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Influence of Trimebutine on Inflammation- and Stress-induced Hyperalgesia to Rectal Distension in Rats

C. LACHEZE, A.-M. COELHO, J. FIORAMONTI AND L. BUÉNO

Department of Pharmacology, INRA, Toulouse, France

Abstract

The effects of trimebutine and its major metabolite, *N*-desmethyltrimebutine on inflammation- and stress-induced rectal hyperalgesia have been evaluated in rats fitted with electrodes implanted in the longitudinal striated muscle of the abdomen.

Intermittent rectal distension was performed before and 3 days after induction of rectal inflammation by local infusion of trinitrobenzenesulphonic acid (in ethanol). Stress consisted of 2h partial restraint and rectal distension was performed before and 30min after the end of the partial restraint session. The animals were treated intraperitoneally with trimebutine or desmethyltrimebutine (5, 10 or 20mgkg^{-1}) or vehicle 15min before rectal distension. Naloxone (1mgkg^{-1}) or saline was injected subcutaneously before trimebutine and desmethyltrimebutine. Before treatment trimebutine at the highest dose (20mgkg^{-1}) reduced the abdominal response to rectal distension for the highest volume of distension (1·6mL) whereas desmethyltrimebutine was inactive. After rectocolitis the abdominal response to rectal distension was enhanced and trimebutine at 5mgkg^{-1} reduced and at 10mgkg^{-1} suppressed inflammation-induced hyperalgesia, an effect reversed by naloxone. Desmethyltrimebutine was inactive. Stress-induced hypersensitivity was attenuated or suppressed, or both, by trimebutine and desmethyltrimebutine at doses of 5, 10 or 20mgkg^{-1}; greater efficacy was observed for desmethyltrimebutine and the effects were not reversed by naloxone.

It was concluded that trimebutine and desmethyltrimebutine are active against inflammation- and stress-induced rectal hyperalgesia but act differently. The effect of trimebutine on inflammation-induced hyperalgesia is mediated through opioid receptors.

Abdominal pain is the major symptom of functional bowel disorders, and reduced threshold to rectal sensation and pain is commonly observed in patients with irritable bowel syndrome (Chaudhary & Truelove 1962; Ritchie 1973; Lembo et al 1994). Even though the existence of gut inflammatory reactions in irritable bowel syndrome is still a subject of controversy, recent reports have emphasized the possibility that previous experience of gut inflammation such as gastroenteritis might trigger the delayed occurrence of irritable bowel syndrome particularly in patients subsequently subject to a stressful life (Gwee et al 1996).

Inflammatory bowel disease is associated with reduced threshold of pain sensation to colonic or rectal distension in man (Rao et al 1987). Colonic or rectal irritation with chemicals induces a drastic increase in barosensitivity to gradual rectal distension in rats (Ness et al 1991; Morteau et al 1994a). Acute physical and mental stress stimuli are known to affect the perception of pain related to barosensitivity in both healthy subjects and irritable bowel syndrome patients (Erckenbrecht et al 1988; Ford et al 1995; Métivier et al 1996). Recently, it has been demonstrated that restraint stress acts in the opposite direction to somatic and visceral sensitivity with a transient lowering of the threshold of rectal distension-induced abdominal cramps in rats (Porro & Carli 1988; Gué et al 1997).

Opioid substances with activity at μ (morphine, Dago) or κ (fedotozine, U50488) receptors have previously been shown to be active on pseudo-affective (cardiovascular) response to colonic distension (Diop et al 1994; Danzebrink et al 1995), with a greater efficacy in the presence of acetic acid-induced colitis (Langlois et al 1994). It has

Correspondence: L. Buéno, Department of Pharmacology INRA, BP3, 180 Chemin de Tournefeuille, 31931 Toulouse Cedex 9, France.

also been reported that mixed μ and κ opioid substances, for example trimebutine, might prevent stress-induced alterations of upper (Gué et al 1988) and lower (Junien et al 1991) gut motility in dogs and rats, respectively.

This aim of this work was to determine whether trimebutine, a classical drug used for the treatment of irritable bowel syndrome and which has mixed μ and κ agonist activity (Valori & Shannon 1987; Pascaud et al 1989) has different effects on rectal sensitivity to distension before and after inflammation or stress. We have also investigated whether such activity is linked to activation of opioid receptors, both by use of naloxone and by comparing its effects with those of its major metabolite *N*-desmethyltrimebutine, a weak opioid agonist.

Material and Methods

Chemicals

Trimebutine maleate and *N*-desmethyltrimebutine were provided by the Institut de Recherches Jouveinal (Fresnes, France) and naloxone hydrochloride was purchased from Sigma (La Verpillère, France).

Animal preparation

Sixteen groups of eight male Wistar rats (Elevage Janvier, Le Genest Saint Isle, France), 250–350 g, were surgically prepared for electromyography, according to a previously described technique (Rukebusch & Fioramonti 1975). Rats were anaesthetized with acepromazine (0·3 mL, 0·5 mg kg^{-1}) and ketamine (Imalgene 1000, Rhône-Mérieux, Lyon, France; 0·3 mL, 120 mg kg^{-1}) injected intraperitoneally. One group of three electrodes was implanted in the abdominal external oblique musculature just above the inguinal ligament. Electrodes were exteriorized on the back of the neck and protected by a glass tube attached to the skin.

Motility recordings

Electromyographic recording began five days after surgery. The electrical activity of the abdominal striated muscles was recorded with an electroencephalograph (Mini VIII, Alvar, Paris, France) using a short time constant (0·03 s) to remove low-frequency signals (< 3 Hz).

Induction of colitis

Trinitrobenzenesulphonic acid (80 mg kg^{-1} in 0·3 mL 50% ethanol) was administered intrarectally through a silicone rubber catheter introduced 1 cm into the anus under light ether anaesthesia, as described previously (Morteau et al 1994a).

Stress procedure

Partial-restraint stress, a relatively mild, non-ulcerogenic model of restraint (Williams et al 1988), was used. Briefly, the animals were lightly anaesthetized with diethyl ether and their fore-shoulders, upper forelegs and thoracic trunk were wrapped in a confining harness of paper tape to restrict, but not to prevent body movement. The animals were then placed in their home cage for 2 h. The rats recovered from the diethyl ether within 2–3 min and immediately moved about in their cages and ate and drank, but the mobility of their forelegs was restricted, thus preventing grooming of the face, upper head and neck. Control animals were anaesthetized but were not wrapped. After recovering from the anaesthesia control rats groomed the face, head and abdomen. Partial-restraint stress was always performed between 1000 and 1200 h.

Rectal distension procedure

To prevent recording artefacts owing to movement during distension, rats were accustomed, three days before distension, to being placed in a polypropylene tube (diam. 6 cm, length 22 cm). A balloon consisting of an arterial embolectomy catheter (Fogarty, Edwards Laboratories, Santa Anna, USA) was introduced into the rectum 1 cm from the anus and fixed at the base of the tail. The balloon (diam. 2 mm, length 2 cm) was increasingly inflated with 0·4 mL water, starting from 0·4 mL up to 1·2 mL. Each inflation step lasted 5 min. The choice of a 5 min duration for each inflation was based on technical considerations because 5 min is the normal duration enabling relevant measurement of abdominal cramp (Morteau et al 1994a). At the end of the distension, the water was withdrawn to enable detection of leakage.

Experimental protocol

In a first series of experiments performed on seven groups of eight rats, rectal distension was performed 1 day before and 3 days after intracolonic instillation of trinitrobenzenesulphonic acid. Ten minutes before rectal distension the animals were treated intraperitoneally with 0·5 mL vehicle (dimethylsulphoxide and water, 50 : 50 v/v) containing trimebutine or *N*-desmethyltrimebutine at doses of 5, 10 or 20 mg kg^{-1}.

In a second series of experiments, seven groups of 8–12 rats were submitted to rectal distension 2 h before and 30 min after a 2-h restraint-stress session. In this series of experiments the animals were

also treated 10 min before rectal distension with trimebutine or desmethyltrimebutine at the same doses as in the first series of experiments.

In a third series of experiments performed on three additional groups of rats, naloxone ($1\,mg\,kg^{-1}$) or vehicle (0·9% NaCl) was injected subcutaneously 10 min before trimebutine or *N*-desmethyltrimebutine.

Data analysis

Statistical analysis of the number of abdominal spike bursts occurring during each 5-min period was performed by Dunnett's procedure for multiple comparisons, after analysis of variance. $P < 0.05$ was considered as indicative of statistical significance. All the values are expressed as means ± s.e.m.

Results

Trinitrobenzenesulphonic acid-induced rectal hyperalgesia

Effects of trimebutine and desmethyltrimebutine on abdominal response to rectal distension. Before treatment with trinitrobenzenesulphonic acid, rectal distension progressively increased the number of abdominal cramps; this increase was significant for rectal distension volumes between 0·8 and 1·6 mL (Table 1, Figure 1). Intraperitoneal trimebutine at doses of 10 and $20\,mg\,kg^{-1}$ significantly ($P < 0.05$) reduced the number of abdominal cramps observed for the highest volume of distension, 1·6 mL, but also for 1·2-mL distension at a dose of $20\,mg\,kg^{-1}$. At the lowest dose ($5\,mg\,kg^{-1}$), trimebutine did not affect the number of abdominal cramps regardless of distension volume (Table 1).

Injected 30 min before rectal distension, desmethyltrimebutine did not affect the abdominal cramps generated by rectal distension regardless of dose (5, 10 and $20\,mg\,kg^{-1}$) or the distension volume (Table 1, Figure 1).

Effects of trimebutine and desmethyltrimebutine on trinitrobenzenesulphonic acid-induced hyperalgesia. Compared with values observed before inflammation, trinitrobenzenesulphonic acid significantly ($P < 0.05$) increased the number of abdominal cramps generated by 0·4, 0·8 and 1·2-mL rectal distension (Figure 1, Table 2).

Injected before rectal distension, doses of trimebutine as low as $5\,mg\,kg^{-1}$ attenuated this increase for a distension volume of 0·8 mL; doses of 10 and $20\,mg\,kg^{-1}$ suppressed abdominal cramps generated by all distension volumes (Figure 1, Table 2). In contrast, doses of desmethyltrimebutine from 5 to $20\,mg\,kg^{-1}$ had no significant effect on the trinitrobenzenesulphonic acid-induced increase in the abdominal response to distension (Table 2). Naloxone, previously administered subcutaneously at a dose of $1\,mg\,kg^{-1}$, suppressed the effects of trimebutine on the trinitrobenzenesulphonic acid-induced increase in abdominal response to rectal distension (Table 3).

Stress-induced rectal hyperalgesia

Effect of partial-restraint stress. Rectal distension applied in control rats significantly and gradually increased the number of abdominal discharges from a threshold volume of 0·8 mL, in a manner similar to that observed in the first series of experiments. Partial-restraint stress applied for 2 h reduced to 0·4 mL the threshold of abdominal response to rectal distension and significantly ($P < 0.05$) increased, by 76·8 and 41·6%, the number of abdominal contractions observed for 0·8- and 1·2-mL rectal distension (Figure 2).

Effects of trimebutine and desmethyltrimebutine. When administered at a dose of $5\,mg\,kg^{-1}$ 10 min before rectal distension and after partial-restraint stress, trimebutine did not modify the stress-induced increase in abdominal response to rectal

Table 1. Effect of intraperitoneal trimebutine and *N*-desmethyltrimebutine on the number of abdominal spike bursts generated by increasing volumes of rectal distension in rats.

Treatment	Dose ($mg\,kg^{-1}$)	Abdominal cramps/15 min Distension volume (mL)				
		0	0·4	0·8	1·2	1·6
Vehicle	–	1·2 ± 0·4	6·7 ± 1·7	17·6 ± 2·3	26·9 ± 2·7	30·3 ± 1·8
Trimebutine	5	0·9 ± 0·6	5·8 ± 0·7	18·1 ± 2·5	24·7 ± 2·3	30·2 ± 1·7
	10	1·3 ± 0·5	5·9 ± 0·6	17·1 ± 1·9	24·8 ± 2·2	26·1 ± 1·9*
	20	0·8 ± 0·7	5·2 ± 1·2	17·2 ± 0·9	21·4 ± 2·3*	23·1 ± 2·1*
N-Desmethyltrimebutine	5	0·8 ± 0·1	4·7 ± 1·1	19·6 ± 2·1	25·1 ± 2·6	27·5 ± 3·3
	10	1·1 ± 0·4	6·7 ± 1·5	18·1 ± 1·3	26·6 ± 1·6	29·3 ± 1·8
	20	1·9 ± 0·7	5·3 ± 1·5	13·7 ± 2·7	28·4 ± 2·0	28·7 ± 2·1

Results are means ± s.e.m. (n = 8). *$P < 0.05$, significantly different from corresponding results for vehicle.

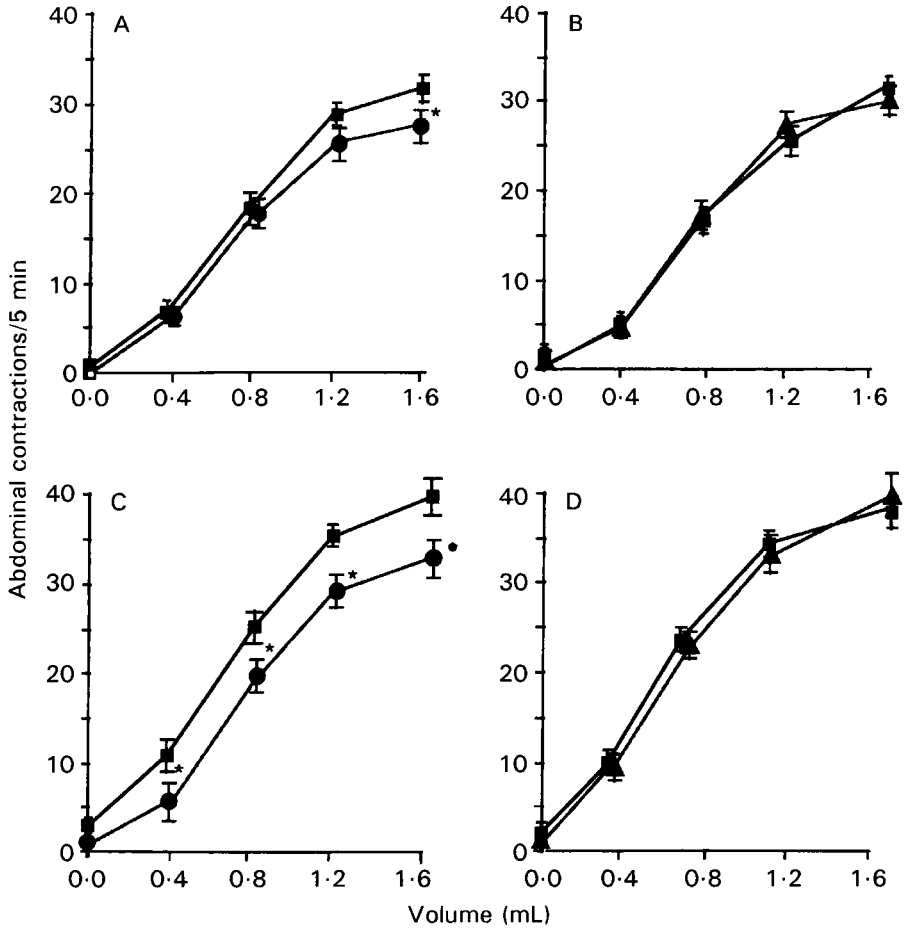

Figure 1. Influence of trimebutine (●) and *N*-desmethyltrimebutine (▲) at intraperitoneal doses of $10 mg kg^{-1}$, compared with vehicle (■), on the number of abdominal contractions induced by step rectal distension before (A, B) and 3 days after (C, D) rectal instillation with trinitrobenzenesulphonic acid. Results are means ± s.e.m. (n = 8). $*P < 0.05$, significantly different from corresponding results for vehicle.

Table 2. Effect of trimebutine and *N*-desmethyltrimebutine on rectocolitis-induced increase in the number of abdominal cramps induced by 0·8-mL rectal distension in rats.

Treatment	Dose ($mg kg^{-1}$)	Abdominal contractions/5 min
Vehicle		6·3 ± 0·2
Trimebutine	5	3·2 ± 0·18*
	10	0·4 ± 0·6**
	20	0·3 ± 0·5**
Vehicle		5·9 ± 1·6
N-Desmethyltrimebutine	5	4·8 ± 1·4
	10	4·7 ± 0·9
	20	3·9 ± 1·5

Results are means ± s.e.m. (n = 8). $*P < 0.05$, $**P < 0.01$, significantly different from corresponding results for vehicle.

distension. In contrast, 10 and $20 mg kg^{-1}$ trimebutine reduced and suppressed, respectively, stress-induced hyperalgesia regardless of distension volume (Figure 2).

When injected intraperitoneally 20 min after the stress session at doses as low as $5 mg kg^{-1}$, desmethyltrimebutine reduced by 56·2% the stress-induced enhancement of abdominal spike discharges observed for 1·2-mL distension. At higher doses (10 and $20 mg kg^{-1}$) desmethyltrimebutine abolished the effects of stress on rectal sensitivity (Figure 2).

Antagonism by naloxone

Injected subcutaneously 20 min before rectal distension, naloxone ($1 mg kg^{-1}$) did not significantly affect the number of abdominal cramps in control animals or stress-induced enhancement of abdominal response. However, when injected 10 min before trimebutine ($10 mg kg^{-1}$) applied 3 days after trinitrobenzenesulphonic acid, naloxone reversed the effects of trimebutine on inflammation-induced hyperalgesia (Table 3, 4). At the same dose naloxone did not affect the effects of trimebutine ($10 mg kg^{-1}$) on partial-restraint-stress-induced hyperalgesia for a distension volume of 1·2 mL. Furthermore, naloxone ($1 mg kg^{-1}$) seemed unable to attenuate significantly the antinociceptive

Table 3. Effect of intraperitoneal trimebutine and *N*-desmethyltrimebutine on the number of abdominal cramps induced by rectal distension after restraint stress in rats.

Treatment	Dose ($mg\,kg^{-1}$)	Abdominal contractions/5 min Distension volume (mL)			
		0	0·4	0·8	1·2
Vehicle	–	0·8 ± 0·5	6·1 ± 0·6	17·9 ± 1·8	25·7 ± 1·4
Trimebutine	5	1·2 ± 0·7	6·4 ± 0·9	18·2 ± 2·1	25·1 ± 2·2
	10	1·1 ± 0·3	6·2 ± 1·5	14·6 ± 2·2	21·5 ± 1·8*
	20	0·9 ± 0·7	7·0 ± 0·7	12·2 ± 1·7*	17·6 ± 1·8*
Vehicle	–	0·8 ± 0·5	6·8 ± 1·1	20·5 ± 1·8	27·4 ± 1·7
N-Desmethyltrimebutine	5	1·4 ± 0·4	6·2 ± 1·3	15·5 ± 1·8	20·9 ± 1·4*
	10	0·9 ± 1·1	6·3 ± 1·9	11·6 ± 1·7*	16·5 ± 1·0*
	20	1·2 ± 1·0	6·3 ± 1·4	12·0 ± 2·2*	17·3 ± 2·6*

Results are means ± s.e.m. (n = 8). *$P < 0.05$, significantly different from corresponding results for vehicle.

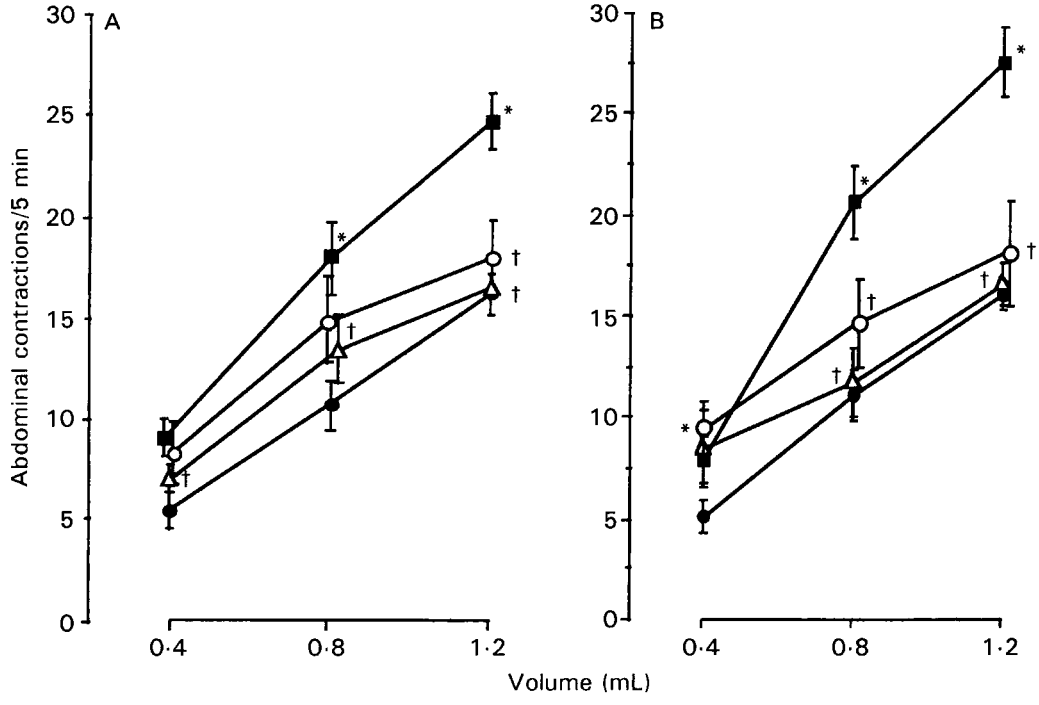

Figure 2. Effects of increasing doses of trimebutine (A) and *N*-desmethyltrimebutine (B) on the restraint-stress-induced increase in abdominal cramps in response to rectal distension in rats. ●, Control; ■, stress + vehicle; △, stress + $10\,mg\,kg^{-1}$ drug; ○, stress + $20\,mg\,kg^{-1}$ drug. Results are means ± s.e.m. (n = 8). *$P < 0.05$, significantly different from corresponding results for vehicle. †$P < 0.05$, significantly different from corresponding results for stress + vehicle.

effects of desmethyltrimebutine on the stress-induced increase in abdominal spike activity in response to rectal distension (Table 3, 4).

Discussion

Our results demonstrate that trimebutine and its major metabolite, desmethyltrimebutine, affect rectal barosensitivity in rats differently, depending upon the basal state. Moreover these drugs seem selectively more active against rectal hyperalgesia induced by local inflammation and stress than on basal sensitivity, these effects being only partly related to action on opiate receptors.

As previously described (Morteau et al 1994a), the induction of rectocolitis by trinitrobenzenesulphonic acid in ethanol evokes an increase in the sensitivity to rectal distension by reducing the threshold of appearance of abdominal cramps and by enhancing the response to rectal distension, an effect unrelated to alterations in rectal compliance. This hypersensitivity induced by locally applied trinitrobenzenesulphonic acid is reduced by 5-HT_3 receptor antagonists but there is no clear evidence

Table 4. Antagonism by naloxone of the effects of trimebutine and *N*-desmethyltrimebutine on inflammation induced by trinitrobenzenesulphonic acid and the stress-induced increase in abdominal response to rectal distension in rats.

	Abdominal contractions/5 min		
	After trinitrobenzene sulphonic acid Distension volume (mL)		After stess Distension volume (mL)
	0·4	1·6	1·2
Vehicle (0·9% NaCl)	6·1 ± 1·2	9·3 ± 0·7	7·0 ± 1·3
Trimebutine (10 mg kg^{-1}, i.p.)	1·7 ± 0·5*	2·6 ± 0·2*	3·2 ± 1·4*
Naloxone (0·3 mg kg^{-1}, s.c.)	6·2 ± 1·4	8·5 ± 0·7	6·4 ± 1·2
Trimebutine + naloxone (1 mg kg^{-1})	6·0 ± ·08	9·0 ± 0·8	2·0 ± 0·2*
Vehicle (0·9% NaCl)		9·3 ± 0·7	9·2 ± 0·6
N-Desmethyltrimebutine (10 mg kg^{-1}, i.p.)		2·6 ± 0·2	2·0 ± 0·8*
Naloxone (0·3 mg kg^{-1}, s.c)		8·5 ± 0·7	8·5 ± 0·7
N-Desmethyltrimebutine + naloxone (1 mg kg^{-1})		9·0 ± 0·8	2·3 ± 1·5*

Results are means ± s.e.m. (n = 8). *$P < 0.05$, significantly different from corresponding results for vehicle.

that the involvement of 5-HT$_3$ receptors is selective for inflammation-induced hyperalgesia (Morteau et al 1994b). In contrast, mediators such as bradykinin seem to be selectively involved in triggering trinitrobenzenesulphonic acid-induced hyperalgesia because a B_2 antagonist (HOE140) is active on rectal nociception only after induction of rectocolitis (Julia et al 1995).

Trimebutine, a drug extensively used for treatment of irritable bowel syndrome has peripheral opioid agonist properties related to affinities for μ and κ opioid receptor subtypes (Pascaud et al 1989). Several studies indicate that opioid agonists might have peripherally mediated antinociceptive properties (Smith & Wilkinson 1982). It has also been shown that selective κ agonists such as U50488 and fedotozine act peripherally to inhibit nociceptive inputs generated by colorectal distension with potent visceral antinociceptive efficacy on hyperalgesia resulting from inflammatory reactions (Langlois et al 1997). Our current studies have shown that trimebutine is four to ten times more potent at reducing abdominal cramps related to rectal distension after trinitrobenzenesulphonic acid-induced rectal inflammation and that this effect is blocked by naloxone, suggesting that it is linked to an activation of opiate receptors.

Recently, pharmacological and electrophysiological data have contributed to the assessment of the peripheral analgesic effects of opiates-μ and κ agonists have been found to block nociception efficiently when given at the site of irritation at doses that are not active systemically (Stein 1993). These effects are blocked by antagonists such as quaternary alkaloids, which penetrate the blood–brain barrier poorly (Smith & Wilkinson 1982), and higher antinociceptive effects of these compounds are found when they are administered locally at the site of inflammation (Stein 1993). Accordingly, the receptors involved in the peripheral mechanism of action of opioids are probably located on the very distal ends of primary afferent neurones or on surrounding cells, an increased number of local opioid receptors being detected at the site of inflammation (Hassan et al 1993).

Partial-restraint stress increases the abdominal response to rectal distension, an effect which has previously been shown to be mediated by the CNS release of corticotrophin-releasing factor (CRF) (Gué et al 1997). In man, peripheral administration of CRF at doses inducing somatic analgesia (Hargreaves et al 1987) reduces the threshold and increases the intensity of sensation of discomfort to rectal distension (Lembo et al 1996). However, the mechanisms by which stress induces rectal hyperalgesia are not well understood. CRF might act by changing the excitability of dorsal horn neurons receiving converging inputs from different afferents (Mayer & Gebhart 1994) or is the consequence of an increase in the size of the receptive fields of dorsal horn neurons and spinal mechanisms (Cervero 1994). CRF can trigger the local release of proinflammatory mediators inducing sensitization of primary afferent endings (Schäfer et al 1997) and can also alter the brain-level processing of visceral sensory information as demonstrated for the locus coeruleus (Valentino et al 1992). Both trimebutine and its major metabolite desmethyltrimebutine are active on stress-induced rectal hyperalgesia at doses as low as 5 mg kg^{-1}, which are not active in the basal state. Unexpectedly, desmethyltrimebutine seems more active than trimebutine and its effects and those of trimebutine are not blocked by naloxone. Desmethyltrimebutine has a

lower affinity than trimebutine for μ and κ opioid receptors. Consequently we can speculate that these two compounds act centrally or peripherally on sensitization of terminals of primary afferents by interfering directly with other mechanisms and possibly by changes in ionic permeability (Roman et al 1998).

Although the causes and mechanisms of irritable bowel syndrome are not well understood, it is admitted that stress might contribute to visceral hypersensitivity because most patients with irritable bowel syndrome suffer from increased levels of anxiety and psychosocial distress (Drossman et al 1988). More recently it has been demonstrated that irritable bowel syndrome symptoms appear more frequently after severe gut-infectious diarrhoea in stressed patients suggesting that stress and gut inflammation act synergistically to trigger gut hyperalgesia (Gwee et al 1996).

Our experiments have shown that intraperitoneal trimebutine, at plasma concentrations equivalent to those obtained during classical treatment of oral irritable bowel syndrome, i.e. 300 to 600 mg twice a day, is active on hyperalgesia induced by both local inflammation and stress. However at this dose trimebutine might influence gut motility with a peripheral site of action (Valori & Shannon 1987) and these effects might also result from primary influence on gut afferents involved in functional reflexes.

Finally, whatever the mechanism involved trimebutine and its major metabolite desmethyltrimebutine are potent drugs inhibiting rectal hyperalgesia evoked by local inflammation and stress in rats and these effects might explain the efficacy of trimebutine in the treatment of functional bowel disorders.

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