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Fedotozine blocks hypersensitive visceral pain in conscious rats: action at peripheral κ-opioid receptors

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Abstract

The effect of fedotozine on visceral hypersensitivity was evaluated in conscious rats. One hour after colonic irritation (0.6% acetic acid intracolonically), a 30 mmHg colonic distension was applied for 10 min. Irritation increased the number of abdominal contractions induced by colonic distension (23.4 ± 4.1 versus 4.8 ± 1.4 in saline-treated rats, $P < 0.001$). Facilitation of colonic pain was reversed in a dose-dependent manner by fedotozine ((+)-(-1*R*)-1-phenyl-1-[(3,4,5-trimethoxy)benzyloxymethyl]-*N*,*N*-dimethyl-*n*-propylamine), (±)-U-50,488H (*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl]cyclohexyl)benzeneacetamide) and morphine (respective ED_{50} values 0.67, 0.51 and 0.23 mg/kg s.c.). The κ-opioid receptor antagonist, nor-binaltorphimine, abolished the effects of fedotozine and (±)-U-50,488H but not those of morphine. Low doses of naloxone (30 μg/kg s.c.) blocked the effect of morphine but not of fedotozine or (±)-U-50,488H. After intracerebroventricular administration, morphine was very potent (ED_{50} 1.7 μg/rat), (±)-U-50,488H poorly active (58% of antinociception at 300 μg/rat) and fedotozine inactive up to 300 μg/rat. These results show that fedotozine blocks hypersensitive visceral pain by acting on peripheral κ-opioid receptors in animals. © 1997 Elsevier Science B.V.

Keywords: Fedotozine; κ-Opioid receptor; μ-Opioid receptor; Visceral pain; Colonic hypersensitivity; (Colonic distension)

1. Introduction

Altered visceral sensation and pain are common major symptoms in non-cardiac chest pain (Paterson et al., 1993; Harford, 1994), functional dyspepsia (Lémann et al., 1991) and irritable bowel syndrome (Müller-Lissner, 1993). In these pathological states, a decreased threshold for sensation of discomfort and pain arising from the gut has been demonstrated by provocative tests like balloon distension (Ritchie, 1973; Lémann et al., 1991; Cannon and Benjamin, 1993). κ-Opioid receptor agonists (for review, see Junien and Rivière, 1995), $5\text{-}HT_3$ receptor antagonists (Prior and Read, 1993) and somatostatin analogs (Bradette et al., 1994b; Hasler et al., 1994) are among the promising pharmacological approaches for the treatment of gastrointestinal sensitivity disorders and pain.

Distension of the digestive tract has been widely used experimentally in animals (Ness and Gebhart, 1990). However, few attempts have been made to irritate the gut in order to mimic visceral hypersensitivity observed in human pathological states. One study has reported a decrease in rectal pain threshold to distension after trinitrobenzene sulfonic acid-induced colonic inflammation in conscious rats (Morteau et al., 1994). In an other study, systemic administration of a low dose of 5-hydroxytryptophan lowered the distension pressure required to induce visceromotor response to colo-rectal distension in conscious rats (Banner and Sanger, 1995). We have previously shown that in anaesthetized rats, the intracolonic administration of dilute acetic acid induces a facilitation of colonic pain to distension without significant tissue injury (Langlois et al., 1994). Fedotozine, which acts as an agonist on peripheral κ-opioid receptors (Gué et al., 1990; Diop et al., 1994b; Rivière et al., 1993, 1994, displayed a greater antinociceptive effect against colonic distension after acetic acid-induced colonic irritation than in non-irritated rats (Langlois

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et al., 1994). The latter observation was obtained with a high-grade distension pressure (75 mmHg). Furthermore, the effect of fedotozine on colonic pain has hitherto not been investigated in conscious rats. Therefore, the present study examined the antinociceptive activity of fedotozine in a model of hypersensitive colonic pain using a low-grade colonic distension pressure in conscious rats. In addition, the antinociceptive effect of fedotozine was compared to that of morphine and (±)-U-50,488H, two reference agonists at μ- and κ-opioid receptors.

2. Material and methods

2.1. Animals and surgical preparation

260 male Sprague-Dawley rats (Iffa Credo, Les Oncins, France) weighing 300–350 g were used. The animals were housed 3 per cage in a regulated environment (20 ± 1°C; humidity 50 ± 5%; light from 8:00 a.m. to 8:00 p.m.). Food (regular laboratory chow, M25, Extralabo, Piètrement, Provins, France) and water were provided ad libitum.

For central injection, animals were implanted one week before the experiment with an intracerebroventricular (i.c.v.) cannula under ketamine anaesthesia. The cannula was anchored with dental cement to the skull according to a technique adapted from Stewart et al. (1978).

Procedures for the maintenance and use of the experimental animals were carried out in accordance with the guidelines of the International Association for the Study of Pain.

2.2. Colonic irritation procedure

After an overnight fast, each animal was placed in a transparent plastic cage with a layer of sawdust on the floor in a 45 min period in order to get used to its surroundings. A 5-cm-long latex balloon mounted on a polyethylene catheter was used for the colonic distension. The balloon was inserted via the anal route and kept in place by taping the balloon catheter to the base of the tail such that the tip was kept 10 cm from the anal verge. Colonic distension was produced by inflation of the balloon with air through the polyethylene catheter. The balloon compliance may be considered infinite since in ambient air, the pressure in the balloon remained at zero for volumes up to 50 ml of air. By contrast, a distension volume of about 7 ml was enough to achieve a balloon pressure of 30 mmHg when the balloon was placed in the rat colon.

Colonic irritation was induced by intracolonic injection of 1.5 ml of 0.6% acetic acid (w/v) followed by a 1 ml flush of air via a small Silastic catheter (i.d. 0.635 mm, o.d. 1.19 mm) mounted along the balloon assembly (Langlois et al., 1994). Control animals received 1.5 ml of isotonic saline solution intracolonically. One hour after the injection, a colonic distension of 30 mmHg was applied for 10 min. Pain was scored by visual counting of the abdominal contractions (Koster et al., 1959) occurring over the 10-min distension period. It has previously been demonstrated that abdominal electromyographic recording and visual evaluation of abdominal muscle contraction are consistent together and lead to the same pain score (Ness and Gebhart, 1988). To evaluate the effect of acetic acid on colonic compliance, the volume of air required to maintain a constant distension of 30 mmHg for 10 min was determined in saline- and acetic-acid-treated rats.

Finally, the warm water (45°C) tail-flick test (Franklin and Abbott, 1989) was used as a non-visceral somatic stimulus to verify that the acetic-acid-induced hyperalgesic response was limited to the visceral stimulus. The latency to tail withdrawal was determined before (control period) and 60 min after intracolonic administration of 0.6% acetic acid in the same animals.

At the end of the experiments, animals were killed with an i.p. overdose of pentobarbital and the colonic mucosa was examined macroscopically.

2.3. Pharmacological experiments in acetic-acid-treated rats

In acetic-acid-treated rats, the colonic distension of 30 mmHg for 10 min (pre-treatment period) was followed by a subcutaneous injection of vehicle or drugs and 20 min later a second period of distension (30 mmHg for 10 min, post-treatment period) was again applied. In all experiments, pressure within the balloon was measured continuously by a pressure transducer (Bioblock, Illkirch, France). To avoid any influence of colonic motor responses (contraction or relaxation) on the magnitude of the stimulus, care was taken to apply a constant pressure distension.

Drugs were given as follows: fedotozine ((+)-(-1*R*)-1-phenyl-1-[(3,4,5-trimethoxy)benzyloxymethyl]-*N*,*N*-dimethyl-*n*-propylamine) at doses ranging from 0.3 to 3 mg/kg s.c. and at 100 and 300 μg/rat i.c.v.; morphine at doses ranging from 0.1 to 1 mg/kg s.c. and from 1 to 10 μg/rat i.c.v.; and (±)-U-50,488H (*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl]cyclohexyl)benzeneacetamide) at doses ranging from 0.3 to 3 mg/kg s.c. and from 30 to 300 μg/rat i.c.v. Naloxone (30 and 300 μg/kg s.c.) was coadministered with the agonist whereas nor-binaltorphimine (10 mg/kg s.c.) was administered 10 min before the injection of the agonist. The doses of naloxone (30 μg/kg s.c.) and nor-binaltorphimine (10 mg/kg s.c.) were previously shown to selectively block μ- and κ-opioid receptors, respectively (Diop et al., 1994a,b).

2.4. Drugs

The drugs were purchased as follows: morphine (Francopia, Paris, France), (±)-U-50,488H (RBI, Bioblock, Il-

lkirch, France) and naloxone hydrochloride (Narcan®; Dupont de Nemours, Paris, France). Fedotozine tartrate was synthesized by Sipsy (Avrillé, France) and nor-binaltorphimine hydrochloride by Jouveinal's Department of Medicinal Chemistry. Fedotozine, morphine, (±)-U-50,488H and naloxone were dissolved in 0.9% saline solution. Nor-binaltorphimine was dissolved in distilled water. Injected volumes were limited to 2 ml/kg and 5 μl/rat for the s.c. and i.c.v. routes, respectively. Acetic acid was obtained from Prolabo (Paris, France), pentobarbital from Sanofi (Libourne, France), ketamine (Ketalar®) from Parke-Davis (Courbevoie, France) and dental cement from De Trey Special Tray Material (De Trey Dentsply, Bois Colombes, France).

2.5. Statistical analysis

Results are expressed as mean ± S.E.M. Statistical significance between two different groups of animals was assessed using the Mann-Whitney *U*-test. Statistical significance in the same group of animals between the pre-treatment period and the post-treatment period was assessed using the Wilcoxon test. Differences were considered statistically significant at $P < 0.05$. The antinociceptive effect of opioid receptor agonists was expressed by the following equation: % antinociception = 100 × [1 − (AC after treatment/AC before treatment)] (AC = cumulative abdominal contraction). The ED_{50} (the dose of drug that produced half-maximum antinociception) was calculated using the method of Litchfield and Wilcoxon (1949).

3. Results

3.1. Colonic irritation procedure

In control rats (isotonic saline intracolonically) a colonic distension of 30 mmHg for 10 min induced a small number of abdominal contractions (cumulative response during the distension period: 4.8 ± 1.4). In contrast, in most of the acetic-acid-treated rats (about 70%), the same distension procedure elicited a significantly greater number of abdominal contractions (cumulative response during the distension period: 23.4 ± 4.1, $P < 0.001$ vs. control rats). Animals were considered to display a hypersensitive response to colonic distension after acetic acid pretreatment, above a cut-off of 15 abdominal contractions. According to this cut-off, about 30% of animals were considered as non-responders and were not included in the study. Furthermore, when the hypersensitive response was present during the first distension period, it was stable and reproducible during the time as shown by the response obtained during a second period of distension applied 20 min later (Fig. 1). Finally, abdominal contractions totally disappeared at the end of the distension periods and neither isotonic saline (control rats) nor acetic acid (experimental rats) alone induced any abdominal contractions.

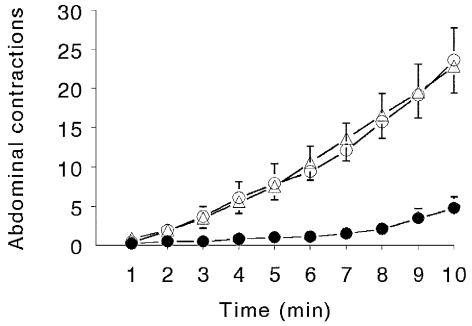

Fig. 1. Cumulative response in abdominal contractions during colonic distension (30 mmHg, 10 min) in saline-treated rats (●, $n = 10$) and in acetic-acid-treated rats ($n = 8$) during the first (○) and the second (△) distension period. Results are expressed as mean ± S.E.M.

The volume of air required to maintain a constant distension of 30 mmHg for 10 min was not significantly different between saline- and acetic-acid-treated rats (7.1 ± 0.6 ml and 6.0 ± 0.7 ml, respectively).

Macroscopic examination of colonic mucosa indicated that acetic acid but not saline induced a moderate area of congestion, and superficial focal hemorrhage; necrosis, gross bowel wall thickening and ulceration were never observed in 0.6% acetic-acid-treated rats.

Eight animals displaying colonic hyperalgesia to distension (24.9 ± 1.8 abdominal contractions) were also used in the warm water tail-flick test. Acetic acid treatment did not affect the latency to tail withdrawal. It was 9.78 ± 0.74 s before and 9.48 ± 0.74 s after intracolonic injection of 0.6% acetic acid.

3.2. Pharmacological experiments in acetic-acid-treated rats

None of the drugs tested in this study significantly modified the volume of air required to obtain a constant

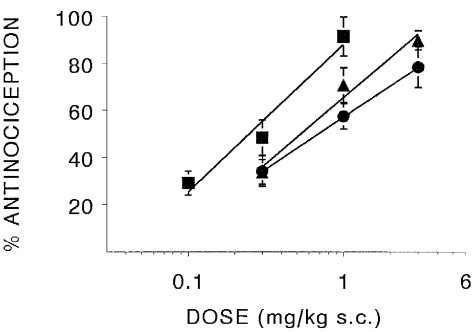

Fig. 2. Dose-response relationships of antinociceptive actions produced by s.c. administration of fedotozine (●), morphine (■) and (±)-U-50,488H (▲) on abdominal contractions during colonic distension (30 mmHg, 10 min) in acetic-acid-treated rats. Results are expressed as mean ± S.E.M. of 5–8 animals per dose.

Table 1
Antinociceptive effect of fedotozine, morphine and (±)-U-50,488H after intracerebroventricular administration

Agonist	Dose i.c.v. (μg/rat)	*n*	Abdominal contractions		% Antinociception
			1st distension period	2nd distension period	
Fedotozine	100	7	19.0 ± 2.0	15.3 ± 1.8	18.0 ± 9.0
	300	7	22.6 ± 2.3	18.7 ± 2.8	19.0 ± 7.6
Morphine	1	6	18.5 ± 1.3	12.2 ± 2.1	32.6 ± 12.5
	3	7	19.4 ± 2.1	5.4 ± 2.0	68.8 ± 12.5 [a]
	10	6	21.0 ± 1.9	1.5 ± 0.6	92.6 ± 3.5 [a]
(±)-U-50, 488H	30	6	19.7 ± 1.3	12.5 ± 1.0	35.4 ± 6.4 [a]
	100	7	17.4 ± 1.6	8.0 ± 1.6	53.1 ± 8.7 [a]
	300	7	18.6 ± 0.8	7.7 ± 0.9	58.1 ± 5.4 [a]

Drugs were given between the two periods of distension. Values are expressed as mean ± S.E.M.; *n* = number of animals per group. Statistical significance was assessed using the Wilcoxon test. [a] $P < 0.05$ vs. the 1st distension period.

distension pressure (data not shown), indicating that the compliance of the colon was not affected and thus did not contribute to the potential antinociceptive effect of the drug tested.

3.2.1. Effect of peripheral injection of fedotozine and opioid receptor agonists

Subcutaneous injection of fedotozine significantly ($P < 0.05$) inhibited in a dose-dependent manner the abdominal contractions induced by colonic distension in acetic-acid-treated rats (Fig. 2). The ED_{50} of fedotozine was 0.67 mg/kg s.c. (95% confidence intervals: 0.20–2.23). Morphine, a μ-opioid receptor agonist, and (±)-U-50,488H, a κ-opioid receptor agonist, also significantly ($P < 0.05$) inhibited abdominal contractions under the same conditions (Fig. 2). The ED_{50} of morphine and (±)-U-50,488H were 0.23 (95% confidence intervals: 0.09–0.59) and 0.51 mg/kg s.c. (95% confidence intervals: 0.20–1.32), respectively.

3.2.2. Effect of central injection of fedotozine and opioid receptor agonists

Morphine administered i.c.v. (1–10 μg/rat) induced a dose-dependent inhibition of abdominal contractions during colonic distension with an ED_{50} of 1.70 μg/rat (Table 1), which corresponds to 1/47 of the ED_{50} by s.c. route. In contrast, (±)-U-50,488H administered i.c.v. (30–300 μg/rat) produced a slight reduction in abdominal contractions during colonic distension (Table 1) with a maximal antinociceptive effect of 58.1 ± 5.4%. On the other hand, fedotozine did not display any significant antinociceptive effect after i.c.v. administration at doses ranging from 100 to 300 μg/rat.

3.2.3. Effect of naloxone and nor-binaltorphimine on the antinociceptive response to fedotozine, morphine and (±)-U-50,488H

When given alone, both naloxone (30 μg/kg and 300 μg/kg s.c.) and nor-binaltorphimine (10 mg/kg s.c.) failed to reduce abdominal contractions during colonic distension in acetic-acid-treated rats (data not shown). However, pre-treatment with a high dose of naloxone (300 μg/kg s.c.) blocked the effect of both morphine (1 mg/kg) and (±)-U-50,488H (3 mg/kg) (Table 2). At a lower dose (30 μg/kg s.c.) naloxone abolished the effect of morphine (1 mg/kg s.c.) but did not alter that of (±)-U-50,488H (3 mg/kg s.c.) (Table 2). Nor-binaltorphimine (10 mg/kg s.c.) abolished the effect of a maximal dose of (±)-U-

Table 2
Inhibitory effect of naloxone (30 and 300 μg/kg s.c.) and nor-binaltorphimine (Nor-BNI, 10 mg/kg s.c.) on the antinociceptive effect of morphine (1 mg/kg s.c.) and (±)-U-50,488H (3 mg/kg s.c.)

Agonist s.c.	Antagonist s.c.	*n*	Abdominal contractions		% Antinociception
			1st distension period	2nd distension period	
Morphine	–	7	21.4 ± 3.2	1.4 ± 7.0	90.7 ± 7.0
	Naloxone 300 μg/kg	5	25.6 ± 3.1	31.2 ± 2.9	−24.7 ± 8.8 [b]
	Naloxone 30 μg/kg	6	22.7 ± 3.8	20.8 ± 3.7	8.5 ± 7.6 [b]
	Nor-BNI 10 mg/kg	6	23.7 ± 3.2	3.0 ± 1.0	88.5 ± 2.9
(±)-U-50,488H	–	6	19.5 ± 3.0	1.7 ± 3.5	90.8 ± 3.5
	Naloxone 300 μg/kg	5	31.6 ± 4.1	34.8 ± 3.3	−12.6 ± 6.0
	Naloxone 30 μg/kg	5	24.0 ± 2.5	1.6 ± 3.5	93.0 ± 3.5 [a]
	Nor-BNI 10 mg/kg	7	24.1 ± 2.0	22.4 ± 2.1	6.3 ± 7.3 [b]

Drugs were given between the two periods of distension. Values are expressed as mean ± S.E.M.; *n* = number of animals per group. Statistical significance was assessed using the Mann-Whitney *U*-test. [a] $P < 0.01$, [b] $P < 0.001$ vs. agonist alone.

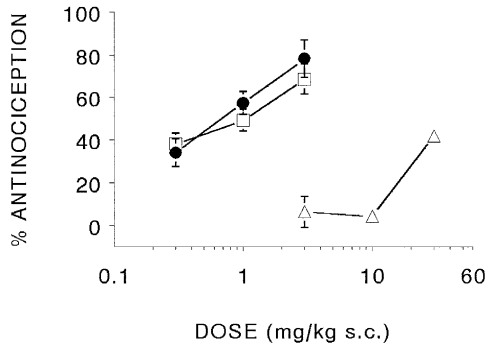

Fig. 3. Inhibitory effect of naloxone (30 μg/kg s.c., □) and nor-binaltorphimine (10 mg/kg s.c., △) on the antinociceptive action of fedotozine (●) against abdominal contractions during colonic distension (30 mmHg, 10 min) in acetic-acid-treated rats. Results are expressed as mean ± S.E.M of 5–8 animals per dose.

50,488H but had no effect on the maximal effective dose of morphine (Table 2). Pretreatment with the high dose of naloxone (300 μg/kg s.c.) totally inhibited the effect of fedotozine (3 mg/kg s.c.), the cumulative response in the second period of distension being 30.2 ± 1.9 abdominal contractions vs. 23.2 ± 1.8 abdominal contractions in the first period of distension. However, the low dose of naloxone did not alter the antinociceptive effect of fedotozine (Fig. 3). Finally, the fedotozine dose–response curve was shifted to the right after nor-binaltorphimine pretreatment (Fig. 3). In these conditions fedotozine at 30 mg/kg s.c. exhibited a maximal inhibitory effect of 41.6 ± 1.9%.

4. Discussion

It is well established that in humans as well as in animals, the distension of hollow organs induces pseudoaffective reflexes such as cardiovascular and visceromotor responses (Ness and Gebhart, 1988). Such responses have been used to quantify the magnitude of gastrointestinal pain stimulus and to evaluate the analgesic activity of drugs in animal models. In the present study pain was scored by visual counting of the abdominal contractions. Visual counting was preferred to electromyographic recording since both techniques give similar results (Ness and Gebhart, 1988), but visual counting of abdominal contractions provides a greater comfort for the animals by avoiding an invasive surgery procedure for implantation of chronic electrodes.

The number of abdominal contractions during colonic distension of 30 mmHg for 10 min remained very low, below 5, in saline-treated rats, while this intensity of colonic distension elicited a significant number of abdominal contractions in acetic-acid-treated rats. This result suggests an increase in colonic pain sensitivity to balloon distension. Using a step-down avoidance behavioral paradigm, Ness et al. (1991) showed that 30 mmHg colo-rectal distension did not affect the acquisition of passive avoidance behavior in control rats. By contrast, this same degree of colo-rectal distension led to avoidance of the stimulus following inflammation induced by topical administration of turpentine, indicating that non-noxious colo-rectal distension turned into a painful stimulus.

The increase in viscerosensitivity following acetic acid-induced colonic irritation is not related to abnormal colonic compliance since the volume of air required to obtain a constant distension of 30 mmHg for 10 min was not significantly different between control animals and the acetic-acid-treated group. In irritable bowel patients, a normally non-painful colonic distension turns into a painful stimulus without change in colonic compliance (Bradette et al., 1994a). Finally, the latency to tail withdrawal in the warm water tail-flick test was not modified after intracolonic injection of acetic acid. This finding indicates that increased visceral pain to colonic distension in acetic-acid-treated rats is not associated with altered somatic sensitivity, similarly to previous observations in irritable bowel patients (Cook et al., 1987). Taken together, the animal model developed here shows interesting features in regard to functional bowel disorders.

As it was previously shown in anesthetized rats (Langlois et al., 1994), κ-opioid receptor agonists such as fedotozine and (±)-U-50,488H as well as the μ-opioid receptor agonist, morphine, display an antinociceptive activity against colonic pain following colonic irritation. The antinociceptive effects were dose dependent and fedotozine was almost equipotent to (±)-U-50,488H and morphine in restoring normal visceral sensitivity to balloon distension.

In order to determine the type of opioid receptor involved in the antinociceptive action of fedotozine, differential blockade with selective antagonists of opioid receptor was carried out. The high dose of naloxone abolished the antinociceptive effects induced by the high dose of fedotozine, (±)-U-50,488H and morphine, indicating involvement of opioid receptors. The low dose of naloxone, known to selectively block μ-opioid receptors (Diop et al., 1994a,b), totally inhibited the maximal effect of morphine but did not affect the antinociception induced by the maximal effective dose of (±)-U-50,488H and did not shift the dose–response curve of fedotozine. Nor-binaltorphimine, which has been reported to be a selective κ-opioid receptor antagonist (Portoghese et al., 1987; Takemori et al., 1988), abolished the effect of the maximal effective dose of (±)-U-50,488H and shifted the dose–response curve of fedotozine to the right but did not modify the maximal effective dose of morphine. This suggests that the antinociceptive effect of fedotozine on colonic pain hypersensitivity following colonic irritation in conscious rats is mediated by κ-opioid receptors, as previously reported for other pharmacological effects of fedotozine (Rivière et al., 1993; Diop et al., 1994b; Langlois et al., 1994).

Fedotozine did not display any antinociceptive action when administered intracerebroventricularly, even at doses up to the ED_{50} observed after subcutaneous administration. This result is consistent with the lack of activity of fedotozine after intracerebroventricular or intrathecal administration (Rivière et al., 1993; Diop et al., 1994b), and suggests that peripheral κ-opioid receptors are involved in the pharmacological action of fedotozine in restoring normal colonic pain sensitivity to balloon distension as shown by the blockade of abdominal contractions in acetic-acid-treated rats. Similarly, the low potency of (±)-U-50,488H after i.c.v. compared to s.c. administration suggests that peripheral rather than supraspinal κ-opioid receptors are involved. On the other hand, the potent activity of morphine after i.c.v. administration was in good correlation with its high affinity for supraspinal and spinal μ-opioid receptors (Martin, 1984). In addition, in the central nervous system, the brain areas involved in sensory integration and pain modulation have a high density of μ-opioid receptors (Mansour et al., 1988).

A peripheral rather than a central action of fedotozine and (±)-U-50,488H, two κ-opioid receptor agonists, has been described in the present study. The increase potency of κ-opioid receptor agonists during inflammation has been extensively detailed (for review see Barber and Gottschlich, 1992; Junien and Wettstein, 1992) and a direct action on primary afferents has been suggested. U-50,488H selectively acts on Ca^{2+} channels in cultured dorsal root ganglion cells (Werz et al., 1987). Such an action could block the release of the afferent transmitter since Ca^{2+} inflow is critical for neurotransmitter release (Millan, 1990). Moreover, inhibitory and facilitatory effects of κ-opioid receptor agonists on C-fiber-evoked responses in dorsal horn neurons have been reported (Haley et al., 1990; Hylden et al., 1991). These findings were initially established in a non-visceral somatic pain model and the concept has recently been validated for visceral pain. Rivière et al. (1994) have suggested that κ-opioid receptor agonists may reverse chemical ileus by a peripheral action on non-vagal sensory afferents. In another study, fedotozine blocked peritonitis-induced c-fos expression in the spinal cord at the level of projection of visceral afferents (Bonaz et al., 1995). Finally, fedotozine and U-50,488H block colonic distension-induced firing of decentralised pelvic afferents (Sengupta et al., 1996).

In conclusion, fedotozine is able to restore normal colonic sensitivity in a experimental model of hypersensitive colonic pain in conscious rats, probably by modulating the activity of afferent fibers carrying the noxious message. This finding is consistent with the ability of fedotozine to raise the painful threshold to gastric (Coffin et al., 1995) and colonic distension (Delvaux et al., 1995) in humans and with its clinical efficacy shown in functional dyspepsia (Fraitag et al., 1994) and in irritable bowel syndrome patients (Dapoigny et al., 1995).

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