Effects of Tachykinin NK₁ Receptor Antagonists on the Viscerosensory Response Caused by Colorectal Distention in Rabbits

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ABSTRACT

Irritable bowel syndrome (IBS) is a common disorder mainly characterized by altered bowel habits and visceral pain. In this study, we investigated the role of tachykinin NK₁ receptors in the visceral pain response (abdominal muscle contraction) caused by colorectal distention in rabbits previously subjected to colonic irritation, using the selective tachykinin NK₁ receptor antagonists TAK-637 ([aR,9R]-7-[3,5-Bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthyridine-6,13-dione) and (±)-CP-99,994 ([±)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine). Intracolorectal administration of 0.8% acetic acid solution enhanced the nociceptive response to colorectal distention, producing a significant increase in the number of abdominal muscle contractions. Under these conditions, intraduodenal TAK-637 (0.1–3 mg/kg) dose dependently decreased the number of distention-induced abdominal contractions, and a significant inhibitory effect was observed with doses of 0.3 to 3 mg/kg. Another tachykinin NK₁ antagonist, (±)-CP-99,994, also reduced the number of abdominal contractions. In contrast, the enantiomer of TAK-637 (which has very weak tachykinin NK₁ receptor antagonistic activity), trimethobutine maleate, ondansetron, and atropine sulfate did not inhibit the abdominal response. The main metabolite of TAK-637, which has more potent tachykinin NK₁ receptor antagonistic activity but permeates the central nervous system less well than TAK-637, produced less inhibition of the viscerosensory response. When given intrathecally, TAK-637 and (±)-CP-99,994 markedly reduced the number of abdominal contractions. These results suggest that tachykinin NK₁ receptors play an important role in mediating visceral pain and that TAK-637 inhibits the viscerosensory response to colorectal distention by antagonizing tachykinin NK₁ receptors, mainly in the spinal cord. They also suggest that TAK-637 may be useful in treating functional bowel disorders such as IBS.

ABSTRACT

Chronic visceral pain and/or discomfort are the most common symptoms observed in patients with IBS (Naliboff et al., 1997). Most patients show a lowered threshold of nociceptive perception, i.e., hypersensitivity to colorectal distention (Mertz et al., 1995). Although the precise mechanisms underlying the changes in visceral sensitivity are not fully understood, recent studies suggest that some previous experiences, such as gastrointestinal inflammation, psychological or emotional stress, and surgery are associated with this dysfunction (Gwee et al., 1996; Accarino et al., 1997). Central sensitization, including spinal plasticity and/or hypersensitivity of the viscera, appears to occur in IBS patients after stress or inflammation (Mayer and Gebhart, 1994).

Among the several experimental models available for estimating visceral pain, gastrointestinal distention with a balloon is one of the most commonly used methods. The noxious visceral stimuli caused by colorectal distention produce reflex responses such as abdominal contractions or cardiovascular responses (Ness and Gebhart, 1988). These responses can be quantified and have been reported to correlate with the intensity of the colorectal distention applied. Sensitivity to distention has also been reported to increase after repeated stress, intestinal inflammation caused by chemicals, or intestinal infection in experimental animals (Gue et al., 1997; McLean et al., 1997; Al-Chaer et al., 2000).

SP is a member of the tachykinin family of peptides. There are three distinct receptors for tachykinins, and tachykinin NK₁, NK₂, and NK₃ receptors have high affinity for SP, NKA, and NKB, respectively (Otsuka and Yoshioka, 1993). SP has been identified in mammalian CNS tissues such as the brain and spinal cord, as well as in the enteric nervous system of the gut (Holzer and Holzer-Petsche, 1997; Quartara and

ABBREVIATIONS: IBS, irritable bowel syndrome; NK, neurokinin; SP, substance P; CNS, central nervous system; TAK-637, (aR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthyridine-6,13-dione; M₁, metabolite I; (±)-CP-99,994, ([±)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine; L-733,060, ((2S,3S)-3-(3,5-bis(trifluoromethyl)phenyl)ethyl)-2-phenylpiperidine.
Numerous reports have indicated that SP mediates efferent neuromuscular and neuromuscular transmission in the enteric nervous system, resulting in the activation of gastrointestinal motility (Scheurer et al., 1994). It also mediates the transmission of afferent perceptual signals from the gastrointestinal tract via capsaicin-sensitive C-fibers (Gamse et al., 1980), and there is considerable evidence that SP in the spinal cord plays an important role in mediating noxious stimuli from the peripheral organs (Chapman and Dickenson, 1993).

TAK-637 ([αR,9R]-7-[3,5-Bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthyridine-6,13-dione) is a novel orally active tachykinin NK1 receptor antagonist with high affinity (IC50 = 0.45 nM) for tachykinin NK1 receptors in human IM-9 cells, but with low affinity (IC50 = 85 nM) for rat tachykinin NK1 receptors (Natsugari et al., 1999). It has been demonstrated that TAK-637 has high selectivity for tachykinin NK1 receptors, and its affinity for tachykinin NK2 and NK3 receptors is at least 2000 times lower than that for tachykinin NK1 receptors (Natsugari et al., 1999). (+)-CP-99,994, i.e., both agents are almost completely blocked the (Sar9,Met(O2)11)-SP-induced depressor response at 0.01 mg/kg, i.v. in rabbits, but not in rats, even at 1 mg/kg, i.v.

The aim of this study was to clarify the possible role of tachykinin NK1 receptors in visceral perception by investigating the effects of TAK-637 and (+)-CP-99,994 on the viscerosensory response caused by colorectal distention. We also attempted to clarify whether TAK-637 acts peripherally or centrally.

Materials and Methods

Animals. Male New Zealand White/Kbl rabbits (Kitayama Research, Ina, Japan) weighing 1 to 2.5 kg were used. Before the experiments, the animals were housed separately under standard controlled environmental conditions with a 12-h light/dark cycle and were given food and water ad libitum. Before the experiments, the animals were deprived of food for 48 h but allowed free access to water. The care and use of animals and experimental protocols of this study were approved by Takeda’s Experimental Animal Care and Use Committee.

Drugs. TAK-637, the enantiomer of TAK-637, the main metabolite of TAK-637 (metabolite I; M-I), and (+)-CP-99,994 were all synthesized at Takeda Chemical Industries, Ltd., Osaka, Japan. Ondanestron was synthesized by Junsei Chemical Co., Osaka, Japan. Atropine sulfate and β-cyclodextrin were purchased from Wako Pure Chemicals, Osaka, Japan. Trimebutine maleate and buprenorphine hydrochloride were obtained from Sigma Chemical Co. (St. Louis, MO) and Diosynth (Apeldoon, The Netherlands), respectively. Methylcellulose and bupivacaine hydrochloride were purchased from Shinetsu Chemical Industries (Tokyo, Japan) and AstraZeneca (Osaka, Japan), respectively. For intraduodenal administration, TAK-637, trimebutine maleate, ondansetron, atropine sulfate, and buprenorphine hydrochloride were suspended in 0.5% methylcellulose solution and administered at a volume of 4 ml/kg. For i.v. administration, (+)-CP-99,994 and buprenorphine hydrochloride were dissolved in saline and administered at a volume of 2 ml/kg, whereas TAK-637 and M-I were dissolved in dimethyl sulfoxide and administered at a volume of 0.05 ml/kg. For i.t. administration, TAK-637 was dissolved in 20% β-cyclodextrin solution, then lyophilized and stored until required. For use, the lyophilized TAK-637 was dissolved in distilled water and diluted with 20% β-cyclodextrin solution. (+)-CP-99,994 was dissolved in saline.

Surgical Procedures. The abdomen was opened by a midline laparotomy under pentobarbital sodium (30 mg/kg, i.v.) anesthesia, and a silicone catheter (o.d., 1.5 mm; i.d., 1 mm) was inserted to allow intraduodenal administration. One end of the catheter was introduced into the duodenal lumen through an incision made 2 cm distal from the pyloric ring. The other end was run subcutaneously along the costal flank and out through an incision between the scapulae, where it was fixed to the adjacent skin with silk sutures.

For i.t. administration, the animals were anesthetized with pentobarbital and respiration was maintained at 60 breaths/minute by mechanical ventilation. A polyethylene intrathecal catheter (o.d., 0.66 mm; i.d., 0.28 mm) was chronically implanted into the T11-L2 spinal segments through a puncture in the atlanto-occipital membrane and was secured to the skull using the method of Yaksh and Rudy (1976) with minor changes. Animals that showed any motor dysfunction after catheter implantation were excluded from the experiments. To verify the placement of the catheter, 80 μl of a local anesthetic, 0.25% bupivacaine hydrochloride, was injected i.t. about 1 week after implantation. If the catheter was correctly placed, the animals developed dragging of the hind legs after the bupivacaine injection, but recovered from this paralysis within 5 min.

Finally, a medical force transducer attached to a telemetry system (IMT-10; Star Medical, Tokyo, Japan) was sutured to the external oblique muscle, 4 cm from the midline, to measure the number of abdominal contractions. The animals were allowed to recover from the operation before the experiments.

Colorectal Irritation. After a 48-h fast, each animal was placed into a clear plastic syringe (i.d., 13–15 cm; length, 45–60 cm; Osaka Riko, Osaka, Japan). To acclimatize the animals to this new environment and the colorectal distention technique, colorectal distention was performed twice before proceeding with colorectal irritation. A 6-cm-long balloon made from the tip of a condom was inserted through the anal canal and advanced 8 cm into the rectum, then the tube was secured to the base of the tail with tape. The balloon was rapidly inflated with air to a pressure of 30 mm Hg, and this pressure was maintained for 10 min. Colorectal irritation was performed according to the method of Langlois et al. (1997) with minor changes. Acetic acid solution (0.8%, 4 ml, 24 ml/min) was applied to the colorectal region through a silicone catheter (o.d., 3 mm; i.d., 2 mm) inserted 2 to 8 cm in from the anal verge. One hour after introduction of the acetic acid solution, the animals displayed a hypersensitive response to colorectal distention as described by Plourde et al. (1997).

Colorectal Distention Procedures. To count the abdominal contractions, the receiver for the wireless force transducer was connected to a polygraph system (WindGraf 980; Gould Inc., Cleveland, OH). Because colorectal sensitivity to colorectal distention after acetic acid treatment differed among the animals, the most appropriate distention pressure (i.e., one that produced more than 10 contractions/10 min) was selected by increasing in 5-mm Hg steps. Any animal that did not exhibit an adequate response after the pressure had been increased to 45 or 50 mm Hg was excluded from the study.

In the first series of experiments, we investigated whether treatment with acetic acid solution would enhance the response to colorectal distention. The colorectal distension was performed by colorectal irritation at 30 mm Hg for 10 min before and 1 h after acetic acid treatment.

In the second series of experiments, the effects of TAK-637 and the various reference drugs on viscerosensory response were investigated. The inhibition rate for each drug (percentage) was calculated by comparing the number of contractions induced by the combined...
acetic acid/colorectal distention procedure before and after administration of each drug; namely, 1 h after administration of acetic acid solution into the colorectum, the colorectum was distended. At this time, the most appropriate distention pressure was selected as described above. The animals showing different distention pressure responses were assigned evenly to each group so that the mean distention pressure was the same among the treatment groups. A 10-min interval was taken between each distention period. TAK-637, the enantiomer of TAK-637, trimebutine maleate, ondansetron, atropine sulfate, and buprenorphine hydrochloride were administered intraduodenally 10 min after distention with the appropriate pressure (first distention). Forty minutes later, the colorectum was distended with the same pressure (second distention). In addition, (±)-CP-99,994 and buprenorphine hydrochloride were given i.v. 3 min before the second distention period. TAK-637 and M-I were given i.v. 10 min before the second distention period. Intrathecal injections of TAK-637 and (±)-CP-99,994 were performed 30 and 5 min before the second distention period, respectively.

In the third series of experiments, we investigated the effect of TAK-637 on the viscerosensory response after administration once daily for 7 consecutive days to determine whether the inhibitory effect of TAK-637 is affected by repeated administration. The seventh dose was administered 40 min before the second distention period.

The total number of animals used in these experiments was 150. In the first series of experiments, 11 animals were used. In the second and third series of experiments investigating the effects of various drugs on viscerosensory response, 5 animals were assigned to each group.

Statistical Analysis. To compare the effects of the various drugs on the viscerosensory response, the inhibition rate (percentage) for each drug was calculated as follows: inhibition rate (%) = (A - B/A) × 100; where A and B represent the number of abdominal contractions induced by colorectal distention before (A) and after (B) drug administration.

All data are expressed as the mean ± S.E.M. The statistical significance of differences among all the groups was determined using Dunnett’s test, whereas differences between two particular groups were analyzed using the paired or Student’s t test.

**Results**

Acetic Acid Solution-Induced Colorectal Irritation. To determine whether 0.8% acetic acid solution induces hypersensitivity in the colorectum, the number of abdominal contractions caused by colorectal distention was counted before and after the administration of acetic acid solution. One hour after the intracolorectal administration of acetic acid solution, the number of distention-induced abdominal contractions showed a significant 4-fold increase (Fig. 1). Because the visceral sensitizing effect of acetic acid treatment remained apparent for at least 4 h, the effects of TAK-637 and the other reference drugs were investigated under this condition.

Effects of Tachykinin NK1 Receptor Antagonists and Reference Drugs on the Viscerosensory Response. In acetic acid-treated rabbits, the number of abdominal contractions caused by colorectal distention was slightly increased after vehicle administration. Intraduodenal administration of TAK-637 dose-dependently inhibited the viscerosensory response to colorectal distention in rabbits (Fig. 2). A significant inhibitory effect was observed with doses of 0.3 to 3 mg/kg, and the inhibition rate at a dose of 1 mg/kg, intraduodenally, was 48.6 ± 7.1% (n = 5). Another tachykinin NK1 receptor antagonist, (±)-CP-99,994, also inhibited the abdominal response dose dependently and significantly when given i.v. (Fig. 3). By contrast, the enantiomer of TAK-637, which possesses only about 1/750 of the affinity for tachykinin NK1 receptors shown by TAK-637, had no effect on the abdominal contractions. The inhibition rates for the vehicle alone and the enantiomer at a dose of 3 mg/kg, intraduodenally were 1.0 ± 9.0 and −2.5 ± 10.8% (n = 5), respectively.

To clarify whether the inhibitory effect of TAK-637 is affected by repeated administration, the effect of consecutive doses of TAK-637 was investigated. After repeated adminis-
tration for 7 days at a dose of 1 mg/kg, intraduodenally, the inhibitory effect of TAK-637 was the same as that after a single dose (inhibition rate $\pm 48.6 \pm 7.1\%$, $n = 5$).

The effects of various other reference drugs on the viscerosensory response were also investigated. A peripheral opiate receptor agonist, trimebutine maleate, a 5-hydroxytryptamine3 receptor antagonist, ondansetron, and a muscarinic receptor antagonist, atropine sulfate, showed no inhibitory effect on the abdominal response caused by distention of the irritated colon (Fig. 4). A central opiate receptor agonist, buprenorphine hydrochloride, whether given intraduodenally or i.v., markedly reduced the abdominal response (Figs. 3 and 4).

**Effects of TAK-637 and M-I on the Viscerosensory Response.** To clarify whether TAK-637 inhibits the viscerosensory response by acting peripherally or centrally, we investigated the effect of its main metabolite, M-I, which has more potent tachykinin NK1 receptor antagonistic activity but is mainly distributed to the peripheral organs, on colorectal distention. Intravenous injection of TAK-637 dose dependently and significantly reduced the number of abdominal contractions in the rabbits (Fig. 5). Although M-I also inhibited the abdominal response, its inhibitory effect was less than that of TAK-637 (Fig. 5).

**Effects of Intrathecal Administration of Tachykinin NK1 Receptor Antagonists on the Viscerosensory Response.** To clarify whether TAK-637 acts at the spinal level, the effect of i.t. administration on the viscerosensory response was investigated. At a dose of 10 $\mu$g i.t., TAK-637 significantly inhibited the viscerosensory response caused by colorectal distention in acetic acid-treated rabbits by $62.7 \pm 12.6\%$ ($n = 5$; Fig. 6A). (+)-CP-99,994 at a dose of 10 $\mu$g, i.t. also significantly inhibited the abdominal response caused by colorectal distention ($n = 5$; Fig. 6B).

**Discussion**

It is well known that, in both humans and experimental animals, distention of the gastrointestinal tract elicits abdominal pain, thereby inducing pseudoaffective reflexes such as viscerosensory or cardiovascular responses (Ness and Gebhart, 1988). Abdominal contractions induced by colorectal distention in rats have been used to quantify visceral perception and to assess therapeutic agents for functional bowel disorders such as IBS (Langlois et al., 1997). Because this response is attenuated by morphine, colorectal distention seems to act as a nociceptive stimulus to organs, leading to an visceral response.

**Fig. 3.** Effects of (+)-CP-99,994 and buprenorphine hydrochloride (BUP) on abdominal contractions caused by colorectal distention (30–45 mm Hg, 10 min) in acetic acid-treated rabbits. The drugs were administered i.v. 3 min before the second distention period. All data are expressed as the mean ± S.E.M. for five animals. *, $P < 0.05$ and **, $P < 0.01$ compared with the vehicle-treated group (Dunnett’s test).

**Fig. 4.** Effects of trimebutine maleate (TRM), ondansetron (OND), atropine sulfate (ATR), and buprenorphine hydrochloride (BUP) on abdominal contractions caused by colorectal distention (30–45 mm Hg, 10 min) in acetic acid-treated rabbits. The drugs were administered intraduodenally 40 min before the second distention period. All data are expressed as the mean ± S.E.M. for five animals. ***, $P < 0.01$ compared with the vehicle-treated group (Dunnett’s test).

**Fig. 5.** Effects of TAK-637 and its main metabolite, M-I, on abdominal contractions caused by colorectal distention (30–45 mm Hg, 10 min) in acetic acid-treated rabbits. The drugs were administered i.v. 10 min before the second distention period. All data are expressed as the mean ± S.E.M. for five animals. *, $P < 0.05$ and **, $P < 0.01$ compared with the vehicle-treated group (Dunnett’s test).
abdominal contractions (Ness and Gebhart, 1988). Furthermore, the abdominal response to colorectal distention in rats is abolished after spinalization but not by decerebration, suggesting that distention acts via brainstem loops (Ness and Gebhart, 1990).

The mean sensory thresholds of hollow organs are generally lower in IBS patients than in unaffected individuals (Mertz et al., 1995). Although the mechanism underlying this hypersensitivity is not fully understood, previous infection, inflammation, and/or psychological stress have been associated with the bowel dysfunction observed in IBS (Gwee et al., 1996; Accarino et al., 1997). Langlois et al. (1997) found that colorectal hypersensitivity could be induced by intracolorectal treatment with 0.6% acetic acid solution in rats. In the present study, we used 0.8% acetic acid solution to induce colorectal hypersensitivity. Our preliminary histological study revealed areas of slight detachment of the epithelium and neutrophilic invasion, but no hemorrhage, in colorectal segments treated with 0.8% acetic acid solution (data not shown). The number of abdominal contractions caused by colorectal distention was markedly increased after treatment with 0.8% acetic acid in rabbits as well as in rats. Buprenorphine, an analgesic, markedly inhibited the abdominal response caused by colorectal distention of the irritated colon, indicating that this response was caused by noxious stimuli. In addition, Plourde et al. (1997) showed that this colorectal hypersensitivity was attenuated by treatment with a large dose of capsaicin in rats, suggesting that this response is, at least in part, mediated via capsaicin-sensitive afferent C-fibers.

In the present study, the tachykinin NK₁ receptor antagonist TAK-637 dose dependently inhibited the viscerosensory response in rabbits, and repeated administration did not decrease this inhibitory effect. (±)-CP-99,994, another tachykinin NK₁ receptor antagonist that differs structurally from TAK-637, also inhibited the abdominal response in a dose-dependent manner. On the other hand, the enantiomer of TAK-637, which has only about 1/750 of the tachykinin NK₁ receptor antagonistic activity of TAK-637 (Natsugari et al., 1999), did not inhibit the abdominal contractions. The first main points of this study are, therefore, that tachykinin NK₁ receptor antagonists exert a potent inhibitory effect on the viscerosensory response, and that TAK-637 inhibited the response specifically via tachykinin NK₁ receptors. Moreover, in our preliminary study, TAK-637 did not change colorectal compliance in rabbits (data not shown). McLean et al. (1998) and Pan et al. (1995) have also shown that tachykinin NK₁ receptor antagonists inhibit nociceptive reflex responses to jejunal distention in rats and gallbladder distention in cats. These results clearly show that tachykinin NK₁ receptors play an important role in visceral perception.

Numerous studies of the distribution of tachykinin NK₁ receptors have shown that, although there are differences among species, tachykinin NK₁ receptors are widely distributed throughout the central and peripheral nervous systems. In the gastrointestinal tracts of rodents, SP is located in SP-containing neurons found almost entirely in the Auerbach and Meissner enteric nervous systems (Holzer and Holzer-Petsche, 1997). Moreover, the sensory afferent neurons known as capsaicin-sensitive C-fibers, which run from the viscera to the spinal dorsal root ganglia, also contain SP (Gamse et al., 1980). The terminals of these C-fibers are known to be located mainly in superficial laminae I of the spinal cord, and SP is one of the most abundant peptides in this region (Todd and Spike, 1993). In somatic pain models, the expression of SP in the spinal cord is increased by arthritis-induced hyperalgesia (Walker et al., 2000). In addition, administration of anti-SP monoclonal antibody by the same route diminished the pain responses caused by tail pinching and arthritis (Kuraishi et al., 1991; Satoh et al., 1992).

**Fig. 6.** Effects of i.t. TAK-637 and (±)-CP-99,994 on abdominal contractions caused by colorectal distention (30–50 mm Hg, 10 min) in acetic acid-treated rabbits. The drugs were administered i.t. 30 (A) and 5 (B) min before the second distention period. All data are expressed as the mean ± S.E.M. for five animals. **+, P < 0.01 compared with the vehicle-treated group (Student’s t test).**
Although the importance of SP or tachykinin NK1 receptors participates in this response. However, further studies will be required to clarify the involvement of these receptors in the viscerosensory responses caused by colorectal distention in rabbits.

It is known that chronic life stresses activate neural and hormonal factors and can result in gastrointestinal dysfunc-

In IBS patients, stress seems to be strongly associated with the occurrence of symptoms such as diarrhea, constipa-

tion, and abdominal pain, since counseling therapy and an-

xioytic or antidepressant agents are reported to be effective treatments (Clouse, 1994). The occurrence of IBS symptoms is also known to be closely associated with the severity of depression (Drossman, 1999). Recently, Kramer et al. (1998) reported that a tachykinin NK1 receptor antagonist showed antidepressant activity in experimental animals as well as in patients with a major depressive disorder. Although there is no conclusive evidence that TAK-637 has an anxiolytic effect, the possibility cannot be ruled out because this agent perme-
ates into the CNS. Furthermore, TAK-637 has been found to inhibit restraint stress-induced defecation in gerbils (Okano et al., 2001). These results suggest that TAK-637 has poten-
tial usefulness in the treatment of IBS.

In summary, our investigation has clearly shown that the tachykinin NK1 receptor antagonist TAK-637 inhibits the viscerosensory response induced by colorectal distention of the irritated colon in rabbits, and that its main site of action seems to be tachykinin NK1 receptors in the spinal cord. Taken together with the recent finding that TAK-637 inhibits stress-induced defecation in gerbils, our results indicate that TAK-637 could be a useful therapeutic agent for the treatment of functional bowel disorders such as IBS.

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