectric and motor activity in monkeys to determine regional differences within the colon in morphine response. In each of 4 monkeys (Macaca arctoides) four combined strain gage transducers and bipolar electrodes were chronically implanted on the ascending colon, hepatic flexure, splenic flexure and sigmoid colon. On each study day, baseline recordings were made for 3 hours in fasted, unanesthetized animals. Morphine sulphate was then given IV in doses of 10,25,50,100,500,1000 µg/kg. The order of dosing was randomized. Sufficient time elapsed between studies for all effects of previous doses to clear.

The basal fasting pattern of colonic motility was characterized by non-migrating clusters of contractions and migrating individual contractions (MIC). The clusters consisted of groups of 5-10 contractions occurring randomly at each recording site. The MIC, originating in the right colon and migrating to the sigmoid colon occurred at a frequency of 3-4/hr. The migration velocity of MIC was approximately 1 cm/sec.

Morphine at very low doses (10-25/µg/kg) had no effect on colonic motility at any site. At doses of 50-200 µg/kg, clusters and MIC's were eliminated but there was an overall increased motility entirely due to increased contraction frequency; there was no alteration in contraction amplitude or duration. At morphine doses of 500 and 1000 µg/kg, contractions clusters and MIC's again were not seen, but at these doses there was a decrease in colonic motility due entirely to decreased contraction frequency. Both stimulation and inhibition were least marked in the right colon, the responses progressively increasing in magnitude at each more distal recording site with the most pronounced effects seen in the left colon. Morphine did not alter slow wave frequency at any site.

We conclude that 1) Morphine at lower doses (50-200 µg/kg) stimulates and at higher doses inhibits random colon contraction frequency without a significant change in mean amplitude or duration of contractions; 2) Morphine at and above doses of 50 µg/kg eliminates the normal contraction clusters and MIC's seen in fasting animals. Both excitatory and inhibitory effects were most marked in the sigmoid colon.

ROLE OF CHOLINERGIC MECHANISMS IN ESOPHAGEAL PERISTALSIS. J.S. Gidda and J.P. Buyniski. Gastrointestinal Research, Pharmaceutical Research and Development Division, Bristol-Myers Co., Syracuse, New York 13221 U.S.A.

The purpose of this study was to examine the role of cholinergic mechanisms in esophageal peristalsis. Studies were performed in ten anesthetized opossums. Swallow induced motility was recorded at 5 and 1 cm above the lower esophageal sphincter, using a manometric catheter assembly. Evoked swallows were marked by mylohyoid activity. Each swallow (n=50) evoked peristaltic contractions. At the 5 cm site the latency, duration and amplitude of contraction were 2.1 ± .12 sec (± SE), 1.8 ± .31 sec and 74.5 ± 6.1 mm Hg, respectively. At the 1 cm site the respective values were 5.2 ± .24 sec, 3.8 ± .32 sec and 42.0 ± 3.8 mm Hg, respectively. The calculated speed of peristalsis was 1.21 cm/sec. After treatment with the cholinesterase inhibitor physostigmine (100 µg/kg) each swallow evoked simultaneous, repetitive and long duration contractions. The values of latency, duration and amplitude of contraction at 5 cm site, after physostigmine treatment were 1.2 ± .16 sec, 6.6 ± .42 sec and 166.2 ± 8.9 mmHg, respectively. At 1 cm site the respective values were 1.5 ± .18 sec, 8.2 ± .38 sec and 86.8 ± 7.4 mmHg. The calculated speed of peristalsis was 13.3 cm/sec. These values were significantly higher than controls ($p < .01$). The characteristics of swallow evoked contractions after treatment with metoclopramide (10 mg/kg, iv), which enhances cholinergic neural component of contraction, were similar to that seen after physostigmine treatment. Atropine (30 µg/kg, iv) reversed the influence of physostigmine and metoclopramide resulting in a significantly slower speed of peristalsis. This data suggests that excessive release of acetylcholine or prevention of its breakdown may contribute to the development of repetitive, high amplitude, long duration contractions similar to those seen in patients with diffuse esophageal spasms.

SEROTONIN MEDIATED EFFECTS OF TRYPTAMINE IN THE MYENTERIC PLEXUS. M.D. Gershon, G.M. Mawe, M. Takaki and J.M. Barasch. Dept. Anat. Cell Biol., Columbia Univ. P&S, New York, NY 10032 U.S.A.

The enteric neural receptor for serotonin (5-HT) has been characterized, electrophysiologically and by radioligand binding with ^{3}H-5-HT. An absolute requirement of 5-HT analogs for affinity at this site is an unsubstituted OH-group on the indole ring. Thus, the non-hydroxylated compound, tryptamine (TRY), does not displace ^{3}H-5-HT. Nevertheless, TRY was found, using intracellular recording, to mimic one of the actions of 5-HT when applied in pulses to the surface of myenteric neurons. This action was a slow depolarization of type II/AH neurons associated with an increase in input resistance. Other actions of 5-HT on other myenteric neurons were not mimicked by TRY. When continuously superfused, moreover, TRY blocked the slow depolarizing action of 5-HT and the slow EPSP elicited in type II/AH neurons by fiber tract stimulation that is thought to be mediated by 5-HT. The hypothesis was tested that these effects of TRY are secondary to the release of endogenous 5-HT. TRY caused the Ca^{+2}-independent but temperature-dependent release of preloaded ^{3}H-5-HT from the myenteric plexus. Furthermore, prolonged exposure to TRY totally depleted the myenteric plexus of endogenous 5-HT. Following the depletion of 5-HT the response of type II/AH neurons to exogenous 5-HT recovered but the slow EPSP did not. Radioautographic studies revealed that axons and perikarya of the myenteric plexus took up TRY; however, the distribution of ^{3}H-TRY in the plexus was different from that of ^{3}H-5-HT and uptake of ^{3}H-TRY was not blocked by excess 5-HT. TRY, therefore, does not enter myenteric neurons via the specific 5-HT uptake mechanism. Despite this, an inhibitor of 5-HT uptake (zimelidine) antagonized 5-HT release by TRY and attenuated its physiological actions. It is concluded that TRY releases physiologically active 5-HT from myenteric neurons. The mechanism of this release is unclear but may depend on the membrane 5-HT transporter. TRY should prove to be a useful tool for studying the neurophysiology of serotonergic elements of the enteric nervous system.

EFFECT OF MORPHINE ON INTRACELLULAR ELECTROPHYSIOLOGICAL CHARACTERISTICS OF CIRCULAR AND LONGITUDINAL SMOOTH MUSCLE. R.J. Gilbert, S.K. Sarna, and D.R. Harder, Medical College of Wisconsin, and VAMC, Milwaukee, WI.

The cellular mechanisms by which opioid peptides influence gastrointestinal smooth muscle function remain largely unknown. In these studies we investigated the effect of morphine (M) on the intracellular electrical behavior of jejunal smooth muscle cells of the dog. Conventional intracellular recording methods were utilized. Electrical activity of the circular muscle was recorded from the mucosal side after removal of the mucosa/submucosa. Longitudinal muscle activity was recorded from mucosal side, after dissection of an area of circular muscle. Both circular and longitudinal muscle cells demonstrated electrical control activity (ECA) on all impalements. The effects of morphine perfusion (10^{-10} - 10^{-5} M) onto the muscle were assessed on the following electrical parameters of the ECA: Resting membrane potential (RMP), frequency (F), amplitude (A), rate of depolarization (RD), plateau duration (PD), and rate of hyperpolarization (RH). M caused a dose-dependent increase in RMP, amplitude, RD and RH while demonstrating no significant effect on F or PD (Table I). These effects were blocked by infusion of Naloxone (10^{-6} M) or TTX (10^{-6} M). M demonstrated no significant effect on any of the electrical parameters studied for the longitudinal muscle.

Table I

Drug	RMP(mV)	F(c/min)	A(mV)	RD(mV/s)	PD(s)	RH(mV/s)
Control	-50.0	13.0	10.3	33.1	2.1	7.5
Morphine 10^{-5}M	-60.0*	12.0	19.2*	52.7*	2.0	12.0*

*$p < 0.05$.

We conclude: 1) in canine jejunal circular muscle morphine causes hyperpolarization of RMP, and increase in the rate of depolarization, hyperpolarization and amplitude of the ECA. 2) in the longitudinal muscle morphine causes no significant effect on electrical parameters of the ECA. 3) The aforementioned effects of morphine on the circular smooth muscle are mediated via enteric nerves.

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(A-15)

HUMAN COLONIC SMOOTH MUSCLE: SPONTANEOUS CONTRACTILE ACTIVITY AND RESPONSE TO STRETCH. R C Gill, K R Cote, D J Waldron, K L Bowes, Y J Kingma. Departments of Surgery and Electrical Engineering, University of Alberta, Edmonton, Alberta, Canada.

Colonic smooth muscle was obtained from 22 patients undergoing partial colectomy for carcinoma. Six specimens from ascending, five from transverse, four from descending and seven from sigmoid colon were studied. Longitudinally-orientated strips were cut from both the taenia and the inter-taenial region; circularly-orientated strips were taken from between the taenia. The strips (mucosa removed) were mounted slack in a horizontal tissue chamber and continuously superfused with oxygenated Kreb's-Ringer solution at 37 $\pm$ 1°C. Following a 30 min. equilibration period, the spontaneous contractile activity of the strips was recorded as their length was increased, stepwise, by increments of 1.0 mm every 15 min. From measurement of the baseline and active contractile forces and estimation of the cross-sectional area of the appropriate muscle layer, passive and active stresses in the longitudinal axis of the muscle strips were determined.

Muscle obtained from the right (ascending & transverse) colon was more distensible than that obtained from the left (descending & sigmoid) colon. This was true for all muscle layers. Maximum active stress was exerted by both circular and longitudinal muscle layers of the right colon at significantly greater ($p<0.001$) degrees of stretch than those of the left colon.

The contractile frequency of longitudinally-orientated strips increased with length although the contractile frequency of inter-taenial strips from the right colon was significantly lower ($p<0.001$) than that of strips from the left colon. The contractile frequency of circularly-orientated strips from the right colon (6.25 ± 0.38 min^{-1}) was significantly higher ($p<0.001$) than that of strips from the left colon (3.25 ± 0.28 min^{-1}).

This marked difference in mechanical behaviour of smooth muscle obtained from the right and left parts of the human colon in vitro may be related, in some way, to their differing embryological origin and function.

NEURAL INVOLVEMENT IN THE RELATIONSHIP BETWEEN INTESTINAL MOTILITY AND TRANSMURAL POTENTIAL DIFFERENCE. Beverley Greenwood and J.S. Davison. Department of Medical Physiology, 3330 Hospital Drive, NW, Calgary University, Calgary, Alberta, Canada.

In the vagally intact anaesthetised ferret bursts of spontaneous motility are associated with fluctuations in transmural potential difference (PD). After bilateral cervical vagotomy stimulation of the vagus nerve induced an increase in jejunal motility, a fluid secretion and a rise in PD in the direction of lumen negativity. Atropine ($100\mu gkg^{-1}$) abolished the vagally induced motility though the rise in PD and the fluid secretion were still apparent. The aim of this study was to examine the possible neural link between spontaneous and vagally induced intestinal motility and fluctuations in PD.

The results demonstrated the resumption of cyclical motility during prolonged vagal stimulation with or without sympathetic blockade with guanethidine ($3mgkg^{-1}$). Associated with the bursts in motility were fluctuations in PD. Atropine ($0.1\text{-}1mgkg^{-1}$) abolished the cyclical motility and associated fluctuations in PD. However, a motility independent vagally induced rise in basal PD was not abolished by atropine (up to $5mgkg^{-1}$).

The results show that motor activity and PD oscillations were seen after vagotomy and sympathetic blockade, thus we believe that the link between both events is intrinsic to the gut wall and involves enteric nerves, though a vagal influence has been demonstrate in providing the background conditions necessary for initiating the event. There also appears to be a direct vagal innervation of the intestinal epithelium involving both cholinergic and non-cholinergic pathways.

Central vagal stimulation in ferrets with one vagus intact reflexely activated this vagal pathway. However, the importance of tonic and reflex vagal control under physiological conditions has yet to be determined.

DO SPECIAL CONTRACTILE MECHANISMS EXIST FOR PRODUCING TONIC CONTRACTIONS IN THE GASTROINTESTINAL TRACT? K. Golenhofen, K. Filipponi, A. Golenhofen, I. Juhnke and E. Lammel. Department of Physiology, Deutschhausstr. 2, 3550 Marburg/Lahn, Federal Republic of Germany.

Considerable differences exist in the membrane processes controlling phasic contractions of canine gastric antrum on the one hand and tonic contractions of canine gastric fundus on the other hand (Golenhofen et al., in: M. Wienbeck, Motility of the digestive tract, Raven Press, New York 1982, pp. 95-102). We have now studied to what extent differences in the basic contractile processes can contribute to the functional differentiation between these two types of preparation. Tension development was measured in preparations after chemical skinning with Triton X-100 or by freeze drying, and the contractile protein content was measured by quantitative sodium dodecyl sulfate/polyacrylamide gel electrophoresis. The maximum tension development of antrum and fundus preparations was similar under normal conditions, and also the total content of contractile protein was similar in fresh preparations. The actin-myosin ratio was significantly larger in fundus (around 2.5) than in antrum strips (around 1.5). After chemical skinning, however, the tenison development was much more reduced in fundus (3-10 mN/mm^2) than in antrum preparations (30-80 mN/mm^2), although the protein content was only slightly changed by the skinning prodedures. This indicates a difference in the contractile machinery between fundus and antrum muscle, and this difference may be related with the specialisation of the fundus muscle for producing tonic contractions. The differences cannot be explained by differences in the content of the classical contractile proteins actin and myosin. Fresh antrum and fundus preparations contained a protein with a molecular weight near 80000 (5-10% of the myosin concentration). This protein was not measurable in fundus muscle after skinning with Triton X-100 or by freeze drying, but it remained present in skinned antrum preparations. This protein may be identical with leiotonin A (Ebashi et al., Fed. Proc. 41, 2863-2867 (1982)), and its loss by skinning procedures may be responsible for the weak contractility of skinned fundus preparations.

STOMACH EMPTYING OF SOLIDS IN THE PIG: RELATION TO FEEDING. P. C. Gregory, V. Rayner. Rowett Research Institute, Aberdeen, Scotland, AB2 9SB

It has been shown that liquid meals empty from the stomach at a constant caloric rate. We have investigated the emptying of dry matter (DM) from the pig stomach in animals trained to consume their feed in 45 min (twice daily) and fed with a barley-based diet where nearly all of the energy is in the solid fraction. When the stomach was evacuated via a gastric cannula immediately prior to feeding there was no difference in DM emptying of the morning meal (448 $\pm$ 49 g, or 26.5 $\pm$ 1.6% of the meal) compared to the afternoon meal (405 $\pm$ 50 g, or 25.8 $\pm$ 1.9%). Immediately prior to the morning meal the stomach retained only 59 $\pm$ 17 g DM from the meal the previous day, while immediately prior to the afternoon meal 503 $\pm$ 21 g remained from the morning meal. When this was not emptied before the afternoon meal an estimated 288 $\pm$ 19 g was emptied during the meal or 14.8 $\pm$ 0.7% of the total contents.

During a meal the pigs ate 628 $\pm$ 34 g DM in 10-15 min and emptied 160 $\pm$ 24 g (25.0 $\pm$ 2.8% of the meal); in 20-25 min they ate 1212 $\pm$ 66 g and emptied 322 $\pm$ 25 g (26.8 $\pm$ 2.5%); in 30-35 min they ate 1648 $\pm$ 125 g and emptied 427 $\pm$ 48 g (25.8 $\pm$ 1.4%) and at 38-45 min they ate 1686 $\pm$ 108 g and emptied 469 $\pm$ 31 g (27.8 $\pm$ 0.9%).

Thus when a pig eats on an empty stomach the rate of emptying varies with the amount eaten and during the period of feeding the stomach empties a constant fraction of what has been eaten. When digesta from previous meals is present in the stomach, emptying is considerably inhibited.

THE INFLUENCE OF FAT ON SMALL INTESTINAL DIGESTA TRANSIT IN THE PIG. P.C. Gregory, V. Rayner and G. Wenham. Rowett Research Institute, Aberdeen, Scotland, AB2 9SB.

Ileal infusion of partially or non-digested fat slows small intestinal transit in man (Read et al 1984). In the pig both ileal and duodenal infusions of a fat emulsion (Intralipid, 20%) accelerates transit (Gregory & Rayner 1984). We now report that intestinal transit is accelerated by a variety of lipids when presented in digestible form. The transit time of phenol red from duodenum to terminal ileum (126 ± 6 min) was reduced by ileal infusion (2 ml/min for 75 min) of Intralipid (74 ± 16) but was not altered by soya bean or vegetable oil. The transit time was reduced by duodenal infusion of Intralipid (40 ± 9), soya bean oil (46 ± 6) and vegetable oil (51 ± 7). Emulsification with bile and lipase reduced the transit time for duodenal (32 ± 4; 33 ± 19; 34 ± 8) and ileal (37 ± 3; 50 ± 3; 82 ± 12) infusions of Intralipid, soya bean and vegetable oil respectively. Transit time was reduced by duodenal (39 ± 5) and ileal (76 ± 13) infusion of monoglyceride (principally monooleate plus monolinoleate, 0.4 g/min) emulsified with bile, but only by duodenal (76 ± 13) and not ileal (107 ± 16) infusion of emulsified oleic acid (0.4 g/min). Transit time was not affected by duodenal infusion (145 ± 14) of the CCK-releasers phenylalanine (0.72 mM/min) and tryptophan (0.36 mM/min).

We suggest therefore that in the pig intestinal transit is stimulated by fat digestion products, perhaps monoglyceride via a mechanism which may not involve CCK. This increased transit rate was seen by radiography to derive from peristaltic rushes passing through long sections of intestine.

Read N. W., McFarlane, A., Kinsman, R. I. et al (1984) Gastroenterol 86, 274–280

Gregory, P. C. & Rayner, V. (1974) Gut 25, A1326.

ON THE PEPTIDERGIC NEURONAL INFLUENCE ON COLONIC MOTILITY AND BLOOD FLOW IN THE CAT. P.M. Hellström. Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.

The non-cholinergic colonic contraction and vasodilatation evoked by pelvic nerve activation, and the non-adrenergic colonic relaxation and vasoconstriction induced by splanchnic and lumbar colonic nerve stimulation were investigated in anesthetized cats. Motility in the proximal and distal colon was assessed by volume recording devices. Colonic blood flow was registered with drop recorders connected to the venous effluent.

Pelvic nerve activation by mechanical stimulation of the anal canal, or direct electrical stimulation of of the pelvic nerves evoked a contraction and vasodilatation. The motility response was blocked by atropine when combined with naloxone but the vasodilatation remained. Naloxone was shown to prevent the contractile resaponse to exogenous met-enkephalin. Further, the substance P (SP) antagonist (D-Arg^1,D-Pro^2, D-Trp^{7,9}, Leu^{11})-SP and SP tachyphylaxis which blocked the response exogenous SP were used, but had no effect on the response to pelvic nerve activation. Thus, at least two nervous mechanisms are involved in the non-cholinergic response to pelvic nerve activation. The non-cholinergic contraction seems to be mediated by enkephalin, or a related agonist, which acts on colonic smooth muscle, while the vasodilatation is mediated via another mechanism.

Electrical stimulation of the splanchnic and lumbar colonic nerves induced colonic relaxation and vasoconstriction, which were partly resistant to α-and β-adrenoceptorblockade. However, the effects of sympathetic nerve stimulation were abolished by guanethidine. Neuropeptide Y (NPY) induced colonic relaxation and vasoconstriction. These responses were not mediated via by noradrenaline, since neither guanethidine nor adrenoceptor blockers prevented the response. Since NPY is stored in sympathetic gut neurons and released upon sympathetic nerve stimulation, an effect which is inhibited by guanethidine, it is suggested that NPY is released during nerve stimulation of the colonic sympathetic nerves to induce relaxation and vasoconstriction of the colon.

THE INTESTINAL TRANSIT OF CAPSULES AND PELLETS John G. Hardy, Elizabeth Wood and Clive G. Wilson Queen's Medical Centre, Nottingham, England

We have monitored the transit of a capsule and a multiparticulate preparation through the gastrointestinal tract, in order to investigate factors affecting drug delivery to the colon.

A non-disintegrating capsule, 25 mm long by 9 mm diameter radiolabelled with technetium-99m, and 0.2 g ^{111}In-labelled cation exchange resin particles 0.5 - 1.8 mm diameter, were administered simultaneously to six healthy subjects after an overnight fast. The preparations were monitored over a 30 hour period using a gamma camera.

The median time (± 1 S.D.) for 50% of the pellets to leave the stomach was 1.2 ± 1.3 h and this was very similar to that for gastric emptying of the capsule, 0.8 ± 1.2 h. Both systems moved through the small intestine together, with median transit times of 3.4 ± 1.0 h for the pellets and 3.2 ± 0.8 h for the capsules. The pellets tended to disperse within the colon but progression of both systems was highly variable. In each subject, however, transit of the capsule within the colon was more rapid than that of the pellets. The median transit time through the large bowel for the capsules was 26 h (range 13 to 68 h).

Small particles disperse widely within the colon and are retained for prolonged periods, and therefore may provide suitable systems for colonic drug delivery.

HOW DOES CHOLINERGIC NEURAL EXCITATION INTERACT WITH NONCHOLINERGIC INHIBITION TO CONTROL PERISTALTIC VELOCITY AND WAVEFORM IN THE OPOSSUM ESOPHAGUS? J.F. Helm, W.J. Dodds, F.D. Loo, W.J. Hogan and R.D. Layman. Medical College of Wisconsin, Milwaukee, WI 53226 U.S.A.

Controversy exists regarding the roles of excitatory cholinergic and inhibitory noncholinergic neural pathways in the mediation of peristalsis in the smooth muscle esophagus. To further evaluate neural control of esophageal contraction, we stimulated the cervical vagi simultaneously in each of 8 anesthetized opossums. Vagal stimulation elicits two types of peristaltic contractions: atropine-sensitive A waves with a latency gradient similar to that of swallow-induced peristalsis, and atropine-insensitive B waves that occur after stimulus termination and with a minimal latency gradient. We stimulated one vagus with parameters chosen to give a B wave (6 s train of 3-5 ms pulses at 40-50 hz), while the other vagus was stimulated to selectively elicit an A wave (2 s train of 0.3-0.5 ms pulses at 3-4 hz). The onset of the A-wave stimulus was varied from 6 s before, to 4 s after the offset of the B-wave stimulus. Depending on the relative timing of the A- and B-wave stimuli, three response patterns were seen: 1) For A-wave stimuli that began more than 0.5 s before offset of the B-wave stimulus, the A-wave was inhibited. 2) For A-wave stimuli that began 0.5 s before offset of the B-wave stimulus, the A and B waves were partially fused to give a double-peaked configuration, the amplitudes of the B-wave contractions (first peaks) were markedly depressed, and the latency gradient of the A wave was minimal and comparable to that of the B wave. In 2 animals, the double-peaked waveform occurred only distally. 3) For A-wave stimuli beginning more than 0.5 s after offset of the B-wave stimulus, the A and B waves separated, the B wave regained normal amplitude, and the A-wave latency gradient was restored. We conclude that depending on timing, 1) An A-wave stimulus depresses the amplitude of a B wave, 2) a B-wave stimulus modifies the latency gradient of the A wave, and 3) A and B waves may fuse. Timing and interplay between cholinergic neural excitation and non-cholinergic inhibition may be important in control of peristaltic velocity and waveform.

PHARMACOLOGIC AND MECHANICAL PROPERTIES OF COLON IN A MODEL OF HIRSCHSPRUNG'S DISEASE. Craig Hillemeier, Don Singer, Jose Behar, Piero Biancani. Brown University and Rhode Island Hospital, Depts. of Pediatrics and Internal Medicine, Providence, RI 02902 U.S.A.

In the mouse the Ls trait is an autosomal recessive allele, that when present in the homozygous Ls/Ls condition, causes a segment of distal colonic aganglionosis resulting in obstruction similar to Hirschsprung's disease. Circular muscle rings from the aganglionic (AGC) and the ganglionic colon (GC) of Ls/Ls mice and from corresponding segments of control mice, were tested in vitro. 1) Electrical field stimulation caused neurally mediated relaxation followed by contraction in GC of both Ls/Ls and control mice while the AGC of Ls/Ls mouse did not respond. 2) AGC responded to direct acting myogenic agents and, in some instances, at lower doses than the GC. AGC was supersensitive to Vasoactive Intestinal Peptide (VIP) and Bethanechol but not to Isoproterenol and ATP. 3) The maximal active force generated by the colon from the Ls/Ls mouse was significantly greater in rings from both the GC and AGC than in control mice. 4) Circular muscle thickness and stress, i.e. maximal active force normalized for the amount of muscle present, were greater in both the GC and AGC of Ls/Ls mouse than in control mice. 5) Isolated muscle cells, obtained by in vitro digestion with collagenase and examined with phase contrast microscopy, were significantly longer in GC of Ls/Ls mouse than in the corresponding segment of control colon (119.9 vs. 83.1 um).

We conclude: the colon in this Hirschsprung model generates greater forces because of greater circular muscle thickness and stress. These changes may be a reflection of the greater cell size. Increased sensitivity to Bethanechol and VIP may represent "denervation" supersensitivity and support the hypothesis that VIP may be an endogenous neurotransmitter responsible for inhibition of normal colon.

COORDINATION OF ELECTRICAL ACTIVITIES IN THE MUSCLE LAYERS OF THE PIG COLON. J.D. Huizinga, E. Chow, N.E. Diamant, and T.Y. El-Sharkawy. Depts. of Physiology and Medicine, University of Toronto, Ontario, Canada.

The electrical control activities of the circular and longitudinal (taenia) muscle of the colon of the pig are distinctly different (Huizinga et al. Am.J.Physiol. 245 (1983) G482-91. The circular muscle has omnipresent slow waves at 1-3 cpm, the longitudinal muscle intermittent slow waves at 20-30 cpm. The question arose how such different control activities could cooperate to form the basis of coordinated propulsive contractions. In vitro, electrical activities were measured at 4-8 locations simultaneously using suction electrodes. Results: (a) Without stimulation, the longitudinal muscle was electrically quiescent, only circular muscle exhibited slow waves at low frequency. (b) With a continuous stimulus present (stretch or cholinergic agent in the presence of tetrodotoxin) a high level of coordination of the activities of the two muscle layers was observed: each slow-wave spike complex from the circular muscle layer occurred at about the same time as the onset of a burst of longitudinal muscle activity. Within the circular muscle layer, slow waves were phase-locked in circumferential direction and along the long axis of the colon. They appeared to propagate in either oral or aboral direction at about 8 mm/sec. Within the longitudinal layer, the bursts of oscillations were phase locked, circumferentially (in the different taeniae!) and longitudinally. (c) With random stimulation by the intramural nervous system, i.e. "spontaneous" activity in Krebs solution, the longitudinal muscle showed irregular intermittent activity and coordination with circular muscle was poor.

This study shows that the distinctly different myogenic control activities of the two muscle layers of the pig colon, can obtain a high level of coordination, when appropriately stimulated.

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EFFECT OF SELECTIVE PROXIMAL VAGOTOMY WITHOUT AND WITH PYLOROPLASTY ON GASTRO-DUODENAL MOTILITY IN THE DOG.

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Truncular vagotomy delays the emptying of solid meal.On the other hand,interpretation of the effect of selective proximal vagotomy (SPV) are contradictory.

Electric and motor activity were tested on six mongrel dogs. 5 bipolar platin electrodes and 5 strain gage transducers were placed in the antrum and the proximal duodenum (as described by P.Bass).Measurements were made before and follow ing the 14 th day after SPV.Feeding motility was tested after administration of 25o grams of dog standard protein meal.X-ray examination were made in the same cycle after a barium enriched standard test meal (the same as for the motility measurements).The emptying time was calculated for 1.first appearance in the duodenal bulb,2. half emptying,3.total emptying.

The animals showed delayed emptying after SPV most markedly in the 1.and 3.phase,with an average of 86 % and 54 % respectively. In antral motility,significant changes were observed only in the interdigestive state,where the motility-index MI decreases parallel to the decrease in contraction freqency.No decrease in antral motility could be detected in the fed state after SPV.Only a non-significant increase of the MI in the interdigestive state and a slight decrease in the fed state were seen in the duodenal bulb after SPV.

In 3 dogs a submucous pyloroplasty was added after a postoperative observation time of three months.

Conclusion of our findings:The observed emptying delay after SPV cannot be caused solely by an impaired duodeno-antral motor gradient.

Other factors are discussed.

ELECTRICAL ACTIVITIES APPARENTLY PROPAGATING IN THE CIRCULAR MUSCLE LAYER OF THE HUMAN COLON. J.D.Huizinga, H.S.Stern, W.E.Waterfall, T.Y.El-Sharkawy and N.E.Diamant. Intestinal Disease Research Unit, McMaster Univ.,Hamilton. Depts. of Physiology and Medicine, Univ. of Toronto. Dept. of Surgery, Mount Sinai Hospital, Toronto, Ontario, Canada.

Motor activities in the human colon probably hold back content most of the time. This may be reflected in poorly coordinated contractions observed at different sites at manometry. Intermittently, transit occurs in the colon which requires coordinated motor activity. This implies coupling of electrical events throughout the segment in which transit occurs. Such coupling was studied in vitro. Electrical activities were recorded simultaneously with 4-8 suction electrodes placed 1.7-10 mm apart, on the circular muscle of segments of human colon, in the presence of tetrodotoxin. Under basal conditions, low amplitude electrical control oscillations were observed from 10-24 cpm, but the frequency could vary within one segment. Spiking activity occurred randomly and usually was not coordinated over more than 2 electrodes. With the continuous presence of a stimulus (carbachol 2-10 x 10^{-8}M), the control activities and the coupling characteristics changed markedly. Carbachol increased the amplitude of the electrical control activity and increased its frequency when below 20 cpm. Two characteristic activities which frequently propagated over all electrodes were observed: (a) a burst of oscillatory activity, at around 25 cpm, lasting about 20 sec, with or without spiking activity, and (b) a prolonged slow depolarization lasting 5-10 sec with superimposed intense spiking activity. The latter activity was only observed at higher doses of carbachol. Both types of electrical activity were generated by circular muscle, the first type can also be recorded from the longitudinal muscle. We have now shown that: (a) under unstimulated conditions the colonic muscle may show little coordination of electrical activities resulting in stationary contractile activity; (b) the colon musculature has the myogenic capability, providing adequate stimulation is present, of producing electrical activities which are coupled over a segment of bowel. This is a basis for propulsive activity.

INITIATION OF THE INTERDIGESTIVE MIGRATING CONTRACTIONS BY ERYTHROMYCIN THROUGH INTRAVENOUS AND INTRADUODENAL ROUTES.
Z. Itoh, I. Takahashi, H. Arai and K. Wakabayashi.
GI Labs, College of Medical Technology and Institute of Endocrinology, Gunma University, Maebashi, Japan 371

Initiation of the interdigestive migrating contractions (IMC) in the stomach by erythromycin (Erythrocin, Abbott labs, EM) in the dog was studied through three different routes, i.v., i.a. and intraduodenal ones. Contractile activity was monitored by means of chronically implanted force transducers. Silastic tubes were placed in the vena cava and the duodenum and a tiny plastic tube was chronically inserted into the short gastric artery as routes for EM administration. Serum concentration of immunoreactive motilin (IRM) was determined by a specific radioimmunoassay for motilin and that of EM by a paper disk technique using Micrococcus luteus ATCC 9341 as the test organism.

It was found that i.v. infusion of EM in a dose of 50-100 µg/kg-hr for 20 min during the interdigestive quiescent period induced a series of strong contractions quite similar to the naturally occurring IMC in the stomach and the contractions migrated in a caudad direction. Serum concentration of IRM started to increase associated with the initiation of the IMC. With termination of the i.v. infusion of EM, serum IRM concentration rapidly decreased. Intraduodenal administration of EM in a dose of 300-500 µg/kg strongly stimulated contractile activity in the stomach and duodenum and finally induced the typical IMC. Serum concentration of IRM (400-600 pg/ml) and EM (5-8 µg/ml) was concomitantly increased with the initiation of the IMC in the stomach. When EM (1µg/kg) was given directly to the stomach through the short gastric artery, strong tonic contractions quite similar to the contractile pattern of the IMC were induced only locally in the gastric body but serum concentration of IRM was not changed.

It is concluded that EM itself has strong activity to stimulate smooth muscle contractions in the stomach, but EM-induced IMC were always associated with the release of endogenous motilin in the dog.

METOCLOPRAMIDE STIMULATES NIFEDIPNE DEPRESSED ESOPHAGEAL MOTILITY.
H.D. Janisch, C. Vassilopulos, P.Thies, D.v.Kleist, K.E.Hampel. Universitätsklinikum Charlottenburg, Freie Universität Berlin, FRG.

Nifedipine is a worldwide used compound for the treatment of cardio-vascular diseases. It is well known that calcium channel blocking agents cause an inhibition of esophageal motor activity and thus may lead to gastro esophageal reflux. It was the purpose of this study to investigate whether metoclopramide (MCP) an intestinal motility stimulating drug is able to antagonize the motility inhibiting effect of nifedipine (NIF).

Methods: 8 healthy volunteers were manometrically investigated in a crossover trial using the Arndorfer perfusion system. Sphincter pressure was measured by rapid pull-through techniques. Esophageal body motor function was investigated every ten minutes after bolus application of 5 ml of water to induce swallowing. At day I subjects received MCP 20 mg i.v., at day II NIF (20 mg) was administered s.l. 10 min. before the i.v. application of 20 mg MCP. Total recording time was 75 min. Tracings were coded and read blindly. Values given are mean ± SEM.

Results: LESP: basal 25.5 ± 3.4, vs. 26.1 ± 3.3 (NIF+MCP), vs. 36.7 ± 3.0 mm Hg (p 0.03) (MCP); Ampl.: basal 78.4 ± 7.4, vs. 87.0 ± 8.9 (NIF+MCP), vs. 105.2 ± 8.0 mm Hg (p 0.03) (MCP); Duration: basal 3.9 ± 0.2, vs. 4.1 ± 0.5 (NIF+MCP), vs. 4.6 ± 0.2 sec. (p 0.005) (MCP).

Conclusion: Metoclopramide is able to antagonize completely the motility inhibiting effect of nifedipine on esophageal motor function and lower esophageal sphincter pressure, but has compared to MCP-monotherapy no further esophageal motility stimulating effect over it after a pretreatment with nifedipine.

COMPETETIVE APPLICATION OF DOPAMINE (DOP) AND METOCLOPRAMIDE (MCP) AND ITS EFFECT ON LOWER ESOPHAGEAL SPHINCTER PRESSURE.
H.D.Janisch, P.Thies, D.v.Kleist, U.Wolf*, E.F.Bauer, K.E.Hampel. Universitätsklinikum Charlottenburg, Freie Universität Berlin & Hannover, FRG.

It has been shown in previous studies that the adminstration of DOP results in a reduction of LESP. The motility enhancing effect of MCP is supposed to be mediated by dopamine receptor blockade. It was therefore the aim of the following study to investigate whether MCP can abolish the dopamine induced LESP reduction.

Method: Manometric investigation was carried out in 9 adult concious dogs (purebred beagles) in a crossover trial using the Arndorfer perfusion system. Pressure recordings were performed by a rapid pull through technique. Tracings were coded then and analysed blindly. On the first day LESP was measured after intravenous administration of 20 mg MCP. On day II DOP (15µg/ kg min) was intravenously infused over a 30 min. period to get a stable pressure plateau. Infusion was then omitted and 20 mg MCP were given i.v. Pressure recordings were continued for another 15 min. period. Data given are mean ± SD.

Results: MCP-monotherapy enhanced LESP from 20.1 ± 7.5 to 28.8 ± 9.8 mm Hg. Dopamine infusion decreased LESP significantly (p 0.005) with a maximum effect after 25 min. (basal: 23.0 ± 5.3 vs. 18.6 ± 4.2 mm Hg). The dopaminergic inhibition was completely antagonized by MCP. MCP increased LESP to a maximum pressure of 30.9 ± 5.9 mm Hg which was statistically different compared to baseline pressure and LESP during DOP-infusion. No difference was seen comparing LESP under MCP-monotherapy and LESP after MCP during combined therapy.

Conclusion: 1. The dog LES responds to dopamine and metoclopramide. 2. The MCP effect on LESP was not influenced by a pretreatment with dopamine. 3. The dopamine antagonism of MCP should be reconsidered.

THE ENKEPHALIN ANALOGUE HOE-825 INHIBITS THE EFFECT OF THE NON-ADRENERGIC, NON-CHOLINERGIC INHIBITORY NERVOUS PATHWAY.
J. Janssens, G. Vantrappen, P. Ceccatelli. Center for G.I. Research, University of Leuven, Belgium.

As the mechanism of action of enkephalins on gastrointestinal motor function is incompletely understood, we studied the effect of the enkephalin analogue Hoe-825 on esophageal motility and on the migrating motor complex (MMC) of stomach and small intestine in 7 volunteers. The esophageal motor activity was examined with an intraluminal perfused catheter system (orifices at 5, 10 and 15 cm above the LES) and a Dent sleeve to monitor LESP. After a 30 min basal period, a 5 min IV placebo infusion was given and motility was followed for 45 min; then 40 µg Hoe-825 was slowly infused IV (5 min) followed by another 45 min registration period. Hoe-825 had no significant effect on the resting LESP but reduced significantly the completeness (in %) of LES relaxations from 88% ± 4% to 70% ± 7% (mean ± SEM). Hoe-825 significantly increased the amplitude of the deglutitive contraction wave in the esophageal body with 30% and its duration with 14%; the progression velocity was significantly increased from 3.9 ± 0.5 to 5.0 ± 0.7 cm/sec (mean ± SEM). The MMC in stomach and small intestine was studied with perfused catheters at 4 levels in the gastric antrum 3 cm apart, and at 3 levels in the small intestine (D II, 25 and 50 cm more distally). When the second spontaneous activity front (AF) occurred at D II + 25 cm, 40 µg Hoe-825 was infused IV over 5 min. Almost immediately a premature AF started in D II and migrated distally. The latency time between this AF and the previous spontaneous front was 36.7 ± 4.0 min as compared to a normal cycle duration of 103.5 ± 8.9 min ($p < 0.001$). At the time of the premature AF in D II, the gastric antrum showed almost no contractile activity. As the normal delay between two AF's seems to be governed, at least in part, by the inhibitory nervous system, and as this system also has a role in the LES relaxation and the peristaltic progression of the esophageal contraction, the effect of Hoe-825 is consistent with an inhibition of this inhibitory nervous pathway, the mechanism of which remains to be established.

(A-19)

RELEASE OF A VIP-LIKE MATERIAL BY DOPAMINE FROM OPOSSUM ESOPHAGUS CIRCULAR MUSCLE: ACTIONS DISTINCT FROM NON-ADRENERGIC INHIBITORY MEDIATOR. J. Jury, L.P. Jager and E.E. Daniel. Program for Control of Smooth Muscle Function McMaster University, Department of Neurosciences, Hamilton, Ontario, Canada.

In isolated strips of circular muscle studied in the double sucrose gap, dopamine (2×10^{-5} M) produced a 7 mV hyperpolarization accompanied by increase in membrane resistance (145%) and secondarily by enhanced rebound depolarizations and eventually continuous membrane oscillations with spikes and contractions accompanying the depolarized phases. These responses were dose-dependent (10^{-7} to 5×10^{-5} M), also produced by epinephrine and norepinephrine, unaffected by phentolamine (10^{-5} M), propranolol (10^{-5} M), both antagonists[3] or domperidone (10^{-5} M)[5] but reduced by haloperidol (10^{-5} M)[6] or bulbocapnine (10^{-5} M), unaffected by tetrodotoxin (10^{-6} M), but abolished by scorpion venom (10 ug/ml) and by low Ca^{2+}, high Mg^{2+} substituted physiological saline, and by substitution of isethionate for chloride in the physiological saline. VIP (Sigma) had identical dose-dependent effects which were similar in all respects to those of dopamine except that they were unaffected by scorpion venom or low Ca^{2+}, high Mg^{2+} saline. We conclude that dopamine releases a VIP-like material. In the same strips, field stimulation (40 V, 0.3 ms, 30 pps for 300 ms) caused inhibitory junction potentials of 20 to 30 mV which were accompanied by decreased membrane resistance, reversed at about -90 mV membrane potential and were dependent in size and reversal potential on external potassium. They were tetrodotoxin and scorpion venom-sensitive. We conclude that dopamine releases endogenous VIP-like material. Release of this material and addition of exogenous VIP have identical electrophysiological effects totally distinct from those of the inhibitory mediator.

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TRANSIENT RELAXATION OF THE UPPER ESOPHAGEAL SPHINCTER (UES) ACCOMPANYS BELCHING P.J. Kahrilas, J.B. Wyman, W.J. Dodds, J. Dent, W.J. Hogan, R.C. Arndorfer. Medical College of Wisconsin, Milwaukee, WI., USA.

Although gastroesophageal activity associated with belching has been investigated previously, the behavior of the UES during belching has not been studied. In this study of 7 healthy subjects, we evaluated the role of the UES in belching. We recorded pressure activity with a flattened sleeve device straddling the UES, a second sleeve straddling the LES, 3 esophageal and 2 pharyngeal side-hole recording sites. Additionally, a large-bore side hole enabled air injection. With the subjects sitting, we injected air boluses of 5-30 ml into the esophageal body while recording pharyngoesophageal motor activity. Belching was also provoked by having the subjects drink two solutions which combined in the stomach to generate 1000 ml of CO_2. Results. Injection of air into the esophageal body caused either complete UES relaxation, partial UES relaxation or, in some cases, no change in UES pressure. The transient complete UES relaxations (0.6-2.2s) were independent of swallowing, but were generally accompanied by a belch. Incomplete UES relaxation was associated with a sensation of "almost belching". LES relaxation occurred only concomitant with secondary peristalsis which was uncommon when belching occurred. The interval between esophageal air injection and the onset of UES relaxation ranged from 0.2 to 17.0s with a median of 0.7s. After gas forming solutions were swallowed, multiple belches occurred by the following sequence of events: 1) transient LES relaxation, 2) gas reflux with a common cavity phenomenon in the esophagus, 3) transient UES relaxation, 4) gas escape into the pharynx. The delay between LES relaxation and gas reflux into the esophagus was variable (1-10s). The delay between the esophageal common cavity and UES relaxation was 0.1-0.3s. Conclusions: 1) In normal subjects, belching is invariably associated with a transient complete UES relaxation. 2) With partial UES relaxation, belching does not occur. 3) Rapid esophageal distension by air injection elicits UES relaxation without accompanying LES relaxation. 4) The UES relaxation is independent of swallowing or LES relaxation. 5) Transient UES relaxation may be an important mechanism in patients with regurgitation.

DEXTROMETHORPHAN AND LOPERAMIDE INHIBIT INTESTINAL SMOOTH MUSCLE CONTRACTILITY IN VITRO BY DIFFERENT MECHANISMS. J. F. Kachur, D. Morgan, and T. S. Gaginella. Dept. of Pharmacology, Hoffmann-La Roche Inc., Nutley, N. J. 07110

Irritable bowel syndrome (IBS) is associated with altered patterns of gastrointestinal motility, often accompanied by visceral pain. Dextromethorphan (DM) recently has been suggested to be useful in the management of IBS. The present study was designed to examine the comparative spasmolytic effect of DM and loperamide (LP) on guinea pig ileum in vitro. To gain insight into the biochemical mechanism of action of these drugs, we also examined their ability to inhibit the activation of smooth muscle actomyosin (SMA) and calmodulin-stimulated phosphodiesterase (PDE). Segments of guinea pig ileum were mounted along their longitudinal axis in physiologic buffer (37°C, pH 7.4) gassed with 5% CO_2 in O_2. Calmodulin-stimulated PDE was measured as the conversion of ^{3}H-cyclic AMP to ^{3}H-5'-AMP. SMA activation was measured spectrophotometrically as the change in optical density at 550 nm due to aggregation of chicken gizzard actomyosin. Results: DM inhibited carbachol (20 µM)-induced phasic and tonic contractions of the ileum in a concentration-dependent manner; 50% inhibition (IC50) occurred at 60 µM and 104 µM for phasic and tonic contractions, respectively. LP also inhibited carbachol-induced contractions, but in contrast to DM, it was more potent in favor of the tonic (IC50 9 µM) versus the phasic (IC50 27 µM)-type contractions. At 50 µM, DM produced a 10-fold shift in the concentration-response curve to calcium in the presence of 40 mM K^+. LP completely inhibited the response to calcium. In preliminary experiments, DM (63 µM) inhibited activation of SMA by 65% while LP did not inhibit the interaction between actin and myosin. DM produced <50% inhibition of calmodulin-stimulated PDE at concentrations up to 1 mM; LP inhibited the enzyme by 56% at 0.1 mM, indicating that these are not potent calmodulin antagonists. Conclusion: The data suggest that the antispasmodic effects of DM and LP are due to different mechanisms, which are probably independent of calmodulin.

PGE_2-MEDIATED RELAXATION OF ISOLATED COLONIC SMOOTH MUSCLE CELLS. H.W. Kao, W.J. Snape, Jr., P.E. Hyman. Department of Medicine, Harbor-UCLA Medical Center, Torrance, CA 90509 U.S.A.

Enhanced prostaglandin production in ulcerative colitis may play a role in the smooth muscle dysfunction seen in this disorder. While PGE_2, a major prostanoid of inflammation, relaxes intact colonic circular smooth muscle, its mechanism of action is unknown. In other smooth muscle, PGE_2 has been shown to stimulate the production of cAMP, an antagonist of contraction for gastric smooth muscle cells. The aim of this study was to evaluate the effect of PGE_2 or a cyclic AMP analogue, 8 bromo-cAMP, on cholinergic-mediated contraction of isolated colonic circular smooth muscle cells of the rabbit. Freshley dispersed cells from the circular muscle layer of the distal colon were prepared by a modification of the technique of Bitar and Makhlouf. The length of at least 50 cells was measured in the control state and after exposure to bethanechol from 10^{-10}M to 10^{-5}M. Contraction was expressed as the percentage decrease in mean cell length from control (mean ± SEM: 79.0±3.0um). Contraction with bethanechol was maximal at 30 sec. Bethanechol-induced contraction was determined with and without preincubation (60 sec) with PGE_2 or 8 bromo-cAMP. Bethanechol stimulated a dose-dependent contraction up to a maximum (23.4±2.0%) occurring at 10^{-6}M. Supramaximal concentrations inhibited the contractile response, reaching a plateau (12.5%) at 10^{-6}M or greater. 8 Bromo-cAMP (10^{-7}M) reduced the maximal contractile response by 16.6% ($p<0.025$) without decreasing the potency of bethanechol. PGE_2 (10^{-8}M), on the other hand, reduced the efficacy of bethanechol by 34.7% ($p<0.05$), as well as its potency with the maximal contraction occurring at 10^{-7}M ($p<0.05$). These studies suggest that cAMP is a noncompetitive antagonist of the action of bethanechol. In contrast, PGE_2 acts as a competititve as well as a noncompetitive antagonist of cholinergic-mediated contraction of isolated colonic circular smooth muscle cells. Thus, cAMP-mediated relaxation can not be the sole mechanism involved in relaxation of colonic smooth muscle cells by PGE2.

DIFFERENTIAL EFFECTS OF GLN-NEUROTENSIN ON LONGITUDINAL AND CIRCULAR MUSCLE OF DOG ILEUM IN VITRO. M. Karaus, S.K. Sarna, Med. College of WI, and VAMC, Milwaukee, WI.

The role of neurotensin as a hormone and as a neurotransmitter in the GI-tract is incompletely understood. We studied the effects of GLN-neurotensin (NT) on isolated dog ileal longitudinal and circular muscle strips (LM, CM) in a perfusion apparatus. Contractile and electrical activities were recorded by FD-Transducers and suction electrodes respectively. LM strips exhibited spontaneous regular phasic contractions and CM exhibited irregular phasic and tonic contractions. All values are means ± SE. The ECA frequency of LM (8.0 ± 0.1) and CM (7.7 ± 0.5) corresponded to the frequency of the phasic contractions. Hexamethonium (HEX), 10^{-5}M, did not change the motor activity of LM and CM; Atropine (AT), 10^{-5}M, inhibited LM partially or totally but did not affect CM-activity. TTX, 10^{-8}M, stimulated CM and inhibited LM. NT inhibited LM in a dose dependent fashion (ED 100, 10^{-8}M, $p < 0.005$)(n=7) without affecting ECA-frequency. NT stimulated CM in a dose dependent manner. NT, 10^{-7}M (ED 100), increased the motor index to 3.1 ± 0.6 ($p < 0.005$) in the first 5 min perf. period and ECA frequency to 9.1 ± 0.6. Higher doses or longer perfusions caused tachyphylaxis. Field stimulation (FS) (10 Hz, 150 V, 1-5 ms) caused inhibitory (CM) and excitatory (CM, LM) neural responses during NT perfusion depending on the pulse width of stimulus. HEX did not block the effect of NT on CM or LM. AT reduced the effect of NT on CM but did not block the inhibitory effect on LM. TTX did not block the inhibitory effect of NT on LM. We conclude that CM and LM of dog ileum are under different neural control. Spontaneous activity of CM in in vitro conditions is primarily myogenic which can not be inhibited by AT or TTX. LM is under constant excitatory cholinergic neural influence, which can be blocked by TTX and AT. NT has different effects on both layers. It stimulates CM partly by its direct action on the muscle and partly through a post ganglionic cholinergic pathway. NT inhibits LM through a TTX-insensitive, non-cholinergic postganglionic pathway leaving neural excitation by FS and ECA-frequency unchanged. These results give strong evidence that NT acts as a complex peripheral neurotransmitter in the ileum.

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GIANT MIGRATING CONTRACTIONS IN THE DOG COLON DURING DEFECATION. M. Karaus, S.K. Sarna, Medical College of Wisconsin, and VAMC, Milwaukee, WI 53193

We investigated the colonic motor mechanisms of defecation in 5 conscious dogs. A set of 6 strain gauge transducers were implanted on the colon of each dog, 7 to 11 cm apart. An implanted fistula gave access to the terminal ileum. After a control period showing at least 2 colonic migrating motor complexes at each recording site, the following stimuli were applied: 2 mg/kg guanethedine (G) (iv), 30 µg/kg neostigmine (N) (iv), 1-4 ml/kg castor oil (C) (po), 200 ml 25% glucose (GL) (into ileum), rectal distension by a balloon (120 cc). Colonic contractions occurring immediately before and during defecation were compared in their amplitude to those in colonic motor complexes and their migration properties were determined. Giant contractions were defined as those whose amplitude exceeded the mean maximal amplitude of contractions in the previous 2 colonic motor complexes by at least a factor of 1.5. Those giant contractions that migrated over at least two recording sites were called giant migrating contractions (GMC). GMC occurred in 91.1% of experiments with GU, N, C and GL, 30.2% of these migrated over the entire colon, 51.2% migrated over more than half the colon, and 18.6% over less than half the colon. The migration velocity varied from 0.2 to 3 cm/sec with a mean of 0.82 + 0.1 SE cm/sec. The mean amplitude of the GMC was 3.7 ± 0.3, 3.3 ± 0.2, 4.3 ± 0.3 SE times the mean maximal amplitude of contractions in motor complexes of the proximal-, middle- and distal colon respectively. GMC occurred simultaneously in 11.1% of experiments; 4% of GMC migrated orad during defecation. GMC stimulated by glucose started preferentially near the ileocecal junction. Balloon expulsion was accompanied by a GMC in only 9% of experiments and then too GMC occurred only in the distal colon. We conclude that defecation is generally accompanied by strong migrating contractions in the colon called GMC. More than 80% of these GMC migrate over more than half the colon. The migrating velocity of GMC is highly variable. Rectal distension only rarely initiates a GMC. The GMC may provide a major force for defecation and be responsible for at least partial evacuation of the colon during defecation.

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SELECTIVE INHIBITION OF SPIKE-DEPENDENT AND SPIKE-INDEPENDENT CONTRACTIONS OF THE FELINE LOWER ESOPHAGEAL SPHINCTER (LES) BY CALMODULIN ANTAGONISTS. D. Katzka, J. Reynolds, and S. Cohen. University of Pennsylvania, Philadelphia, Pennsylvania, 19104, U.S.A.

Contractions in the LES are either spike associated or spike independent. Aim: to determine if these two type contractions may be mediated by distinct calcium channels. Pressures were measured via perfused catheters and myoelectric spike activity via bipolar electrodes in chloralose anesthetized cats. Basal tone or bethanechol (B), phenylephrine (P) and Bombesin (BN) induced contractions were recorded during continuous iv infusions of nitroprusside (NP), verapamil (V) or trifluoperazine (TFP). Results: V, NP and TFP gave dose dependent inhibition of both tonic and phasic contractions. The ED_{100} dose for tonic and phasic contraction inhibition was the same for each individual antagonist. V-64 (64 ug/kg/m), NP-3 (3 ug/kg/m) and TFP-5 (5 ug/kg/m) inhibited LES resting tone by ~ 50%. NP-3 and TFP-5 were more potent in inhibiting resting tone than phasic contractions ($p < .05$). V-64 was a more potent inhibitor of phasic contractions than NP (35%±11 vs 4%±3, $p < .05$). V-16 and NP-3 inhibited phasic contractions by 50%. NP-3 was a more potent inhibitor of BN induced contractions than P induced contractions (47%±9 vs 4%±3, $p < .025$). Spike activity corresponding to phasic contractions showed a dose dependent inhibition to V and NP, closely correlating to contraction inhibition. In contrast, inhibition of resting tone by these agonists did not correlate with changes in spike activity. Conclusions: 1) Tonic and phasic contractions are equally inhibited by high doses of calcium channel antagonists. 2) NP and TFP show greater potency in inhibiting spike independent LES tone than spike associated phasic contractions. 3) V is a more potent inhibitor of spike associated contractions than NP. 4) BM induced LES contractions are more sensitive to NP inhibition than P induced phasic contractions. Spike associated and spike independent contractions of the LES may be a function of varying dependence on distinct calcium channels.

DIFFERENTIAL SENSITIVITIES OF HUMAN GALLBLADDER (GB) AND INTESTINE TO CHOLECYSTOKININ (CCK). J. Kellow, L. Miller, S. Phillips, A. Haddad, A. Zinsmeister, W. Charboneau, Mayo Clinic, Rochester, MN 55905.

CCK has been implicated in the genesis of the irritable bowel syndrome. However, it is uncertain whether CCK's effects on intestinal muscle are physiological, since responses of the GB and bowel have not been compared in vivo. Aims: to compare in man the sensitivities of GB and bowel to a range of physio- and pharmacological doses of CCK-8 and to determine whether CCK's effects on the intestine vary regionally. Methods: A 12-lumen catheter (side holes spanning 0-170 cm) recorded intraluminal pressures from sites in the jejunum (n = 2-4), ileum (3-6) and proximal colon (1-2). In healthy volunteers (5F, 3M; 24-53 yr), fasting recordings (15-20 hr) were followed by IV control (1 hr saline) and CCK-8 (3 hr) infusions. CCK-8 was given as 6 x 30-min doses (mean, 2.2, 4.6, 9.6, 18.5, 37.0, 73.2 pmol kg^{-1} hr^{-1}, assayed at point of infusion). Motility indices (MI) were quantified by planimetry at each intestinal locus each 10 min. GB volumes (real-time ultrasound, sum of cylinders) were measured each 10 min during CCK-8 infusions and, on another occasion, after a test meal (395 Kcal, 37% fat) was ingested (n=4) or instilled intraduodenally (n=4). Results: GB volume decreased during IV CCK-8, showing significant linear ($P<0.001$) trend with increasing doses. CCK-8 increased jejunal MI with a linear dose response ($P<0.05$). Ileal and colonic MIs initially decreased, then increased ($P<0.05$). The GB's response to nutrients by mouth (mean max. vol. reduction 29%) was comparable to that during 4.6 pmol kg^{-1} hr^{-1} CCK by vein; intraduodenal nutrients caused a 54% reduction, similar to that during 18.5 pmol kg^{-1} hr^{-1} CCK. Significant ($P<0.05$) effects of CCK-8 on the GB, jejunum and ileum occurred after doses of 2.2, 18.5, and 73.2 pmol kg^{-1} hr^{-1}, respectively. Conclusions: 1) doses of CCK-8 given by vein included the "physiological" range, 2) using the GB's response as a "simultaneous bioassay" for CCK, the intestine was less sensitive to CCK-8 than was the GB, and 3) sensitivities of the gut to CCK-8 vary regionally.

PROPERTIES OF DRUG-INDUCED GASTRIC DYSRHYTHMIA (GD) IN FASTING AND FED STATES. C.H. Kim, F. Azpiroz, A.R. Zinsmeister and J.-R. Malagelada. GI Unit, Mayo Clinic, Rochester, MN 55905 U.S.A.

The aims of this study were to characterize different types of GD and to compare the relative susceptibility of the stomach to GD in fasting and fed states. In 4 conscious dogs, we compared the 50% dysrhythmic dose (ED_{50}) of epinephrine, PGE_2, met-enkephalin and glucagon (estimated by Dixon's up-and-down method) in fasting and fed states. A bolus of saline or drug was injected through a catheter chronically implanted in the left gastric artery either following 14 hr of fasting or 1 hr after ingestion of a solid meal (400 g of ALPO). After the injection, the electrical activity was recorded for 1 hr by Ag-AgCl electrodes implanted on the serosa of the stomach along the greater curvature (4 electrodes) and the proximal duodenum (1 electrode). GD was defined as pacesetter potentials of $\geqslant$8/min (tachygastria [TG]) or $\leqslant$3/min (bradygastria [BG]). The focus of origin of GD was determined by the level at which GD was first detected. Results: 1) All 4 drugs tested induced intermittent episodes of TG, BG or both whereas saline did not. The ED_{50} for epinephrine, PGE_2, met-enkephalin and glucagon postprandially (16.6, 16.6, 35.1, >221 µg/kg, respectively) were higher than during fasting (1.7, 5.2, 11.1, 61.0 µg/kg, respectively). Thus, the stomach was less susceptible to GD for all drugs following a meal. 2) During fasting, we recorded 14 episodes of TG (mean duration ± SE = 4.4 ± 1.9 min) and 7 episodes of BG (1.2 ± 0.1 min). Postprandially BG was more frequent (17 episodes, 2.2 ± 0.2 min) than TG (1 episode, 1 min). 3) In both fasting and fed states, TG originated from an ectopic focus in the distal antrum, its pacesetter potentials spread orally and it was followed by a compensatory pause. BG appeared in both the corpus and the antrum and its pacesetter potentials spread aborally. None of GD propagated into the proximal duodenum. We conclude that ingestion of a meal makes the stomach less susceptible to drug-induced GD but does not alter the electrical properties of TG or BG.

AUTONOMIC NEURONS IN INTRINSIC GANGLIA IN THE MAMMALIAN PANCREAS. B. F. King and J. H. Szurszewski. Mayo Medical School, Rochester, MN 55905 U.S.A.

Although mammalian pancreata possess an intrinsic network of autonomic ganglia, few direct observations have been made on the neurons therein. We have identified two types of pancreatic ganglia by their location. One type (para-fascicular ganglia) lay on major nerve bundles entering the pancreas. The other type (intrapancreatic ganglia) were found in the bed of the pancreas. Histological studies showed both types of ganglia to contain small (< 20 µm) ovoid neurons. Ultrastructural studies showed nerve terminals in close apposition to the somal body of neurons and to contain predominantly small agranular (cholinergic) vesicles as well as a few large opaque (peptidergic) vesicles. Electrophysiological studies were made on both types of ganglia using intracellular recording techniques. All autonomic neurons responded to depolarizing current by discharging exclusively in a phasic (fast-adapting) firing pattern. Neurons received cholinergic input in the form of fast EPSPs which summated to elicit action potentials. Cholinergic input was observed from the efferent (central) nerves and also from the post-ganglionic (peripheral) nerve fascicles extending from both types of ganglia. The conduction velocity of the peripheral nerves was low (< 1 $m.s^{-1}$) indicating they were C-fibers. Further ultrastructural studies showed axon bundles to be unmyelinated and therefore C-fibers. Following cholinergic blockade, antidromic invasion of action potentials was observed in both sets of ganglia. Intrapancreatic ganglia received antidromic invasion following stimulation of peripheral nerves, para-fascicular ganglia with central nerves. Slow excitation was seen following high frequency (30 Hz) stimulation of central nerves to both types of ganglia. Substance P also caused slow excitation and may be the mediator of the nerve-mediated response. Taken together, these observations suggest that intrinsic pancreatic ganglia are centers for integration of various synaptic and neural inputs. (Supported by NIH AM 17632.)

DOES THE ELECTRICAL 'SLOW WAVE' EXIST IN CIRCULAR MUSCLE OF HUMAN COLON? Y.J. Kingma, M.M. Chambers and K.L. Bowes. University of Alberta, Edmonton, Alberta, Canada, T6G 2G3.

Electrical slow-wave activity, which corresponds to contractile activity, has frequently been measured in canine circular colon muscle. Similar electrical activity has been measured in in-vivo human studies using extra-cellular electrodes. Can such activity be measured in human in-vitro studies, using microelectrodes?

Samples were obtained from patients undergoing surgery of the large bowel and were immediately immersed in oxygenated Krebs' solution. The mucosa was removed and two types of specimens were prepared: 'intact' circular muscle strips and 'isolated' circular muscle strips. The tissues were mounted in an organ bath for microelectrode recordings in the usual way: a force transducer was attached to one end of the specimen.

All specimens contracted vigorously. Electrical signals were difficult to obtain, but eventually various patterns of activity emerged. The membrane potential was -59 ± 11mV; in some cases, irregular triangular depolarizations (amp 7 ± 4mV) were recorded, either singly or in groups, confirming our observations using the sucrose gap technique; in other recordings, continuous oscillations (13 - 23 cpm) were superimposed on the resting potential. None of the electrical recordings corresponded to the concomitant contractile activity.

Our measurements show no evidence of slow-wave activity of the type measured in human stomach or canine colon. One possible explanation for the 'slow-wave' activity measured in-vivo with intra-luminal or wire electrodes, is that it may be due to motion artifact. However, wire-electrodes mounted on the human stomach or small bowel give well defined and repeatable signals, despite considerable motion in both these organs. Why should the colon differ in this respect? Since no slow-wave-type of electrical activity is measured with micro-electrodes, we conclude that the electrical signal in the circular muscle of human colon is not merely masked by motion, but that activity such as is seen in canine circular colon muscle does not exist.

NEUROPEPTIDE CONCENTRATIONS AND ELECTROPHYSIOLOGICAL PROPERTIES OF COLONIC SMOOTH MUSCLE FROM THE TWO-TOED SLOTH. TR Koch, VLW Go, DR Roddy, DL Lucas, SR Michener, and JH Szurszewski. Mayo Clinic, Rochester, MN 55905 USA

The two-toed sloth (Choloepus didactylus) is known to accumulate fecal material for several days and has "extreme smooth-muscle sluggishness" by barium x-ray studies (Quart. Rev. Biol. 1941). To elucidate the basis for this pattern of colonic motility, we determined the concentrations of 4 neuropeptides and measured some smooth muscle properties. Colon proximal to the rectal pouch was removed to obtain the muscularis externa (n=3). Neuropeptides were extracted into boiling 0.1 N HCl. After neutralization, immunoreactive vasoactive intestinal peptide (VIP), peptide histidine-isoleucine (PHI), substance P (SP), and met-5-enkephalin (ENK) were measured by specific radioimmunoassays, and their molecular species in respect to porcine standards were characterized by reverse phase HPLC. Circular muscle strips (3 x 8 mm) were pinned in an organ bath superfused at 36°C with Krebs solution or with Krebs solution containing atropine, phentolamine, and propranolol (each 1 µM). Mechanical and intracellular electrical activity were recorded to obtain resting membrane potential (RMP), and inhibitory junction potential (IJP) produced by electrical field stimulation (1 H, 10 s). Results: Neuropeptide concentrations (mean ± SD; ng/g wet weight) were: VIP 275 ± 26; PHI 225 ± 18; SP 97 ± 17; and ENK 128 ± 32. By HPLC, sloth extract contained individual peaks of immunoreactivity with retention times identical to authentic SP and VIP; immunoreactive PHI was present in one peak different from authentic PHI; immunoreactive ENK was present in 3 peaks (the largest was identical to the retention time of authentic ENK). Spontaneous mechanical activity consisted of individual phasic contractions with a range of 5-6 contractions/4 min period. RMP was -58 ± 4 mV (mean ± SD; n=6). The amplitude of IJP's ranged from 1 to 3 mV, and there was no associated muscle relaxation. Summary: The absence of prominent inhibitory innervation, as evidenced by small amplitude IJP's with no circular muscle relaxation, may be associated with low concentrations of VIP and PHI. These findings may account for this animal's in vivo pattern of colonic motility. Supported by AM 17238.

INTRACELLULAR MYOELECTRICAL ACTIVITY OF CANINE GALLBLADDER. J.W. Konturek and G.W. Scott. Surgical-Medical Research Institute, University of Alberta, Canada.

The gallbladder has only a single very thin muscle layer made up of a three dimensional mesh of muscle fibers. We simultaneously recorded the intracellular myoelectrical activity and contractility in strips from the fundus, body and the neck of 12 freshly removed canine gallbladders. The strips (15 x 1 mm) were cut in transverse, longitudinal and both oblique axes and mounted in a specially constructed organ bath at 37°C. Electrical activity was recorded using a single sucrose gap method and contractility with a Grass force displacement transducer. The tension put on the tissue was 1 g. The relationships between the electrical pattern versus mechanical activity, localization (fundus, corpus, neck) and the orientation of tissue strips were analysed.

Spontaneous intracellular myoelectrical activity showed a slow wave pattern. In 71.7% of recordings, slow waves showed a regular, rhythmical pattern at a mean frequency of 9.07±4.51 per min. They consisted of an initial potential followed by a plateau potential and could bear superimposed spiking activity at the frequency of 1 spike per slow wave. In 73.9% cases, electrical activity correlated with mechanical activity and preceeded it. The mean values of the frequency of slow waves were 11.31±2.48 per min in fundus, 9.3±5.1 per min in corpus and 10.25±2.47 per min in the neck of a gallbladder. We did not notice any significant difference between the electrical pattern and the orientation of the tissue preparation (transverse, longitudinal and oblique direction).

Conclusions: In vitro intracelular myoelectrical activity of canine gallbladder exhibits spontaneous activity that consists mainly of regular, rhythmical slow waves. No significant differences could be seen in myoelectrical pattern obtained from different regions of gallbladder (fundus, corpus, neck).

A NEW CIRCUMFERENTIAL CUFF TUBE FOR PROLONGED SPHINCTER MANOMETRY MULTILUMEN: K. Kraglund, A. Mølgaard-Nielsen, H. Gregersen and S.A. Pedersen. Aarhus Kommunehospital, W. COOK Europe and Odense University Hospital, Denmark.

Recent studies have emphasized the importance of the phasic motor activity in gastrointestinal sphincters. Sphincters often maintain a tonic contraction at rest and an active or phasic activity in other periods. Until now the sleeve catheter has been used for prolonged registration of activity in the lower oesophageal sphincter (LOS) and the ileocecal sphincter. Several studies have emphasized that a sleeve catheter does not permit analysis of phasic activity, however. This is due to rapidly increasing damping in the sleeve and further the sleeve only measures the pressure in one direction. To this end we have developed a new type of perfused assembly, which measures pressure in the whole circumference and also seems to be able to measure phasic contraction.

The manometric assembly is a 14 Fr(4.7 mm) tube in outer diameter and has a total length of 250 cm. The tube contains 7 channels, 6 with an internal diameter of 1 mm and 1 with a diameter of 1.4 mm allowing a giude wire to facilitate rapid position. The lateral orifices are placed in the area of interest(in this study in the oesophagus, stomach and duodenum). The tube incorporates a circumferential cuff sensor, 6 cm in length, to monitor sphincter contractions. The assembly is made of polyvinyl chloride. The catheter is perfused with deoxydized water from a modified low compliance hydraulic system. The perfusion rates vary between 0.16-0.50 ml/min.

Results: The assembly was tested in vivo and in vitro. In vitro testing was done by calculating pressure rise rate in response to occlusion at 0.5 cm steps along the cuff and sleeve. The Dent sleeve showed a rapidly increasing damping following an exponential curve, only allowing reliable recordings within the first cm of the sleeve. The cuff showed a nearly linear rise rate response higher than 150 cm H_2O. In vivo the cuff tube clearly demonstrated the increase in LOS tone parallel to antral phase III activity. Conclusions: We have constructed a circumferential cuff tube permitting reliable prolonged recordings from LOS. It is easily placed and well tolerated.

QUANTITATIVE MEASUREMENT OF COLONIC TRANSIT IN MAN-A NEW TECHNIQUE. B. Krevsky, L. Malmud, F. D'Ercole, A. Maurer, J. Siegel and R. Fisher. Depts. of Medicine & Diagnostic Imaging. Temple Univ. School of Med., Philadelphia, PA.

Methods for quantitative measurement of colonic transit have not been available previously. Colonic scintigraphy was employed to measure colonic transit in 10 normal subjects. Following 3 days of a controlled diet and passage of a catheter into the cecum, 50 µCi of In-111-DTPA in an 8 ml. volume were instilled into the cecum. Progression of the labeled cecal instillate was followed for 48 hrs. using a gamma camera on line to a digital computer. Movement of the labeled cecal instillate was evaluated visually, by time distribution analysis, and by calculation of the geometric center. The field of view was divided into 7 Regions of Interest: cecum and ascending colon (1), hepatic flexure (2), transverse colon (3), splenic flexure (4), descending colon (5), sigmoid and rectum (6), and excreted feces (7). Representative data showing regional distribution of the instillate with time is shown in percent in the table below.

HOUR \ REGION	CAC (1)	HF (2)	TC (3)	SF (4)	DC (5)	SR (6)	FECES (7)
1	53	30	12	5	0	0	0
3	25	25	18	15	7	5	5
24	4	10	10	7	6	32	31
48	2	3	5	5	5	6	74

Cecum and ascending colon emptying was exponential with 28 ±7, 48±7, 55±11, 75±7 and 96±1% having emptied at 0.5, 1, 2, 3, and 6 hrs., respectively. The mean half emptying time was 79±22 min. The geometric centers for progression of the chyme were 1.4±0.2, 1.6±0.3, 2.7±0.5, 3.6±0.5, 4.3±0.5, 5.2±0.3, and 6.0±0.3 at 1,2,3,4,6,24 and 48 hrs. Movement in the first 4 hrs. was exponential followed by a prolonged linear phase. Conclusions: 1) Fifty percent of the chyme which entered the cecum at any instant was propelled distally after 79 min.; 2) emptying of the proximal colon was exponential, in contrast to the distal colon which emptied linearly. This study suggests that the residence time of chyme within the cecum and ascending colon may be too brief for these regions to serve as major fecal storage sites.

INTRACELLULAR RECORDINGS FROM NEURONS IN SACRAL DORSAL ROOT GANGLIA OF THE CAT. J. Krier, Department of Physiology, Michigan State University, East Lansing, Michigan 48824.

Intracellular recording techniques were used to study the passive and active electrical properties of neurons in the first and second sacral dorsal root ganglia (SDRG) of cats. An in vitro preparation consisted of the SDRG, sacral dorsal and ventral roots, peripheral nerve trunk and pudendal nerve. The mean transmembrane potential of neurons was -55 mV ± 2.4. The input resistance ranged from 15.3 to 41 MΩ (Mean 25 MΩ ± 4.0). Neurons generated action potentials in response to direct depolarizing current stimulation and to electrical stimulation of afferent fibers in sacral dorsal roots, peripheral nerve trunk and pudendal nerve. Neurons were classified into two groups: A and C. A neurons exhibited action potential durations ranging from 2 to 4 msec. The average conduction velocity was 13 m/sec (range 2.0 to 33 m/sec). C neurons exhibited action potentials with delayed repolarizations (action potential duration range 8 to 12 msec). The average conduction velocity was 1.5 m/sec (range 0.9 to 2.0 m/sec). Tetrodotoxin (TTX) (10^{-6} to 10^{-5} M) blocked action potentials of A and C neurons in response to electrical sitmulation of afferent axons but did not block action potentials evoked by direct depolarizing current. In conclusion, action potentials evoked in A and C neurons by afferent fibers may be largely by sodium dependent whereas action potentials evoked by direct depolarizing current stimulation may involve TTX-resistant sodium channels (AM 29920).

ELECTROPHYSIOLOGICAL PROPERTY OF INTERNAL ANAL SPHINCTER OF SOME MAMMALS. M. Kubota and J.H. Szurszewski. Mayo Medical School, Rochester, MN 55905 U.S.A.

We studied circular muscle layer within 2 cm from the anal verge in dog, cat, rabbit, guinea pig and man. Mechanical and intracellular electrical activity were recorded simultaneously. The sphincter muscle could be identified by its characteristic pattern of spontaneous activity. In dog and cat, sphincter muscle (up to 5 mm from the anal verge) exhibited electrical oscillations of 24.2 c/min and 34.4 c/min, respectively, while nonsphincteric muscle (15 mm from anal verge) showed a regular potential change of < 10 c/min. The mean resting membrane potential of sphincteric and nonsphincteric muscle in dog was -52.7 mV and -52 mV, respectively, while corresponding values in cat were -47.7 mV and -60.8 mV. Sphincter muscle of rabbit also exhibited electrical oscillations of a similar frequency (24.5 c/min) though irregularities of membrane activity were much more commonly observed than in dog and cat. Nonsphincteric muscle (15 mm from anal verge) was characterized by membrane fluctuations of a small amplitude and spike generation was observed in some cells. The mean membrane potential of sphincteric and nonsphincteric muscle was -40.3 mV and -48.4 mV, respectively. In guinea pig, the muscle cells examined were electrically quiescent but resting membrane potential of the sphincter muscle (up to 3 mm from anal verge) was significantly lower than that of nonsphincteric muscle (15 mm from anal verge). Mean membrane potential of sphincteric and nonsphincteric muscle was -45.1 mV and -58.1 mV, respectively. Phasic contractions triggered by electrical oscillations fused to produce a sustained muscle tone in the sphincter of dog, cat and rabbit, while muscle tone was maintained without spontaneous activity in the guinea pig. Human muscle from this part uniformly exhibited electrical oscillations (13-15 c/min) with sustained muscle tone. Mean membrane potential was -51.5 mV. These results suggest regional and species differences in electrical activity in the terminal part of circular muscle layer and correspondingly in internal anal sphincter. (Supported by NIH Grant AM 17238.)

PROLONGED INTESTINAL MANOMETRY: IS IT NECESSARY? D Kumar and DL Wingate. GI Science Research Unit, The London Hospital Medical College, London E1 2AJ, UK.

Small bowel motor abnormalities are of two types; persistent as in neuropathies or myopathies or, as reported recently (GE 1985, abstract in press), intermittent or paroxysmal. Patients with suspected motility disorders are usually studied for relatively short periods (<8 hours) with perfused tube manometry. Ambulant manometric techniques, such as radiotelemetry, have made prolonged intestinal manometry possible but the clinical value of such recordings is not established. To answer the question of whether prolonged recording is helpful in the diagnosis of motility disorders, we have reviewed our recent experience of proximal small bowel manometry in 30 patients. Manometry was carried out for 8 hours using a conventional multi-lumen perfused tube system (n=3), or for 24 hours or more using dual pressure-sensitive 'radiopills' (n=26), or both techniques (n=1). Three patients with suspected pseudo-obstruction had the diagnosis confirmed by 8-hour manometry and subsequently by histology. Another 3 patients had abnormal motility records, characterised by abnormal fasting contractions, seen only on prolonged manometry, and in one, total absence of MMCs over 24 hours. In 5 of the remaining 24 patients investigated for abnormal intestinal motility, abnormal motility was not noted until at least 14 hours after the onset of study. With the conventional recording, the abnormality would have been missed in these patients. Reviewing management strategies, it is clear that neuropathic or myopathic motor abnormalities can be as easily diagnosed on short recordings, but our data show that transient deviations from normal fasting motility patterns require prolonged, preferably overnight, recordings if they are not to be missed.
(DK is a Beecham Clinical Research Fellow)

DECREASING POTENCY OF REPETITIVE PSYCHOLOGICAL STRESS IN THE INHIBITION OF HUMAN MIGRATING COMPLEXES (MCs). D Kumar, P C Kao*, D L Wingate. GI Science Research Unit, London Hospital Medical College, London E1 2AJ, UK and *Section of Clinical Chemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

To avoid the problem of adaptation to prolonged psychological stress (Gut 1982, 23:404), we adopted a protocol (GE 1983, 84:1340) in which 3 two-hour stress periods were separated by one-hour rest periods; controls for these periods were the equivalent periods in the preceding day during which stress was absent. We have analysed the incidence of duodenojejunal MCs during control and stress periods in 9 healthy volunteers and 21 'irritable bowel' (IBS) patients submitted to the stress protocol to test the hypothesis that intermittent stress effectively abolishes adaptation. In addition, since plasma levels of beta-endorphin appear to be an effective index of nociceptive stress (GE 1983, 85:83), these were measured with radioimmunoassay during the control and stress days in 6 healthy controls. In both study groups, there were approximately 0.5 MCs/hour/subject throughout the eight-hour control period and during the 2 one-hour rest periods on the stress day. In spite of the apparently complete recovery from each stress episode, the effectiveness of stress in inhibiting MCs progressively diminished during the stress day in both groups. The same trend was visible in beta-endorphin plasma levels; the mean increment in the 1st stress period being 20 pg/ml, in the second 10 pg/ml, and nil in the third. In spite of the wide variability of plasma levels, and the small number of subjects, the trend of beta-endorphin diminution was statistically significant ($P<0.05$ ANOVA). We conclude that adaptation to psychological stress is probably a diurnal phenomenon, which might be overcome by increasing the intensity of the stressors. Our data are consistent with the possibility that stress-related IBS symptoms tend to occur at the beginning of the day because subjects are then most susceptible.

CHOLECYSTOKININ-OCTAPEPTIDE (CCK-OP) ACTIVATES THE INTESTINAL MOTOR CORRELATES OF VOMITING BY A PERIPHERAL MECHANISM. I.M. Lang, S.K. Sarna and R.E. Condon, Medical College of WI, and VAMC, Milwaukee, WI 53193 USA.

We examined the effects of CCK-OP on the contractile and electrical activities of the gastrointestinal tract of 8 dogs. The dogs were chronically implanted with seromuscular strain gage transducers or bipolar electrodes along the gastrointestinal tract. The electrical and contractile responses to bolus injections of CCK-OP (10-500 ng/kg, i.v.) were compared to responses activated by apomorphine (APO) (1-15 µg/kg, i.v.). APO activates the GI motor correlates of vomiting at a central site. The effects of vagotomy (3 dogs), splanchnectomy (3 dogs), and the following agents (8 dogs) on the responses to APO and CCK-OP were examined: atropine (100 µg/kg, i.v.), domperidone (0.5 mg/kg, i.v.), and proglumide (300 mg/kg, i.v.). We found that CCK-OP ($\geq$ 50 ng/kg) initiated the retrograde peristaltic contraction (RPC) of the intestine only. The CCK-OP-induced RPC occurred at the same sites with the same magnitudes (160 $\pm$ 8% of phase III height) as that initiated by APO, and the myoelectric correlates of these contractions were the same also. Like APO, the CCK-OP-induced RPC magnitude was independent of dose. Unlike APO, the CCK-OP-induced RPC did not begin at a fixed position (175 $\pm$ 20 cm) from the pylorus but within a range (100 to 175 cm). The RPC velocity activated by CCK-OP (32 $\pm$ 3 cm/s) was significantly faster ($p < .01$) than the APO-induced RPC (11 $\pm$ 1 cm/s). Other gastrointestinal motor responses initiated by CCK-OP were similar to those activated by APO. CCK-OP did not activate emesis or its prodromal signs. Atropine blocked both the CCK-OP and APO-induced RPC but splanchnectomy had no effect on either response. Vagotomy or domperidone blocked the APO-induced responses but had no effect on CCK-OP-induced responses. Proglumide blocked the CCK-OP-induced responses but not APO-induced responses. These results indicate that CCK-OP activated the motor correlates of vomiting in the intestine by a peripheral mechanism, part of which may be in common with the APO-induced responses. This common pathway included muscarinic, but not CCK receptors. These results suggest that CCK may mediate a peripherally activated RPC.
This research was supported in part by VA grant 5120-02P.

VIP AS A POSSIBLE NEUROTRANSMITTER OF LIPID INDUCED CHANGES OF LES-TONE IN DOGS.
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The ingestion of a meat or glucose meal causes an increase of lower oesophageal sphincter pressure (LESP). In contrast, a lipid meal causes a decrease of LESP. The mechanisms of these reactions are unknown. In a previous study it has been shown that in the dog intestinal contents of the duodenum play an important role of the postprandial rise or fall of LESP. VIP is a potent inhibitor of opposum LESP, and it has been reported that its inhibitory effect is exerted directly on the sphincter muscle. In 6 mongrel dogs (weight 15-20 kg) we studied the effect of duodenal instillation of 100 ml of peptone 20 %, Intralipid® 20 %, Glucose 20 % and NaCl on LESP and plasmaconcentrations of VIP. A special surgical preparation allowed a direct perfusion of the duodenum via an intestinocutaneous fistula. LESP was measured manometrically by rapid-pull-throughs during 15 minutes before and 75 minutes after the beginning of the 10 minutes lasting perfusion of the duodenum. Blood samples for VIP-measurement were taken every 15 minutes. NaCl-perfusion causes no significant changes in LESP and VIP-concentration. Glucose-perfusion of the duodenum slowly rises the LESP up to a maximum difference of 13 mmHg ($\bar{x}$, 70. min) meanwhile the VIP-concentrations are unaltered. Following peptone-perfusion the LESP rises up to a high pressure difference of 20 mmHg ($\bar{x}$,35.min). Again there was no change in VIP-concentrations. Duodenal perfusion of lipidsolution causes a prompt fall of LESP with a pressure difference of -6 mmHg ($\bar{x}$, 15. min). At the same time VIP-concentration rises from 14.7 pmol/l ($\bar{x}$) up to 24.3 pmol ($\bar{x}$). When the LESP reaches resting levels the VIP-concentrations are low again.

ANORECTAL MANOMETRY AND DEFECATION STUDIES IN CHILDHOOD ENCOPRESIS. Vera Loening-Baucke. University of Iowa, Dept. of Pediatrics, Iowa City, Iowa, USA.

It has been previously suggested that constipation with encopresis, a frequent and often persistent problem in childhood, is associated with an inability to defecate. The aims of this study were to evaluate with intraluminal transducers and surface electrodes anorectal function and external sphincter (exSp) activity during trials to defecate and during balloon distention. 37 encopretics (P) (31 boys, 6 girls; ages 6-15 years) and 16 age-matched healthy children (H) underwent anorectal studies which included thresholds (ml of air) of the internal sphincter relaxation (TRSR $\geq$ 5 mm Hg), of exSp contraction (TexSp $\geq$ 5 mm Hg), and of rectal sensation (Tsens is the smallest transient air volume sensed and CV is the volume which produced a strong urge to defecate). We determined the initial pressure (mm Hg) in the lower rectum during balloon distention of the upper rectum with 60 ml air (iPr), and 20 seconds after adaptation had taken place (aPr). All H showed a $\geq$ 25% decrease in amplitude of exSp action potentials together with decreased anal tone of $\geq$ 5 mm Hg during defecation trials (EMG+). 35% of Pdef+ and 77% of Pdef- had increased exSp contraction during trials to defecate. P were divided by their ability to defecate $\geq$ 2 of 3 waterfilled (30, 50, 100 ml) balloons (Pdef+) and $\leq$ 1 balloon (Pdef-). Mean $\pm$ SD of the measurements are given in the table.

	TRSR	TexSp	Tsens	CV	iPr	aPr
H	11+5	19+ 6	14+ 7	101+ 39	34+21	14+19
Pdef+	16$\pm$5*	42$\pm$35*	24$\pm$13*	185+ 90*	20$\pm$15	9$\pm$15
Pdef-	16$\pm$8*	44$\pm$39*	29$\pm$15*	219$\pm$127*	24$\pm$21	8$\pm$12

TRSR, TexSp, Tsens, and CV were significantly larger in Pdef+ and Pdef- than in H ($p < 0.05$). The rectum adjusted similarly in all 3 groups during rectal distention. In P, the inability to defecate balloons did not appear to be related to a more severe abnormality in rectal sensation or rectal wall elasticity ($p > 0.2$). The ability to defecate balloons was related to EMG+ in P ($p < 0.02$). After six months treatment with laxatives 3 of 3 Pdef+ had recovered from chronic constipation and encopresis, but only 1 of 4 Pdef-. Abnormal exSp contraction during defecation may contribute to fecal retention in some P.

ELECTRICAL AND MECHANICAL ACTIVITIES IN THE LOWER ESOPHAGEAL HIGH PRESSURE ZONE OF THE CAT IN VIVO
D.Liebermann-Meffert. Dept.Surgery, Kantonsspital, University, CH Basel, Switzerland

we have recorded intraluminal pressures and myoelectric activity simultaneously in situ from the lower esophagus, its high pressure zone (LEHPZ) and stomach of 20 Ketamine anesthetized cats using a multi channel Beckman Dynograph at various amplifications and paper speeds.

After surgical removal of the phrenoesophageal membrane needle electrodes were sticked into the thickened LES muscle lesser curve sides in 10 cats at the site of maximal LEHPZ pressure and at distances of 5mm orad and caudad. Recording the interelectrode activity four wave types were identified:

1) Sinus-waves of regular 12 sec/rhythm with periodically changing wave magnitude (0.2 to 1.3mV). Manipulations on the LEHPZ shortened the waves.
2) A high amplitude "negative/positive" activity (SW-signal) of up to 8mV strongly correlated with the oncomming swallowing wave (SW) and LES relaxation.
3) Waves up to 0.02mV amplitudes correlated with respiration and
4) Waves of EKG type correlated with the heart action (femoral artery pulse).

The sinus-wave pattern, the SV signal and the superimposed activities were a constant feature recorded from chronically implanted intramuscular LEHPZ miniature electrodes up to 6 months in the other 10 cats, although the pattern was less regular.

This study shows that there is LES myoelectrical activity consisting of regular rhythmic waves,contraction related activity and superimposed respiration and heart activities. LES - and stomach EMG were different.

COMPARATIVE STUDIES IN HUMAN AND CANINE GASTRIC MUSCLE: SPONTANEOUS ACTIVITY AND EFFECTS OF VARIOUS PEPTIDES. F.E. Lüdtke, K. Golenhofen, C. Köhne, K. Milenov and H.J. Peiper. Dept. of General Surgery, D-3400 Göttingen, FRG; Dept. of Physiology, D-3550 Marburg/Lahn, FRG; Institute of Physiology, Sofia, Bulgaria.

Method: Circular and longitudinal strips from fundus, corpus, antrum, pylorus and duodenum were transferred to an organ bath, and the mechanical activity was recorded to examine the species differences between man and dog. Results: 1. Spontaneous activity. Human fundus strips produced a predominantly tonic activity which was similar to the spontaneous activity of canine fundus preparations. Canine corpus and antrum strips showed rhythmic activity, with a marked frequency gradient from corpus (4-5/min) to distal antrum (1/min). In contrast, circular strips from human stomach developed strong rhythmic activity, the frequency of which reached - after an adaptation period of 1-2 hours - 4-5/min (which is higher than the normal in situ-frequency of 3/min). No significant frequency gradient from corpus to distal antrum could be observed in human stomach. The spontaneous activity of the canine inner pylorus was qualitatively different from that of the neighbouring preparations (strong phasic activity of minute-rhythm type). The spontaneous activity of human inner pylorus was more variable, and the differentiation between inner and outer pylorus was not so marked in man as in the dog. 2. Bombesin produced only weak excitatory responses in isolated canine gastric muscle. In human strips, however, it was the most powerful excitatory agent in all types of preparation. 3. Neurotensin produced strong activations in human strips from distal stomach and duodenum. In canine stomach, however, the effects of neurotensin were negligible in most types of preparation. 4. In dog cholecystokinins (CCK 33, CCK 8 and caerulein) all produced an identical pattern of responses: they predominantly increased the frequency of the phasic contractions in circular corpus and antrum strips. The effects of CCK in human preparations were much weaker. A significant increase of the frequency could not be observed. Conclusion: There are marked differences in the basic properties of human and canine gastric smooth muscle, both in the spontaneous activity and in the responses to various peptides.

(A-25)

MMC-RELATED INTRADUODENAL pH CHANGES IN SHEEP.
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Since the pancreaticobiliary duct in sheep opens into the duodenum 20 cm from the pylorus and gastric emptying is almost continuous, the proximal duodenum is, in contrast to many monogastric animals, daily exposed to large amounts of acidic digesta. However, periodic interruption of abomasal motility, coincident with ISA and RSA (phase II & III) development on the duodenum, suggests that some changes in intraduodenal pH, related to MMC activity, could occur. To test this in 4 ewes fitted with antroduodenal nichrome wire electrodes and a duodenal T-shaped cannula, EMG activity was continuously monitored and changes in pH of intraduodenal contents (IDC) were measured by opening the cannula and letting the IDC flow out, or via small pH electrode into the duodenal lumen via the cannula. In the IDC studies, MMC-related mean pH/vol. (ml) for 10 min aliquots were: ISA-2.9/63; RSA-3.2/41; quiescence-4.8/18. Probe studies showed more precise pH-MMC relationships, i.e. rapid pH oscillations between 2-5 during ISA and a steady rise in pH to 4.5-6.5 at the end of RSA. The increased MMC rhythmicity by methysergide treatment was accompanied by concomitant cyclical changes in IDC pH (Fig.). We conclude that the MMC has marked effects on the pH of ovine IDC and that the highest values occur during duodenal quiescence when antral motility is also inhibited.

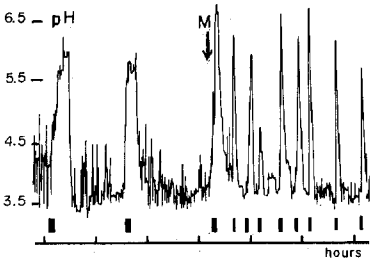

Fig. : MMC-related changes in intraduodenal pH before and after 50 µg/kg methysergide IV (arrow). Solid bars indicate periods of RSA. Note the rise in pH at the end of RSA to 4.5-6.5 during the phase of quiescence.

REVERSAL OF NEGATIVE PRESSURE VENTILATION INDUCED LOWER ESOPHAGEAL SPHINCTER (LES) DYSFUNCTION WITH METOCLOPRAMIDE.
W.D. Marino, N.K. Jain and C.S. Pitchumoni. Our Lady of Mercy Medical Center, Bronx, NY 10466 U.S.A.

We have previously demonstrated that LES dysfunction is induced in healthy volunteers placed in negative pressure body ventilators (GE 1984;86:1123). This is important since regurgitation of gastric contents and peptic esophagitis are frequent complications of the use of such ventilators. The present study was conducted to determine whether LES dysfunction during the use of these ventilators also occurs in patients with chronic respiratory failure, and whether this dysfunction can be pharmacologically reversed. Five patients with documented chronic respiratory failure were studied. After an overnight fast, esophageal, LES and gastric pressures were simultaneously recorded in the unassisted state and during mechanically assisted ventilation. After measuring pressures in the steady state during mechanical ventilation, 10 mg IV metoclopramide was administered to each patient and pressure recordings continued for one hour more. In all 5 patients, baseline LES pressures were in the normal range (mean 15 mmHg). During the inspiratory cycle of mechanical ventilation, 3 of the 5 patients demonstrated a significant reduction in LES pressure to a mean of 3 mmHg, while it was unchanged in the other 2. Within 15 minutes of metoclopramide administration there was an increase in LES pressure to 15 mmHg in the 3 patients in whom a significant decrease in LES pressure had occurred. Metoclopramide did not have any effect on the LES pressure of the other 2 patients. Thus, we conclude that in patients with chronic respiratory failure, as in normals, there is a subset of individuals in whom negative pressure mechanical ventilatory assistance induces dysfunction of the LES and that this dysfunction is reversible with metoclopramide. The effect of negative pressure mechanical ventilatory assistance on LES function should thus be evaluated by esophageal manometry in patients requiring such therapy. The use of metoclopramide should be considered in those patients found to develop LES dysfunction.

EFFECT OF KETANSERIN, A SELECTIVE ANTISEROTONINERGIC DRUG,ON HUMAN INTERNAL ANAL SPHINCTER(IAS) IN VIVO.
L.Marzio,M.Neri,AM.Di Giammarco,C.De Angelis, F. Cuccurullo.Istituto di Fisiopatologia Medica,Università di Chieti, Chieti, Italy.

Five-hydroxytriptamine has been shown to produce an excitatory effect on human IAS muscle strips in vitro(Gastroenterology 1979;77:484-90); however a role for serotonin in IAS function has not yet been demonstrated in vivo. Eight normal subjects have been studied.In each subject IAS pressure and the rectoanal inhibitory reflex were evaluated by means of a probe with a balloon of 4.5x4.5 cm mounted on the tip,and an open tip catheter(1mm OD)placed 3 cm distal to the balloon, continuously perfused by a low infusion system.In each subject the probe was slowly pushed through the anal canal in a stepwise manner,in order to obtain a pressure profile;the probe was then withdrawn till the open tip recorded maximal pressure.The rectoanal inhibitory reflex was firstly checked and was normal in all subjects.A saline infusion was continuously administered throughout the study.Twenty min after recording a stable pressure in the IAS,Ketanserin(20 mg i.v. as bolus)or placebo(2 ml i.v. as bolus)were administered in a double blind fashion,and recordings continued 45 min afterward.The results show a striking fall in IAS pressure from 1 to 2 min after Ketanserin(basal:78.3±22;Ketanserin 1 min 49.5±18;15 min:40.1±13;30 min:36.1±11;mmHg,mean±SE). Placebo,unlike Ketanserin,did not produce any variation in the IAS pressure recording. A serotoninergic involvement in the maintainment of IAS basal tone may therefore be suggested

DOPAMINE INDUCES A PHASE III-LIKE ACTIVITY IN FED HUMANS.
L.Marzio,M.Neri,A.Iacobucci,AM.Di Giammarco,F.Cuccurullo.Istituto di Fisiopatologia Medica, Università di Chieti,Chieti,Italy.

In a previous work(Gastroenterology 1984;86:1175)we showed that dopamine induces a phase III-like activity in the human duodenum during the interdigestive state.The aim of the present study has been to investigate if dopamine has the same effect on duodenal motility during the fed state. After an overnight fasting a four lumen manometric probe was passed nasally in five subjects and positioned fluoroscopically with the edge below the angle of Treitz.Each catheter was perfused with deionized water at the rate of 0.5ml/min by a low compliance infusion system,and connected through a pressure transducer to a polygraph.A respiration belt monitored breathing.The study began after a 500ml whole milk meal,when a stable fed pattern was established.After a 20min base-line activity,dopamine was infused i.v. for 15min at the dose of 5µg/Kg/min.Dopamine at this dose has been shown to produce a specific dopaminergic effect.The results show that dopamine in all subjects interrupts the fed state motility pattern, inhibiting the high antral pressure waves and activating in three subjects a duodenal motility pattern strikingly similar to the phase III of the interdigestive migrating motor complex,followed by a period of quiescent motor activity.In the remaining two subjects the increased motility induced by dopamine did not fullfill the criteria of phase III identification.These findings may support the hypothesis that a dopaminergic mechanism might modulate the cycling of motor complexes in humans.

GALLBLADDER ELECTRICAL ACTIVITY IN VIVO. T. Matsumoto, S.K. Sarna, and R.E. Condon, VAMC, and Medical College of WI, Milwaukee, WI.

Electrical oscillations are the basis of most types of contractions in the gastrointestinal tract. The electrical basis of gallbladder contractions has not been defined as yet. We investigated if gallbladder smooth muscle has an electrical activity and, if so, how it may be related to its contractile activity? The gallbladder electrical and contractile activities were recorded by a teflon coated stainless steel bipolar wire electrode and a strain gauge transducer implanted on the infundibulum. Additionally, 4 bipolar electrodes and 2 strain gauge transducers were implanted on the small intestine and antrum respectively. The electrical signals were filtered in the frequency ranges of 0.3 to 0.5 Hz, 0.5 to 1.5 Hz, and 1 to 5 Hz to separate out different components of electrical signals. The gallbladder smooth muscle showed a distinct and omnipresent electrical activity in the frequency range of 18-30 c/min. The mean frequency of this electrical activity was 22.1 $\pm$ 1.2 SE c/min. In contrast, the frequency of duodenal ECA was 18.7 $\pm$ 0.2 c/min. The extracellularly recorded amplitude of gallbladder electrical activity increased 5-10 fold when gallbladder smooth muscle contracted, but there was no significant change in the frequency of oscillation (24.5 $\pm$ 0.6 c/min). We did not observe any burst of electrical response activity (ERA) or spikes superimposed on each oscillation during a contraction. During phase III contractions of gallbladder, the increase in amplitude of electrical oscillation occurred at a repetition rate of 6.6 $\pm$ 0.3/10 min which was the same as the frequency of phasic contractions. The amplitude of electrical oscillations was also increased after a meal or after insulin administration when gallbladder strain gauge transducer recorded tonic and phasic contractions. We conclude that gallbladder contractile activity is also controlled by an electrical activity. There may, however, be some differences in the excitation-contraction coupling in the gallbladder smooth muscle as compared with that in the rest of the gastrointestinal tract where ERA is usually associated with in vivo contractions.

Supported in part by grants VA 7722-01P and NIH AM 32346.

GASTRIC EMPTYING OF SOLIDS AND LIQUIDS IN PATIENTS AFFECTED BY SEVERE REFLUX ESOPHAGITIS. S.Mattioli,V.Stanghellini,V.Pilotti,C,Raiti,A.Parmeggiani,C.Corinaldesi, L.Barbara,G.Gozzetti. University of Bologna.

Twenty consecutive patients(16 M,4 F, $\bar{m}$ age 52.75 yrs $\pm$ 8.82)affected by endoscopically and radiologically proven esophageal severe lesions (confluent erosions,ulcer and/or acquired short esophagus) underwent the following examinations: a)basal and pentagastrin stimulated gastric acid secretion(BAO,MAO); b)24-hr combined esophago-gastric home pH-monitoring:% total time of esophageal pH$\leq$4(%TT pH$\leq$4 Es.) and of gastric pH>4(%TT pH>4 St.)were calculated; c)gastric emptying(GE)of solids and liquids, measured by radioisotopic gamma camera techniques in two different occasion one week apart: data were analysed by a power exponential function and expressed respectively as T/2S and T/2L.The solid meal(640cc,703KCal)was labelled by 99mTc-SC in vitro infiltrated chicken liver; the liquid meal(300cc,570kCal) by 99m Tc-DTPA. Data were compared with those obtained in a group of 17 controls (14 M, 3 F, $\bar{m}$ age 39.7 yrs $\pm$9.1).

Results

	BAO	MAO	T/2L	T/2S	%TT pH$\leq$4 Es.	%TT pH>4 St.
Ctrs $\bar{m}$	3.20	15.07	89.82	104.88	2.09	11.82
S.D.	1.79	4.25	9.98	20.24	1.43	7.61
Pts $\bar{m}$	4.79	25.76	141.65	136.00	22.28	30.96
S.D.	4.51	12.15	49.40	65.43	22.33	15.51
t-test	N.S.	p<.01	p<.01	N.S.	p<.02	p<.01

Furthemore, no correlation was found between esophago-gastric pH and GE parameters.

Conclusions Severe esophagitis patients present: 1) a delayed GE of liquids but not of solids, suggesting a major impairement of fundic rather than antral gastric motility; b) %TT pH$\leq$4 Es. higher than controls but not correleted to T/2S and T/2L; c) %TT pH>4 St. higher than controls, further confirming the presence of gastrointestinal motor abnormalities.

FECAL INCONTINENCE: CONTRIBUTION OF RESTING AND SQUEEZE PRESSURES S.McHugh & N.E.Diamant, Univ. of Toronto,Canada

The contribution of resting anal pressure (RAP) and maximal squeeze pressure (MSP) to the problem of fecal incontinence (FI) was assessed by comparing 148 incontinent patients (101 females;47 males:ages 19 - 87) to a control population of 145 healthy subjects (85 females;59 males:ages 20 - 89). These parameters were determined with a multi-lumen continuously perfused (0.7cc/min/orifice) catheter (OD6mm) using a validated mechanized rapid pullthrough technique. In the control population RAP did not differ between the two sexes. MSP, however, was significantly higher in men than in women under 50 years of age. In women there was a good correlation between age and RAP (coef.-0.589, p<.0005) but only a fair correlation with MSP (coef.-0.337, p<.0005). Parity showed only a weak correlation with RAP (coef. -0.137, p>.05). Multiple linear regression showed that age and not parity accounted for changes in RAP (F-ratio = 44.146, p<0.00005) and MSP (F-ratio = 10.616, p=0.002). In males, there was a fair correlation between age and RAP (coef.-0.278, p = 0.03) and MSP (coef. -0.361, p=0.002). Normative data for these parameters was constructed for each sex on a decade basis for comparison with the FI population. The wide range of pressures (mean +/- 2SD) for these parameters resulted in 39% of female patients and 44% of male patients falling within the normal range and 41% and 17% of patients having impairment of one or both parameters. Ten percent of FI patients had a RAP within the normal range for their age and sex but which was less than 35 mm Hg. CONCLUSIONS: In women, aging effects RAP more than MSP and parity has little effect on either parameter. In men, aging has less effect on both parameters. Normality of anal sphincter function represents a broad range for both RAP and MSP. Impaired RAP and MSP significantly contribute to about 60% of problems of FI. A significant number of patients had a RAP within the normal range but less than pressures commonly attained in the rectum with physical activity. Variation in colonic function may account for some of the desychrony between sphincter pressure measurements and clinical problems of bowel control.

CHARACTERISTICS OF HUMAN SPHINCTERIC MUSCLE IN VITRO. H.C. McKirdy, R.W. Marshall, B.A. Taylor, P. Griffin and H.L. Duthie. University of Wales College of Medicine, Cardiff, CF4 4XN, Wales, United Kingdom.

The high pressure zone (HPZ) found in the junctional regions of the gut has been variously attributed to an inherent property of smooth muscle, to local mechanical features or to neural or humoral control. We have studied muscle strips (0.2-2mm thick and 0.3-2cm long) from surgical specimens, 23 of oesophagogastric junction (OGJ), 20 of ileocaecal junction (ICJ), 18 of internal anal junction (IAJ) and from 15 fresh autopsy specimens of choledochoduodenal junction (CDJ). Strips were set up for isometric recording and subjected to electrical field stimulation (EFS) using 0.3 msec square wave pulses at 10 Hz for 5 sec.

Strips from OGJ and IAJ consistently developed a high sustained myogenic resting tension (i.e. resistant to tetrodotoxin 5μM) which showed a relaxation on EFS (1). A lower myogenic resting tension developed in a majority of strips from CDJ and ICJ which gave a relaxation or a biphasic response to EFS. Strips from muscle adjacent to all these junctional zones developed little or no resting tension and contracted in response to EFS. A similar pattern of tension and response to EFS has been found in the gastroduodenal area (2).

Thus there is an overall pattern of response in strips of smooth muscle taken from the HPZ of the human gut: they have a resting tone which has a myogenic component which can be measured in vitro: the response to EFS relates to the level of tone developed and can help to characterise sphincteric muscle.

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THE EFFECT OF FEEDING AND CHOLECYSTOKININ (CCK) ON THE CANINE CYSTIC DUCT. L.J.McMullin*, C.V. Nally, A.S. Clanachan, C.M. Rodkiewicz and G.W. Scott. Biliary Research Group, University of Alberta, Canada.

As CCK constricts the cystic duct in anaesthetised dogs we compared the effects of feeding(F) with CCK infusions on cystic duct diameter and gallbladder(GB) emptying in conscious dogs.

Cannulae were placed in the GB, common bile duct(CBD) and duodenum and a double marker system was used to measure GB emptying. Pressures in the GB and CBD were measured. The migrating myoelectric complex(MMC) was monitored with 3 electrodes on the bowel. Changes in cystic duct diameter were calculated from GB emptying rates and pressure differences between the GB and CBD. During phase 1 of the MMC the dogs were either fed, or infused for 30 min with CCK 30pmol.kg^{-1}.hr^{-1} (CCK_1) mimicking post prandial levels, or 300pmol.kg^{-1}.hr^{-1} (CCK_2). GB and CBD pressures, GB emptying and changes in cystic duct diameters during CCK infusions were compared with those during feeding(Mean±SEM).

GB pressure during CCK_1 (9.9±1.0cmH_2O) and F (11.9±1.3cmH_2O) were similar; GB pressure during CCK_2 (25.0±0.8cmH_2O) was significantly higher($P<.001$). There was no difference in CBD pressures (CCK_1=8.3±0.6, CCK_2=6.8±2.3, F=10.2±0.6). The resulting pressure differences between GB and CBD induced by F and CCK_1 were similar but were significantly less($P<.01$) than that induced by CCK_2. GB emptying during F(9.1±0.8ml.30 min^{-1}) and CCK_1 (8.6±1.6ml.30min^{-1}) were similar. CCK_2 caused a significantly($P<.05$) greater emptying (16±2.2ml.30min^{-1}). There was no significant difference in cystic duct diameter between CCK_1 and F but CCK_2 reduced the diameter by 53%. We conclude that CCK_1 and F have similar effects on the GB, CBD and cystic duct. CCK_2 increases the pressure in the GB and the pressure gradient between the GB and CBD. Although CCK_2 increases emptying it appears that this may be impeded by constriction of the cystic duct.

*Alberta Heritage Foundation for Medical Research Fellow

PYLOROSPASM IN DIABETIC GASTROPARESIS. F. Mearin, M. Camilleri and J.-R. Malagelada. Gastroenterology Unit, Mayo Clinic and Foundation, Rochester, MN 55905 U.S.A.

Gastrointestinal motor disturbances have been characterized in diabetics with the gastroparesis syndrome. However, pyloric activity has not been specifically investigated. We have quantified the pyloric manometric profile in 24 diabetics with the clinical syndrome of gastroparesis without radiologic and/or gastroscopic evidence of structural abnormalities in the upper gut. Twelve healthy volunteers served as controls. A multilumen assembly, with 5 side openings each 1 cm apart, was positioned fluoroscopically across the antroduodenal junction. Pressure activity was monitored for 5 hr (3 hr fasting and 2 hr after a 511 calorie mixed solid-liquid meal) in each subject by means of a low compliance, pneumohydraulic perfusion manometric system. Three patterns of pyloric activity were defined and quantified: 1) baseline elevation of ⩾3 mm Hg for ⩾1 min (tonic pattern); 2) antral-type phasic pressure activity mixed with duodenal phasic activity (mixed phasic pattern); 3) phasic pattern superimposed on tonic activity (combined tonic-phasic pattern). Results: During fasting (FAST) and postprandially (FED), the duration of the total pyloric activity quantitated was greater in diabetics than controls (FAST: 18±4 min vs 3±0.6; FED: 26±5 min vs 9±3 [mean±SE], $P<0.005$ for both by Wilcoxon rank sum test). The relative proportions of the three patterns of pyloric activity were not different between diabetics and controls. However, episodes of unusually prolonged (⩾3 min) and intense (⩾10 mm Hg) tonic contraction, "pylorospasm," were found in 14 of 24 diabetics but in only 1 control (1 fasting episode). Episodes of pylorospasm in diabetics had a peak amplitude of tonic activity of 13±1 mm Hg and a duration of 7±0.7 min (mean±SE). Conclusion: Pylorospasm is a common and previously overlooked manifestation of diabetic autonomic dysfunction in the gastroparesis syndrome.

ROLE OF THE PYLORUS IN FASTING ANTRODUODENAL RESISTANCE TO FLOW. F. Mearin, F. Azpiroz, A.R. Zinsmeister and J.-R. Malagelada. Gastroenterology Unit, Mayo Clinic, Rochester, MN 55905 U.S.A.

Using a recently developed pneumatic resistometer (Clin Res 32:747A, 1984) we have demonstrated cyclic changes in antroduodenal resistance to flow during fasting in a chronic canine model. To study the pyloric contribution to this resistance we studied 4 control dogs and 4 dogs with extramucosal pyloric myotomy. Changes in antroduodenal resistance were measured as changes in air flow through a flaccid polyurethane cylinder (7.5 cm long) positioned along the antroduodenal area and maintained at a constant pressure gradient (2 mm Hg) by the resistometer. Antral and duodenal pressure activity were simultaneously monitored by manometric catheters. In each of the 8 fasted conscious dogs two consecutive interdigestive motor complexes (IMC) were recorded in triplicate experiments. Air flow was averaged for each IMC phase: phase I, "early half" and "late half" phase II, and phase III. Statistical analysis compared the linear and quadratic trends in air flow per IMC phase for control and myotomized dogs. Results: Changes in air flow were related to the different phases of the IMC and were preserved after pyloric myotomy (Table; mean ± SE). However, the linear as well as the quadratic trends were significantly different between the two groups ($P<0.001$). During the periods of relative motor quiescence flow was significantly higher (decreased resistance) in the myotomized group when compared to controls. These differences decreased during phases of high motor activity.

	Air Flow (ml/min)			
IMC phases	I	II (early)	II (late)	III
Control	364±60	263±48	212±46	93±26
Pyloric myotomy	840±48	744±91	487±87	148±25

Conclusion: The pylorus plays a major role in fasting antroduodenal resistance to flow during gut motor quiescence. During high motor activity other factors (antral and/or duodenal) predominate.

EFFECT OF SUBSTANCE P ON THE ISOLATED GUINEA PIG GALL BLADDER. L.A.Meldrum, J.H.C. Bojarski and J. Calam. Royal Postgraduate Medical School, Hammersmith Hospital, London W12 OHS.

Substance P-like immunoreactive fibres have been shown to be present in guinea pig gall bladder smooth muscle. However, functional studies have not been performed and the role of this peptide has not been examined. Guinea pig gall bladder strips were mounted in 5ml overflow organ baths; changes in tension were measured isometrically.

Gall bladder strips were contracted with substance P (0.1-10uM) in a concentration-dependent manner. Non-cumulative concentration-response curves were constructed, with 15 mins between additions of substance P to avoid tachyphalaxis. These concentration-response curves to substance P were unaffected by tetrodotoxin (1uM), atropine (10uM) or chlor-amphenicol (10uM). In other smooth muscles of the gastrointestinal tract, these drugs have been shown to be potent blockers of substance P responses. The substance P antagonist, (D-Arg^1, D-Pro^2, D-Trp^{7,9}, Leu^{11})substance P (10uM), caused a parallel shift to the right of the substance P concentration-response curve.

These results indicate that substance P acts directly on smooth muscle and not via other mechanisms, such as release of acetyl choline from cholinergic nerves or histamine release from mast cells. Since the non-adrenergic, non-cholinergic nerves in this tissue are inhibitory, the role of substance P fibres remains unclear, but it may prove to be an important modulator of gall bladder function.

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RECTOANAL DYSYNERGIA IN CONSTIPATED CHILDREN. P.Meunier, Manometric Investigation Laboratory, INSERM U45, Pavillon Hbis, Hôpital E.Herriot, 69374 - Lyon Cédex 08. France

In normal subjects, the Valsalva maneuver decreases the electrical activity of the external anal sphincter, inducing a decrease of anal pressure as observed in manometry. The aim of this study was to observe if this normal sphincteric response is affected in constipated children. For this, a manometric study of the anorectum was undertaken in 21 control children (aged 6-13 yr, median : 9 yr), as well as in 35 patients (aged 6-14 yr, median 9.5 yr) with primary chronic constipation. There was no encopresis in this latter group of patients, and all of them have had a recent failure to lactulose therapy. The method of investigation has already been described (Meunier et al., Gastroenterology, 1984, 87:1351), except for a point which was added : i.e., that 5 successive Valsalva maneuvers were done by both controls and patients, and recorded manometrically.

The rectoanal inhibitory reflex was found in each subject, thus excluding Hirschsprung's disease in this series. During Valsalva maneuvers all control children showed an anal relaxation at at least 1.5 kPa. For the constipated patients, in 26 cases, instead of a relaxation, an increased anal pressure (of at least 1.5 kPa) was recorded in each of the 5 maneuvers ; in 1 patient the Valsalva maneuver induced no significant change in anal pressure. Absent anal relaxation was called "rectoanal dysynergy". In the 27 patients with rectoanal dysynergy other miscellanous rectoanal disorders were observed : anal hypertonia in 7 cases, increased rectal compliance in 13 cases, impaired rectal conscious sensitivity in 11 cases.

In conclusion, it appears that a high percentage (77%) of rectoanal dysynergy is observed in primary chronic constipation in children. This fact certainly explains, at least in part, the failure of lactulose therapy observed in these children. The finding of such a rectoanal dysynergy is, in our opinion, the clear indication of biofeedback therapy.

CAN BREATH TESTS BE USED TO MEASURE INTESTINAL TRANSIT TIME IN RATS? B.M. Meyer, C.A. Sninsky, D.F. Lynch. VA Medical Center and Dept. of Medicine, Univ. of Florida, Gainesville, FL, USA.

Small bowel transit time (SBT) in rats is delayed by clonidine (J Pharmacol Exp Ther 212:487, 1980), but its effect on myoelectric activity has not been evaluated. We investigated the effect of clonidine, 10 µg/kg s.c., on intestinal myoelectric activity and SBT in rats. A ^{14}C-lactose breath test was used to measure SBT. Adult rats are relatively lactase-deficient thus lactose may be a suitable substrate for measuring SBT. Intestinal myoelectric activity was monitored in fasted rats by 4 indwelling bipolar electrodes. Saline and clonidine were administered s.c. on separate days. A second group of fasted male rats had orogastric gavage of 3 µCi of ^{14}C lactose in 500 mg of unlabeled lactose. Exhalation of $^{14}CO_2$ and total CO_2 was monitored in each animal with and without clonidine, 10 µg/kg s.c. A third group of rats with surgically created ileostomies was studied to quantitate the influence of the small bowel flora on breath $^{14}CO_2$ after orogastric ^{14}C-lactose. Results: Clonidine abolished the activity front of the migrating myoelectric complex 9.7± 0.4 min after injection; this inhibition persisted for 71.7±6.9 min. $^{14}CO_2$ excretion in the rats with ileostomies showed a blunted curve different from that of nonoperated rats. The breath test data for the nonoperated rats was tabulated to include the time of peak $^{14}CO_2$ excretion. Linear regression and its coefficient of determination (r^2) were also calculated because the data seemed to closely follow a linear pattern.

$^{14}CO_2$	Peak (min)	Slope	r^2
Control	154±7	0.69±0.04	0.92±0.02
Clonidine	214±13*	0.52±0.02*	0.89±0.05

Mean±SEM; *p < 0.05 compared with control

Conclusion: 1) clonidine, 10 µg/kg, inhibits myoelectric activity and delays transit of the small intestine, and 2) linear regression of breath $^{14}CO_2$ after orogastric administration of ^{14}C-lactose is an effective way to do repeated measurement of SBT in rats.

IDENTIFICATION OF AN ACID CLEARANCE ABNORMALITY IN PATIENTS WITH HIATAL HERNIA (HH). R.K. Mittal, R.C. Lange, L. Magyar, R.W. McCallum. Depts. of Medicine and Nuclear Medicine, Yale University School of Medicine, New Haven, CT.

The significance of HH in the pathophysiology of gastroesophageal reflux (GER) remains unclear. Our aim was to determine if HH contributes to the delayed acid clearance present in patients with GER. We studied esophageal acid clearance by simultaneously monitoring the esophageal pH and transit of a bolus of HCl labeled with ^{99m}Technetium (^{99m}Tc). 15 subjects with HH (10 symptomatic, 5 asymptomatic) and 3 GER patients with no HH were studied. All subjects had normal peristaltic motor function and the mean lower esophageal sphincter (LES) pressure in patients with and without HH was 17 and 26 mm Hg, respectively. A pH probe was positioned 5 cm above the LES. Subjects lay supine under a gamma camera and a 15 ml bolus of 0.1 N HCl labeled with 200 µc ^{99m}Tc was injected 15 cm above the LES. Beginning 15 sec after this injection, subjects swallowed every 30 sec. Two such sequences were done. An additional study was performed with the pH probe 10 cm above and acid injection 20 cm above the LES. The number of swallows to attain an esophageal pH of 5 was determined. Results: 1) Acid clearance was delayed in symptomatic as well as asymptomatic HH subjects (mean=25.3 swallows) compared to GER patients with no HH (mean=10.0); 2) At 5 cm above the LES, each swallow resulted in a biphasic pH response (an initial fall, followed by a rise) in all but one HH subject, but only a monophasic (rise) response in non-HH subjects; 3) acid clearance was faster at 10 than at 5 cm above the LES and more biphasic responses were observed at 5 cm; 4) On radionuclide scanning 11 of the 15 subjects with HH showed a biphasic response to initial 1-3 swallows (i.e., an initial reflux followed by clearance). Swallow-induced reflux was not seen in non-HH patients. Conclusions: Acid clearance in HH subjects is impaired because of an initial reflux of acid from the HH sac during each swallow-induced LES relaxation. These data illustrate a mechanism by which HH can contribute to the pathogenesis of GER.

CIRCADIAN RHITHMS OF THE HUMAN COLONIC MOTILITY. F. Narducci, G. Bassotti, M. Gaburri, A. Morelli. Dept. Medicine, University of Perugia, Perugia, Italy.

Despite colonic transit is slow and bowel movements occur approximately every 24 hours, colonic motility has been studied only over short times. Aim of this study was to evaluate the circadian rhithms of the transverse and distal colon motor activity in healthy humans. Multilumen manometric catheters were introduced into the transverse colon at colonoscopy in ten healthy volunteers. The manometric recordings lasted 24 consecutive hours (12 am to 12 am), during which the subjects ate two 1000 kcal mixed meals and one continental breakfast, slept overnight and changed body position (recumbent/sitting) according to a fixed protocol. Motor quiescience alternated cyclically with motor activity at all the recording sites. Motor activity was mostly represented by isolated non-propagating contractions and by non-migrating bursts of contractions (non--migrating motor complexes). Phases of motor activity were greater in number and longer after feeding, after awaking and after assuming the sitting position, so that the motility index increased significantly at these times. After the morning awake and/or after breakfast, but rarely during the day, high-amplitude (80-150 mm Hg) isolated peristaltic contractions were also seen. These contractions migrated distally over long distances at a propagation velocity of 1.4±0.4 cm/sec. In 1/4 of the occasions these peristaltic contractions were felt by the subject as a need to defecate or preceded the defecation. In conclusion, these studies show that colonic motility: 1) shows circadian fluctuations related to feeding, sleep and body position; 2) is mostly represented by sporadic non-propagating contractions and non-migrating motor complexes; 3) shows infrequent but vigorous peristalsis that may represent the manometric equivalent of the mass movements.

MULTIPLE ACTIONS OF VASOACTIVE INTESTINAL POLYPEPTIDE ON GUINEA PIG DUODENUM. M.C. Ngu. Dept Medicine & Clinical Science, John Curtin School of Medical Research, Australian National University, Canberra ,Australia.

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide which has been shown to relax smooth muscle preparations from the gastrointestinal tract. It has been suggested that VIP is a transmitter of the non-adrenergic, non-cholinergic (NANC) inhibitory innervation in the enteric nervous system. The aim of the present study was to test this hypothesis by examining the actions of VIP in the guinea pig duodenum where there is a dense network of VIP-immunoreactive nerves. Tension recordings were made from isolated segments of guinea pig duodenum. Addition of VIP caused a transient rise in tension . The threshold concentration ranged from 2nM to 10nM. The response was abolished by tetrodotoxin (TTX 0.3μM) and by atropine (1.4μM) indicating that it was mediated by activation of cholinergic neurones rather than by any direct action on the musculature. In the presence of atropine or hyoscine (2.3μM), addition of VIP caused a biphasic response with an initial contraction followed by transient relaxation below baseline tension. The non-muscarinic contractile response was abolished by TTX suggesting that it too was a result of neural activation. The relaxation component of the response to high concentration of VIP however was resistant to TTX suggesting a direct effect on the smooth muscle. Furthermore, the VIP induced relaxation persisted in the presence of apamin (1μM) which blocked the relaxation induced by stimulation of NANC inhibitory nerves.

It is concluded that VIP has three different actions on the guinea pig duodenum: cholinergic excitation , non-cholinergic excitation and apamin-resistant muscle relaxation. These actions are incompatible with VIP being the NANC transmitter in this tissue.

THE PROJECTION OF ENTERIC NERVE PATHWAYS TO THE GUINEA PIG DUODENAL BULB . M.C. Ngu. Dept Medicine & Clinical Science, John Curtin School of Med. Res., Australian National University, Canberra, Australia.

The aim of the present study was to examine the pattern of innervation of the duodenal bulb by enteric nerves and to compare it with that of other regions of the small intestine. The gastric antrum and the whole duodenum were removed en bloc from the adult guinea pig and intracellular recordings were made from smooth muscle cells in the wall. Localised transmural stimulation (Stim) with single pulses (0.1-0.6 ms ,70V) in all distal parts of the duodenum (maximum distance 6cm) evoked excitatory junction potentials (ejp's) in the bulb. This response was blocked by tetrodotoxin (0.3μM) and by atropine (1.4μM) indicating that it resulted from activation of cholinergic excitatory pathways in the enteric nervous system. In the jejunum and ileum such ascending excitatory pathways projected only over 2-3 cm and the predominant response to Stim applied < 1cm distally was an inhibitory junction potential (ijp) although an ejp could be produced by increasing the stimulus strength or by repetitive stimulation (1Hz). In the duodenal bulb, proximal Stim within the bulb evoked mainly ejp's whereas in the remainder of the small intestine proximal Stim produced an ijp or a combination of ijp and ejp in the first 1-1.5 cm and ijp up to 5 cm distally. Only small ijps were seen in the bulb when Stim was applied to the distal antrum. Ejp's and ijp's evoked by single pulses along the whole small intestine were abolished by atropine (1.4μM) and apamin (0.1μM) respectively .

It is concluded that the intrinsic innervation of the duodenal bulb is different from that of other parts of the small intestine. It is predominantly excitatory and the projection of ascending excitation occurs over longer distances. This pattern of innervation may be important in protecting distal regions from excessive gastric emptying or in preventing duodeno-gastric reflux.

STRESS INDUCED DISTURBANCES OF HUMAN POST-PRANDIAL ANTRODUODENAL MOTILITY AND OROCAECAL TRANSIT. THE CONTRIBUTION OF ADRENERGIC PATHWAYS. J D O'Brien, D G Thompson, S Day, W R Burnham, E Walker, Dept. of Gastroenterology, The London Hospital, London, E1, England.

Stress, induced experimentally in man by hand immersion in cold water (CW), stimulates catecholamine secretion and delays orocaecal transit, principally by inhibiting gastric emptying (GUT 25,A1310). The present studies aimed to identify the coincident antral and duodenal motor responses, associated with this effect and to explore the possible role of adrenoreceptor mediated pathways.

Antroduodenal motility was studied after a standard meal in 7 healthy individuals, intubated using a multilumen perfused tube system. Stress was induced by 10 minutes CW, warm water (WW) immersion acted as a control. CW reduced the frequency of both antral contractions (CW 10.2 ± 3.3 (mean/10 min. ± SEM) vs WW 21.7 ± 4.7 $P<0.05$), and duodenal (CW 24.8 ± 7.6 vs WW 30.9 ± 6.8, $P<0.05$).

Adrenoreceptor pathways: After a pilot study on one subject had shown an effect of beta, but not alpha blockade on reducing CW-induced transit delay, a randomised, double-blind study was conducted in 9 normal individuals to study the effect of atenolol (a) 100mg (a selective beta 1 blocker) vs placebo (p) on post-prandial orocaecal transit, measured by breath hydrogen sampling, after CW or WW. Atenolol did not alter control transit (WW + a 56.0 ± 4.8 min vs WW + p 58.5 ± 4.4 $P>0.05$), but abolished the stress effect (CW + a 56.7 ± 5.4 min vs CW + p 82.2 ± 10.1 min $P<0.02$).

The effect of atenolol on antroduodenal motility was also studied using a similar protocol in 7 subjects. Atenolol did not effect the frequency of antral or duodenal contractions during either WW, or CW stimulation compared to placebo.

These results indicate the presence of a beta-1 adrenoreceptor mediated pathway in the transit, but not the antroduodenal-motor, responses to CW stress. Since CW effects on transit are exerted principally via gastric emptying, a role for beta adrenoreceptors in the reduction of gastric fundal tone, during stress, is suggested.

MOTOR CORRELATES OF DEFECATION AFTER ILEAL POUCH-ANAL ANATOMOSIS. P.R. O'Connell, J.H. Pemberton, K.A. Kelly, Gastroenterology Unit, Mayo Clinic, Rochester, MN 55905.

The aim was to determine whether the volume of each stool and the frequency of stooling after ileal pouch-anal anastomosis were related to the motility of the ileal pouch. We studied 19 patients who had colectomy, mucosal rectectomy and ileal pouch-anal anastomosis for chronic ulcerative colitis (15 "J" pouch, 4 "S" pouch) 23.4±2.5 (mean±SEM) months following closure of the defunctioning ileostomy. After an overnight fast and following evacuation of the ileal pouch, a non-compliant flaccid bag (maximum capacity, 600 ml) was inserted per anum into the ileal pouch and inflated with 10-ml increments of air each min. Intrapouch pressures were recorded using a non-perfused catheter and a strain gauge transducer. The volume at which large pressure waves appeared (threshold volume), the maximum tolerable capacity, and pouch distensibility ($\Delta V/\Delta P$) were determined. A correlation was sought between the motor parameters and the stool volume and stool frequency recorded over 24 hours while on a standard diet. Results: All patients experienced crampy discomfort and a desire to defecate with the appearance of large amplitude waves in the ileal pouch. The larger the threshold volume at which the waves appeared, the larger the maximum tolerable capacity ($r=0.75$, $P<0.001$) and the greater the pouch distensibility ($r=0.66$, $P<0.005$). The mean volume of each stool varied directly with the threshold volume ($r=0.69$, $P<0.005$), and the mean stool frequency varied inversely with the threshold volume ($r=-0.66$, $P<0.005$). Patients with a stool frequency of >6/24 hr had a lower threshold volume (126±14 ml) than patients with a stool frequency of ≤6/24 hr (176±20 ml, $P<0.05$). We concluded that the volume of each stool and the frequency of stooling were related to ileal pouch motility. The higher the threshold volume at which large amplitude pouch waves appeared, the greater the volume of each stool and the smaller the stool frequency.

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CALCIUM AND POTASSIUM CURRENTS RECORDED FROM FRAGMENTS OF SINGLE SMOOTH MUSCLE CELLS OF THE RABBIT ILEUM.
Y. Ohya, K. Terada, K. Yamanaka, R. Inoue, K. Okabe, K. Kitamura and H. Kuriyama. Department of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan.

Ionic current was recorded from fragments of the isolated smooth muscle cell of the longitudinal muscle layer of the rabbit ileum using the chopped clamp procedures with the electrode for the patch clamp method. The fragment (10 -20μm in width and 30-50μm in length) was prepared by collagenase treatment. The membrane potential was -40mV and application of outward current provoked an action potential with overshooted potential. With the holding potential of -60mV, the inward current could be recorded at -30mV, and the peak current at -10mV, the reversal potential at +45mV. The inward current and spike potential evoked from the fragment were blocked by $MnCl_2$, Ca-free solution and Ca antagonists in the presence or absence of Na. In low concentrations of Ca (0.1mM) the inward current and action potential ceased, but in 10uM Ca in the presence of Na, the inward current and spike potential were again generated by depolarization which possessed different properties; i.e. the onset potential for generation of inward current, the peak and reversal potentials and the shape of action potential differed from that recorded in Krebs solution. These inward currents and action potentials ceased by application of Ca antagonists. Therefore, the Ca channel may pass the Na ion when Ca concentrations are reduced below 10μM, such being a general feature of the voltage dependent Ca channel in excitable cells. The outward current was the K current composed of the Ca dependent and less dependent K currents. The latter was inhibited by TEA in a dose dependent manner. From the values of the single channel conductance, at least three different K channels were observed in this smooth muscle membrane. Only two were dependent on cytoplasmic Ca concentrations and membrane potential, but one channel depended on the external Ca concentration. Action of TEA also differed in case of each K channel. Such differences in the K current were also observed using the excised membrane patch, as estimated from voltage, Ca and TEA dependencies.

PEPTIDERGIC MODULATION OF EXCITABILITY IN MYENTERIC PLEXUS NEURONS. J.M. Palmer, D.H. Zafirov, P.R. Nemeth, and J.D. Wood. Dept. of Physiology, School of Medicine, University of Nevada, Reno, Nevada 89557, U.S.A.

The aim of our investigation was to identify and characterize the actions of brain/gut-related peptides on the electrical behavior of myenteric ganglion cells in the guinea-pig small intestine in vitro. Conventional intracellular methods with 3 M KCl-filled microelectrodes were used to record and inject electrical current in neurons from myenteric plexus preparations superfused with carboxygenated Krebs solution. Vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP), bombesin, cholecystokinin-octapeptide (CCK-8), caerulein and substance P were applied either in the superfusion solution or by pressure ejection from micropipettes. Applications of each of the brain/gut-related peptides mimicked slow synaptic excitation (slow EPSP) in subpopulations of myenteric neurons. Each peptide evoked membrane depolarization associated with increased input resistance, enhanced excitability and suppression of hyperpolarizing after-potentials. Enhanced excitability was reflected by spontaneous spike discharge, a significant increase in the number of action potentials discharged during depolarizing current pulses and by appearance of anodal-break excitation. The reversal potential for the depolarizing effects of all of the peptides was near the estimated potassium equilibrium potential. This suggested that the depolarization and increased membrane resistance resulted from closure of potassium channels by the peptides. The effects of the peptides occurred after blockade of axonal spike generation and synaptic transmission in the presence of tetrodotoxin indicating a direct action on impaled neurons. Adenosine pretreatment suppressed the actions of all peptides except substance P. Adenosine acts to inhibit activation of adenylate cyclase and intracellular increase of cyclic AMP. Failure of adenosine to offset the actions of substance P while blocking actions of the other peptides in these neurons suggest that receptors for all of the peptides except substance P are coupled with adenylate cyclase. Results are consistent with a synaptic or neuromodulatory role for these peptides in integrative functioning of the enteric nervous system. (Supported by NIH Grant ROl AM26742).

THE EFFECT OF GLUCAGON AND GLUCAGON 1-21-PEPTIDE ON DUODENAL PRESSURE ACTIVITY IN HEALTHY SUBJECTS.
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The effects of glucagon and the glucagon-1-21-peptide were studied on duodenal pressure activity and compared to that of placebo in a randomized double blind latin square designed trial. The pressure activity was recorded by intraluminal transducers. A 1 mg bolus of each drug was given intravenously at the end of the first observed migrating motor complex and was followed by intravenous infusion of 2 mg of each drug during the subsequent two hours in 12 healthy subjects. Recordings were performed for at least 3 hours after the bolus injections of the drugs.

Both glucagon and the 1-21-peptide of glucagon caused significant changes in the duodenal pressure activity ($p < 0.05$), as the length of the cycle was significantly increased and the migrating motor complexes were significantly reduced. The changes caused by glucagon were significantly larges than those observed with its fragment.

The frequency of sideeffcts and the degree of discomfort during the recordings were significantly higher ($p < 0.01$) in the glucagon period, compared to that of its fragment and placebo. There was no difference in sideeffects in the 1-21-petide period and that of placebo. Glucagon caused a significant increase in both serum glucose and insulin ($p < 0.01$) Such an increase was neither detected after the glucagon fragment nor the placebo periods.

From a clinical point of view we feel the importance of significant effect of the glucagon-1-21-peptide on motility pattern without the side effects of glucagon.

NEUROTRANSMITTERS INTERACTIONS IN THE CAT INTERNAL ANAL SPHINCTER.
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The contractile activity of strips (15x2mm) isolated from cat internal anal sphincter (IAS) was studied under isometric conditions. Noradrenaline (NA) above 10^{-10}mol/l induced contraction of IAS, antagonized by phentolamine (Ph). Ach and carbachol above 10^{-6}mol/l resulted in relaxation of IAS which was blocked only by simultaneous administration of atropin (A), 10^{-6}mol/l and hexamethonium (H), 10^{-4}mol/l. The Ach-induced relaxation was not influenced by guanetidine (G) and reserpine, but was antagonized by TTX (10^{-7}g/ml). Nicotine (N), 10^{-6} to 10^{-4}mol/l, also caused IAS relaxation which was not influenced by A but was blocked by H and was antagonized by TTX. The Ach-relaxation effect on IAS turned into a contractile one after treatment with depolarizing agents (increased K^+ to 16-20 mol/l, scorpion venom and oubaine) which was blocked by Ph, G, H and was antagonized by TTX. High N concentrations induced a three-phase effect whose second contractile component was Ph and G sensitive. Field electrical stimulation (FES) induced a biphasic response in IAS: an initial contraction which increased after an increase in $[K^+]_o$ and was blocked by Ph and G with subsequent relaxation which was not affected by adrenergic and cholinergic blockers. The effect of FES was TTX sensitive.

It is assumed that the release of NANC neurotransmitter and of NA occurs via presynaptic N-cholinergic receptors and that this release depends on the different threshold values of the membrane potential of the nerve terminals whereby excitatory-secretion coupling takes place.

(A-31)

REGIONAL AND TEMPORAL VARIATIONS OF MOTILIN RECEPTOR DENSITY IN THE HUMAN AND RABBIT GASTROINTESTINAL TRACT. T.L.Peeters, V.Bormans and G.Vantrappen. Center for Gastroenterological Research, University of Leuven, B-3000 LEUVEN, Belgium.

In vivo and in vitro studies suggest that in several species motilin mainly effects the upper gi tract. We therefore examined the distribution of motilin receptors along the gastrointestinal tract of man and rabbit. Human antral, duodenal, jejunal and ileal tissue removed at laparotomy, and tissue from rabbit fundus, corpus, antrum and 5 intestinal regions spaced 50 cm apart (DI-DV) were examined. Smooth muscle tissue was dissected from mucosa and submucosa, homogenized, centrifuged at 800 g for 15 min, washed 4 times, and resuspended in buffer for binding studies with labeled porcine motilin (25000 cpm, 18 fmol). The binding characteristics of human motilin receptors in antral tissue were slightly different from those recently described by us in rabbits : higher density 70.6 fM/mg protein, similar affinity 1.8 nM, lower pH optimum 7.4, similar kinetics. Expressed as a percent compared to antral binding, human duodenal tissue contained 70% receptors, jejunum and ileum 0%. The results in rabbit were as follows: fundus: 0%,corpus: 20%,antrum 100%, DI:96%, DII:10%, DIII:9%, DIV:6%, ileum:0%. By differential centrifugation and enzymatic analysis, receptors were shown to be associated with the plasma membrane fraction. Motilin binding was destroyed by trypsin and by collagenase treatment. In rabbits feeding reduced receptor density in the antrum (25+8% of fasting control). Experimental hypermotilinemia approximately doubled receptor density in antrum and duodenum. This is the first report of motilin receptors in man. In rabbit motilin receptor density seems to be regulated by physiological conditions. The presence of a gradient of receptor density suggests that the rise in plasma motilin, which precedes only gastric and upper duodenal phase 3 in man, promotes excitability of antral and upper duodenal smooth muscle tissue, and is a causal factor in the initiation of phase 3 at this level.

SPREAD OF MECHANICAL ACTIVITY ACROSS THE ISOLATED GASTRO-ESOPHAGEAL JUNCTION (JCT) OF THE OPOSSUM. W. Percy, K. Schulze-Delrieu, S. Shirazi and K. Von Derau. Gastroenterology Research Laboratory, VA Medical Center, Iowa City, IA 52240

The intramural nerves of the esophagus and the stomach are continuous. We used a modified Trendelenburg preparation to determine whether intrinsic neural mechanisms allow the spread of mechanical activity from one organ to the other. The esophagus and the stomach were opened lengthwise. One cut edge of the specimen was fastened to the bottom of the bath containing carboxygenated Krebs' solution at 37°C; the opposite cut edge was connected to force transducers at the level of the LES, and 4 and 2 cm above it and 2 cm below it. Stroking of the esophagus led to a contraction wave along the esophagus and relaxation of the LES. LES tension and LES spontaneous relaxation were enhanced by physostigmine, 10^{-6} M. Contraction waves were consistently produced by electrical stimulation through shielded electrodes (3s trains of 0.5 ms pulses, at 10 Hz, given for 3s and 10-50V). Stimulation of the proximal esophagus produced the well known on and off responses of the esophageal body; in addition, such distant stimulation produced LES relaxation which preceded the on response and outlasted the off response. The stomach showed a variable response to stimulation of the esophagus (out of a total of 9 experiments: predominant contraction in 3, predominant relaxation in 4, no response in 2). Electrical stimulation of the distal stomach also led to a relaxation of the LES. The LES relaxation was as complete as with esophageal stimulation and over a variety of voltages lasted about twice as long (e.g. 10s rather than 5s). The esophageal body never responded to stimulation of the stomach. Stimulus responses were diminished by tetrodotoxin, 10^{-6} M. We conclude that LES relaxation can be produced by stimulation of the intrinsic nerve of both the esophagus and the stomach and that the esophageal muscle coat contains motor nerves for the stomach, but the gastric muscle coat does not contain any motor nerves for the esophageal body.

THE ROLE OF GASTRIN RECEPTORS FOR THE GASTROINTESTINAL MOTILITY IN MEN. W. Peitsch. Dept. of Surgery, University of Göttingen, D-3400 Göttingen, FRG.

Gastrin receptors of the rat stomach and their regulation by serum gastrin were demonstrated by Takeuchi, Speir and Johnson (Am.J.Physiol. 237(3): E 284 - E 294, 1979). Using their modified gastrin receptor assay, specific gastrin binding was found in the mucosa and muscularis of the human stomach and large bowel.

Corpus and antrum of the stomach and large bowel, resected for cancer, were divided into mucosa and muscularis. Binding studies were done with the 270-30,000 g tissue fraction, using I^{125}-Gastrin-I-(human). The receptor levels were correlated with the tissue gastrin concentrations and serum gastrin.

Results: 1. Tissue gastrin: The muscularis of the corpus and antrum of human stomachs and large bowel contain less than 0.3 µg gastrin/g tissue.

2. Specific gastrin binding: Significant amounts of specific bound gastrin were demonstrated in the muscularis of all parts of the stomach and large bowel.

3. In patients with gastric or duodenal ulcer diseases the number of gastrin receptors increases significantly in the corpus mucosa, while the tissue gastrin concentrations and the gastrin receptor binding do not change in the muscularis of corpus and antrum.

Summary: For the first time significant amounts ofgastrin receptors were demonstrated in the muscularis of human stomachs and large bowel. Gastroduodenal ulcer diseases increases significantly the gastric acid output, tissue gastrin concentrations of the antral mucosa and gastrin receptor binding to the corpus mucosa, but do not change the tissue gastrin concentration and number of gastrin receptors in the muscularis of the corpus and antral part of the human stomach.

In contrast to the acid stimulatory effect,gastrin does not play an important role in motility of the human stomach.

CHARACTERIZATION OF THE DEPOLARIZATION INDUCED IN GUINEA PIG INFERIOR MESENTERIC GANGLION BY DISTENSION OF THE COLON. S. Peters and D.L. Kreulen. Department of Pharmacology, University of Arizona College of Medicine, Tucson, AZ 85724 U.S.A.

Distension of the distal colon of the guinea pig evokes cholinergic and noncholinergic synaptic depolarizations in neurons of the inferior mesenteric ganglion of guinea pigs. Using in vitro preparations that consisted of the inferior mesenteric ganglion and a 2-3 cm segment of distal colon attached by the intervening mesentery and nerves, we characterized the intracellular electrical responses of the ganglionic neurons to distension of the colon with a fluid-filled catheter. In 44% of the cells tested, colon distension from 0 cm H_2O to 20-25 cm H_2O resulted in a 1 to 7.2 mV depolarization (mean: 3.4 ± S.E. 0.3 mV). This depolarization persisted in the presence of nicotinic and muscarinic antagonists. The average duration of the depolarization was 221 ± 40 s (mean ± S.E.) and reached its peak in 64 ± 14 s (mean ± S.E.). The depolarization was associated with a 20 ± 3% (mean ± S.E.) increase in cell input resistance. The amplitude of the slow depolarization was proportional to the distending pressure up to 25 cm H_2O. During prolonged distensions, the membrane potential returned to predistension value even though the colon remained distended. During this period of desensitization the amplitude of electrically-evoked slow excitatory postsynaptic potentials was diminshed in 2 of 9 cells suggesting a common transmitter in these two cells. Treatment of the ganglia with capsaicin in vitro ($2x10^{-5}$M) to deplete endogenous substance P diminished the distension-induced depolarization to 42% of control and reduced the electrically-evoked slow EPSP to 25% of control in 2 of 4 cells. These experiments demonstrate the existence of a slow excitatory synpatic potential in abdominal sympathetic ganglion that is induced by distension of the distal colon and suggest that the depolarization in some cells is mediated by substance P. Support: HL27781, HL01136 to DLK.

CISAPRIDE ACCELERATES GASTRIC EMPTYING OF SOLID AND LIQUID MEAL COMPONENTS IN PATIENTS WITH GASTRIC STASIS. J.M. Petersen, R. Lange, R.W. McCallum. Depts. of Medicine and Nuclear Medicine, Yale University, New Haven, CT.

Cisapride (R 51,619, Janssen), a benzamide derivative, is a new prokinetic agent without dopamine antagonism effects, whose mechanism of action is thought to be through facilitation of acetylcholine release from the myenteric plexus and also possibly by inhibition of serotonin. Our purpose was to investigate the effects of acute IV Cisapride on gastric emptying (GE) in patients with subjective and objective evidence of non-obstructive gastric stasis. 9 patients, 8 females and 1 male, aged 33-62 yrs (mean 42) with gastric stasis had GE. The etiology of the gastric stasis in 4 patients was regarded as "idiopathic", 4 were post-gastric surgery (2 after vagotomy and pyloroplasty, 2 after Billroth II), and 1 had diabetic gastroparesis. The GE technique utilized the dual isotope method. The solid (S) component of the meal was chicken liver labeled in vivo with ^{99m}Tc-sulfur-colloid and mixed with beef stew. The liquid (L) was 4 oz water labeled with ^{111}In-DTPA. The patients had a baseline GE to establish objective evidence of delayed emptying and returned on a separate day for a second GE when IV Cisapride 10 mg was administered 5 min before ingesting the same test meal. GE was monitored for 2 hrs while patients lay supine under a gamma camera and results are below (* indicates $p<0.05$ after Cisapride (C) versus baseline (B) gastric emptying).

		30 min		60 min		90 min		120 min	
% Isotope		B	C	B	C	B	C	B	C
Retained	S	91.5	84.0	88.0	70.6	86.0	63.4*	83.4	54.7*
in Stomach	L	72.9	58.3*	61.8	34.3*	56.9	22.6*	52.9	15.4*

7 of 9 patients had faster solid food emptying after Cisapride, and 5 of the 7 normalized their emptying rate (<70% retained at 2 hrs). No side effects were noted. In summary: Cisapride significantly accelerated GE of solids and liquids in patients with gastric stasis associated with different etiologies. We conclude that Cisapride is a promising new gastric prokinetic agent and well controlled trials to establish its clinical efficacy are warranted.

TWO TYPES OF SLOW ELECTRICAL RHYTHMIC ACTIVITY IN INTESTINAL MUSCLE C. L. Prosser, N. Suzuki and V. Dahms. Department of Physiology and Biophysics, University of Illinois, Urbana, Illinois 61801

Electrical "slow waves" of small bowel, 4-6 sec duration, in cat, rabbit, rat and dog are generated by an electrogenic Na^+-K^+ pump. These waves are abolished by ouabain (10^{-7} to 10^{-6} M) by K^+-free medium; they are not sensitive to TTX or atropine, and are abolished when Na_o^+ is less than 10 mM or when Ca_o^{2+} is less than 10^{-4} M, or when Li^+ is substituted for Na^+. The pump-generated waves are absent below 20°C, are sensitive to hypoxia and to CN^-. Ouabain depolarizes, and subsequent repolarization by voltage clamp fails to restore the waves. Na^+ efflux is maximal during the repolarizing phase. After blocking by ouabain, acetylcholine (10^{-5} M) can induce a second type of rhythmic waves which have a prepotential, fast depolarizing phase, spike, and after-hyperpolarization; these ACh-induced waves are blocked by atropine and potentiated by physostigmine; they require Na^+ at 50 mM, Li^+ can substitute for Na^+, Ca^{2+} is needed at higher concentrations. The ACh-induced waves are less sensitive to cold or hypoxia than the Na^+ pump generated waves. ACh waves are similar in frequency to Na^+-pump waves. The Na^+ pump-generated waves originate in cells near the boundary between longitudinal and circular layers and are of diminished amplitude in the cells toward the submucosa. Waves can be induced by ACh in circular muscle at a distance from the boundary between layers. In guinea pig normal slow waves resemble the ACh-induced waves of other species. Slow waves recorded in vivo from cat and rabbit are ouabain-sensitive. In these species the two types of slow waves provide redundancy of rhythmic activity.

ALTERED MYOELECTRIC ACTIVITY OF THE SMALL INTESTINE AFTER RESERPINE DEPLETION OF CATECHOLAMINES AND SEROTONIN WITHIN THE MYENTERIC PLEXUS. V.M. Piñeiro-Carrero, M.H. Clench, R.H. Davis, J.M. Andres, J.R. Mathias. Depts. of Pediatrics and Medicine, Univ. of Florida and VA Medical Center, Gainesville, Fla.

We have previously reported 1) that chemical destruction of the adrenergic varicosities that contain norepinephrine unmasks the migrating action potential complex (MAPC) from the migrating myoelectric complex (MMC) and 2) that destruction of the serotonergic neurons by indolamine neurotoxins causes marked distortion of the MMC. We have now investigated how reserpine, which depletes the stores of catecholamines and serotonin, affects the myoelectric activity of the small intestine. In a rat model, we implanted 4 bipolar electrodes 5 cm apart on the upper jejunum. After a 10-day recovery, the rats were fasted and a 2-h baseline myoelectric recording was obtained. Reserpine (1 mg/kg, s.c.) was injected into the rats (n=5) on days 1 and 5. Control rats (n=5) were given saline. Continuous recordings, immediately after injection and on days 2, 6, and 10, were analyzed for periodicity (P), duration (D), and propagation velocity (PV) of the MMC, for % disrupted MMCs, and for % MMCs with MAPCs. Results:

	Control	Day 2	Day 6	Day 10
P (min)	10.90±0.51	11.81±0.62	16.19±3.50*	15.07±0.85†
D (min)	2.65±0.06	3.36±0.13†	2.95±0.58*	3.50±0.13†
PV (cm/min)	2.58±0.09	2.97±0.16*	1.95±0.10†	2.23±0.11*
% disr. MMCs	9.0±1.6	76.1±0.3†	100±0†	75.1±1.2‡
% MAPCs	2.9±1.3	60.1±1.6†	64.0±0.7†	27.7±6.1
Weight (g)	322.2±5.23	312.8±5.86	288.4±7.9‡	266.2±7.5†
Diarrhea	0	++	+++	+

Mean ± SEM; *$p<0.05$, †$p<0.001$, ‡$p<0.01$, vs. controls.

Summary: 1) Acute depletion of catecholamines by reserpine unmasked the MAPC--as did destruction of the varicosities. 2) Acute depletion of serotonin disrupted the organized MMCs, much as indolamine neurotoxins had done. 3) Diarrhea developed, and all treated animals lost weight. Our findings support the cellular-based concept that norepinephrine and serotonin are major neurotransmitters in the enteric nervous system.

DIFFERENTIAL ACTION OF TWO MACROLIDE ANTIBIOTICS ON PRE AND POST PRANDIAL MOTILITY PATTERNS. XY Qin, M-A Pilot, HH Thompson, G Maskell. GI Science and Microbiology Research Units, The London Hospital Medical College, 26 Ashfield Street, London E1 2AJ, England

Intravenous infusions of erythromycin cause disturbances of the basal fasted motility patterns in dogs and human, provoking nausea, abdominal cramps and vomiting. We compared the action of erythromycin with josamycin, another macrolide sharing the same basic structure to study this effect.

After a 3-hour basal period, 4 fasted dogs were given 250 or 500 mg of either josamycin or erythromycin orally, and the activity was monitored for a further 3 hours. Blood samples were taken serially to measure plasma levels and the bioavailability of both drugs. The experiments were repeated in the same dogs after feeding.

Following josamycin, there was no change in the motility pattern of any of the dogs, either in the fasted and fed states, neither was there any sign of discomfort, retching or vomiting. After 250 and 500 mg of erythromycin, all the fasted dogs retched and vomited. The basal pattern was disrupted for the next 3 hours, with a large initial increase in spiking activity. In the fed dogs, there was an increase in irregular spiking activity and emesis in all but one dog. The lack of effect seen with josamycin was not due to poor absorption of the antibiotic, as peaks in blood levels were comparable to erythromycin.

The differential action of the two antibiotics must be due to small side-chain differences, as the two compounds are structurally very similar. An analysis of chemical characteristics of compounds such as macrolide antibiotics may explain their mode of action and reveal something of the mechanism of motility control.

DOES THE PIG STOMACH EMPTY ISOENERGETICALLY? V. Rayner, P. C. Gregory. Rowett Research Institute, Aberdeen, Scotland, AB2 9SB.

Isoenergetic emptying of fat or glucose test meals has been implicated in the control of food intake in the monkey (McHugh & Moran 1979). We have investigated the control of gastric emptying of dry matter (DM) in pigs fed a barley-based diet, where nearly all of the energy is in the solid fraction. The rate of stomach emptying was measured by evacuating the stomach through a gastric cannula before and then immediately after the pig had consumed a 700 g meal (66% of the ad libitum intake). Isoenergetic amounts (0.026 MJ/min) of fat (Intralipid 20%) and glucose (40%) were infused through the duodenum for 30 min before and during feeding and the rate of emptying was compared with that during a meal alone.

Neither infusion altered the rate of eating, and the meal was consumed in 22 ± 3 min (Intralipid); 20 ± 3 min (glucose); and 18 ± 3 min (meal alone). Glucose and Intralipid both inhibited emptying (% DM emptied: Intralipid 20.6 ± 1.6%; glucose 20.8 ± 0.7%; meal alone 25.9 ± 1.9%). The total energy reaching the duodenum (meal plus infusions) was 3.0 ± 0.1 MJ (Intralipid); 3.0 ± 0.2 MJ (glucose) compared to 2.1 ± 0.2 MJ (meal alone). The total energy reaching the duodenum during the meal minus the 30 min pre-infusion was 2.2 ± 0.2 MJ (Intralipid), 2.2 ± 0.1 MJ (glucose) and 2.1 ± 0.2 MJ (meal alone) and expressed as a percentage of the total energy input (meal plus infusion) it was 25.7 ± 1.9% (Intralipid), 25.8 ± 1.2% (glucose) and 25.9 ± 1.9% (meal alone).

Duodenal infusion of isoenergetic amounts of Intralipid and glucose thus inhibited stomach emptying of DM to an equal extent during the period of feeding. We suggest that stomach emptying of DM in pigs fed a solid meal is regulated to give an isoenergetic flow of nutrients to the duodenum during the feeding period and is such that a constant fraction of the total energy input reaches the duodenum during the period.

McHugh, P. R. & Moran, T. H. (1979) Am. J. Physiol. 236, R254-R260.

PHYSIOLOGICAL MEASUREMENTS IN YOUNG CONSTIPATED WOMEN
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Manometric, radiological and electrophysiological measurements were carried out in 34 women aged between 14 and 53, who suffered from chronic constipation, refractory to treatment with drugs or dietary fibre and 27 age-matched normal female controls.

The constipated patients had signficantly lower anal pressures, an abnormal degree of perineal descent, obtuse anorectal angles findings compatible with pudendal neuropathy, possibly caused by prolonged straining at stool.

Lower percentages of constipated patients than control subjects could pass simulated stools from the rectum (for example, 10% constipated subjects could pass a 1.8 cm sphere from the rectum compared with 78% control subjects ($p < 0.01$); and 7 out of 8 showed increased activity in their external sphincter as they strained down compared with 1 out of 6 controls.

Finally constipated patients required significantly greater degrees of rectal distension than controls ($p < 0.05$) to elicit rectal contractions, sustained anal relaxations or a desire to defecate.

Constipated subjects may be unable to relax their pelvic floor when they strain because they do not perceive a desire to defecate.

Measurement	Controls (27)	Constipated Group (34)
Mean Highest Basal Pressure (cmH_2O)	103(54-170)	81(39-130)*
Mean Highest Squeeze Pressure (cmH_2O)	235(115-319)	172(87-377)*
Anorectal angle (degrees)	89(78-96)	106(70-127)*
Distance of anorectal angle below pubococcygeal line on straining (cm)	1.7(0.9-2.7)	2.6(0-7.0)*

Mean and range, * = $p < 0.05$

ISOLATED PYLORIC CONTRACTIONS (IPC) IN FASTED AND FED HUMAN SUBJECTS
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It is controversial whether phasic pyloric contractions occur in humans independently from antral and duodenal contractions. If present isolated pyloric phasic contractions would be difficult to detect, since they probably occur over a very short pyloric segment. We have recorded pyloric pressures in 9 healthy subjects (8 male & 1 female aged between 19 & 39) with a 4.5 cm long sleeve sensor. The position of this sensor was monitored by measurement of transmucosal potential difference at either end of the sleeve. Pressures were also measured with perfused side holes at 4 sites in the duodenum and 3 sites in the antrum.

Fasting activity was recorded for at least 140 minutes in each subject. Five subjects exhibited sequences of between 18 and 89 regular pyloric contractions which occurred at a frequency of between 2.9 and 3.3 min^{-1} and were not associated with any detectable phasic contraction in the antral or duodenal recording sites situated 1 cm from either end of the sleeve. IPC occurred immediately before the onset of phase III of the MMC in 4 subjects and within 15 minutes of the end of phase III in 4 subjects. In 3 subjects IPC occurred both before and after phase III.

In 7 subjects recordings were also carried out for between 80 and 165 minutes after drinking 300 ml of chocolate milk. All 7 showed post prandial IPCs which commenced within an hour of ingestion. These IPC sequences lasted from 19 to 153 contractions at a frequency of between 2.5 and 2.9 min^{-1}. After ingestion of the milk, IPCs occupied 25 ± 8% (SEM) of recording time compared with 7+ 4% during fasting. Post prandial IPCs were also more likely to be interspersed with episodic peristaltic waves which swept from the antrum into and along the duodenum. Intrinsic pyloric contractions occur in man, and have been triggered consistently by feeding milk. These contractions may play a role in the control of transpyloric flow, especially in the fed state.

α-ADRENERGIC CONTROL OF DUODENAL INHIBITION BY ANTRAL CONTRACTIONS. S.N. Reddy and E.E. Daniel, Dept. of Neurosciences, McMaster University, Hamilton, ON, Canada.

One means of antroduodenal coordination is the inhibition of duodenal contractions by antral contractions. We reported previously that the neural control of such inhibition in dogs was mediated primarily via the sympathetic nerves and secondarily via the intrinsic nerves through the pylorus (inhibition was reduced markedly by phentolamine, but only slightly by pyloric transection)*. In this study, we examined the nature of α-adrenergic neural control of duodenal inhibition. In four anaesthetized dogs, bipolar stimulating electrodes were placed on cervical vagi tied toward the cranial side. Nerves between spleen and stomach were cut and the anterior nerve of Laterjet was tied. Four strain gauges, with bipolar stimulating electrodes, were sutured on antrum (A1 & A2) and duodenum (D1 & D2) 5 and 10 cm from the pylorus. Cannulae were placed in areas A1 and A2 for local infusion of drugs. A quiescent duodenum was excited by vagal or D2 field stimulation (FS). Antral activity was obtained by either FS or carbachol (1 ug). Inhibition was elicited after the pylorus was transected; then changes in responses were studied after the i.v. administration of 1) yohimbine (2 mg/Kg) followed by prazosin (1 mg/Kg) or, 2) vice-versa.

After yohimbine was administered, inhibition to both FS and carbachol was nearly abolished and administration of prazosin had no further effect. When prazosin was administered first, inhibition could still be elicited; it was completely abolished by the subsequent administration of yohimbine. Inhibition was elicited more easily when antral or duodenal contractions were closer to the pylorus.

We conclude that inhibition of duodenal motor activity by antral activity is mostly mediated by sympathetic nervous system and that α2 adrenergic mediation (inhibition by α2 antagonist Yohimbine) is more predominant than mediation by α1 receptors (inhibition not abolished by prazosin).

*Dig. Dis. Sci., p.554, May 84. Supported by MRC, Canada.

EFFECT OF TRANSECTION AND PACING ON HUMAN JEJUNAL PACESETTER POTENTIALS. H.M. Richter, III, K.A. Kelly, Gastroenterology Unit, Mayo Clinic, Rochester, MN 55905.

The aim was to determine whether transection and pacing alter the frequency of the jejunal pacesetter potentials (PPs) in man, as they do in the dog (Am J Physiol 1975; 229:1188). Methods: Three temporary stainless steel bipolar electrodes were sewn to the jejunal seromuscularis of 8 patients undergoing elective operation. In 6 patients with Roux-en-Y gastrectomy, 1 electrode was placed on the jejunum 5 cm proximal to the transection and 2 electrodes were placed on the Roux loop 10 and 20 cm distal to the transection. In 2 control patients without transection, 3 electrodes were placed at 10-cm intervals on the proximal jejunum. After recovery, fasting myoelectrical activity was recorded on 2 or 3 separate days. In 6 patients, jejunal pacing was attempted by stimulating the middle electrode with pulses of 50 msec duration and up to 10 mA strength given at frequencies slightly faster than the natural PP frequency. PP frequency was determined by counting PPs in at least five 1-min intervals in each channel each day, during periods of minimal spike activity. For each patient, mean PP frequency at each site was determined, and grand means for each site calculated. Results: In the Roux patients, the jejunal PP frequency was slower distal to the transection (10.8±0.2 and 10.9±0.2 cpm) than proximal to the transection (11.3±0.3 cpm, $P<0.05$), but the difference was slight. In contrast, the jejunal frequency in the controls was similar at the 3 sites of recording (11.7, 11.8 and 11.7 cpm). In 1 control patient, pacing increased the PP frequency by 0.5 cycle/min, but it had no effect in the other 5 subjects studied. Conclusion: Transection of the human jejunum decreases the PP frequency distal to the cut, but in contrast to the dog, the effect is slight. Human jejunal segments are not readily entrained by electrical stimulation, and, unlike the dog, separation from the native duodenal pacemaker may not facilitate pacing.

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NIFEDIPINE: A POTENT INHIBITOR OF ESOPHAGEAL CONTRACTIONS. IS IT EFFECTIVE IN THE TREATMENT OF NON-CARDIAC CHEST PAIN? JE Richter, CB Dalton, DO Castell. Bowman Gray School of Medicine, Winston-Salem, North Carolina.

Acute drug studies have shown the calcium channel blocker nifedipine to be a potent inhibitor of lower esophageal sphincter pressure (LES) and distal contractions in the esophageal body. Controlled studies of clinical efficacy in the treatment of painful motility disorders are not available. We investigated the effects of nifedipine on symptoms and esophageal contractions in 17 patients ($\bar{x}$ age 52, 10M, 7F) with chronic non-cardiac chest pain (CP) and high amplitude peristaltic contractions, the "nutcracker esophagus" (NC). All patients had normal coronary angiograms and UGI x-rays/endoscopy. Seven patients had CP replicated during manometry by edrophonium, 80mcg/kg IV. In a double-blind crossover study, patients were begun on identical-appearing intact capsules of nifedipine (10mg) or placebo, 2 TID, then titrated according to CP and side effects. Study duration 14 weeks: 6 weeks on each drug with 2 week washout period before crossover. CP frequency, intensity (scale 1-10) and CP index (frequency X intensity) were recorded daily in a diary. At end of each 6 weeks on drug, esophageal manometry was performed 30 min after ingestion of last capsule. Mean LESP and distal esophageal pressures in response to 10 wet swallows were recorded. Results:

	PLACEBO ($\bar{x}$±SE)	NIFEDIPINE	P
Amplitude (mmHg)	198±13	119±10	<.001
Duration (s)	4.5±0.3	3.8±0.1	<.05
LESP (mmHg)	28.4±3.7	15.8±1.4	<.001
CP Index ($\bar{x}$ of 6 weeks)	6.8±2.1	5.6±1.6	n.s.

CP frequency, index and weekly scores also did not improve with nifedipine. Edrophonium responders did no better than nonresponders. Conclusions: 1) long-term oral nifedipine therapy in NC patients markedly decreases LESP and distal amplitude; 2) CP, however, is not significantly improved; 3) these preliminary results question the importance of abnormal esophageal contractions in the etiology of non-cardiac CP.

ON THE MECHANISM OF ESOPHAGEAL CHEST PAIN: EVIDENCE FOR ABNORMAL SENSORY PERCEPTION. JE Richter, CF Barish, CB Dalton, and DO Castell, Bowman Gray School of Medicine, Winston-Salem, NC.

Many cases of recurrent chest pain (CP) are considered to be of possible esophageal origin. Although some will show typical esophageal spasm, the mechanism of pain production is not clear in most patients. We studied the response to intraesophageal balloon distension in 30 CP patients ($\bar{x}$ age 52) with negative coronary angiograms and 30 controls ($\bar{x}$ age 41). A polyvinyl balloon (length 30mm; maximum diameter after 10cc distension 27mm) was positioned 10cm above the LES and inflated with 1cc increments of air to total volume 10cc. Pressure was monitored within the balloon and 5cm proximally. Using a double-blind design, symptom response (pain) was recorded both during and without (placebo) balloon distension. EKG was monitored during studies. Results: 18/30 (60%) CP patients and 6/30 (20%) controls ($p<0.05$) experienced pain. Controls only noted pain at ≥9cc volume while 15/18 CP patients had pain at ≤8cc volume. Symptoms were identical to patients' CP, unassociated with EKG changes and resolved immediately with balloon decompression. During pain neither balloon pressures nor esophageal contractions proximal to the balloon differed significantly in the two groups. Intraballoon pressure/volume curves were identical for patients and controls with and without production of CP.

Conclusions: 1) esophageal chest pain can be reproduced (60%) by small volume (10cc) balooon distension; 2) no evidence for excessive esophageal contractions was found during pain; 3) similar pressure/volume curves show identical esophageal compliance with and without pain; 4) abnormal sensory perception to distension may at least partially define the mechanism of pain production.

PHARMACOLOGICAL CONTROL WITH CISAPRIDE OF GASTRO-ESOPHAGEAL REFLUX IN INFANTS. H. Rode and S. Cywes. Department of Paediatric Surgery, University of Cape Town, Red Cross Children's Hospital, Cape Town, South Africa.

Gastro-intestinal drug receptors allow for the inotropic manipulation of esophageal and gastric function. A new gastro-intestinal prokinetic substance, Cisapride, which has a profound acetyl-cholimetric effect limited to gastro-intestinal motility was evaluated to determine the mode of action of the drug and the pharmacological efficacy of controlling pathological gastro-esophageal reflux. Thirty-two infants - mean age 6.2 months - were studied with continuous esophageal pH monitoring for a period of 36 hours. Five parameters were constantly recorded and individually assessed in the erect, supine and prone positions and the results compared before and during pharmacological stimulation. The oral dose given was 1 mgm/kg in 3 divided doses. No untoward drug side-effects were recorded.

Parameters	No medication	Cisapride	% Improvement
Total no. of reflux episodes/36 hours	32.7	17.8	45.6
% time pH <4	8.9	3.0	66.3
No. of reflux >5 min.	2.5	0.9	64
Longest reflux episode (min.)	8.6	3.1	64
Average acid clearance time (min.)	13.5	6.8	49.6

$P_2 = 0.003$

An overall improvement of 58% was observed in the 5 parameters following Cisapride administration. Three factors contributed to poor response in 7 infants, viz. Roviralta syndrome, large hiatus hernia and near SIDS. Conclusion: Cisapride improved lower esophageal sphincter competence and motor function, making it an effective drug in the management of pathological gastro-esophageal reflux in infants.

ENHANCEMENT OF THE CYCLICAL PATTERN OF ACTIVITY OF BOTH SMALL AND LARGE INTESTINE BY LOPERAMIDE. Y. Ruckebusch and Ch. Cherbut. Dept. of Physiology, Ecole Nationale Vétérinaire, 31076 Toulouse Cédex (France).

Loperamide (LOP) is a synthetic opiate only poorly absorbed from the gut and thus could be of interest to study locally-mediated motor effects. In contrast, when given parenterally, LOP effects may involve central sites of action which result, as for morphine, in a short-lived stimulation followed by a long-lasting inhibition. Since gut motility in the pig is organized in cyclical phases on the small intestine (0.8/hr) and on the transverse colon (2.5 to 3.8/hr), we examined the effects of local versus systemic administration of LOP (0.5 mg/kg) on the upper and lower digestive tract motility. In four animals fitted with bichrome wires and catheters on the duodenum and colon, intraduodenal LOP (0.5 mg/kg) increased the cyclical activity of the small intestine to 2.5 phases/hr for 4-5 hrs (Fig.). A similar dose into the proximal colon doubled the frequency of colonic cyclical activity for 6-8 hrs. LOP subcutaneously (0.5 mg/kg) inhibited duodenal and colonic motility for 3-4 hrs (Fig.). All these effects, systemic and local on small and large intestine, were dose-dependently blocked for 1 and 2 hrs by IV naloxone (0.5 and 1 mg/kg. The data are consistent with a local drug-opioid receptor interaction modulating the inherent cyclical motor activity of the small and large intestine.

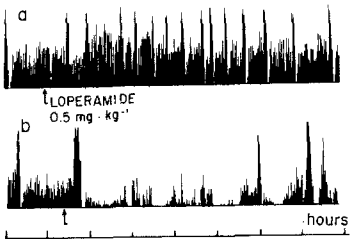

Fig. : Integrated MMC recordings of the local (a) versus systemic (b) effect of loperamide on the cyclical activity of of the duodenum.

SLOW WAVE PROPAGATION IS IMPAIRED WHEN ANTRAL MUSCLE IS DRIVEN AT PHYSIOLOGICAL FREQUENCIES. K.M. Sanders, and N.G. Publicover. Univ. Nevada Sch. Medicine, Reno, NV 89557 USA.

The corpus normally generates slow waves at a frequency of 4.5 - 5.7 CPM in conscious dogs. Electrical records from the canine antrum in vivo show variability in the waveforms from event to event. Experiments were performed to determine whether antral muscles could propagate slow waves at the frequencies they are presented with in vivo. Electrical activity was recorded from canine antral muscles in vitro with intracellular electrodes so that the effects of frequency on the waveform of slow waves could be quantitated. Slow waves were evoked by an extracellular electrode. At frequencies less than 3.0 CPM all slow waves were similar in waveform to spontaneous events. Between 3.0 and 4.8 CPM slow waves occurred in an alternating waveform pattern, in which every other event had a significantly depressed plateau amplitude and duration. At frequencies between 4.8 and 5.5 CPM, the plateau phase was abolished and upstroke velocity was reduced. Above 5.5 CPM many stimuli failed to evoke slow waves. These data suggest that at physiological frequencies antral muscle is incapable of consistently propagating mechanically productive slow waves. Experiments were performed to determine the cause of the alternating slow wave pattern. We found that the time between repolarization of the plateau and the next stimulus determined the waveform of the next slow wave. Following slow wave repolarization, the upstroke mechanism recovered after 3 seconds and an interval of at least 12 seconds was required for the plateau mechanism to fully recover. These experiments defined the propagation refractory periods of the 2 components of the slow wave. We also tested the effects of acetylcholine (ACh) on the propagation refractory period. ACh, 10^{-6} M, reduced the interval required for the plateau potential mechanism to reset and permitted conduction of mechanically productive slow waves at or above physiological frequencies. This is a previously undescribed role for cholinergic stimulation in gastric motility.
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MYOELECTRIC SPIKE BURSTS ASSOCIATED WITH COLONIC PROPULSION. J.C. Schang, M. Hémond, Centre Hospitalier Universitaire, Sherbrooke, Québec, Canada, J1H 5N4.

The relationships between colonic myoelectric spiking activity and the movements of fluids introduced into the colon were studied in 9 subjects. We used a 50cm long silastic tube equipped with 3 AgAgCl bipolar ring electrodes fixed 15cm apart at its proximal end, and 3 polyethylene slowly perfused open catheters which tip was located 1cm distal from each electrode. A solution of PEG 4000 at 10g/l was infused at 12ml/min into the colon through another tube opening 5cm orad from the most proximal electrode; the fluid was collected through a rectal tube which tip was 10cm aborad from the most distal electrode. The tracings were divided in 1-minute time intervals during which the different types of spike bursts were compared to the intraluminal pressure waves and to the volume of fluid collected.

The colonic spiking activity was made of Rhythmic Stationary Bursts that were seen at only one electrode site (RSB) and of Sporadic Bursts that were either propagating over all 3 electrodes (SPB) or not propagating (SNPB) as previously reported (Gastroenterology, 1983, 85: 1045-1053). Sporadic bursts were always associated with intraluminal pressure waves which amplitude was significantly higher than that associated with rythmic bursts. The volume of fluid collected from the colon did not change significantly whether stationary bursts were present or not. The volume increased significantly when sporadic bursts were occurring, and reached a maximum value when the bursts were propagating.

These results indicate that 1)- Sporadic bursts, particularly when propagating, are associated with significant propulsive movements; 2)- stationary bursts do not seem to be involved in colonic propulsion since they are associated with no increase nor decrease of intraluminal flow.

	NUMBER OF MEARESEMENTS	PRESSURE (cmH2O)(m+SD)	VOLUME COLLECTED (ml/min) (m+SD)
No spiking	35	-	3.9±1.7
RSB	102	6.0±1.2*	3.3±1.9
SNPB	186	35.3±5.2	9.4±4.1*
SPB	72	39.1±8.2	21.6±8.8*

* Significantly different from all others ($p < 0.01$).

EFFECT OF MORPHINE ON COLONIC MOTILITY: INHIBITION OF THE PROPAGATING MYOELECTRIC SPIKING ACTIVITY. J.C. Schang, M. Pilotte and M. Hébert Centre Hospitalier Universitaire, Dept. Chirurgie, Sherbrooke, Québec, Canada, J1H 5N4.

A paradoxical effect of morphine on colonic motility is to slow down colonic transit while stimulating smooth muscle activity. This effect was investigated by recording the colonic myoelectric spiking activity -that correlates well with motor activity- by means of a 50 cm long silastic tube equipped with 4 bipolar AgAgCl ring electrodes fixed at 10 cm intervals. This tube was introduced into the left colon in 8 healthy subjects by flexible sigmoidoscopy so as the electrodes be located at 50,40,30,20 cm from the anal verge. Tracings were performed for 1 hour in the fasting state and for another 1 hour after i.m. injection of morphine sulphate 0.15 mg/kg. The different types of spike bursts were compared before and after morphine injection. The control tracings showed that the spiking activity of the colon was made of 2 types: 1)- Rhythmic Stationary Spike Bursts (RSB), that were seen at only one electrode site; 2)- Sporadic Bursts, that were either propagating over all 4 electrodes (SPB) or non propagating (SNPB). Injection of morphine was followed, within 15 minutes, by 1)- a considerable increase in the number of rhythmic stationary spike bursts; 2)- the complete disappearance of the sporadic propagating bursts.

These results indicate that 1)- stimulation of colonic smooth muscle activity by morphine seems to result from an increase in the number of rhythmic stationary bursts; 2)- however inhibition of colonic transit may be related to the decrease in the number of sporadic propagating bursts.

	NUMBER OF BURSTS (nb/hour)(mean±sem)		INDIVIDUAL BURSTS DURATION (seconds) (mean±SD)	
	Before	After	Before	After
RSB	107±43	491±23*	3.1±0.2	3.0±0.8
SNPB	52±4	57±5	13 ±13	15 ±5
SPB	7.3±2.0	0.3±0.2*	22 ±6	24 ±8

* Significantly different from before MORPHINE ($p < 0.001$).

CORRELATIONS BETWEEN THE INTESTINAL MOTILITY AND TRANSIT OF DIGESTA IN VIVO. M. Schemann, H.-J. Ehrlein Institute of Zoophysiology, University of Hohenheim, Stuttgart, FRG

Many studies dealed with correlations between motility and transit of chyme, but definite interactions remained unclear. Therefore, we investigated in six dogs the effects of several nutrients and hormones (n=14) on jejunal motility by means of six closely spaced strain gages. Transit rates of digesta were assessed fluoroscopically. A computer was used to analyse the motor pattern, especially the length of spread of contractile waves. All meals and hormones changed the motor profile characteristically. A technique for fitting theoretical equations to experimental data - measured transit rate (t) against evaluated parameters - was used to prove the functional significance of the contractile patterns. As best fitting parameters we used the length of spread of contractile waves (l), which determines the propulsive ability of contractions, their propagation velocity (v), and their frequency (f). A multiple regression model describes the linear relation between the parameters. Each of the 177 experiments were expressed in the formula: $t = a_1 l + a_2 v + a_3 f$. Matrix algebra was used to determine the best values for the coefficients, which were $a_1 = 0.318$, $a_2 = 0.094$, $a_3 = -0.108$. After comparing the measured transit rate with that predicted by the model, there was a correlation coefficient of $r = 0.92$ indicating a high relevance of the model. The fact that a_1 exhibited the greatest value indicates that the length of spread of contractile waves is the most important factor in regulating transit of digesta. It was shown that transit of digesta can be described by combining several factors of contractile patterns. CONCLUSION. The study focussed attention to the importance of the length of spread of contractile waves in understanding transit of chyme along the small intestine. Analysing motor patterns and interactions between parameters is more important and informative than measuring mere quantity of intestinal activity.

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DOES PROSTAGLANDIN (PG) $F_{2\alpha}$ MEDIATE THE METENKEPHALIN (FK) STIMULUS ON THE TONE OF THE ISOLATED RAT COLON? U. Scheurer, E. Drack, F. Halter. Gastrointestinal Unit, University Hospital, Inselspital, 3010 Bern, Switzerland.

FK dose-dependently stimulates rat colonic tone. We have recently found that the FK stimulation is abolished by cyclooxygenase inhibitors like aspirin (ASA). This suggested that PG's may be involved. The present study was done in order to identify mediator(s) of the FK stimulus. Intraluminal perfusion manometry was performed in an in vitro preparation of the rat colon. Dose-response curves were obtained with the test drugs (10^{-9}M to 10^{-5}M) added to the nutrient. ASA treatment (0.3 mM) was initiated 30 min before other test drugs were added.

Results: Stimulation by FK started at 10^{-9}M and was maximal at 10^{-6}M with an integrated tonic pressure response of 40.0±4.2 AU (arbitrary units, mean±SEM, n=6). $PGF_{2\alpha}$ (10^{-5}M) produced similar responses of 37.2±3.5 AU. In the presence of ASA, the same dose of $PGF_{2\alpha}$ caused stimulation to 21.7±3.0 AU. $PGF_{1\alpha}$, PGD_2, PGE_2 produced only small pressure increases, and PGI_2 significantly reduced basal tone. When PG's were added to a submaximal dose of FK (10^{-7}M), $PGF_{2\alpha}$ (10^{-5}M) increased FK-stimulated tone from 32.1±3.7 to 44.8±5.0 AU; $PGF_{1\alpha}$ and PGD_2 had no significant effect, whereas PGE_2 and PGI_2 were inhibitory. Furthermore, $PGF_{2\alpha}$ completely reversed the ASA-induced inhibition of FK-stimulated tone. In the presence of ASA combined with PGE_2 (10^{-7}M) or PGI_2 (10^{-7}M), only $PGF_{2\alpha}$, but not PGD_2 or $PGF_{1\alpha}$, was able to reverse the inhibitory actions of these drugs on the submaximal FK stimulus.

Conclusion: It is suggested that $PGF_{2\alpha}$ is a part of the mediator system of metenkephalin stimulus on rat colonic tone, because $PGF_{2\alpha}$ stimulated the tone to a similar degree as FK, increased the tone during submaximal FK stimulation and reversed inhibitory actions of ASA alone and in combination with PGI_2 or PGE_2.

EFFECTS OF HORMONES ON PROPULSIVE ABILITY OF CANINE JEJUNAL MOTILITY. M. Schemann, H.-J. Ehrlein. Institute of Zoophysiology, University of Hohenheim, Stuttgart, FRG

The purpose of this study was to investigate the influence of neurotensin (NT), somatostatin (SST), secretin (SE), cholecystokinin (CCK), and 5-hydroxytryptophan (5-HTP) on the temporal and spatial distribution of jejunal contractions measured by means of 6 closely spaced strain gages. The hormones were given intraveneously after the administration of a non-caloric cellulose meal. A computer determined the length of spread of contractile waves (LSCW) by analysing the occurrence of time-related contractions at adjacent recording sites. The transit of digesta was measured fluoroscopically. In comparison to the NaCl control infusion CCK and 5-HTP increased significantly the length of the contraction spread, the incidence of propagative contractions, the contractile force, and the transit rate of digesta, but not the contractile frequency. In contrast, NT, SST, and SE significantly decreased the contraction spread, the incidence of propagative contractions, and the transit rate of chyme. NT increased the contractile force, but had no effect on contractile frequency. SST and SE decreased both the contractile force and the contractile frequency.

	LSCW cm	PC %	FORCE mN	FREQU. c/min	TRANSIT cm/sec
NaCL	9.6±0.8	76	85±14	12.9±1.2	2.5±0.8
CCK	12.8±2.3 *	85 *	102±4 *	14.4±0.6	3.7±0.9*
5-HTP	12.4±1.6 *	83 *	103±18 *	14.1±1.0	3.1±0.8*
NT	3.7±1.8 *	47 *	105±11 *	10.9±1.1	0.5±0.3*
SST	4.9±1.0 *	53 *	54±6 *	7.3±1.8 *	1.2±0.7*
SE	4.5±0.8 *	50 *	61±13 *	7.8±0.9 *	0.8±0.2*

* p<0.05 compared to NaCl control

CONCLUSION. Each hormone exhibited a characteristic action on the length of spread of contractile waves and thereby modified the propulsive and segmenting activity of the small intestine.

PROSTAGLANDINS (PG) AND THE METENKEPHALIN (FK) STIMULATED CONTRACTION OF THE ISOLATED RAT COLON U. Scheurer, E. Drack, F. Halter. Gastrointestinal Unit, University Hospital, Inselspital, 3010 Bern, Switzerland.

We have previously shown that FK dose-dependently stimulates rat colonic tone. The aim of this study was to investigate the role of PGs in the FK stimulated tonic contraction of the rat colon. Intraluminal manometry was performed in an in vitro preparation of the rat colon. Dose-response curves were obtained with test drugs (10^{-9}M - 10^{-5}M) added to the nutrient. Prior to some experiments aspirin (ASA) was given orally for 3 days (300mg b.d.).

Results: FK stimulation started at 10^{-9}M and was maximal at 10^{-6}M with an increase of integrated colonic tone of 40.0±4.2 AU (arbitrary units, mean±SEM, n=6). ASA given orally or added to the nutrient (0.3-3.0mM) subtotally abolished FK stimulation. $PGF_{2\alpha}$ stimulation of colonic tone started at 10^{-9}M and was maximal at 10^{-5}M with 37.2±3.5 AU, while at the same concentration $PGF_{1\alpha}$, PGE_2 and PGD_2 caused a small increase only. PGI_2 decreased basal tone at 10^{-9}M with the peak reaction at 10^{-7}M (-9.8±0.9 AU), but stimulated at 10^{-5}M (3.5±0.2 AU). Oral pretreatment with ASA or addition of ASA to the medium (0.3mM) markedly reduced stimulation by $PGF_{2\alpha}$, while the stimulatory effect of $PGF_{1\alpha}$ and PGD_2 was enhanced. ASA did not affect PGE_2 stimulation, but it reduced the inhibitory effect of PGI_2. $PGF_{2\alpha}$ enhanced the stiumulatory action of 10^{-7}M FK. $PGF_{1\alpha}$ and PGD_2 did not affect it. PGE_2 and PGI_2 dose-dependently inhibited this FK stimulus. In the presence of constant ASA (0.3mM) combined with constant FK (10^{-7}M) $PGF_{2\alpha}$ completely and $PGF_{1\alpha}$ subtotally reversed the inhibition of the FK stimulus, whereas the inhibitory action of PGI_2 was reduced.

Conclusion: Inhibition of the FK stimulation by ASA, stimulation of colonic tone, even in presence of ASA as well as the reversal of ASA induced inhibition of the FK stimulated tone by PGs strongly suggests an involvement of PGs in the metenkephalin stimulation-contraction coupling in the isolated rat colon.

(A-37)

THE ULTRASTRUCTURE OF RABBIT GASTRIC SMOOTH MUSCLE IN RELATION TO ITS FUNCTION. K. Schulze-Delrieu and B. Wright. Gastroenterology Research Laboratory, VA Medical Center, Iowa City, IA 52240.

Smooth muscle of the proximal stomach generates tension, of the distal stomach phasic contractions. Whether there is a correlation in the ultrastructure is not known. We filled stomachs with 100 ml of Krebs' solution and marked squares on the fundus and antrum. Antral squares changed little with changes in luminal volume; fundic squares about doubled their length and width when the gastric volume was increased from 50 to 200 ml. The dimensions of each square were maintained during fixation, osmication and embedding of the muscle. Ultrathin cross and longitudinal sections of circular muscle were studied by electronmicroscopy. The nuclei of the fundic and antral muscle cells showed invaginations, the cells themselves did not. Most nuclei were capped on their ends by endoplasmatic reticulum with associated ribosomes and many of the cells' mitochondria. The perinuclear cell segment was always straight, whereas other cell segments and the myofibrils in their interior were often wavy. Dense bodies and glycogen granules were scattered throughout the cells. All collagen fibers between the cells were 30-35 nM in diameter. Many fibers occurred in bundles with varying orientation to the cell axis. Gap junctions in the circular muscle increased from about $60{,}000/mm^2$ in the corpus to about $155{,}000/mm^2$ in the antrum. None were seen in the longitudinal muscle or mucosal muscle. Both antral and fundic cells were staggered, but fundic cells appeared longer at all volumes. Also, antral muscle cells were strapped down by short collagen fibers on all sides, and the extracellular space of antral muscle appeared narrower than in fundic muscle. Fundic muscle cells were connected to adjacent cells mostly on their poles, leaving the remainder of the cell free for contraction and expansion. Cell density was highest ($155{,}000$ cells/mm^2) at 100 ml, and decreased both on filling and emptying of the stomach. We conclude that differences exist in the cell-to-cell connections of smooth muscle in the proximal and distal stomach.

INTERACTION OF CISAPRIDE WITH 5-HYDROXYTRYPTAMINE-RECEPTORS CANNOT EXPLAIN ITS MOTOR-STIMULATING ACTION ON THE GUINEA PIG ILEUM. J.A.J. Schuurkes and J.M. Van Nueten. Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium.

Recent reports suggest that 5-hydroxytryptamine (5-HT) was involved in the motor-stimulating action of cisapride on the guinea pig ileum. Our aim was to determine the 5-HT-antagonistic or -agonistic properties of cisapride on the guinea pig ileum and their contribution to the effects of cisapride.

5-HT-agonism. 5-HT-induced contractions on rat fundus (EC_{50} = 2.4 x 10^{-9} M), rat caudal artery (EC_{50} = 9.0 x 10^{-7} M) and guinea pig ileum (EC_{50} = 1.5 x 10^{-6}M), whereas it inhibited the contractile response of the guinea pig ileum to electrical stimulation (IC_{50} = 4.9 x 10^{-7} M). In contrast, cisapride did not exert any intrinsic agonistic effect. On the guinea pig ileum it enhanced the contractile responses to electrical stimulation at low concentrations (EC_{50} = 9.2 x 10^{-9} M), but inhibited them at higher concentrations (IC_{50} = 5.8 x 10^{-6} M). This inhibition could not be reversed by methiothepin, which antagonized the 5-HT-induced inhibition on the same preparation.

5-HT-antagonism. Cisapride antagonized the 5-HT-induced contractions on the rat caudal artery (IC_{50} = 4.7 x 10^{-9} M) and the guinea pig ileum (IC_{50} = 1.1 x 10^{-7} M), but not on the rat fundus. Ketanserin and R 53 434 also antagonized the effects of 5-HT on artery and ileum respectively, even at lower concentrations than cisapride. However, these compounds did not enhance the response of the ileum to electrical stimulation nor did they affect the response of the preparation to cisapride.

In conclusion. Cisapride did not exert 5-HT-agonistic properties in the tests used. Instead it did antagonize contractile responses to 5-HT. However, our findings do not support the involvement of these 5-HT-antagonistic properties in the stimulating effect of cisapride on electrically evoked contractions of the guinea pig ileum.

EFFECT OF DUODENAL BILE ACID DELIVERY ON FASTING INTESTINAL MOTOR ACTIVITY. R.B. Scott. Dept. of Pediatrics, and GI Research Group, University of Calgary, Alberta, Canada.

Fasting duodenal bile acid delivery is pulsatile with peak rates of delivery preceding the cyclic appearance of the migrating myoelectric complex (MMC) in the duodenum. To determine if duodenal bile acid concentration exerts dose-response control over the duodenal cycle period (CP) of the MMC, or over intensity of duodenal motor activity, 3 dogs were surgically prepared with a duodenal cannula permitting cannulation of the common bile duct, duodenal infusion, and manometric recording. Fasting duodenal motor activity was recorded in multiple experiments. CP was measured under control conditions with the enterohepatic circulation (EHC) intact, and after cannulating the common bile duct to divert endogenous bile from the duodenum during continuous duodenal infusion (1.6ml/min) of 0, 2.5 12.5 or 25mM sodium taurocholic acid (TCA) in 154mM NaCl. In a 2nd protocol with the EHC intact, a control and subsequent CP were measured and a pulse (1ml/min x 10 min) of pooled dog bile (112mM total bile acids), or 0, 20, 80, 140 mM TCA in 154mM NaCl was infused into the duodenum at 40% of the 2nd CP (as estimated from control CP). The integral of duodenal pressure with respect to time was determined for 2 consecutive 16-min intervals of both control and succeeding CP, commencing at 40% of the control CP and at the start of pulse infusion of the succeeding CP. CP was significantly different ($p<0.001$) between dogs, however there was not significant difference in CP with the EHC intact compared to during continuous duodenal infusion of 0, 2.5, 12.5 or 25 mM TCA. Also, there was no significant change in CP or integral of duodenal pressure with respect to time after pulse infusion of 0, 20, 80, 140mM TCA or pooled dog bile. Thus, in fasted conscious dogs, the CP was not significantly altered by diversion of endogenous biliary secretion, or by continuous duodenal infusion of TCA at concentrations spanning the physiologic range. Premature delivery of pulses of pooled dog bile or a range of concentrations of TCA, which simulated pulsatile duodenal bile acid delivery during fasting, did not initiate premature MMC's or an increase in duodenal motor activity.

EFFECT OF BILE ACIDS ON GALLBLADDER CONTRACTILITY AND BILIARY LIPIDS. E.Shaffer, J.Davison, H.Parsons, C.St.George, D.Kirk. University of Calgary, Calgary, Alberta, Canada.

Gallbladder stasis is a factor in gallstone formation and perhaps medical dissolution. To determine any effect of bile acid therapy, we measured gallbladder contractility in a model of cholesterol gallstones: Richardson ground squirrels fed either a trace (Control) or 1% cholesterol (Test) diet. Animals also received the following capsules for 28 days: placebo, chenodeoxycholic acid 10 or 30mg/kg/d (C-10, C-30), or ursodeoxycholic acid 10 or 30mg/kg/d (U-10, C-30). Isometric tension measured *in vitro* used whole gallbladder responses to increasing doses of cholecystokinin-octapeptide (CCK), from 2.5x10^{-9} to 1.9x10^{-7}M. Lithogenic index (LI) and tensions (T) at 100% maximal response are shown as $\bar{X}\pm SE$. *p<.05 vs Control; †p<.05 vs Test

Diet:	trace cholesterol					1% cholesterol				
	Control	C-10	C-30	U-10	U-30	Test	C-10	C-30	U-10	U-30
n=	9	6	5	4	5	14	5	5	5	5
L.I.	.49	.42	.55	.52	.44	1.02*	.54†	.98	.95*	.56†
±SE	±.08	±.03	±.06	±.09	±.04	±.16	±.05	±.28	±.21	±.03
T(g)	2.92	2.67	2.37	3.45	3.10	1.96*	2.60†	1.52*	1.14*†	2.48
±SE	±.30	±.27	±.52	±.32	±.17	±.20	±.34	±.25	±.24	±.18

Neither bile acid had any effect on lithogenicity or motility when animals consumed the regular diet. The 1% cholesterol diet increased bile lithogenicity and reduced tension significantly ($p<.05$). Addition of chenodeoxycholic acid 10mg/kg and ursodeoxycholic acid 30mg/kg decreased LI and improved contractility to control values. C-30mg/kg worsened lithogenicity and contractility, whereas U-10mg/kg failed to reverse the defect caused by the high cholesterol diet. Thus, bile acids fed to animals on a normal diet do not affect gallbladder contractility or lithogenicity. High dietary cholesterol increases bile lithogenicity and impairs contractility. Chenodeoxycholic acid at a low dose and ursodeoxycholic acid at a high dose restores lipid composition and contractility to normal. The ability of both agents to correct gallbladder stasis appears dependent on their reducing cholesterol saturation, features which should be considered when assessing the response to medical dissolution of gallstones.

MATHEMATICAL ANALYSIS OF MYOELECTRIC CYCLING IN THE OPOSSUM SPHINCTER OF ODDI. S.W. Sharp, J.M. Becker and J.J. Sullivan. University of Utah School of Medicine, Salt Lake City, UT 84132 U.S.A.

The sphincter of Oddi (SO) of the fasted opossum exhibits spontaneous cyclical myoelectric activity in association with the migrating myoelectric complex (MMEC) of the stomach and duodenum. Our aim was to demonstrate mathematically that myoelectric cycling in the SO continues after feeding. In four adult opossums, bipolar electrodes were implanted on the SO. After a 2 week recovery period, animals underwent 8 hour recording sessions while fully conscious. After 2 fasting cycles of the MMEC, the animals were fed a 200 kcal fat meal and recording continued for 4-6 hours. This caloric value had been previously found to elicit maximal SO myoelectric spike response. Recordings were visually scored for spike burst frequency. Pre- and postprandial values were entered into a computer and subjected to three mathematical analyses: moving average using a 5 point window, curve fitting to a 5th degree polynomial by curvilinear regression, and spectral density analysis. It was demonstrated that the cycles observed in the fasted state continued after feeding with approximately the same mean ± SD period (91.3±18.9 vs 91.8±13.6 min) but with elevated minimum spike burst frequencies (Table). We conclude using three methods of mathematical analysis that cycling of myoelectric spike activity of the opossum SO continues after feeding but is masked by the decrease in the difference between maximum and minimum spike burst frequency per cycle.

	Spike Burst Frequency (mean + SD)				% Variance
	Overall	Maximum	Minimum	Delta	
Fasted	3.9±1.4	5.7±1.3	2.1±1.6	2.7±1.0	43.5±15.0
Fed	6.5±1.1	8.1±1.5	4.9±0.8	1.9±0.5	23.3± 1.0

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MECHANICAL RESPONSES OF X-IRRADIATED INTESTINAL MUSCLE. L. Sillin, A. Bortoff, D. Terasaka, A. Sterns, R. Sagerman, K. Snyder. Upstate Medical Center, Syracuse, NY 13210.

The purpose of these studies was to study the effect of X-irradiation on the mechanical properties of intestinal smooth muscle. Six anesthetized adult cats underwent laparotomy, and three received 2,000 rads of intra-operative X-irradiation to a 12 cm segment of jejunum. The other three cats served as non-irradiated controls. Two months later the irradiated segment was removed. Five rings of circular muscle, approximately 2 mm wide, were dissected away from each specimen and used for the mechanical studies. The muscle rings were placed in a chamber (10 ml in volume) perfused at 5 ml/min with oxygenated Krebs solution, warmed to 32°C and containing 10^{-6} M physostigmine. The rings were fixed by small stainless steel rods near the bottom of the bath and were attached to strain gage transducers by pre-stretched silk threads at the top of the bath. Tension-length curves were generated by passing alternating current (20 V/cm, 60 Hz) between two platinum plates at either end of the chamber, in order to determine the optimal length (L_o) for each muscle ring. Dose-response curves were then generated at L_o for acetylcholine (ACh). Tension was calculated as $Nx10^5/m^2$ by using L_o, the blotted wet weight of the tissue and assuming a density of 1.0. Five jejunal muscle rings from each of the control animals were treated the same way. Peak tensions were attained at ACh concentrations of 10^{-3} M for both groups of tissue. Peak tensions ($Nx10^5/m^2$ ± SEM) were: control, 3.59±.48; irradiated, 1.46±.33 ($p<0.025$, Student's t-test, 4 degrees of freedom). The ACh concentration producing one-half maximal tension was: control, $4x10^{-6}$ M; irradiated, $4x10^{-5}$ M. These data indicate that irradiated intestinal muscle is intrinsically weaker than normal, and furthermore, that it has a decreased number of cholinergic receptors, and/or that these receptors have a decreased affinity for ACh. (Supported by the Veteran's Administration and NIH grant 2 S07 RR0540223)

ROLE OF ENDOGENOUS PROSTAGLANDINS IN THE REGULATION OF GASTRIC EMPTYING IN PRIMATES. T. Shea-Donohue, E. Montcalm, A. Dubois. Uniformed Services University, Bethesda, MD, 20814-4799, USA.

We have shown previously that PGE_2 and $PGF_{2\alpha}$ increase, while PGI_2 decreases gastric emptying. The present study was designed, therefore, to examine the role of endogenous prostaglandins (PG) on gastric emptying. Seven conscious chair-adapted rhesus monkeys were pretreated (16 hrs and 45 min) with aspirin (ASA; 25, 50, 100, 150 mg/kg s.c.). Using a 99m-Tc-DPTA dilution technique, gastric fractional emptying rate (FER) was determined during a fasting period (FP) and at 2 initial 5 min intervals and 5 subsequent 10 min for a total of 60 min after the administration of an 80 ml water load (PL) (pH 7.0, 37°C). FER was inhibited significantly by 150 mg/kg ASA (see Table) and was suppressed significantly by all doses of ASA after the water load. At 5 min PL, ASA produced a 12-95% decrease in FER that was dose-dependent and significant ($p<0.05$) for 50, 100, and 150 mg/kg when compared to controls (15.1±7.8; 10.6±2.7; 10.6±2.7; 0.9±4.6 respectively vs 17.3±4.9 %/min). In contrast, the effects on the later phase of emptying do not appear to be related to the dose of ASA. After 40 min, all doses of ASA produced an equal (>50%) inhibition ($p<0.05$) of FER.

ASA (mg/kg)		0	25	50	100	150
FER	FP	3.4±1.3	1.7±1.5	2.11±1.2	1.6±0.9	0.3±0.4*
%/min	PL	5.7±1.0	3.6±0.7*	2.40±0.4*	3.5±0.7*	0.7±0.4*

* $p<0.05$ vs. 0 (Control). Values are means ± S.E.

These data demonstrate that inhibition of endogenous PG significantly inhibits gastric emptying. However, the aspirin-induced suppression of the early phase (5 min) of emptying appears to be dose-dependent, in contrast to the inhibition observed in the later phase (>40 min). These results suggest that endogenous PG play a physiological role in the regulation of the gastric emptying response to a water load. As PGE_2 and $PGF_{2\alpha}$ enhance FER, the suppressive effect on FER following the inhibition of endogenous PG implies that PGE_2 and $PGF_{2\alpha}$ have a greater role than PGI_2 in the physiological control of gastric emptying.

THE CARBOHYDRATE-INDUCED INCREASE IN WAVE AMPLITUDE OF THE SURFACE ELECTROGASTROGRAM IS BLOCKED BY ATROPINE. DR Sinar, JM Joyce. Departments of Medicine and Physics, ECU School of Medicine, Greenville, NC.

In our previous studies of the electrogastrogram (EGG), an increase in power (wave amplitude) after a meal was influenced by the meal carbohydrate content. We examined the mechanism of the postprandial increase in power (PWR) by studying the EGG response to a 50 ml bolus of 0.2 gm/ml glucose (GLU) solution with and without pretreatment with atropine (AT) or an equicaloric IV infusion of GLU (IVGLU). Sedated cynomolgus monkeys were studied with bipolar recordings from surface abdominal electrode positions for two 32 min periods; before and after test injection or infusion of GLU. Analogue data were collected through 0.016 Hz-0.3Hz (1-18 cy/min) filters and passed to a lab computer for Fourier analysis. The frequency resolution was 0.3 cy/min. Power spectra were divided into equal bands of 1.8 cy/min increments; band 2 contained the frequency of gastric ECA. Serum GLU was measured during the 30 min period after GLU injection. Total PWR in each frequency band, and band 2 frequency were compared in groups over time. Results: Serum GLU after injection was similar (range 120-240 mg%). Mean band 2 frequency did not change significantly after any injection. Total PWR increased significantly after GLU (464 vs 3450 units; $p < 0.05$); and decreased after GLU + AT (726 vs 571 units; NS). There was no significant increase in PWR after IVGLU (602 vs 837 units; NS). There was a significant increase ($p < 0.05$) in PWR after GLU in the frequency range 1.9-7.5 cy/min that was not present in animals treated with GLU + AT. Conclusions: 1) Intragastric GLU is a potent stimulus for the increase in PWR (wave amplitude) in the EGG after a meal. 2) Intragastric GLU produces the maximum PWR increase in the frequency range of gastric ECA, with lower magnitude, but significant increases in the frequency range 3.8-7.5 cy/min. 3) The GLU-induced postprandial increase in PWR is completely blocked by AT. 4) Intravenous GLU does not induce a significant increase in PWR when compared with intragastric GLU.

REGULATION OF SLOW WAVES BY MOTOR NEURONS OF THE SUBMUCOUS PLEXUS IN THE CANINE COLON. T.K. Smith and K.M. Sanders. Univ. Nevada School of Medicine, Reno, NV 89557 USA.

It is thought that the myenteric plexus contains the motor neurons that activate GI smooth muscles. In contrast, the submucous plexus appears to have a modulatory role on intrinsic reflexes and is mainly concerned with regulation of the mucosa. Experiments were performed to determine the effects of directly stimulating the submucous plexus on slow waves. Segments of canine proximal colon were removed and strips of muscle (2mm x 20mm) consisting of the entire thickness of the muscularis were cut and the mucosa was removed. The muscle was pinned to expose the submucous plexus lying on top the circular muscle. Single circular muscle cells were impaled with microelectrodes which were advanced through the submucosa. Microinjection of ACh (10^{-3}M) onto the submucous plexus produced a slow wave of reduced amplitude that was followed by a slow wave of increased duration (up to 42 sec). In the presence of atropine (10^{-6}M), microinjection of ACh produced an inhibitory junction potential (IJP) that further reduced the amplitude and duration of the first slow wave after the stimulus. The second, large duration slow wave was also decreased by atropine, but by increasing the duration of the ACh pulse the long duration of the second slow wave was restored. The duration of the second slow wave was not related to the size of the IJP suggesting that this secondary excitation was not a "rebound" phenomenon. These changes in the waveforms of slow waves were manifest in the force and duration of corresponding contractions. The responses to ACh microinjection were blocked by either TTX (10^{-6}M) or hexamethonium (10^{-4}M), confirming their neural origin. Removal of the longitudinal muscle and myenteric plexus did not affect these responses suggesting that cholinergic and noncholinergic excitatory motor neurons as well as inhibitory motor neurons are located within the submucous plexus of the canine colon. Thus in the colon, where slow waves are generated in the inner layer of circular muscle, the submucous plexus appears to play a major regulatory role in motility. (Supported by NIH Grants AM32176 and AM01209)

'INAPPROPRIATE' LOWER ESOPHAGEAL SPHINCTER RELAXATIONS IN NORMAL SUBJECTS. A.J.P.M. Smout, L.M.A. Akkermans, J.W. Bogaard, O.J. ten Thije, P. Wittebol. Departments of Gastroenterology and Surgery, University Hospital, Utrecht, the Netherlands.

The human lower esophageal sphincter (LES) exhibits relaxations that are not elicited by esophageal peristalsis. The mechanism causing these 'inappropriate' relaxations (IRs) is still obscure. The objective of this study was to investigate whether occurrence and duration of IRs are related to interdigestive and postprandial motor activities of the upper digestive tract.
In 15 healthy volunteers intraluminal pressures in esophageal body, LES, fundus, antrum and proximal duodenum were continuously recorded, during a complete cycle of the interdigestive migrating complex (IMC), and during 2½ h after a test meal.
RESULTS: A total of 181 complete IRs was recorded. IRs occurred in all subjects. In the interdigestive state the hourly rate of occurrence was 1.90 ± 0.35/h (mean ± sem). There were no significant differences between the hourly rates in phases 1,2, and 3 of the IMC. IRs occurred with the highest frequency in the first half hour after the meal (4.93 ± 0.15/h). Thereafter the frequency gradually decreased, but remained higher than in the interdigestive state. IR duration varied from 8 to 49 seconds. There were no motor phase-related differences in IR duration. The frequency of occurrence of IRs was not correlated with the frequency of primary peristaltic waves in the esophagus, nor with mean LES pressure. Most IRs were accompanied by a measurable drop in fundic pressure, but changes in the motor activity of antrum and duodenum did not occur. It was observed, however, that 12 of the 181 IRs were immediately preceded by a simultaneous rise in pressure at all recording sites, caused by body movement or straining.
CONCLUSIONS: IRs occur most often in the early postprandial period. Apart from this, IRs seem to occur at random, at all levels of LES pressure, and unaccompanied with motor changes in stomach and duodenum. About 7% of the IRs appear to be elicited by a rise in abdominal pressure.

EFFECT OF ACUTE COLITIS IN THE RABBIT ON COLONIC SMOOTH MUSCLE FUNCTION. W.J. Snape, Jr., J. Cohen, T. Tan, H.W. Kao, J. Lechago, Department of Medicine, UCLA Medical Center, Torrance, CA 90509

The purpose of this study was to determine the effect of acute experimental colitis on the membrane potential (MP) and contractile activity of colonic circular smooth muscle. Experimental colitis (EC) was induced in the distal colon of New Zealand white rabbits by rectal infusion of formalin followed by an intravenous infusion of soluble immune complexes. Macroscopic and microscopic mucosal inflammation occurred within 1 week. Despite active mucosal disease, there was little inflammation in the smooth muscle layers. The resting MP was measured using intracellular microelectrodes. Passive membrane properties were measured using the double sucrose gap. Isometric tension was measured at the length for optimal tension development (L_o) after exposure to 80mM $[K^+]_o$. The MP measured with intracellular microelectrodes in tissue from healthy rabbits was -52±.9mV (n=200cells). In EC the MP was decreased (-38±1.8mV) (n=75 cells) ($p<.001$). A constant hyperpolarizing current (0.1-2.5uA) passed through the tissue initiated an electrotonic potential (EP). In muscle from EC the EP after a 0.6uA current pulse was decreased (11±3mV) compared to the muscle from healthy animals (22±3mV) ($p<.05$). The voltage response was decreased in EC throughout the entire range of current pulses. In muscle from EC, the time constant (τ) of the EP was decreased (139±13msec) ($p<.001$) compared to muscle from healthy animals (291±23msec). The isometric tension in muscle from EC after exposure to 80mM $[K^+]_o$ was 52% of the response by muscle from healthy animals ($p<.01$). These studies show that in muscle from animals with EC 1) the resting membrane potential is decreased 2) the membrane resistance is decreased as reflected by the decreased EP and shortened τ 3) Contractile activity is reduced. These studies suggest that a functional abnormality is present in the electrical and mechanical activity of muscle from animals with acute experimental colitis, despite absence of light microscopic changes.

EFFECT OF NEUROTENSIN ON ELECTRICAL AND MECHANICAL ACTIVITY IN THE RABBIT COLON. W.J. Snape, Jr., S.T. Tan, J. Wang, Dept. of Medicine, Harbor-UCLA Medical Center, Torrance, CA.

The aim of these studies was to determine the mechanism by which neurotensin (NT) stimulates isolated distal colonic circular smooth muscle of the rabbit. Isometric tension was measured at the length for optimal tension development (L_o). The changes in the membrane potential (MP) after the administration of NT was measured using intracellular microelectrodes and the double sucrose gap. NT (10^{-12}M-10^{-7}M) stimulated a dose dependent increase in isometric tension. The D_{50} for NT stimulation of muscle tension was $5X10^{-9}$M and the peak tension development occurred at 10^{-8}M. The increase in tension after NT, was not blocked by phentolamine (10^{-6}M), propranolol (10^{-6}M), atropine (10^{-6}M) naloxone (10^{-6}M) or TTX (10^{-7}M). Verapamil (10^{-6}M) inhibited NT stimulated contraction of the tissue. Studies were performed to correlate changes in mechanical and electrical activity. Using intracellular microelectrodes the MP of the muscle during perfusion with Krebs solution was -52±2mV. NT caused a concentration dependent decrease in MP. After perfusion with NT (10^{-8}M) the MP was -47.7±1.9mV ($p<0.05$). The maximum rate of rise (dV/dt_{max}) of an electrically induced spike potential was increased by NT (10^{-8}M) (835±96mV/sec) compared to Krebs solution (685±82mV/sec) ($p<.05$). The passive membrane properties associated with the decrease in MP were measured using a double sucrose gap. The amplitude of the electrotonic potential (EP) and the time constant (τ) after hyperpolarizing current pulses were similar during perfusion with Krebs and NT. Thus, NT did not alter membrane resistance. These data suggest that 1) NT stimulates colonic smooth muscle contraction directly without the mediation of neural agonists. 2) The increase in muscle tension after exposure to NT may be related to depolarization of the muscle and an increase in dV/dt_{max} of the spike. 3) NT may stimulate colonic smooth muscle contraction through a receptor-activated increase in a specific ion conductance, possibly Ca^{2+}.

DELAYED GASTRIC EMPTYING IN PATIENTS WITH ANOREXIA NERVOSA AND BULIMIA: EFFECTS OF CISAPRIDE. G. Stacher, H. Bergmann, S. Wiesnagrotzki, A. Kiss, J. Hobarth and G. Mittelbach. Psychophysiology Unit, University of Vienna, A-1090 Vienna, Austria.

Patients with anorexia nervosa often complain of postprandial gastric fullness or discomfort, which is relieved by spontaneous or self-induced vomiting. As previous studies have shown, these symptoms seem to be due, at least in part, to a delayed gastric emptying. In the present study we investigated, in ten patients with anorexia nervosa (mean age, 24.7 yr ± 1.7 SEM; mean percentage of desirable weight, 63.3 ± 3.3%) and in two patients with bulimia (age 19 and 37 yr; % desirable weight, 93 and 96%), gastric emptying time and whether delayed emptying could be accelerated by cisapride. Cisapride has been shown to enhance, presumably via a stimulation of acetylcholine release in the gut wall, gastric emptying and antroduodenal coordination in animals as well as in humans. All patients were studied on two occasions one week apart on which they received, according to a double-blind crossover design, either 10 mg cisapride or saline placebo by i.v. injection. Gastric emptying was studied by means of a radioisotope technique and a semisolid test meal. In six of the ten anorexia patients and in both bulimic patients, gastric emptying was grossly delayed, the half emptying times (T 1/2) ranging from 117 to 193 min and being more than 120% longer than those of a group of 24 healthy volunteers (mean T 1/2: 52.9 ± 4.3 min). Of the remaining four anorexia patients, three had slightly prolonged T 1/2 (65, 67, and 72 min), while only one (T 1/2 = 50 min) emptied faster than, on average, the healthy controls. Cisapride accelerated emptying markedly in all patients, the mean T 1/2 being 44.7 ± 5.0 min as compared to 115.8 ± 13.5 min with placebo (t-test, t (11) = 4.82, $P < 0.001$). It is concluded that cisapride reliably accelerates delayed gastric emptying in patients with anorexia nervosa and bulimia. A long-term medication of the drug might prove benefitial in diminishing the patients' symptoms and, in those with anorexia nervosa, probably also might help to attain weight again.

IS THE MOTILITY OF THE PANCREATIC SPHINCTER DISTINCT FROM THE BILE DUCT SPHINCTER ? M.Staritz, M.Manns, T.Poralla, K.-H.Meyer zum Büschenfelde. 1 st Medical Department, Johannes-Gutenberg-University Mainz, D 6500 Mainz, West Germany.

To date it is not yet established whether the pancreatic sphincter has a motility, distinct from the bile duct sphincter's motility. Several authors found a higher contraction frequency in the pancreatic sphincter. We, therefore, investigated the pancreatic sphincter in patients before and after complete sphincterotomy (endoscopic papillotomy) of the bile duct sphincter.
Methods: 6 patients were included in the study. Endoscopic papillotomy had been performed for removal of bile duct stones more than 1 cm in diameter. The pancreatic sphincter motility and baseline pressure was recorded before papillotomy and 6 weeks after the procedure. The completeness of the bile duct sphincterotomy was confirmed by measuring the bile duct pressure which was zero, and by endoscopic inspection showing the bile duct wide open. All endoscopic manometric recordings were obtained in standard conditions as recently published (Gut, 1985, 26: 194 -197).
Results:
Before sphincterotomy the bile duct sphincter and the pancreatic sphincter showed no difference regarding its contraction frequency. The baseline pressure of the pancreatic sphincter amounted to 16.3 ± 0.9 mmHg, its contraction amplitude to 88 ± 1.6 mmHg. After sphincterotomy in the bile duct sphincter no motility was obtained. The motility of the pancreatic sphincter was unchanged.
Conclusions: The pancreatic sphincter is distinct from the bile duct sphincter. Its motility, however, does not differ from the bile duct sphincter. Endoscopic papillotomy does not affect the function of the pancreatic sphincter

CISAPRIDE STIMULATES DOSE-DEPENDENTLY FASTING JEJUNAL MOTOR ACTIVITY IN HEALTHY MAN. G. Stacher, H. Steinringer, C. Schneider, S. Winklehner and G. Gaupmann. Psychophysiology Unit, University of Vienna, A-1090 Vienna, Austria.

Cisapride enhances, in animals as well as in humans, gastric emptying, gastroduodenal coordination, and the segmenting activity of the colon. This study investigated whether cisapride stimulates the interdigestive contractile activity of the jejunum in healthy humans. Twelve male volunteers participated, in one week intervals, in three experiments each. Five minutes after the end of an activity front (phase III of the migrating motor complex) they received, in random double-blind fashion, 10 mg cisapride, 4 mg cisapride, or saline placebo by i.v. injection. Jejunal pressures were recorded continuously for four hours by means of a pressurized capillary infusion system with six catheters with orifices spaced 3 cm apart and positioned 10 to 30 cm beyond the ligament of Treitz. The pressure recordings were analyzed by computer. Cisapride dose-dependently diminished phase I ($P < 0.001$) and increased phase II-type activity ($P < 0.001$) and reduced the number of activity fronts. Phase II-type activity after cisapride was significantly more propulsive than after placebo (4 mg cisapride, $P < 0.02$; 10 mg cisapride, $P < 0.01$). The number and amplitude of jejunal contractions, the area under the pressure curve as well as self-rated abdominal grumbling increased markedly after administration of both doses of cisapride to reach peak values after 30 min and to last for the entire recording period. Both doses of cisapride were significantly more active than placebo ($P < 0.001$), but differed only slightly from each other. Blood pressure, heart and respiratory rate, psychomotor function as well as self-rated well-being were not altered, however, self-rated drowsiness and tiredness increased significantly after cisapride. Conclusion: Cisapride stimulates fasting jejunal motility and might prove useful in clinical conditions of impaired small intestinal motor activity.

INVESTIGATION OF THE EFFECT OF MODERN MORPHINE-LIKE ANALGESICS ON THE SPHINCTER OF ODDI. M.Staritz, T.Poralla, M.Manns, K.Ewe, K.-H.Meyer zum Büschenfelde. 1 st Medical Department, University of Mainz, D 65 Mainz, West Germany.

Opiates hamper the function of the sphincter of Oddi by inducing papillary spasm. We therefore examined modern analgesics with morphine-like molecular structure.
Methods: 23 healthy persons were included in the study. The sphincter of Oddi motility and baseline pressure was examined before and 10 minutes after administration (i.v.) of the drugs by using ERCP-manometry as recently described (Gut, 1985; 26, 194 - 197). We applied in 5 persons 30 mg Pentazocine, in 8 persons 0.3 mg Buprenorphine, in 8 persons 50 mg Tramadol, and in 5 subjects 1 ml NaCl 0.9 % (controls).
Results: After Pentazocine administration the duration of the sphincter of Oddi contractions rose from 6.2 ± 0.2 per sec. to 8.1 ± 0.28 ($p<0.005$) and the sphincter baseline pressure rose from 5.1 + 0.6 mmHg to 8.9 ± 0.7 mmHg ($p<0.005$, Wilcoxon test). The frequency of the sphincter contractions and the contraction amplitudes in the Pentazocine group and all these parameters in the other groups remained unchanged.
Conclusions: By inducing longer closing phases of the sphincter and elevation of its baseline pressure Pentazocine hampers the function of the sphincter muscle. Since this effect will cause reduced flow of bile and pancreatic juice pentazocine should not beused as analgesic drug of the first choice in patients with pancreato-biliary disease. It should be also omitted as premedication for endoscopic procedures concerning the sphincter of Oddi. For chronic administration it should be mentioned that Pentazocine probably could cause cholestasis.

(A-41)

SPECTRAL ANALYSIS OF TACHYGASTRIA RECORDED DURING MOTION SICKNESS. R. M. Stern, W. R. Stewart, I. M. Lindblad, and K. L. Koch. Departments of Psychology and Medicine, The Pennsylvania State University, University Park and Hershey, PA 16802. U.S.A.

Clinical investigators have determined that nausea is sometimes accompanied by tachygastria, 5-8 cpm. The purpose of the present experiment was to study frequency changes in gastric myoelectric activity of healthy human subjects as a function of motion sickness brought about by visual-vestibular mismatch. Fifteen healthy human subjects were fasted and seated inside a drum, the inner surface of which was painted with alternative black and white vertical stripes. Rotation of the drum produces visual signals of self-motion which are in conflict with vestibular signals (i.e., mismatched sensory input). A cutaneously recorded electrogastrogram (EGG) was obtained for three 15 min periods: before the drum was rotated (baseline), during rotation, and after drum rotation stopped. Respiration, symptoms volunteered by subjects, and a continuous measure of intensity of symptoms were recorded. Running spectral analyses, with over-lapping power spectra displayed as a function of time, were obtained from each EGG recording. With this new technique, frequency, power and time are depicted two-dimensionally with a pseudo 3-D display. Examination of the 15 displays, one for each subject, revealed the following results: (1) The dominant frequency of gastric myoelectric activity before drum rotation was 3 cpm; (2) Five subjects showed a continuation of 3 cpm activity during drum rotation and reported no symptoms of motion sickness; (3) Ten subjects during drum rotation showed a shift of their dominant gastric frequency from 3 cpm to 5-8 cpm and reported symptoms of motion skckness. The running spectral analysis and the continuous measure of intensity of symptoms revealed a close correspondence over time between tachygastria and reports of symptoms of motion sickness. In conclusion, visual-vestibular mismatch induces tachygastria in approximately two-thirds of healthy human subjects. Disturbance of normal gastric myoelectric activity may produce symptoms of motion sickness.

COLONIC SLOW WAVE ANALYSIS: LIMITATIONS OF THE FAST FOURIER TRANSFORM (FFT). A. Sunshine, A, Ouyang, R. Perry, L.Baker, J. Reynolds and S. Cohen. University of Pennsylvania and Villanova University, Philadelphia, PA 19104, U.S.A.

The FFT has been used to determine frequency components of colonic slow wave activity. We studied the effect on the frequency spectrum (FS) of a) recorder filter characteristics, b) sampling rate, c) FFT length and d)FFT averaging. Human colonic slow wave activity was recorded on a Beckman recorder and stored on FM tape for computer analysis. The Beckman low and high frequency filters were set at 0.16HZ and 0.3Hz. The Beckman frequency response characteristics were tested using square wave signals. Derived frequency compensation factors were applied to the FFT results. Results: 1) This dynograph filter setting attenuates low frequencies non-linearly, 2) sampling at 512 cpm prevents aliasing and determines the FS range, 3) increasing FFT length with a constant sampling rate increases the resolution of the FS: a 2048 length gives a resolution of 0.25 cpm. Shorter FFT lengths decrease resolution, 4) FFT of less than 4 min data requires padding with zeros which broadens the peaks of the FS. 5) FFT of 4 min or greater of data yields poor frequency peak resolution despite averaging via an overlapping FFT technique, 6) FFT of 1 min data gives optimum frequency peak resolution and shows rapidly changing frequency spectra, 7) the major frequencies in the normal human rectosigmoid lie between 2 and 8 cpm. Conclusions: 1) Failure to compensate for the dynograph filter results in inaccurate detection of slow wave frequencies, 2) Dynograph filter characteristics are non-linear and special compensation is required. 3) Sampling frequency depends on high frequency filter attenuation and frequency of interest, 4) FFT of 1 min data gives better frequency peak resolution, despite padding with zeros, due to the unstable frequency patterns of colonic slow waves. This continuously changing waveform may not be best represented by an FFT of data of short duration. Techniques to analyze the relationship of frequency peaks over time may prove valuable in determining the predominant colonic slow wave pattern.

PROSTAGLANDINS AND JEJUNAL MOTILITY AFTER IRRADIATION. R. Summers, A. Flatt, M. Prihoda and D. Loven. Veterans Administration Hospital, Iowa City, IA 52240, U.S.A.

We have examined the effect of irradiation on jejunal motor activity after irradiation and explored the role of prostaglandins (PG) in the process. Methods: Six dogs underwent abdominal irradiation with 1250 cGy and the "fed pattern" of jejunal myoelectric activity was compared with that measured before irradiation. The concentration of PG's in plasma from mesenteric veins was measured by RIA in another group of animals before, 1d and 4d after irradiation. Jejunal muscle PG synthesis was measured by incubating tissue homogenates with H^3-arachidonate; metabolites were analyzed by HPLC. Myoelectric activity was monitored in another group of 4 dogs which received i.v. indomethacin (2 mg/kg 3x/d) before and after irradiation. Results:

	#bursts/ min	venous conc† PGE_2	$PGF_{2\alpha}$	6-keto $F_{1\alpha}$	% Arachidonate Converted
Control	8.4±0.7	1	0.4	0.8	4.5
1-day	7.5±1.1*	2*	0.7*	2.4*	9.3*
4-days	2.6±1.4	22	6.8	9.9	10.6

* $p < 0.05$ † Plasma concentration - $1x10^2$ pg/ml

The myoelectric activity progressively diminished following irradiation. The concentration of PG's in mesenteric venous blood increased 10-20 fold and conversion of arachidonate to its metabolites by jejunal muscle homogenates doubled. The metabolite of prostacyclin (6-keto $F_{1\alpha}$) increased the most. Indomethacin inhibited PG synthesis, but failed to prevent the reduction of spike burst activity after irradiation. Therefore, irradiation reduces intestinal motor activity, but mechanisms other than the increase in PG synthesis are responsible.

ROLE OF KAPPA OPIOID RECEPTORS IN THE CONTROL OF INTESTINAL MYOELECTRIC ACTIVITY IN DOG. G.L. Telford. Medical College of Wisconsin, Milwaukee, WI 53226 U.S.A.

Mu opioid receptor agonists stimulate spiking activity and initiate migrating myoelectric complexes (MMC's) in the small intestine. The effects of kappa receptor agonists like ketocyclazocine (Keto) are not known. Eight dogs (15-20 kg) had twelve bipolar electrodes for recording myoelectric activity sutured to the serosal surface of their G.I. tract. Two were sutured to the distal stomach, two to the mid duodenum and the remaining were evenly spaced along the jejunoileum. Animals were fasted for 18-24 hours. Recordings were continued until the second MMC was observed and the MMC cycle time calculated. Keto (1.0 mg/kg, i.v.) was administered at a time after the initiation of the second MMC equal to 30-35% of the MMC cycle time. Keto disrupted the migration of the MMC and abolished all spiking activity in the stomach and small intestine in 17 of 17 experiments. MMC cycle time was 102.4 ± 12.6 min ($\bar{x}$ ± SD) prior to and 247.4 ± 59.7 min after Keto administration (n=8) ($p < 0.001$). Keto (1 mg/kg, i.v.) inhibited the fed pattern of activity for 85.5 ± 25.5 min when given 15 min after feeding. Naloxone (N) (2 mg/kg, i.v.) administered 5 min prior to Keto blocked the effects of Keto on MMC migration in 8 of 8 experiments. MMC cycle time was 98.8 ± 13.5 min prior to N plus Keto administration and 146.3 ± 48.7 min after (n=4) ($p > 0.05$). To investigate the possibility that Keto was blocking cholinergic receptors rather than acting as a kappa receptor agonist, bethanecol (5 mg. subq.) was administered at 50% of the MMC cycle with and without pretreatment with Keto. Bethanecol initiated intense spike activity in the small intestine when administered in mid MMC cycle and this was not blocked by Keto. Based on these data, we concluded that Keto blocks the initiation and disrupts the migration of MMCs by stimulating an opioid receptor, most likely the kappa receptor, and that kappa agonists are potent inhibitors of the fed pattern of motility. Therefore kappa opioid receptors may play a role in the inhibition of G.I. motility.

OPIOID AND ADRENERGIC EFFECTS ON GASTROINTESTINAL MOTILITY: INTERACTIONS WITHIN AND BETWEEN SPINAL CORD AND GUT. G.M. Thomforde, M. Camilleri, T.L. Yaksh and J.-R. Malagelada. Gastroenterology Unit, Mayo Clinic and Foundation, Rochester, MN 55905 U.S.A.

Our aims were to determine: first, whether spinal and peripheral opioid and adrenergic systems influence gut motility; and second, whether interactions between these systems occur within and between the spinal cord and gut. We studied the effects of such agents in a chronic dog model with surgically implanted intrathecal (i.t.) infusion catheter (tip at T_5 level) and 6 manometric catheters (2 antral, 4 small intestinal). In each experiment, dogs (n=8) were fed a solid meal and 30 min later, agents were infused either i.t. (over 5 min) or i.v. (over 1 hr). Gut manometry was recorded for 3 postcibal hours. Three sets of experiments were performed. I) Dixon's up-and-down method (with ½ log changes in dose) was used to determine i.t. and i.v. minimal effective doses (MED) for alteration of gut motility by morphine (M), naloxone (N), ST91 (an α_2-adrenergic agonist that does not cross the blood-brain barrier) and phentolamine plus propranolol (P+Pr). II) We determined the minimal effective morphine-antagonist dose (MEMAD) of agents when administered by the same route (i.v. or i.t.) with M (at MED). III) Inhibition of effects of i.v. M (at MED) during i.t. infusion of agents was tested. Results: I) MED for M intestinal activity fronts was 150 µg/kg and 450 µg/kg by i.t. and i.v. routes respectively; mean latency for appearance of the front was 50 min by i.t. and 26 min by i.v. route. ST91 inhibited antral and intestinal pressure activity with similar MED (100 µg/kg) for both routes. N and P+Pr did not alter gut motility. II) N and ST91 both inhibited effects of M when administered in the same compartment as M. MEMAD for N and ST91 were the same (36 and 100 µg/kg respectively) by i.t. and i.v. routes. III) These same doses of i.t. N and ST91 blocked i.v. M activity fronts. Conclusions: 1) Spinal opioid and α_2-adrenergic receptors can modulate fed gastrointestinal motility; 2) interactions between these systems occur at spinal and target organ levels, and between spinal cord and gut. (Support AM34988)

INTERACTIONS BETWEEN INTESTINAL SMOOTH MUSCLE AND INTERSTITIAL CELLS OF CAJAL (ICC) IN TISSUE CULTURE. A FILM DEMONSTRATION. L.Thuneberg and G.Burnstock. Anatomy Dept.C, Panum Instituttet, DK-2200 Copenhagen N, Denmark, and Univ. College London, Dept. of Anatomy and Embryology, Gower Street, London WC1E 6BT, England.

A specific role as intestinal pacemaker cells was suggested from morphological studies (Thuneberg, Adv.Anat.Embryol. Cell Biol. 71 (1982)1-130) for one type of ICC (ICC-I), that forms a dense cellular plexus in the interval between longitudinal and circular muscle layers of small intestine. By ultrastructure ICC-I were more similar to smooth muscle cells than to other cell types, although ICC-I appeared to lack the full complement of contractile filaments. The pacemaker hypothesis was supported by the observations that slow waves were abolished by a selective uptake of methylene blue by the ICC-I plexus, followed by illumination of the stained area (Thuneberg et al., Proc.9th Int.Symp.Gastrointestinal Motility. C.Roman, ed., MTP Press Ltd., 1984).

To facilitate studies of interactions between ICC-I and smooth muscle, we have sought to optimize conditions for culturing explants of muscularis of mouse small intestine. Our results, recorded on film, are: 1) Spontaneous, rhythmic contractility of intestinal muscle is preserved in cultured, growing explants, with a frequency similar to the one in vivo. 2) Two main types of contractile cells are present in the spontaneously contracting outgrowths. One is ribbon-shaped, very similar by all light microscopical criteria to the ordinary smooth muscle cell; the other is by light microscopy (incl. a selective staining with methylene blue) apparently identical with the ICC. Both cell types have been identified in explants by electron microscopy. 3) Outgrowths which appear to contain smooth muscle cells alone, have not been seen to contract spontaneously. 4) Frequently, spontaneous contractions of smooth muscle cells were limited to cell parts in contact with thin processes of putative ICC. 5) Upon selective staining with methylene blue of putative ICC-I the spontaneous contractions of the entire explant become extremely sensitive to illumination with red light. Our results support a role of ICC in the generation of patterns of spontaneous contractions in the gut.

EFFECTS OF INTRA-VEINOUS ATROPIN (AT) ON COLONIC RAPID MYOELECTRIC ACTIVITY IN IRRITABLE BOWEL SYNDROME (IBS). R.Tournut , M.Dapoigny , J.F.Trolese , L.Montcharmont G.Bommelaer , Dept of Gastroenterology ,CHU de Clermont-Ferrand, 63003 Clermont-Ferrand Cedex France.

Anti-cholinergic drugs are often prescribed to patients with IBS. This study has been started in order to clarify the effects of such drugs on colonic activity. AT, used as typical anti-cholinergic drug, has been given to IBS patients in whom colonic myoelectrical activity was recorded.

PATIENTS AND METHODS:15 patients, 10 males and 5 females,mean age 46 y, all presenting with IBS were studied.All had abdominal pain, without constipation. Colonic myoelectric activity was recorded 24 hours after introduction of a silastic probe with 15 groups of 3 electrodes,for 1 hour before a 800 Cal meal, then for the next three hours, then the patients were fed another similar test meal. One mg of AT was injected I.V. randomly either 1 hour before the second test-meal (group A) or during the second meal (group B) or 1 hour after the second meal (group C). Rapid myoelectric activity was studied as Long Spike Bursts and Short Spike Bursts and analysed with a micro-computer. Activities were measured by 10 min-intervals. To monitor the effects of AT,cardiac rythm was also recorded throughout the experiment.

RESULTS:During the first period without AT: before meal, all patients had a mean hourly LSB activity of 30,1±2,9; LSB activity significantly increased during the first hour after meal to 41,7±4,7($p<0,001$).The myoelectric response was made of 2 peaks (10-40min and 60-80 min).SSB activity was not modified by feeding. During the second period with AT: In group A: AT inhibited myoelectric activity in the pre-prandial period ($p<0,02$) as during the post-prandial period ($p<0,01$). SSB activity was not modified. In group B:AT inhibited LSB activity during the 2 post-prandial hours ($p<0,02$) and SSB activity was not modified. In group C: AT inhibites significantly the late post-prandial LSB activity. ($p<0,03$). In 3 groups AT increase cardiac rythm for more than 60 min ($p<0,01$).

CONCLUSION:AT inhibits LSB activity in basal and post-prandial periods in IBS patients and that could be correlated the effects of AT on patient's pain. The long effect of AT on colonic activity and cardiac rythm suggests a specific response to AT in IBS patients.

EFFECT OF A NON-ANTIDOPAMINERGIC NON-CHOLINERGIC COMPOUND (CISAPRIDE) ON GASTRIC EMPTYING IN DYSPEPTIC PATIENTS. J.L. URBAIN, S. PAUWELS. University of Louvain Medical School, Brussels, Belgium.

The dual radionuclide technique was employed to evaluate the effect of a new gastrokinetic agent Cisapride (cis-4-amino-5chloro-N-(1-(3-(4-fluorophenoxy)propyl)3 methoxy-4-piperidinyl)-2methoxybenzamide) on gastric emptying in 17 dyspeptic patients : 8 idiopathic dyspepsia (IDP) and 9 postantrectomy dyspepsia (ADP). Following a basal study, and on a separate day, each patient received a IV bolus of 10 mg of Cisapride, 10 min after ingestion of the test meal. Ten out of the 17 patients (3IDP, 7ADP) were restudied after a two week oral administration of the drug (40mg/day). Gastric emptying for solids (GES) and liquids (GEL) was determined using Tc-99^m-SC-scrambled eggs and In-111-labeled water. Images were obtained at 20 min intervals over a 2 hours period and data were corrected for radioactive decay, downscatter and changes in depth. The t1/2 of the emptying for the solid (S) and liquid (L) meal are summarized below (min, mean± SEM) :

GROUP	N	BASAL		IV adm.		ORAL adm.	
		S	L	S	L	S	L
IDP+ADP	17	174±33	96±15	91±17	61±7	-	-
IDP	8	164±55	88±26	102±35	61±14	-	-
ADP	9	182±41	103±15	82±11	61±6	-	-
IDP+ADP	10	183±37	98±13	82±11	64±8	110±16	64±6

Bolus injection of Cisapride improved significantly GES in IDP ($p<0.05$) and ADP ($p<0.01$) whereas GEL improvement reached statistical significance only in ADP ($p<0.005$). After oral administration of Cisapride both GES ($p<0.02$) and GEL ($p<0.05$) were significantly shortened. We concluded that single IV and chronic oral administration of Cisapride significantly improve gastric emptying in dyspeptic patients. The dual radionuclide technique appears to be a useful physiologic test for evaluating and predicting the efficacy of a gastric motility therapy in man.

A NEW SENSOR FOR THE MEASUREMENT OF INTERDIGESTIVE AND DIGESTIVE GASTRIC MOTILITY IN MAN. E.J. van der Schee and H. Geldof. Faculty of Medicine, Erasmus University, P.O.Box 1738, 3000 DR Rotterdam, The Netherlands.

Interdigestive gastric motility in man is commonly quantified by pressure sensitive devices. These methods provide for reliable results since pressure waves are recorded at the moment the antral wall occludes a recording site. After food intake only in the very terminal antrum occlusion may be expected, depending on the strength of the contractile force. We developed a sensor system capable of the detection of displacement of the stomach wall. The device is a modification of a formerly developed sensor for the measurement of inner diameters of arteries (1). A spring-steel wire, folded into an ellips forms the sensor part. The coupling factor between two coils of a miniature transformer varies with the diameter of the ellips since a rod moves in a catheter around which the coils are twisted. The catheter is perfused (rate 0.6 ml/min.) enabling pressure recording. The sensor is easy to swallow and does not mechanically irritate the mucosa wall more than commonly used manometric devices: the force needed for 1 mm displacement amounts about 0.02 N. The probe was used in 5 healthy volunteers before and after a test meal consisting of 250 ml of yoghurt and 20 mg of sugar. The sensor was positioned in the terminal antrum by fluoroscopic control. Results: During the interdigestive state in all subjects the pressure recordings coincided with the displacement signal. Within one minute after food intake contractions were detected by the sensor whereas no pressure waves were observed. In three subjects no pressure waves were recorded during the whole postprandial recording period of 1 hour. In two subjects about 50% of the contractions as measured with the displacement sensor and occurring 3 times per minute, were missed by the pressure recording. Conclusion: The performance of the sensor is superior with respect to manometrical methods in the study of postprandial gastric contractile behaviour in man.

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ELECTRICAL STIMULATION OF THE HUMAN STOMACH. W.E. Waterfall, D. Miller, D.N. Ghista. Depts. of Surgery and Bioengineering, McMaster University Medical Centre, 1200 Main St., W., HAMILTON, Ontario CANADA L8N 3Z5

Electrical signals were obtained from four patients with normal stomachs following recovery from elective laparotomy using a temporary implanted electrode technique. Six pairs of electrodes were implanted on the anterior wall of the stomach in a linear fashion from the most proximal part of the corpus to within 2 cm of the pylorus.

On the fifth and sixth post-operative days, and after re-establishment of normal gastrointestinal function recordings were made in fasted subjects. Control waves were recorded at 3.1 to 3.4 cycles per minute (cpm). Though frequency varied between subjects, individual frequencies varied less than 0.2 cpm. Phase lead was observed proximally in all cases.

Electrical stimulation was delivered to either the most proximal or most distal electrode pair, after a control period. During proximal stimulation (and for a variable period after its discontinuation), the frequency of the control wave was raised from the intrinsic 3.1 through to 4.7 cpm. Entrainment was achieved at all electrode sites, with phase lead proximally during proximal stimulation. Stimulation with a lower frequency than intrinsic did not result in entrainment. Distal stimulation resulted in identical entrainment at a frequency of 4.7 cpm driven from the intrinsic of 3.1 cpm. Phase lead was now observed to be distal. Both forward and reverse pacing resulted in entrainment for periods of up to one hour.

The stomach exhibited memory for the stimulation parameters, for it continued to exhibit the entrained frequency until it abruptly resumed the usual resting frequency. Just before entrainment was achieved, a variety of rhythms were observed, including a one-to-one response to the stimulus, bradygastria - less than intrinsic resting frequency, and tachygastria - higher than maximum driven frequency.

A COMPARATIVE STUDY OF THE CHOLINERGIC VS ANTI-DOPAMINERGIC PROPERTIES OF BENZAMIDES WITH GASTROINTESTINAL PROKINETIC ACTIVITY. J.M. Van Nueten, J.E. Leysen, C.J.E. Niemegeers and J.A.J. Schuurkes. Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium.

Metoclopramide and clebopride possess both dopamine-antagonistic as well as indirect cholinomimetic properties. Recently two novel substituted benzamides, cinitapride and cisapride, have been introduced. The aim of our study was to compare the dopamine-antagonistic properties of the four benzamides with their indirect cholinergic effects. Dopamine-antagonism. Binding affinity for dopamine-receptors was tested on rat striatum (ligand H^3-haloperidol). Both metoclopramide and clebopride showed high binding affinities (K_1-values 6.6×10^{-8} M and 1.1×10^{-8} M respectively). Cinitapride appeared even more effective (6.2×10^{-9} M) whereas cisapride (2.5×10^{-7} M) showed much less affinity for the dopamine-receptor. Apomorphine induces vomiting in conscious dogs via dopamine-receptors. The benzamides antagonized this effect; their ED_{50} values were 0.011, 0.056, 0.28 and 3.3 mg/kg for clebopride, cinitapride, metoclopramide and cisapride respectively. Indirect cholinergic effect. The four compounds enhanced the contractile response of the guinea pig ileum to electrical stimulation. Cisapride appeared most potent: EC_{50} = 9.4×10^{-9} M. The values for clebopride, cinitapride and metoclopramide were 7.3×10^{-8} M, 1.7×10^{-7} M and 1.6×10^{-6} M respectively. A similar order of potency was obtained for their effect on antroduodenal coordination of the guinea pig (in vitro). The ratio K_1 (DA-binding)/EC_{50} ileum was 27 for cisapride, but only 0.15, 0.041 and 0.037 for clebopride, metoclopramide and cinitapride respectively.

In conclusion. Cinitapride shares with metoclopramide and clebopride mixed dopamine-antagonistic and indirect cholinomimetic properties whereas the indirect cholinomimetic, cisapride appears to stimulate gastrointestinal tissues of the guinea pig without appreciable anti-dopaminergic properties.

MYOGENIC CONTROL: A QUANTITATIVE EVALUATION OF ITS ROLE AS A REGULATOR OF INTESTINAL FLUID PROPULSION. W.A. Weems. University of Texas Medical School, Houston, TX 77225 U.S.A.

Intestinal muscle contractions are regulted by both myogenic and neurogenic control systems. It is unclear; however, how these systems interact to produce fluid movement within the intestinal lumen. Experiments were conducted to determine what patterns of propulsive behavior occur when only the myogenic system is expressed and to evaluate the extent to which neural modulation of this fundamental myogenic oscillator contributes to the generation of known patterns of intrinsic propulsive behavior. In vitro segments of cat jejunum and terminal ileum, 17 cm in length, were connected to a propulsion evaluation system that required the attached segment to do known amounts of hydrostatic work to eject fluid from either end. The capacitance of this system was 0.025 ml/cm H_2O and the maximum resistance to flow was 0.049 cm $H_2O \cdot min \cdot ml^{-1}$. Arterial infusion of 1×10^{-7}M tetrodotoxin (TTX) into jejunal segments induced simultaneous sinusoidal ejections of equal fluid volumes from both ends. Similar activity was observed in only 16% of ileal segements infused with TTX. Arterial infusion of both TTX and 1×10^{-3} M atropine sulfate, a procedure known to increase the amount of spike activity per slow wave, increased the amplitude of jejunal ejections by an average of 210% and induced a similar pattern of sinusoidal activity in ileal segments. Sinusoidal ejections enhanced by atropine occurred at frequencies of either ~8 or ~16 cycles min^{-1}, produced maximum flow rates that varied from 9 to 114 ml min^{-1} and had an average peak pressure of 38.5±21.0SD cm H_2O. A quantitative comparison of the myogenic propulsive pattern with patterns having an obligatory neurogenic component indicated that the enteric nervous system produces distinct spatiotemporal forms of propulsive behavior that cannot be generated by simple enhancement or inhibition of myogenic control activity. (Supported by NIH Grant AM23028.)

COMPARISON OF RECTAL AND SIGMOID MOTOR AND MYOELECTRIC ACTIVITY. W.E.Whitehead, P. Enck, H.S. Shabsin, and M. M. Schuster. Johns Hopkins University School of Medicine and Francis Scott Key Medical Center, Baltimore, Md. USA

Previous reports have differed in their characterization of the motility and myoelectric activity of the distal colon. This study sought to determine whether such differences were due to the location from which recordings were made. Five asymptomatic subjects were studied for 5 to 6 hours each. A flexible tube was inserted so that one pair of silver pins was held to the mucosa by suction at 30 cm. from the anal margin and a second pair was positioned at 15 cm. Motility was measured by perfused catheter at the same locations. Recordings were made for 4 out of every 5 min. Polygraph records were inspected, and all samples containing 10-sec or more of movement artifact were discarded. For each 4-min sample of digitized data (4.2 Hz sample rate), a computer program calculated the motility index by summing the deviations of each data point from the mean for the 4-min sample. This sum approximates the area under the curve. These data were log-transformed to normalize the distributions of values. For each subject the correlation between the sigmoid and rectum was calculated for both pressure activity and slow waves. The median correlation between sigmoid and rectal pressure for 5 subjects was .28 (range .18 to .60), suggesting a substantial amount of independence. The median correlation between sigmoid and rectal slow waves was -.02 (range -.43 to +.49), suggesting no relationship between sites. Each 4-min sample was also analyzed by FFT to identify dominant frequencies, and for each subject the distribution of dominant frequencies in the sigmoid was compared to that seen in the rectum. The modes and means of these distributions lay at 2-3 cpm for all subjects for both rectum and sigmoid and for both pressure and slow wave data. Less than 15% of samples contained dominant frequencies greater than 4 cpm. Conclusion: The types and amounts of motor and slow wave myoelectric activity are similar in the sigmoid and rectum, but this activity waxes and wanes independently at the two sites. (Supported by grants AM31369 and MH00133.)

NEURAL MECHANISM MEDIATES ACTION OF HORMONES ON COLONIC MOTILITY: EFFECT OF CHOLECYSTOKININ AND NEUROPEPTIDE Y J. Wiley and C. Owyang, Dept. of Internal Medicine, The University of Michigan, Ann Arbor, MI.

Gastrointestinal hormones are abundantly distributed in the colon. Among them, cholecystokinin stimulates while neuropeptide Y inhibits colonic motility. However, their mechanism of action is unknown. In this study we evaluate the effect of octapeptide of cholecystokinin (CCK-8) and neuropeptide Y (NPY) on longitudinal (LM) and circular (CM) muscle from the colon of the guinea pig. Isolated muscle strips of LM and CM were suspended in organ baths and responses to agonists, electrical stimulation and neural antagonists were charted on a pen recorder via an isotonic transducer. Results: In colonic CM, CCK-8 demonstrated no effect. In contrast CCK-8 (10^{-10}M-10^{-7}M) generated dose dependent contractions in colon LM which were abolished by tetrodotoxin (TX). Since cholinergic, serotonin (5-HT) and substance P (SP) containing neurons are present in abundance in the myenteric plexus, we evaluated their role in the action of CCK. The contractile effect of CCK-8 was only partially blocked by atropine (AP). Studies using SP antagonist and desensitization to 5-HT demonstrated the primary pathway of CCK's action involves 5-HT acting via SP to stimulate LM. In colonic CM, NPY demonstrated no effect. In contrast NPY (10^{-8}M-10^{-6}M) caused dose dependent relaxation of colonic LM. This inhibitory effect was unaffected by hexamethonium but abolished by AP and TX. NPY did not affect acetylcholine-induced contraction of colonic LM. NPY also inhibited electrical twitch response of colon LM which was reversed by yohimbine (α_2 antagonist), but unaffected by other adrenergic/dopaminergic antagonists. Additional studies on colonic muscle strips loaded with ^{3}H-choline confirmed that NPY inhibited potassium induced release of ^{3}H-ACh which was reversed by yohimbine. Thus NPY relaxes colonic LM by inhibiting cholinergic transmission. This appears to be mediated through the α_2-adrenoreceptors on the postganglionic cholinergic neurons. In conclusion despite their opposite effect on colonic LM, CCK-8 and NPY both act via a neural mechanism involving cholinergic and/or 5-HT/substance P pathways. These findings suggest that the myenteric plexus may serve as an integrative center for signal processing to mediate the effect of neuropeptides on colonic motility.

IS GUT MOTILITY AFFECTED BY EXORPHINS? M. Wienbeck, P. Bielfeld, M. Karaus, J. F. Erckenbrecht. Gastroenterology Research Laboratories, Dept. of Internal Medicine, University of Düsseldorf, F. R. Germany

Exorphins are opiate-active peptides occurring in food before and after digestion. They have been implicated with the release of gastrointestinal hormones and a delay of gastrointestinal transit. We, therefore, set out to study the effects of exorphins on gut motility. 5 healthy cats weighing 2.1-3.5 kg were implanted bipolar needle electrodes along the small and large intestine. A permanent duodenal catheter served to instill the test agents in the unanesthetized animals starting 2 weeks after surgery. We tested casopeptone (2 ml/kg) containing a mixture of different exorphins, β-casomorphin-5 (0.5 mg/kg) and 0.9 % NaCl as a control. Results: The gut of all cats exhibited regular slow waves (SW) and intermittently occurring spike potentials (SP). Three hours after the application of the tested agents the mean values of the SW frequency/min were:

	duod.	ileum	proximal	dist. colon
control	17.4	13.2	5.2	5.2
casopeptone	18.0	13.2	5.3	5.4
casomorphin	17.7	12.4	5.3	5.3
and SP (% of time):				
control	1.8	3.5	2.2	2.4
casopeptone	2.0	5.2	2.2	1.6
casomorphin	2.4	4.8	2.8	3.2

The data following exorphin application were not different from control at 3 h and before. Also, bowel movements did not change.
Conclusions: Exorphins which naturally occur in cat food do not affect gut motility. It is questionable, therefore, that they play a physiological role in the control of the motor activity of the small and large intestine.

COMPARISON AND EVALUATION OF TWO DIFFERENT AMBULATORY 24 HOUR pH MONITORING SYSTEMS. WC Wu, BW Ward, KW Lui, DO Castell. Bowman Gray School of Medicine, Winston-Salem, NC.

Two different ambulatory pH monitoring systems, the Bio-search Ambi-24 system (B) and the Oxford Medilog 1000 System (M) were tested on 27 healthy asymptomatic subjects (x̄ age 31.4, range 24-55). Thirteen subjects had both tests performed on separate days. B uses a nasally-inserted antimony pH probe connected to a recording unit. M is a pH-sensitive telemetry capsule passed orally. Normal values for 11 parameters for reflux were characterized. Subjects evaluated both systems using a score of 0-3 for each of 9 parameters, and participating physicians assessed relative pros and cons of the system. Results: normal values for both systems are similar to published data with non-ambulatory systems. Subject assessment: B subjects complain more ($p<.05$) about nose discomfort, feeling of foreign body in the esophagus and physical appearance, whereas M subjects complain about mouth discomfort and difficulties in swallowing solids ($p<.05$). There were no differences when discomfort in swallowing the probe, throat discomfort and difficulties with swallowing liquids were compared.

Physician assessment:	B	M
1) Simplicity of operation and maintenance:	yes	yes
2) Ability to calibrate at room temperature:	yes	no
3) Ability to monitor pH during recording:	no	yes
4) Internal clock for symptom correlation:	no	yes
5) Ability for post-study calibration check:	no	yes
6) Ability to store study on computer disk:	yes	no
7) Hour-by-hour summary of episodes and duration:	no	yes
8) Life of probe (number of recordings/probe):	4-10	20+
9) Need for external reference electrode:	yes	no
10)Need to review tracing to assure accuracy:	yes	yes

Conclusions: 1) Both systems provide adequate 24 hour pH recordings. Results obtained with both are comparable and similar to previously published data with non-ambulatory systems. 2) Significant differences in patient acceptance are equally divided between the 2 systems. 3) Each system has its own unique advantages and disadvantages.

EVIDENCE FOR CYCLIC AMP AS THE PHYSIOLOGIC MEDIATOR FOR ACETYLCHOLINE RELEASE FROM MYENTERIC PLEXUS. W.M. Yau, J.A. Dorsett & M.L. Youther. School of Medicine, Southern Illinois University, Carbondale, IL 62901 U.S.A.

Forskolin is an activator of the adenylate cyclase system presumably by a direct action on the catalytic subunit causing an increase in intracellular cyclic AMP (cAMP). It can elicit a variety of cellular responses which have been linked to cAMP. This report describes a stimulation of ^{3}H-acetylcholine (ACh) release from guinea pig myenteric plexus-longitudinal muscle strips by forskolin in vitro. Innervated muscle strips from the small intestine were prepared and loaded with Krebs containing ^{3}H-choline while under supramaximal stimulation (20 v, 0.1 Hz). After the choline uptake, efflux of ^{3}H-ACh was measured in the presence of hemicholinium-3. Our results are: 1) Forskolin evoked the release of ACh in a dose-dependent manner. The threshold dose for a significant increase in ACh release was 6 X 10^{-7} M. 2) Forskolin-induced ACh release was inhibited by 1 X 10^{-6} M tetrodotoxin. A 130% increase in ACh output over basal was noted with 5 X 10^{-6} M forskolin while the release was not significantly changed from basal if tetrodotoxin was also present. 3) Release of ACh was stimulated by theophylline in the dose range from 1 X 10^{-6} to 1 X 10^{-4} M; however, the increase in ACh release was never greater than 80% over basal. 4) When forskolin was combined with theophylline, there was a further increase in ACh release (250% over basal level). Our data have shown that forskolin evoked the release of ACh from myenteric neurons. This stimulation was susceptible to blockade by tetrodotoxin. When theophylline was tested, it was also found to elicit ACh release. A combination of forskolin and theophylline have further enhanced the release of ACh, supporting the view that cAMP mediated mechanisms may be involved in the release of ACh from myenteric neurons. There is recent electrophysiological evidence to suggest that forskolin mimics slow synaptic excitation in myenteric neurons. These data provide supportive evidence for cAMP as the physiologic mediator/activator for ACh release from myenteric neurons. (Supported by NIH AM-26860)

IN-VIVO GASTRODUODENAL NERVE ACTIVITIES IN CHRONIC DOGS, J.J.L. Yu, S.N. Reddy, E.E. Daniel, I. Berezin, N.K. Sinha, and L. Belbeck, Depts. of Electrical Eng. and Neurosciences, McMaster University, Hamilton, ON Canada.

While approaches to the investigation of myogenic and hormonal controls in the mediation of gut motility are well understood, the methods to analyze neural control, even in animal models, remain to be developed. We have developed a cannula system with nerve cuff electrodes, subserosal bipolar electrodes, and extraluminal strain gauges to simultaneously monitor the vagal nerve, myoelectric (ECA), and contractile activities in chronic dog. The cuff electrodes were used to both stimulate and record nerve signals. Five healthy dogs were implanted with such cannulae on the gastroduodenal area, with the cuff electrodes placed on the anterior nerve of Laterjet and its branches. The condition of the cuff electrodes was monitored by impedance measurements, while that of nerves under the cuff electrodes was studied by electron microscopy after the animals were sacrificed. Computer algorithms were developed to study sensory and motor nerve activity patterns.

Preliminary results indicated 1) constant impedance of cuff electrodes after 14 days; 2) synchronized nerve activities that corresponded with antral and duodenal ECA rates; 3) nerve activities that appeared to alternate between adjacent nerves; 4) changes in contractile and nerve patterns upon nerve stimulation as compared to those before stimulation; 5) sensory and motor patterns in the compound nerve signals; and, 6) progressive damage to very small nerve branches with selective loss of large axons, but with no inflammatory cells, in the large nerve bundles after 2 to 4 months.

We conclude that the cannula system developed in our laboratory makes it possible to explore crucial topics on normal and abnormal motility patterns in animal models as mediated by the extrinsic nervous system. Further development is needed to minimize nerve damage.

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