



Proteinase-Activated Roceptor-2 (PAR-2) Activation Produces Delayed Rectal Hyperalgesia In Awake Rats

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progesterone antagonist RU486 (4mg/rat s.c.) or vehicle before the stress session. Four groups of ovariectomized rats were treated with either vehicle, progesterone (500µg/rat s.c.), estradiol (5 µg/rat s.c.) or both progesterone and estradiol before the restraint stress. Animals were sacrificed 20 min after stress and colonic samples were taken off. Histamine release was measured in vitro on colonic samples using a RIA method, and the effect of NK1 receptor antagonist SR140333 (1.10-3 M) on substance P (3.10-5 M)-induced histamine release was determined. Results: In intact female, SR140333 inhibited SP induced histamine release in stressed animals pretreated with vehicle. This antagonistic effect was abolished when animals were pretreated with RU486. Similarly, SR140333 failed to abolish SP-induced histamine release in ovariectomized rats even when they received estradiol or progesterone. In contrast a combined treatment with estradiol and progesterone restored the antagonistic effect of SR140333 on SP-induced histamine release. Conclusion: In female rats, stress-induced activation of NK1 receptors participates in substance P-induced histamine release and depends upon the sexual hormone status. Combined treatment with estradiol and progesterone is required to elicit the stress-linked NK1 receptor mediation of substance P-induced mast cell histamine release.

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Proteinase-Activated Receptor-2 (PAR-2) Activation Produces Delayed Rectal Hyperalgesia in Awake Rats

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PAR-2 is a recently characterized G-protein receptor that is cleaved by trypsin and mast cell tryptase and activated by the tethered peptide. It is highly expressed throughout the gastrointestinal tract and can participate in widespread inflammatory reactions. According to the role of mast cells in visceral sensitivity, this study was aimed to determine whether PAR-2 activation, located peripherally, may affect sensitivity to rectal distension (RD) in awake rats. Methods: Three groups (n=6-7) of male Wistar rats were surgically equipped with a polyethylene catheter in the colon for intracolonic (IC) infusion (0.25 ml/20 min) and electrodes implanted in abdominal muscles to record abdominal contractions (indication of pain). RD was performed with a balloon inflated by 5 min steps of 0.4 ml (0 to 1.6 ml). Groups 1 and 2 were infused IC with saline (0.25 ml/rat), control inactive peptide (LSIGRL) and active peptide of PAR-2 (SLIGRL, tethered-ligand sequence of rat PAR-2) at doses of 0.05 and 0.2 mg/rat, respectively. Group 3 was infused IC with saline (0.25 ml/rat), boiled trypsin and trypsin at dose of 200 U/rat. In a last group was performed barostatic colorectal distension using a balloon inflated by 5 min steps of 15 mmHg (0 to 60 mmHg) to record colorectal volume. Rats were infused IC with saline, LSIGRL or SLIGRL at dose of 0.2 mg/rat. In all groups, RD and volume measurements were performed 2, 6, 10 and 24 hours after infusions. Results: RD induced abdominal contractions, this being significant when the RD volume reached 0.8 ml (p<0.05). Infused IC, saline and LSIGRL had no effect on the number of contractions in response to RD. At a dose of 0.2 mg/rat, SLIGRL significantly (p<0.05) increased this number for high volumes of distension (from 0.8 to 1.6 ml), 10 and 24 hours post-infusion compared to LSIGRL, without affecting the threshold of abdominal response. At other times (2 and 6 hours) and a lower dose (0.05 mg/rat), SLIGRL had no effect. Moreover, SLIGRL did not affect colorectal volume whatever the pressure applied (from 0 to 60 mmHg). Trypsin, but not boiled trypsin, increased (p<0.05) the number of contractions only at 24 hours post-infusion for high volumes of distension (0.4 to 1.6 ml) compared to saline. Conclusion: Intracolonic infusion of either a selective PAR-2-activating peptide or trypsin produces a delayed (10-24 hours) rectal hyperalgesia without affecting colorectal compliance in rats, suggesting the possible involvement of PAR-2, located in colonic wall, in visceral hyperalgesic states.

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Effects of IL-1β on Prostaglandin EP Receptor Mediated Stimulation of Jejunal Motility and Afferent Discharge in the Rat.

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Background: The relative role of neural and humoral pathways in the febrile response to IL-1β is controversial although vagal pathways and endogenous prostanoids are implicated (Ek et al., J Neurosci. 18: 9471-9, 1998). Prostaglandin E2 (PGE₂) stimulates mesenteric afferent discharge via direct and indirect actions on nerve terminals and intestinal muscle, that are mediated by EP1 and EP2 receptor subtypes respectively (Haupt et al., Gastroenterol. 119: in press, 2000). Our hypothesis was that these sensory and motor responses to different EP-receptors would be potentiated by treatment with IL-1β, which could contribute to CNS representation of peripheral inflammations. Method: Mesenteric afferent recordings were made in pentobarbitone (60mg/kg) anaesthetised rats, from segments of jejunum cannulated to record intraluminal pressure. The EP1 (17-phenyl-ψ-trinor PGE₂) and EP2 (misoprostol) receptor agonists (250 nmol/kg) were administered intravenously in animals treated with either IL-1β (5 mg/kg, i.p.) or vehicle 20 hrs prior to experimentation. Data are presented as the mean±SEM (n=6) and compared using un-paired t-test (* = P<0.05). Results: 17-trinor PGE₂ and misoprostol had similar effects on luminal pressure (LP) but evoked very different patterns of afferent discharge (AD). After IL-1β the motor and afferent response to misoprostol, but not 17-trinor PGE₂, were prolonged while the magnitude of the increase was unchanged. Conclusion: Peripheral IL-1β enhances mesenteric afferent response to PGE₂ via an action on EP2 rather than EP1 receptors. This specific interaction between IL-1β and PGE₂ does not appear to be exerted at the level of the afferent nerve endings, since it is mirrored by changes in motor activity. Funded by the DFG (Kr. 1816/3-1)

		Control		IL-1β	
		17-trinor PGE ₂	Misopros to	17-trinor PGE ₂	Misoprostol
AD (imps)	Duration (min)	0.7±0.1	33.1±3.4	0.7±0.1	67.9±13.1*
	Peak increase	254.9±36.8	65.9±14.4	263.8±12.4	78.9±11.2
	Duration (min)	15.6±0.5	34.1±3.0	13.8±2.4	83.8±15.5*
LP (cmH ₂ O)	Peak increase	5.5±0.9	4.5±0.8	5.5±0.6	4.9±0.5

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Nicotinic Activation Of Vagal Afferent Fibres Supplying The Rat Jejunum: "Cross-Talk" Between The Enteric And Extrinsic Innervation?

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Introduction A population of vagal afferent fibres supplying the gastrointestinal tract terminates with interganglionic laminar endings (IGLEs) in the myenteric plexus. Recent evidence suggests that these endings may serve a mechanosensory function (Zagorodnyuk & Brookes, J Neurosci 20: 6249-55). However, in this location they may also be exposed to mediators released during ganglionic transmission. In this respect nodose ganglion cells express a variety of receptors to enteric neurotransmitters including acetylcholine (Zhuo et al, Prog Neurobiol 52: 79-107, 1997). Whether nicotinic receptors are functional at the level of the sensory nerve terminal has not been demonstrated. Therefore the aim of the present study was to determine the sensitivity of mesenteric afferent nerve bundles to nicotinic receptor stimulation. Methods Extracellular recordings of jejunal afferent discharge and intraluminal pressure were made from pentobarbitone (60mg/kg) anaesthetised Hooded-Lister rats as detailed previously (Kirkup et al., 1999, J. Physiol., 520, 551). Responses to systemic administration of the nicotinic agonist N,N-Dimethyl-N'-phenyl-piperazinium iodide (DMPP) were quantified in control and vagotomised animals and following treatment with ω-conotoxin GVIA (ω-CTX GVIA, N-type Ca²⁺ channel blocker, 30µg/kg) or hexamethonium (10mg/kg). Data are presented as mean±SEM and were compared using paired and un-paired t-test as appropriate. Results DMPP (0.3 to 300 µg/kg) evoked a dose-dependent increase in afferent discharge (AD) accompanying by a fall in intraluminal pressure. 300µg/kg dose increased AD from 44.3±11.1 to 137.1±18.8 imps⁻¹ (P<0.0005, n=6) and was unaffected by ω-CTX GVIA but completely abolished after treatment with hexamethonium indicating a direct effect on either extrinsic afferent nerve terminals or intestinofugal fibres. The motor response was unaffected by either treatment. In three vagotomised animals the afferent response to DMPP was markedly attenuated, 100 µg/kg evoking an increase in discharge of 14.5±2.8 imps⁻¹ compared to 57.1±7.1 in control animals (P<0.005) indicating that vagal afferents contribute considerably to nicotinic sensitivity. Conclusion: Our data show functional nicotinic receptors on the terminals of extrinsic gastrointestinal afferents supporting the concept that sensory information relating to activity in enteric nerve circuits may be transmitted to the CNS. Supported by DFG (Kr 1816/3-1)

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Pelvic Vs Splanchnic Colonic Primary Afferents

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Background: In the upper gastrointestinal tract, afferent fibres following parasympathetic (vagal) pathways mediate non-noxious events, whereas those following sympathetic (splanchnic) pathways mediate both noxious and non-noxious events. In the colon, the pattern is less clear: both pelvic and splanchnic afferents have been suggested to mediate both types of sensation. However, there are discrepancies in the literature between studies using different methods. We have initiated an investigation to compare pelvic and splanchnic afferents in identical *in vitro* preparations of colon in the rat. Methods: Distal colon and inferior mesenteric ganglion (IMG) were removed together from rats. The lumbar splanchnic nerve (LSN) was kept intact with the IMG in earlier studies and the hypogastric branch of the pelvic nerve (HGN) was kept additionally in later studies. In a specialized organ bath, the colon was opened and pinned flat. The mucosa was superfused with fatty acid-containing Krebs', and the serosa with regular Krebs'. The LSN ± HGN were led through a hole and single units recorded from either nerve in an oil-filled chamber. Results: From the LSN 3 classes of primary afferents were recorded as classified previously (Lynn & Blackshaw, J. Physiol. 1999; 518: 271-282): 82 high threshold serosal (probing sensitive, distension-insensitive) afferents, 22 low threshold muscular (distension sensitive) afferents, and 18 mucosal (stroking sensitive) afferents. From the HGN 7 serosal fibres and 2 muscular fibres have been recorded thus far. Preliminary data indicate that responses to stretch were slowly adapting in HGN fibres, but rapidly adapting in LSN fibres. Conclusions: Colonic pelvic afferent recordings are feasible alongside splanchnic recordings in the rat *in vitro*. Preliminary data show that pelvic afferents signal high intensity, potentially noxious events in addition to signalling the degree of colonic distension. The splanchnic pathway transmits a wide range of noxious and non-noxious sensory information, but is more likely to signal muscular contraction than continuous distension. Supported by NHMRC Australia, University of Adelaide and AstraZeneca