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Effects of tachykinin receptor antagonists on the rat jejunal distension pain response

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Abstract

Distension of the rat intestine causes a cardiovascular response which is indicative of nociception. Since tachykinins are involved in nociception, we tested the effect of neurokinin receptor antagonists against the distension-induced response. The jejunal distension-induced depressor responses were inhibited in a dose-dependent fashion by CP 99,994 (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine, tachykinin NK_1 receptor antagonist, $ED_{50} = 0.8$ mg/kg) and SR 48968 (*S*)-*N*-methyl-*N*[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]benzamide, tachykinin NK_2 receptor antagonist, $ED_{50} = 0.7$ mg/kg). SR 142801 (*S*)-(*N*)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-*N*-methylacetamide, tachykinin NK_3 receptor antagonist, 0.3–10 mg/kg) did not significantly affect the depressor responses to jejunal distension. In addition, CP 99,994 (3 mg/kg) and SR 48968 (3 and 10 mg/kg) reduced sensitivity to distension as revealed by a 2.7-fold (CP 99.994, 3 mg/kg), 2.6-fold (SR 48968, 3 mg/kg) and 4.7-fold (SR 48968, 10 mg/kg) increase in the threshold pressure. Intestinal compliance was not affected by the antagonists. In conclusion, these results suggest that tachykinin NK_1 and NK_2 but not NK_3 receptors are possibly involved in the rat jejunal distension pain response. © 1998 Elsevier Science B.V.

Keywords: Tachykinin; Visceral sensation mechanism; Intestinal distension pain response; Visceral nociception; Tachykinin receptor

1. Introduction

Distension of the human jejunum (Bentley and Smithwick, 1940), ileum (Lipkin and Sleisenger, 1958) or colon (Swarbrick et al., 1980) is considered to be a noxious stimulus causing pressure-dependent abdominal pain. In anaesthetised rats, distension of the gastrointestinal tract produces 'pseudoaffective' reflexes (Ness and Gebhart, 1990) including a cardiovascular depressor response and bradycardia. This depressor response is considered to be indicative of visceral nociception as it is potentiated by naloxone, blocked by morphine (Ness and Gebhart, 1990) and abolished by capsaicin (Lembeck and Skofitsch, 1982). As such, the visceral distension depressor response is a useful tool in the characterisation of visceral nociception.

Only limited data are available with regard to the mechanisms and pharmacology of the visceral distension depressor response. 5-HT_3 receptor antagonists (Moss and Sanger, 1990) and opioid receptor agonists (Diop et al., 1994; Scott et al., 1997) have been shown to inhibit the response. However, cholinergic and α-adrenergic mechanisms appear not to be involved (Lembeck and Skofitsch, 1982). The neurones involved in the mediation of the response possibly include capsaicin-sensitive peptidergic afferent fibres as the response is abolished in capsaicin-treated rats (Lembeck and Skofitsch, 1982).

The involvement of capsaicin-sensitive fibres suggests that tachykinin containing nerves are involved as it is well documented that capsaicin treatment causes a depletion of tachykinins in the dorsal horn of the rat spinal cord (Gamse et al., 1980) and a degeneration of substance P containing fibres originating from the submucous ganglia (Furness et al., 1982).

Numerous reports have implicated tachykinins in the transmission of somatic nociception (e.g., Seguin et al., 1995) mediated by tachykinin NK_1 and NK_2 receptors. As such, tachykinins are possibly also involved in visceral

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nociception. To date, the involvement of tachykinins in the visceral distension depressor response has not been investigated. However, tachykinin NK_1 and NK_2 receptors have been implicated in the viscerosensitive response to rectal distension in rats (Julia et al., 1994). It has also been suggested that tachykinin NK_3 receptors are involved in visceral pain (Julia and Bueno, 1995). In a preliminary report (McLean et al., 1997), it was shown that tachykinin NK_2 receptors are involved in the nematode infection-induced hypersensitivity of the depressor response. Thus, the aim of the present study was to investigate the possible physiological role of tachykinins in the response by the use of the following nonpeptide, neurokinin receptor antagonists; tachykinin NK_1 receptor selective: CP 99,994 (Desai et al., 1992); tachykinin NK_2 receptor selective: SR 48968 (Emonds-Alt et al., 1992); and tachykinin NK_3 receptor selective: SR 142801 (Emonds-Alt et al., 1995; Patacchini et al., 1995).

2. Materials and methods

2.1. Surgical and experimental procedure

Male Wistar rats weighing 300–400 g were used. The animals were deprived of food the night prior to experimentation but were given free access to water. They were anaesthetised with pentobarbitone sodium (60 mg/kg s.c.). Anaesthesia was maintained by re-administration of pentobarbitone sodium (15 mg/kg per h). Anaesthetised animals were maintained at approximately 35°C by placing them on a heat pad. The trachea was cannulated to prevent any airway obstruction.

A second cannula was introduced into the thoracic aorta via the left common carotid artery for constant retrograde intra-arterial infusion of saline and for further administration of anaesthetic. The rate of infusion was 40 μl/min. Systemic blood pressure was recorded from a side-arm off the carotid cannula by means of a Statham pressure transducer (P231D) connected to a Beckman (R411 Dynograph) polygraph.

A midline incision along the length of the abdomen was made to expose the small intestine. A section of jejunum, 7 cm from the ligament of Treitz was used in the investigation. A cut was made at one end of the selected segment of intestine on the antimesenteric side to introduce a 5-cm long deflated latex balloon which was loosely secured by cotton thread. The latex balloon was connected via a polyethylene catheter to a 10-ml syringe which was connected to a second pressure transducer to record intraluminal pressure. The intestinal segment was then replaced in the peritoneal cavity and the abdomen closed.

Jejunal distension (12.5–100 mmHg, 25 s every 5 min) has been shown to produce a stimulus-related decrease in diastolic blood pressure (Ness and Gebhart, 1990; McLean et al., 1997). The jejunum was distended by a rapid inflation of the latex balloon and the inflation volume and subsequent intraluminal pressure noted.

2.2. Effects of neurokinin receptor antagonism

2.2.1. Repeated distension pressure

The inhibitory effects of the neurokinin receptor antagonists were quantified by applying repeated distension with a submaximal, noxious intraluminal pressure of 75 mmHg every 5 min until a constant response was achieved. In all rats, the constant response was achieved by the fourth distension and no significant differences ($P > 0.05$) were observed between any of the responses to the pre-control distensions. CP 99,994 (0.3–3 mg/kg), SR 48968 (0.1–10 mg/kg) and SR 142801 (0.3–10 mg/kg) or an equivalent volume of vehicle were given intraperitoneally (i.p.), intestinal distension was then recommended 10 min after drug administration and repeated at 5 min intervals up to 25 min following administration. The i.p. route was chosen based on a previous study (Julia et al., 1994) in which the i.p. administration of tachykinin NK_1 and NK_2 receptor antagonists were shown to inhibit viscerosensitive responses to rectal distension in rats.

2.2.2. Graded distension pressure

Separate experiments were performed to determine threshold pressures and to investigate the effects of SR 48968 (3 and 10 mg/kg, i.p.) and CP 99,994 (3 mg/kg) on the calculated threshold pressures. In these experiments, graded intestinal distension pressure (12.5–100 mmHg)-response curves were constructed in the presence of SR 48968, CP 99,994 or vehicle. Pressure–response curves were constructed 20 min after drug or vehicle administration.

All procedures were approved by the local INRA animal care and use committee.

2.3. Data analysis

The apparent potency of the inhibitory effect of the antagonists was quantified according to a modification of the method of Moss and Sanger (1990). Briefly, responses to repeated jejunal distension (75 mmHg every 5 min) following antagonist administration were expressed as a percentage of the response immediately prior to dosing (taken as 100% response). The maximal effects observed over the test period were subjected to regression analysis (Graph Pad Prism, Graph Pad Software, San Diego, USA). ED_{50} values were calculated using linear regression analyses from the 50% response level and expressed as the mean with 95% confidence limits (95% C.L.). The statistical difference between the depressor responses to intestinal distension in the presence and absence of antagonists was assessed by using Student's unpaired (graded pressures) or

Table 1
Resting mean arterial blood pressure and mean magnitude of the depressor response produced by a control distension pressure of 75 mmHg

Group	Mean resting blood pressure (mmHg)	Mean depressor response (mmHg)
A vehicle	121.1 ± 3.1	20.3 ± 3.1
0.3 mg/kg	120.4 ± 1.1	28.0 ± 3.8
1 mg/kg	118.5 ± 3.1	29.0 ± 7.4
3 mg/kg	128.1 ± 2.7	26.3 ± 5.0
10 mg/kg	129.3 ± 2.3	25.0 ± 3.9
B vehicle	121.1 ± 3.1	20.3 ± 3.1
0.3 mg/kg	125.6 ± 2.3	31.5 ± 4.6
1 mg/kg	125.9 ± 2.1	20.2 ± 6.0
3 mg/kg	127.0 ± 3.5	26.3 ± 5.0
C vehicle	120.6 ± 8.7	39.0 ± 8.4
0.1 mg/kg	129.4 ± 2.2	26.8 ± 5.2
0.3 mg/kg	123.5 ± 1.9	28.0 ± 3.8
1 mg/kg	122.3 ± 2.9	26.1 ± 3.0
3 mg/kg	117.3 ± 2.2	30.2 ± 6.2
10 mg/kg	125.6 ± 5.2	21.6 ± 3.2

Values are means ± S.E.M. of 4–8 data points for each treatment group; (A) SR 142801, (B) CP 99,994 and (C) SR 48968.

paired (repeated pressures) *t*-test. Means were considered significantly different if $P < 0.05$.

The equation as described by Ness and Gebhart (1988):

$$(\text{A blood pressure})^2 = (\text{slope} \times \text{distension}) + \text{intercept}$$

allowed a transformation of the graded pressure–response function. The distension threshold represented the calculated distension value that would evoke a measurable change in diastolic blood pressure of 10 mmHg.

Intestinal pressure–volume curves were constructed as a measure of intestinal compliance according to the methods described by Gregersen and Kassab (1996) to determine whether changes in intestinal compliance occurred following antagonist administration. Intestinal compliance was calculated from the slope of the linear portion of the intestinal pressure–volume curves.

2.4. Drugs

CP 99.994 (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine), SR 48968 (*S*)-*N*-methyl-*N* [4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]benzamide) and SR 142801, (*S*)-(*N*)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl) propyl)-4-phenylpiperidin-4-yl)-*N*-methylacetamide were dissolved in dimethylsulfoxide (DMSO) and made up to volume with an equivalent volume of 0.9% saline. The 'SR' compounds were kindly supplied by Dr. Emonds-Alt, Sanofi Laboratories (Montpellier, France) and CP 99,994 from Dr. Kadin, Central Pfizer (Groton, CT, USA).

3. Results

3.1. Effects of jejunal distension

Jejunal distension (12.5–100 mmHg, 25 s every 5 min) elicited a rapid pressure-dependent decrease in diastolic blood pressure (see Fig. 3) in 85% of rats. The data from nonresponding rats were not included.

3.2. Effects of neurokinin receptor antagonists on the depressor response to jejunal distension

Intraperitoneal administration of the DMSO/saline vehicle (0.6 ml/kg), CP 99,994 (0.3–3 mg/kg, $n = 13$), SR 48968 (0.1–10 mg/kg, $n = 27$) and SR 142801 (1–10 mg/kg, $n = 21$) had no significant sustained effect on resting blood pressure.

3.2.1. Repeated distension pressure

Table 1 shows the resting mean arterial blood pressures and the magnitude of the depressor responses produced by the control, 75 mmHg distension pressure in each treatment group. No significant difference ($P > 0.05$) was ob-

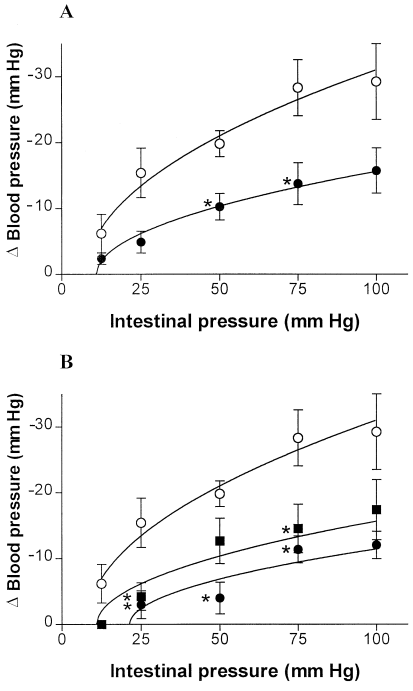

Fig. 1. Regression analyses of the fall in blood pressure induced by graded jejunal distension pressures (12.5–100 mmHg, 25 s every 5 min). Data obtained in the absence (○, $n = 5$), or presence of (A) CP 99,994 (3 mg/kg, ●, $n = 4$) or (B) SR 48968 (3 mg/kg, ■, $n = 4$; 10 mg/kg, ●, $n = 4$). Each point represents the mean ± S.E.M. * $P > 0.05$, unpaired *t*-test. Regression analyses have the equations: control, $y^2 = 10.4x - 81$; CP 99,994 (3 mg/kg), $y^2 = 2.7x - 30$: SR 48968 (3 mg/kg), $y^2 = 4.4x - 87$; (10 mg/kg), $y^2 = 1.7x - 35$.

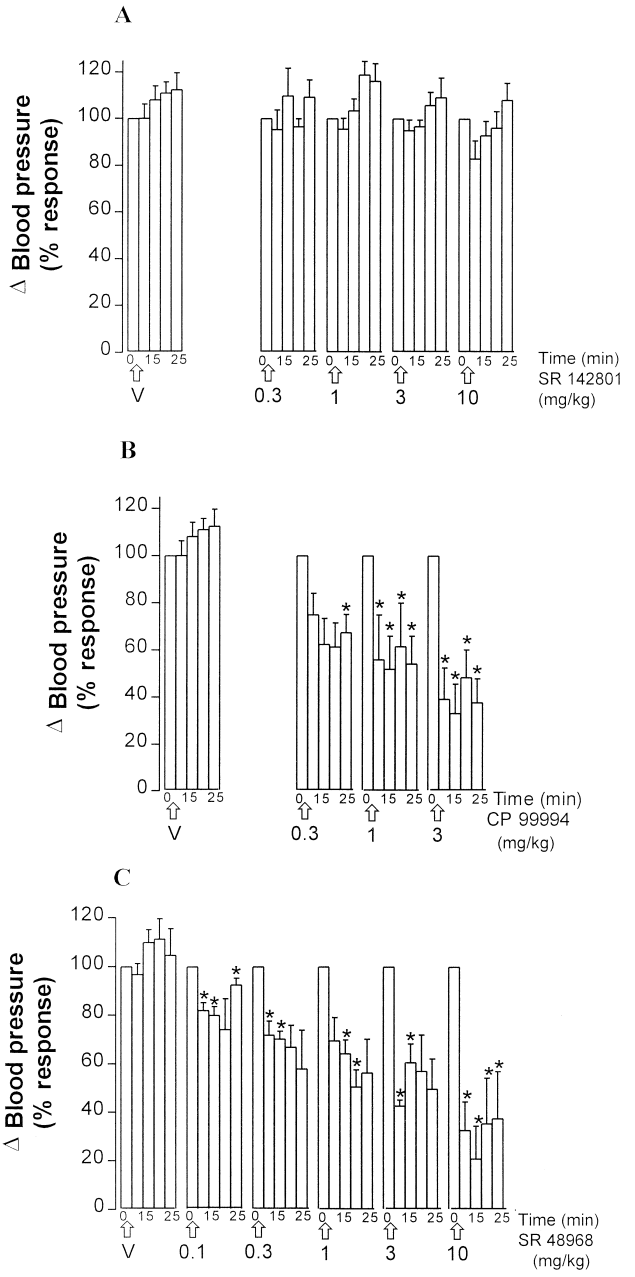

Fig. 2. Effects of (A) SR 142801 (0.3–10 mg/kg i.p.). (B) CP 99,994 (0.3–3 mg/kg i.p.) and (C) SR 48968 (0.1–10 mg/kg i.p.) or vehicle ($V = 0.9\%$ saline:dimethylsulfoxide; 50:50, v/v) administered after a control distension (⇑) on the fall in blood pressure induced by repeated jejunal distension pressures (75 mmHg, 25 s every 5 min). The first column in each group represents the pre-dose control response taken as 100%. Each column represents the mean ± S.E.M. of 4–8 data points. $* P < 0.05$, paired *t*-test.

served between the depressor responses in any of the groups. The i.p. administration of the tachykinin NK_1 receptor antagonist CP 99,994 (0.3–3 mg/kg) and the tachykinin NK_2 receptor antagonist SR 48968 (0.1–10 mg/kg) produced dose-dependent inhibition of these depressor responses (Fig. 1B,C) giving rise to ED_{50} values of 0.8 mg/kg (95% C.L., 0.1–6.1, $n = 11$) and 0.7 mg/kg (95% C.L., 0.4–1.5, $n = 19$), respectively (Fig. 2).

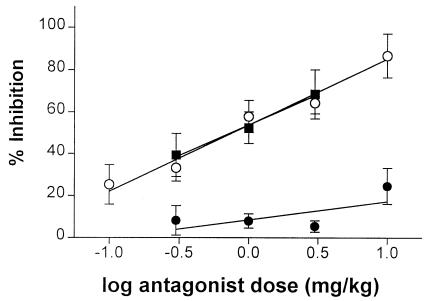

Fig. 3. Linear regression analysis of the effects of CP 99,994 (0.3–3 mg/kg, ■, $n = 11$), SR 48968 (0.1–10 mg/kg, ○, $n = 19$) and SR 142801 (0.3–10 mg/kg, ●, $n = 21$) on the fall in blood pressure induced by repeated jejunal distension pressure (75 mmHg, 25 s every 5 min). The effects of the antagonists are plotted as the percentage inhibition of the response immediately prior to dosing. Each point represents the mean ± S.E.M. of 4–7 data points.

There was no statistically significant effect of the tachykinin NK_3 receptor antagonist SR 142801 (0.3–10 mg/kg, $n = 21$) on the responses to jejunal distension at any of the doses tested (Fig. 1A). However, a trend towards inhibition was observed at the highest concentration of 10 mg/kg (Fig. 1A and Fig. 2).

In all repeated distension pressure experiments, the administration of each of the antagonists, at all doses tested, did not significantly affect the volume of air required (3.0–3.2 ml) to induce a constant intestinal pressure of 75 mmHg.

3.2.2. Graded distension pressure

In separate experiments, graded jejunal distension pressures (12.5–100 mmHg, 25 s every 5 min) elicited pressure-dependent depressor responses (Fig. 3). These experiments were designed to investigate the effects of CP 99,994 and SR 48968 on threshold pressures and, hence, intestinal sensitivity. The resting mean arterial pressures from these experiments was 121 ± 1.2 mmHg ($n = 17$).

Following CP 99,994 (3 mg/kg, i.p.) or SR 48968 (3 and 10 mg/kg, i.p.) administration depressor responses to jejunal distension were significantly reduced relative to

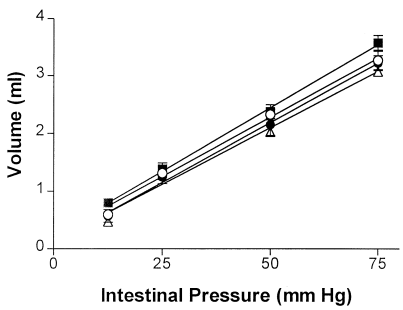

Fig. 4. Intestinal compliance determination over the pressure range 12.5–75 mmHg in the absence (○, $n = 5$) or presence of CP 99,994, 3 mg/kg (△, $n = 4$), SR 48968, 3 mg/kg (●, $n = 4$) and 10 mg/kg (■, $n = 4$). (compliance = 0.04 ± 0.002) (control, CP 99,994 (3 mg/kg) and SR 48968 (10 mg/kg) and 0.04 ± 0.005 (SR 48968, 3 mg/kg) volume in ml/mm Hg, $P > 0.05$).

vehicle controls ($n = 5$) and a 2.7-fold (CP 99,994, 3 mg/kg, $n = 4$), 2.6-fold (SR 48968, 3 mg/kg, $n = 4$) and 4.7-fold (SR 48968, 10 mg/kg, $n = 4$) increase in threshold pressure was observed (Fig. 3) increasing from 17.4 mmHg (control, $n = 5$) to 47.4 mmHg (CP 99,994, 3 mg/kg, $n = 4$), 44.6 mmHg (SR 48968, 3 mg/kg, $n = 4$) and 81.7 mmHg (SR 48968, 10 mg/kg, $n = 4$).

Intestinal pressure–volume curves were constructed as a measure of intestinal compliance (Fig. 4). The curves were significantly linear over the pressure range and compliance values following the administration of CP 99,994 (3 mg/kg) and SR 48968 (3 and 10 mg/kg) were not significantly different to vehicle controls ($P > 0.05$, Fig. 4).

4. Discussion

Distension of the gastrointestinal tract elicits visceral pain in man (Prochacci et al., 1979) and increased visceral perception of distension or motility of digestive organs has been described in patients with functional bowel disorders (Kellow et al., 1991; Mayer and Raybould, 1990). The present study has added to the knowledge of visceral sensation mechanisms via an investigation into the involvement of neurokinin receptors in the rat jejunal distension pain response.

The data obtained with the tachykinin NK_1 receptor selective antagonist, CP 99,994 in the present study suggests an involvement of tachykinin NK_1 receptors in the response. The involvement of tachykinin NK_1 receptors in visceral nociception is supported by other studies in which viscero-visceral reflexes were inhibited by tachykinin NK_1 receptor antagonism (Julia et al., 1994). The apparent potency of CP 99,994 in the present study ($ED_{50} = 0.8$ mg/kg) indicates an activity on tachykinin NK_1 receptors as it is in line with its in vivo potency in other studies such as in guinea pig (1 mg/kg, Foulon et al., 1993; 1–3 mg/kg, Rupniak and Jackson, 1994), ferret (0.3–3 mg/kg, Tattersall et al., 1993, 1994), rat (1.8 mg/kg) and mouse (1.1 mg/kg). Thus, if differences exist between the potency of CP 99,994 at rat tachykinin NK_1 receptors and other species as suggested previously (Beresford et al., 1991; McLean et al., 1993), the present study shows that they are not discriminated by the visceral distension depressor response in the anaesthetised rat.

The data obtained with the tachykinin NK_2 receptor antagonist SR 48968 (Emonds-Alt et al., 1992) is also in line with previous studies in which tachykinin NK_2 receptor antagonists have been shown to have antinociceptive properties against somatic pain (e.g., Seguin et al., 1995). The apparent in vivo potency of SR 48968 determined in the present study ($ED_{50} = 0.7$ mg/kg) correlates well with its potency against other tachykinin NK_2 receptor-mediated responses in the anaesthetised rat (0.5 mg/kg, i.v.; Santucci et al., 1993); the conscious guinea pig (0.1 mg/kg, i.p.; Advenier et al., 1993) and in mice (0.15 mg/kg, i.p.; Poncelet et al., 1993). In another study, Julia et al. (1994) showed that a dose of 5 mg/kg of SR 48968 was submaximal against the viscerosensitive response to rectal distension in rats.

The lack of activity of the tachykinin NK_3 receptor antagonist SR 142801 at concentrations which have been shown to be active in vivo in other studies (Emonds-Alt et al., 1995; Patacchini et al., 1995) suggests that tachykinin NK_3 receptors are not involved in the rat visceral distension depressor response. However, this could also be explained by the observation by Emonds-Alt et al. (1995) that SR 142801 possesses a reduced potency at rat tachykinin NK_3 receptors compared to other species.

Intestinal compliance and therefore the degree of stretch (which is the stimulus to visceral mechanoreceptors (Gregersen and Kassab, 1996) induced by distension was not affected by the antagonists. As such, the inhibitory effects observed can not be attributed to changes in intestinal compliance and are most likely to result from an effect on the pathway mediating the depressor response.

In summary, this study has shown that CP 99,994 and SR 48968 inhibit the jejunal distension-induced pain depressor response in rats, thus, suggesting an involvement of tachykinins, acting via tachykinin NK_1 and NK_2 receptors, respectively, in the perception of noxious visceral stimuli. These findings are possibly relevant to functional bowel disorders in which altered pain perception can result from visceral hypersensitivity. The lack of activity of SR 142801 suggests either that tachykinin NK_3 receptors are not involved in the response or that SR 142801, at the concentrations tested, was not active against rat tachykinin NK_3 receptors.

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