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DIFFERENTIAL EFFECTS OF NMDA RECEPTOR ANTAGONISTS ON MYOELECTRIC ACTIVITY AND TRANSIT OF THE SMALL INTESTINE.

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Gastrointestinal dysmotility and visceral hypersensitivity may be the mechanisms responsible for functional bowel disorders. The influence of N-methyl-D-aspartate (NMDA) receptors on gastrointestinal motility and visceral sensitivity is not well understood. We demonstrated previously that the NMDA receptor antagonists, phencyclidine (PCP) and ifenprodil disrupted activity fronts (AF) of the migrating myoelectric complex (MMC) (Gastroenterology, A1085, 1999). We hypothesized that alterations of the MMC would delay intestinal transit. Transit of the small intestine was measured in fasted, unrestrained, and unanesthetized rats, previously implanted with a duodenal catheter. PCP, a nonspecific NMDA receptor antagonist, and ifenprodil, an antagonist at the NR1NR2B subtype, were tested. PCP at 30 mg/kg and ifenprodil at 5 and 10 mg/kg were administered parenterally. Transit of the small intestine was measured by the movement of radioactive chromate and was quantitated by calculating the geometric center (GC) for its distribution in the small intestine (Gastroenterology 1987; 472-8). The lower the value for the geometric center the slower the transit. The results are expressed as mean \pm SEM and the data from the previous myoelectric studies are also shown for comparison in the table. In summary, ifenprodil but not PCP significantly delayed small intestinal transit while both agents disrupted AFs of the MMC with an increase in random spike activity. We conclude that NMDA receptors are intimately involved in GI motility but surprisingly different subtypes of NMDA receptor antagonists exert differential effects on intestinal myoelectric activity and transit. Furthermore, our findings support the concept that more than one subtype of NMDA receptor may be involved in the control of GI motility. Future development of compounds that interact with NMDA receptor will need to be carefully screened regarding their effect on motility and visceral sensitivity. * $p < 0.05$ from baseline.

	MMC Disruption (min)	AF Pro.Vol.(cm/min)	GC
Control	0.0	3.2 \pm 0.4	4.0 \pm 0.5
PCP 30 mg/kg	139.5 \pm 45.2*	4.6 \pm 0.8*	4.5 \pm 0.6
Ifenprodil 10mg/kg	77.7 \pm 9.6*	3.1 \pm 0.2	1.8 \pm 0.3*

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INTESTINAL MOTILITY IN AN *IN SITU* RAT MODEL OF INTES-TINAL ISCHEMIA-REPERFUSION AND EFFECTS OF L-NAME ON THE MOTILITY CHANGES.

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To clarify the relationship between intestinal ischemia-reperfusion (IR) and dysmotility, we investigated changes in the motility pattern in the duodenum (Du: non-ischemic site) and jejunum (Je: ischemic site) in an *in situ* rat model of IR by means of miniature strain gauge force transducers (FT). We also studied the involvement of nitric oxide (NO) in the IR-induced motility changes caused by the administration of L-NAME (10 mg/kg injected in a bolus and 10 mg/kg/hr continuously infused). FT were sutured onto the Du or Je of male Wistar rats. After a 3 day recovery period contractions were recorded during periods of preischemia (p-Is: 60 min), ischemia (Is: 60 min) and reperfusion (Re: 90 min). The IR was produced by clamping and releasing the mesenteric artery and vein with artery forceps. In control rats one minute clamping was done. Results: (1) A cluster of contractions (CC) were cyclically observed in the Je (n=10) and Du (n=9) during the p-Is period. A frequency and duration of CC, and a total number of contractions (TNC) in Je were 31.4 \pm 0.5/1 min, 51.2 \pm 9.0 second, 154 \pm 12.4/30 min, respectively. (2) In the Je the frequency and duration of CC, and the TNC were significantly less in IR rats than in control rats (n=8) both during the Is period (25.4 \pm 0.9 vs 29.6 \pm 0.7/1 min, 24.3 \pm 4.0 vs 41.3 \pm 9.5 second, 49.8 \pm 14.7 vs 81.6 \pm 18.6 % compared p-Is, respectively) and during the Re period (26.0 \pm 0.8 vs 29.6 \pm 1.0/1 min, 27.2 \pm 3.7 vs 34.9 \pm 6.7 second, 45.7 \pm 7.8 vs 102.0 \pm 15.4 % compared p-Is, respectively). Same trends were observed in the Du only during the Re period. (3) Prolonged high amplitude contractions (PHAC) appeared in the Je during the IR period (Is: 5.0/1 rat/1 hr, Re: 6.3/1 rat/1 hr). (4) L-NAME did not have any effect on the IR-induced changes in CC pattern or the appearance of PHAC in either Du (n=6) or Je (n=6). However, after L-NAME pretreatment there was no decrease in the TNC during the 45-90 min after Re. These results indicate that intestinal IR induces two distinct dysmotilities during the IR period. The changes in CC pattern could not depend on NO, but on hypoxia. The decrease in the TNC observed soon after Re could depend on NO.

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MIGRATING MOTOR COMPLEX (MMC) PERSISTS DURING CONTINUOUS FEEDING IN CHILDREN.

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Many clinicians believe that continuous drip feedings are "less natural" or "a step backward" from bolus tube feedings. One concern is that continuous feedings might interrupt the MMC, the "digestive housekeeper" and marker for neuromuscular integrity of the small bowel. Recent work suggests this may be true for adults (EurJ Clin Invest 1999; 79:615). We used 24 hr small bowel manometry to evaluate if phase 3 of the MMC persists during continuous feeding or during short fasting periods between bolus feedings in children. We studied 6 children (age 4.1 \pm 3.3 yr., range 10 mo. to 12 yr., 2 male) with gastrostomies (n=2) or jejunostomies (n=4) for tube feeding. We placed a solid state manometry catheter with 3-5 channels 3-4 cm apart and a feeding tube through the ostomy into the small bowel under fluoroscopic guidance. After a 4 hr fasting recording we used a programmable Zevex enteral feeding pump to infuse the duodenum with a complex liquid formula in two 10h cycles in random sequence. One cycle consisted of 3 hr feeding, 2 hr fasting, repeated twice, the other cycle was 10 hr continuous feeding. Volume and formula content during the two cycles were identical and sufficient to provide 100% of the patient's daily nutrition requirements. We recorded intraluminal pressures into a portable device. We measured the number of phase 3 episodes/hr during each cycle. In every child phase 3s persisted during continuous duodenal feeding. There was no significant difference in phase 3 frequency (0.6 \pm 0.3/h during bolus feeding vs. 0.7 \pm 0.5/h during continuous feeding, p=0.7), duration (averaging 6.6 min bolus and 5.5 min continuous), propagation speed (averaging 5.5 cm/min bolus vs 4.8 cm/min continuous), or mean contraction amplitudes (37mm Hg bolus and 34mm Hg continuous) during the 2 cycles. There was no difference in symptoms during the two types of feedings. We conclude that in children continuous feedings into the small bowel do not inhibit the MMC. Phase 3 of the MMC is preserved during both continuous and bolus tube feeding.

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JEJUNAL CONTRACTILITY RESPONSES TO BRADYKININ AND NEUROKININ A ARE ALTERED AFTER NEMATODE EXPOSURE-INDUCED INTESTINAL MASTOCYTOSIS IN RATS.

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Functional gastrointestinal disorders are often linked to previous infection of the gut which may have led to neuroimmune changes and, further, to alterations of motility and visceral sensitivity. Exposure of the rat jejunum to *Nippostrongylus brasiliensis* (Nb) results in persistent mastocytosis and hypersensitivity to distension involving two inflammatory mediators: bradykinin (BK) and neurokinin A (NKA). We investigated whether the *in vitro* responses of jejunal smooth muscle to these mediators was altered in rats previously exposed to Nb. Methods: Two groups of 8 male Wistar rats (250-300 g) were used: "Nb" group infected with 3000 L3 larvae of Nb (in 0.5 ml 0.9 NaCl; s.c.); "Control" group given 0.5 ml 0.9 NaCl (s.c.). Jejunal tissue (20-30 cm aboral to LT) was collected from each rat 30 d after injections. Strips (8x2 mm) were placed longitudinally in a superfusion system (Krebs, 37°C, 2 ml/min); isometric contractions were quantified. Concentration-response curves (0.1 nM-10 μ M) were constructed for BK and NKA: EC₅₀ (mean[95%CI]; μ M) and Emax (max response; mean \pm SE; % of that to 60 mM KCl) were determined. Histology (structure, mast cell number) and myeloperoxidase (MPO) assays were performed. Results: At 30 d after infection the jejunum presented no inflammation and MPO levels were similar to controls; in contrast mast cell numbers were increased: 342 \pm 124/mm² vs. 67 \pm 28/mm² (p<0.01). BK and NKA concentration-dependently contracted the strips; although no differences were respectively recorded for EC₅₀s, significant differences were measured for Emax (Table 1). Conclusion: Increased smooth muscle reactivity to NKA agrees with the *in vivo* enhanced visceral sensitivity involving NK₂ receptors already reported in nematode-exposed rats. In contrast lower response to BK was unexpected but could result from a down-regulation of constitutive BK-selective B₂ receptors, switched, in this model, to inducible B₁ receptors less selective of BK.

	Bradykinin		Neurokinin A	
	EC50 (μ M)	Emax (%)	EC50 (μ M)	Emax (%)
Controls (n=8)	0.14 [0.01-2.19]	196.9 \pm 13.5	0.09 [0.03-0.28]	155.0 \pm 9.4
Nb (n=8)	0.09 [0.02-0.51]	130.0 \pm 9.0*	0.12 [0.03-0.48]	220.9 \pm 10.7*

*: significantly different from controls (p<0.01; ANOVA and Bonferroni test)