● EFFECT OF SHORT-CHAIN FATTY ACIDS ON THE PHASIC AND TONIC MOTOR ACTIVITY OF THE HUMAN COLON. P.Jouët, B. Coffin, B. Flourié, M. Lémann, C. Cherbut, C. Franchisseur, R. Jian, J.C. Rambaud. INSERM U 290, Hôpital Saint Lazare,75010 Paris and INRA Nantes, 44026, France.

Short-chain fatty acids (SCFAs) are the main metabolites of the colonic fermentation. Their effects on motility have been studied in vitro and in vivo in animals and the results found are contradictory. In humans the effects of SCFAs on colonic motor activity are unknown but could be involved in the action of dietary fiber on intestinal transit and in the mechanism of diarrheas with excessive bacterial fermentation.

The aim of our study was to assess in healthy subjects the phasic and tonic motor activity of the unprepared colon during intracolonic infusions of SCFAs at physiological concentrations and at 2 different pH.

Methods: 7 healthy subjects swallowed a multilumen tube (3.5m long) consisting of a bag (10 cm long, 700ml maximal volume) connected to an electronic barostat and of 6 perfused catheters located orad and caudad to the bag. The tube migrated to the proximal or distal colon (delay 24-48 h). Recordings of colonic motor activity were performed during a 60-min basal period in the fasting state, for 60 min during the continuous infusion of different solutions (flow rate 2ml/min), and 60 min after. The infused solutions were saline (n=4) and a SCFA mixture (acetic acid 66%, propionic acid 24% and butyric acid 10%; concentration 100mM) at pH 7 (n=4) or 4.5 (n=4). Phasic activity was expressed as a motility index (MI) and tonic activity as the mean volume of the barostat bag, with exclusion of rapid changes in volume caused by phasic events. Results are expressed as a percentage of the basal period value.

Results: (mean ± SEM, ANOVA)

Solutions	Motility index (% of the basal MI)		Barostat volume (% of the basal volume)	
	0-60 min	60-120 min	0-60 min	60-120 min
Saline	90±3	116±15	96±5	104±5
SCFAs pH 7	108±5	116±7	99±3	97±8
SCFAs pH 4.5	108±13	98±5	99±4	91±4

Compared to the basal period, the motility indexes and barostat volumes were not significantly changed by the infusions of either saline or SCFAs at the 2 pH tested.

Conclusions: In healthy subjects, the infusion into the unprepared colon of small amounts of a SCFA mixture at physiological concentrations and at 2 different pH does not alter the fasting basal phasic and tonic motor activity of the colon.

PINAVERIUM BROMIDE INHIBITION OF SUBSTANCE P-INDUCED DESCENDING ACTIVATION IN THE GUINEA-PIG DISTAL COLON. Y. Julé, M.O. Christen. Dept de Physiologie, Faculté des Sciences de Saint-Jérôme, Marseille. Laboratoires Solvay Pharma/LTM, Suresnes, France.

We previously reported that in the isolated distal colon of guinea-pigs, transmural stimulation induces an atropine-resistant descending activation which is suppressed by desensitizing the distal colon to substance P (SP). The purpose of this study was to analyse the effects of pinaverium bromide, a calcium antagonist which is known to reduce intestinal motility, and other calcium antagonists, on the SP-dependent descending activation of the guinea-pig distal colon. In addition to our pharmacological study, immunohistochemical investigations based on lazer confocal microscopy were carried out on the intramural nervous plexus-muscular layer complex of the guinea-pig colon with a view to characterizing and quantifying SP-containing neurons and nerve varicosities. Electrophysiological study was performed *in vitro* on isolated segments of the distal colon (6 animals) using the extracellular electromyographic recording technique. Administration of SP (0.01-0.1 µM ; 10-20 sec) in the presence of atropine (1 µM) elicited burst of action potentials, lasting 10 to 15 min, which propagated in the oral to aboral direction. This excitatory effect of SP was prevented in the presence of pinaverium (1 µM). When the pinaverium administration was stopped, the SP-induced descending activation was gradually restored within 30 min. A similar inhibitory effect was observed upon administrating the calcium antagonists verapamil, diltiazem and nifedipine at a concentration of 1 µM. Using double immunohistochemical labelling (neuron specific enolase/SP ; synaptophysin/SP), it was observed, after colchicine treatment, that many neurons containing SP were located in the myenteric plexus and some in the external submucous plexus. Numerous SP-containing nerve varicosities were present in the intramural plexus, particularly in the deep muscular plexus located in the inner part of the circular muscle layer. The present study indicates that pinaverium bromide, a gastrointestinal selective calcium antagonist, reduces colonic motility by involving the SP nervous component inplicated in the descending activation.

● INVOLVEMENT OF 5HT3 RECEPTORS IN VISCERAL PAIN INDUCED BY INTRACOLONIC INFUSION OF GLYCEROL IN RATS. V. Julia, A. Botella, C. Eeckhout * and L. Buéno, Department of Pharmacology. INRA. Toulouse FRANCE, * Kali-chemie Pharma Gmbh Hanover Germany.

Serotonin and 5-HT3 receptors are involved in the activation of nociceptive afferent pathways induced by rectal distension. In rats, intracolonic infusion of glycerol is able to trigger nociceptive inputs as evidenced by the occurrence of abdominal constrictions. This work was designed to evaluate the influence of 5-HT3 antagonists on this reflex and to localize the site of action by comparing their relative efficacies according to the route of administration.

Male Wistar rats weighing 250 to 350g were surgically prepared for electromyography. Three electrodes were implanted in the striated muscles of the abdominal wall and a catheter was placed in the colonic lumen. Electromyographic recordings began 5 days after surgery and electrical activity of abdominal muscles was recorded from 20 min before to 40 min after colonic infusion of glycerol (60% glycerol + 40% saline, rate 0.75ml/h). Cilansetron was administered intraperitoneally, 15 min before glycerol infusion, at doses of 5, 20, 100 and 500 µg/kg. Granisetron, ondansetron and cilansetron were administred at the dose of 20 µg/kg by intraperitoneal (IP), intravenous (IV) or intracolonic (IC) routes. The number of abdominal spike burst was used as an index of visceral pain.

Intracolonic infusion of glycerol increased significantly ($p<0.05$) the number of abdominal spike bursts during the time of infusion compared with saline alone (30.6 ± 6.6 vs 4.5 ± 3.4 spike bursts / 20 min).When administered IP, cilansetron reduces significantly and dose-dependently the increase of the frequency of abdominal spike bursts from the dose of 20 µg/kg. IP administration of granisetron, ondansetron and cilansetron reduced significantly the increase of the number of abdominal spike bursts that reached to 21.0 ± 5.1, 18.3 ± 6.9 and 19.0 ± 6.0 respectively. IV and IC administration, for cilansetron, ondansetron and granisetron, showed similar effect, with a greater efficacy compared with IP route, cilansetron being the most active by IC route. Indeed, the number of abdominal spike bursts was 23.4 ± 2.8 (IV) and 18.8 ± 5.8 (IC), 13.1 ± 5.5 (IV) and 17.3 ± 5.5 (IC), 15.0 ± 6.0 (IV) and 10.0 ± 5.0 (IC) after granisetron, ondansetron and cilansetron respectively.

Serotonin via 5-HT3 receptors is involved in the mediation of visceral pain induced by intracolonic infusion of glycerol. 5-HT3 antagonists are particularly active by IC route suggesting a local site of action.

● INVOLVEMENT OF NK1 AND NK2 RECEPTORS IN VISCEROSENSITIVE RESPONSES TO ACUTE INFLAMMATION IN RATS: EVIDENCE FOR A CGRP INDUCED-RELEASE OF TACHYKININS. V. Julia and L. Buéno. Department of Pharmacology. INRA. Toulouse. FRANCE

NK1 and NK2 receptors are involved in viscerosensitive responses induced by rectal distension. CGRP and tachykinins are co-localized in sensitive afferent fibers. The aim of this study was to determine the role of NK1, NK2 and CGRP receptors in nociceptive response to acute inflammation and to determine the relationship between these neuropeptides in the mediation of slowing gastric emptying (GE) and abdominal cramps related to intraperitoneal (IP) administration of acetic acid (AA).

Male Wistar rats (250 to 350g) were surgically prepared for electromyography. A group of three electrodes were implanted in the striated muscle of the abdomen. Electromyographic recording began 5 days after surgery and electrical activity of abdominal muscles was recorded starting from 20 min before the test meal ingestion until decapitation of rats (30 min after the test meal). Gastric emptying was evaluated by measuring percentage evacuation of ^{51}Cr. AA or NaCl 9‰ was injected at the dose of 10ml/kg IP, 5 min before the test meal. In a first series of experiment, NK2 antagonist SR-48,968 (1 and 5mg/kg IP), NK1 antagonist RP-67,580 (0.1 and 0.2mg/kg IP), hCGRP(8-37) (10 and 50µg/kg IV) was injected 10 min before AA or saline. In a second series of experiment, RP-67,580 or SR-48,968 or their vehicle was injected 5 min before CGRP (50µ/kg IV) which was administered 5 min before saline (10ml/kg IP) and 15 min before the test meal. The number of abdominal spike burst was used as an index of visceral pain.

AA induced an inhibition of GE (27.9±3.2% vs 52.3±3.8%) and an increase of the number of abdominal spike burst (49.6±6.1 vs 28.0±7.4/35min). RP-67,580 (0.2mg/kg IP) reduced the GE inhibition induced by AA (43.4±4.2%) without affecting the abdominal response. SR-48,968 (5mg/kg IP) reduced the AA induced-increase of abdominal contractions without modifying the GE inhibition. CGRP antagonist reduced both responses induced by AA which reached 40.7±3.5% for gastric emptying and 33.7±3.3/35 min for abdominal response. CGRP agonist reproduced both responses induced by AA. RP-67,580 (0.2mg/kg IP) abolished the CGRP induced-GE inhibition without affecting the increase of abdominal contractions, whereas SR-48,968 diminished CGRP induced-visceral pain but did not influence the GE inhibition evoked by CGRP.

Acute inflammation induces visceral pain and inhibition of gastric emptying. NK1 and NK2 receptors mediate the inhibition of gastric emptying and visceral pain respectively. It is likely that these responses involve a release of CGRP which in turn induces a release of tachykinins .