

Oxytocin increases thresholds of colonic visceral perception in patients with irritable bowel syndrome

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Abstract

Aim—The effects of oxytocin on colonic perception of intraluminal distension were evaluated in 26 patients with irritable bowel syndrome (IBS), using a flaccid bag placed in the descending colon and connected to a computerised barostat.

Method—Symptomatic responses (first sensation and pain) were evaluated during isobaric distensions (4 mm Hg increments, five minute duration, five minute interval with return to zero pressure between each step), performed automatically by the barostat, during a continuous infusion of placebo or various doses of oxytocin (10, 20, 30, and 50 mU/min).

Results—The distension pressure (mean (SD)) required to induce a first abdominal sensation was 17.3 (5.5) mm Hg on placebo, 19.9 (5.8) on oxytocin 10 mU/min (NS), 22.3 (6.0) mm Hg on oxytocin 20 mU/min ($p < 0.01$), 23.1 (6.6) mm Hg on oxytocin 30 mU/min ($p < 0.01$), and 24.0 (7.1) mm Hg on oxytocin 50 mU/min ($p < 0.01$). The distension pressure required to induce pain was 24.8 (6.3) mm Hg on placebo, 26.0 (5.8) on oxytocin 10 mU/min (NS), 33.3 (7.8) mm Hg on oxytocin 20 mU/min ($p < 0.01$), 34.2 (7.6) mm Hg on oxytocin 30 mU/min ($p < 0.01$), and 34.3 (7.9) mm Hg on oxytocin 50 mU/min ($p < 0.01$). Compliance curves were not different after placebo and oxytocin injection at the different doses. Naloxone did not inhibit the effect of oxytocin. Oxytocin also did not alter somatic perception, characterised by the RIII reflex at the level of the biceps femori.

Conclusion—Oxytocin significantly increases thresholds for visceral perception in IBS patients at doses equal or to greater than 20 mU/min, possibly by acting at the level of visceral afferents.

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stimulation.⁶⁻⁸ It has become apparent that an abnormally decreased threshold for visceral sensitivity may also play an important part in the pathophysiology of IBS. Previous studies in humans have found lowered visceral sensory thresholds during intraluminal distension of the oesophagus in patients with non-cardiac chest pain⁹⁻¹⁰ and of the stomach in patients with functional dyspepsia.¹¹⁻¹² Similar hypersensitivity to distension has also been reported for the colon in IBS patients.¹³⁻¹⁸

Besides opioid peptides, several neuro-peptides play an important part as mediators of the antinociceptive pathways: vasopressin, substance P, and neurotensin.¹⁹ It has been recently shown that somatostatin may decrease abdominal symptoms in patients with IBS, increasing visceral sensory thresholds in the colon, up to the level of controls, without modifying pressure-volume relation (compliance).²⁰ It is well known that oxytocin is widely distributed in many areas of the central nervous system and the spinal cord.²¹ Its effects include both hormonal and neuronal processes. Among the latest, oxytocin may modify behaviour of learning and memory. Oxytocin given intraperitoneally as well as intracerebrally to rodents exerts an antinociceptive action.²²⁻²³ In a patient with opiate resistant cancer pain, the injection of oxytocin into the third ventricle was reported to result in effective analgesia.²⁴⁻²⁵ On the other hand, animal studies have shown that the analgesic effect of oxytocin could be opiate mediated.²²

Consequently the aim of this study was to investigate the effects of oxytocin on thresholds of visceral perception and pain sensation during isobaric colonic distensions in IBS patients, using a computerised barostat and to investigate a possible mediation of these effects by an opioid pathway. In addition, we analysed the effects of an effective dose of oxytocin on somatic perception thresholds, as characterised by the RIII cutaneous reflex.

Methods

PATIENTS

Twenty six patients (15 men) were included. Their mean age was 45 years (range 24-63). All patients had a clinical diagnosis of IBS, based on the Rome criteria²⁶: they presented with abdominal pain at least three times a week and constipation (≤ 3 bowel movements per week). Patients gave informed consent to participate in the experimental procedures that

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The pathophysiology of irritable bowel syndrome (IBS) remains largely unknown. A variety of motility disorders have been described but there is no consensus regarding changes in colonic motility under basal conditions,¹⁻² during emotional stress,³⁻⁵ after a meal,¹⁻⁶⁻⁷ or in response to pharmacological

had been approved beforehand by the Institutional Ethical Board.

All patients were required to have a normal physical examination and a normal colonoscopy (to eliminate an organic disease) before acceptance in the study and none were taking medication other than oral contraceptives, at least 15 days before the study. All women were negative for β -HCG blood test. Patients were admitted to the clinical research unit the day before the study and were prepared by ingesting four litres of polyethyleneglycol 4000. Bowel cleansing was completed by repeated tap water enemas until all faecal effluent was clear fluid, free of any particulate matter.

RECORDING ASSEMBLY

Barostat

The device (Barostat INRA, Toulouse, France) consisted of a sensitive pressure transducer (range 0–80 mm Hg, SCXOIDN, Sensym, 91 Savigny sur Orge, France) coupled through a computer (32 Kbytes ROM, 32 Kbytes RAM, 80C32, Intel, 78 St Quentin en Yvelines, France) and a stepping motor to a bellows with a reservoir capacity of 600 ml.²⁷ The system could be activated with a lag time of 10 ms and the maximal air flow was 30 ml/s. The volume of air inside the bag was determined electronically by the computer from the known excursion of the bellows within the

reservoir system. The barostat apparatus included a built-in computer system that could be programmed to automatically perform distensions with fixed time lag (five minute duration, five minute interval with return to baseline volume between each successive increment) and bag pressure increments (4 mm Hg increments). Distensions could therefore be performed by completely deflating the bag between each pressure increment.

Colonic probe

A single lumen silicone tube (8 mm diameter, Silastic, Dow Corning, Midland, MI, USA) was assembled so that the lumen was located within the barostat bag and the open end of the tube connected to the output of the bellows chamber. A thin wall polyethylene bag (40 μ m thick) was fastened tightly to the tube. The maximal capacity of the bag (during table top inflation) was 500 ml with a maximal length of 10 cm. Before each experiment, the barostat bag was checked for air leaks at a pressure of 20 mm Hg maintained during 15 minutes. Within the range of volumes used in our study, the barostat bag compliance was considered infinite.¹⁸

CONDUCT OF THE STUDY

Effect of oxytocin on sensory thresholds and dose response relation

Selected patients presented to the endoscopic unit after a 12 hour fast and adequate bowel preparation. Colonoscopy was performed on day 0 (D0) at 9 00 am with the patients in the left lateral position using minimal air insufflation. Colonoscopy was performed to the caecum in all patients and no retained particulate matter was observed in any case. Pre-medication included intravenous propofol (2 mg/kg) (ICI Pharma, Cergy, France), under surveillance of an anaesthetist. A thread attached to the tip of the colonic probes was used to pull it up into the colon alongside the colonoscope (CFV10, Olympus, Tokyo, Japan), by using a biopsy forceps to carry it. The barostat bag was positioned in the descending colon. Patients were then transported to a recovery room where they were allowed to rest. All experimental procedures began on day 1 (D1) to permit full recovery from anaesthesia. Positions of the colonic probe and barostat bag were verified fluoroscopically before and after experimental procedures. Patients were requested to remain in a 30° supine position during the entire recording sessions.

The barostat bag was used to perform intracolonic isobaric distensions at 8 30 am and 6 00 pm on day 1 and 8 30 on day 2 (Fig 1). Twenty patients received, in a random order, a continuous infusion of placebo (saline solution) or two doses of oxytocin (10 mU/min: n=8, 20 mU/min: n=16, 30 mU/min: n=12, 50 mU/min: n=4), starting 30 minutes before the distension session began and maintained constant during the whole distension

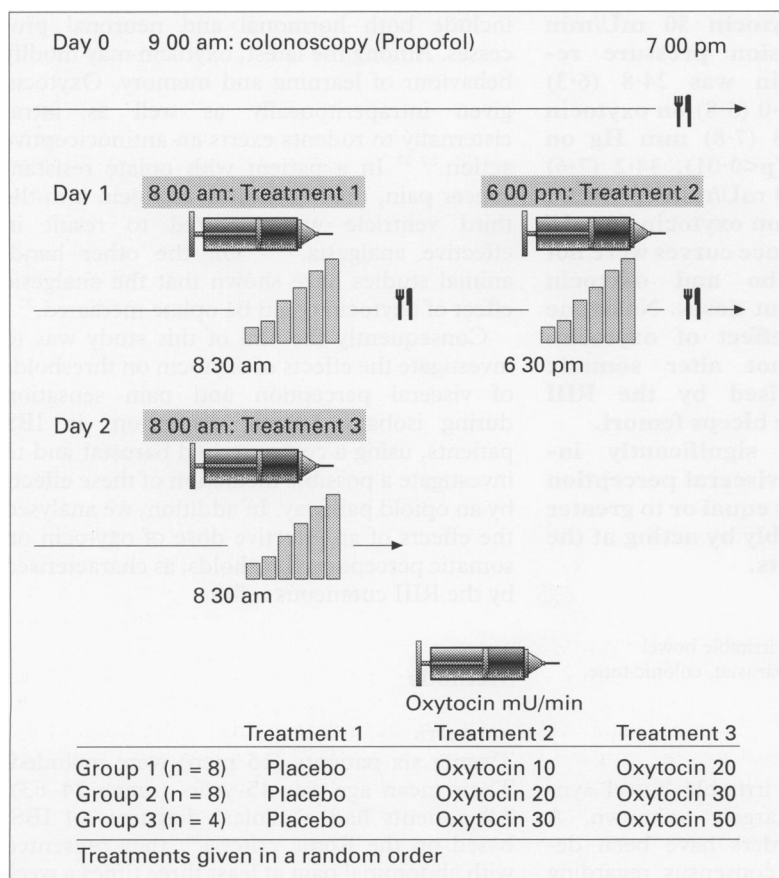


Figure 1: Design of the distension part of the protocol. After placement of the probe, patients underwent three distension sessions with random administration of treatments, either placebo or two consecutive doses of oxytocin.

session. Distensions were performed automatically by the computerised barostat to achieve successive increments of 4 mm Hg every five minutes preceded by completely deflating the barostat bag during five minutes before the next distension, until pain threshold was obtained. The average duration of distension experiments on placebo could be estimated at 60 to 70 minutes from the previous studies performed with this distension protocol in our laboratory.^{18 20} Using a standardised visceral perception questionnaire, patients were requested to indicate when they first felt an abdominal sensation (threshold of first perception) and then when they first felt a sensation of abdominal pain (threshold of pain). At the pain threshold or when the maximum pressure of 40 mm Hg was reached, the bag was deflated and this completed the experimental procedure.

Effect of naloxone on sensory modulation by oxytocin

In six patients, the effect of naloxone was tested on the modulation of the sensory thresholds by oxytocin. The barostat bag was used to perform intracolonic isobaric distensions at 8 30 am and 6 30 pm on day 1, according to the same protocol as described above (Fig 1). Each patient received a continuous infusion of oxytocin (30 mU/min), starting at 8 00 am and 6 00 pm – that is, 30 minutes before the beginning of the distension session. At 8 15 am and 6 15 pm on D1 each patient received in a random order an intravenous injection of placebo (5 ml saline solution) or naloxone (0.4 mg diluted in 5 ml saline solution). Then the distension was performed.

EVALUATION OF SOMATIC PERCEPTION BY THE RIII REFLEX

Somatic perception was evaluated in 12 patients who participated in other parts of the study. Forty eight hour washout periods were systematically observed between the two trials.

The method for stimulating the sural nerve and recording the RIII reflex activity from biceps femoris was similar to that used in other studies.^{28 29} The sural nerve was stimulated behind the lateral malleolus through a pair of surface electrodes on skin covered with cream. The electrical stimulus was delivered by a constant intensity stimulator and consisted of a 20 ms train of six rectangular pulses (1 ms duration each). A warning signal predicted the stimulation. The time interval between two successive stimulations varied with an approximate mean interval of 10 seconds. Reflexes responses were recorded from the ipsilateral biceps femoris muscle using a pair of surface electrodes on the skin overlying the muscle. The latency of a reflex activity corresponding to a RIII response ranged from 90 to 180 ms. The response was considered present when the amplitude of the electrical signal was greater than 50 μ V. The calculation used to define the threshold stimulus inducing a RIII reflex was based upon the frequency of occurrence of this

RIII reflex^{28 29} rather than on the 10% RIII maximal amplitude.³⁰ The frequency of occurrence of the RIII response was calculated for each intensity level.

After an initial sequence of stimulus performed within treatment and a recovery period of 45 minutes, an infusion of oxytocin (30 mU/min) was given to six patients and placebo to the six others, in a random order, as described for distension studies. Thirty minutes later, a new sequence of stimuli was applied and the RIII threshold measured.

DATA ANALYSIS

Pressure and volume of the barostat bag were simultaneously recorded on a potentiometric recorder (BS 270, Gould, Paris, France) for later visual analysis, to permit comparison of pressure-volume curves on placebo and on the different doses of oxytocin. Visceral perception thresholds were characterised by the pressure of inflation of the barostat bag triggering a definite abdominal sensation. All values were expressed as mean (SD). Statistical analysis was performed by a non-parametric paired test when comparing the sensory thresholds on placebo and oxytocin. Pressure-volume curves were compared using the analysis of variance (two way ANOVA).

The influence of treatment on the sensory perception of colonic distension was also evaluated by comparing the number of subjects in whom a sensation was elicited at a certain level of distension. The cumulative number of patients taking placebo and the various doses of oxytocin were compared by the χ^2 test, with Bonferroni's correction, for each step of distension.

Although the treatment sequences were carefully randomised between subjects, we further tested the possibility of a carry over effect of repeated distensions, using a fully factorial (m)ANOVA to test the influence of order of distension, treatment, and interaction of both on the sensory thresholds. All p values <0.05 were considered significant in this study.

Results

TOLERANCE OF THE PROBE AND TECHNICAL ASPECTS OF RECORDING SESSIONS

A total of 26 patients were included in this study. Placements of probes under colonoscopy was not responsible for any complication. In each patient, the duration of the experiments including distensions never exceeded a 36 hour recording. The probe was well tolerated in all patients: diarrhoea, urgent bowel movement or probe migration did not occur. At the end of the recording session, the position of the probe was checked on a plain film of the abdomen. The tip of the probe was still in the descending colon in all patients.

TOLERANCE OF OXYTOCIN INFUSION

No side effect was seen during or after intravenous infusion of oxytocin at doses ranging

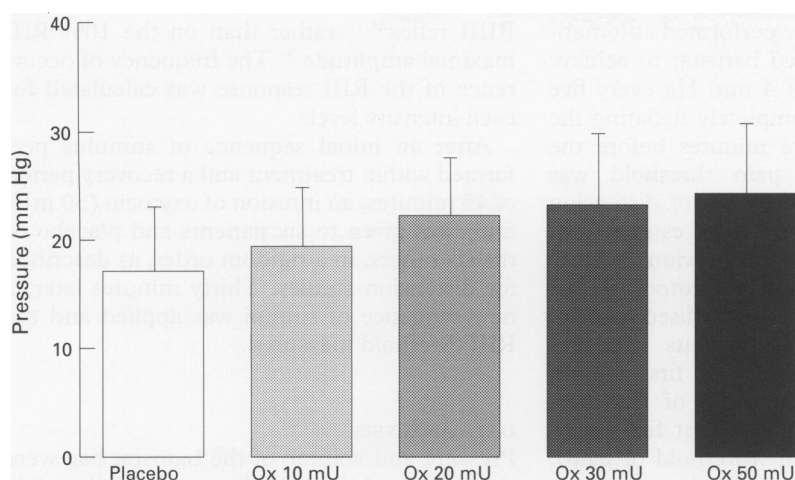


Figure 2: Mean barostat bag pressure at the first sensation threshold in IBS patients taking placebo and the various doses of oxytocin (Ox) (10, 20, 30, and 50 mU/min). Oxytocin at 10 mU/min had no effect on visceral perception. The mean bag pressure required to induce visceral perception was significantly increased after oxytocin (20, 30, and 50 mU/min) ($p < 0.01$).

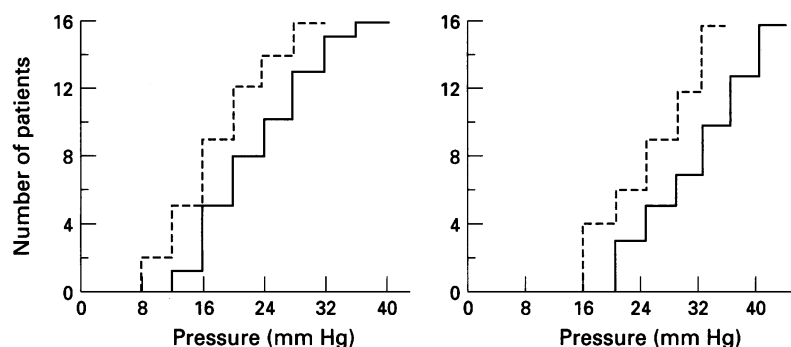


Figure 3: Cumulative number of patients who experienced a first abdominal sensation (left panel) or pain (right panel) during isobaric colonic distension with placebo (dotted line) or oxytocin at the dose of 20 mU/min (plain line). The curves for IBS patients receiving oxytocin show a significant shift toward higher pressures compared with placebo (χ^2 test; $p < 0.001$).

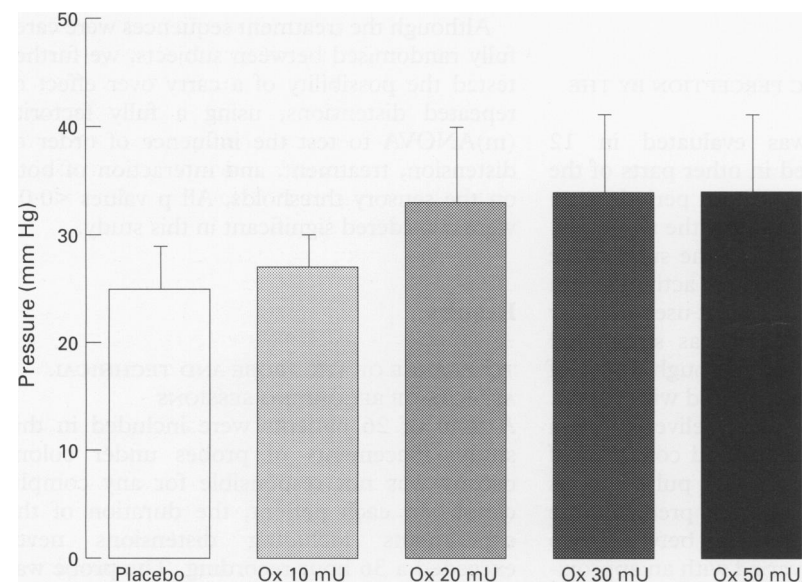


Figure 4: Mean barostat bag pressure at the pain threshold in IBS patients taking placebo and the various doses of oxytocin (Ox) (10, 20, 30, and 50 mU/min). Oxytocin at 10 mU/min had no effect on visceral perception. The mean bag pressure required to induce pain was significantly increased after oxytocin (20, 30, and 50 mU/min) ($p < 0.01$).

EFFECT OF OXYTOCIN ON VISCERAL PERCEPTION IN IBS PATIENTS

First sensation threshold

The mean (SD) distending pressure inducing a first abdominal sensation was 17.3 (5.5) mm Hg with placebo (Fig 2). After the infusion of oxytocin at the dose of 10 mU/min, the mean distension pressure inducing a sensation of discomfort was 19.0 (5.8) mm Hg (NS versus placebo). With oxytocin, at the dose of 20, 30, and 50 mU/min, there was a significant increase of the mean distending pressure required to induce an abdominal sensation, up to 22.3 (6.0) mm Hg (20 mU/min) ($p < 0.01$), 23.1 (6.6) mm Hg (30 mU/min) ($p < 0.01$), and 24.0 (7.1) mm Hg (50 mU/min) ($p < 0.01$) respectively.

Figure 3 shows the cumulative number of patients experiencing a first abdominal sensation with either placebo or oxytocin at the dose of 20 mU/min for a given distending pressure. Twelve of 20 patients who received placebo experienced a first sensation at a pressure ≤ 24 mm Hg. With oxytocin (20 mU/min) eight of 16 patients experienced discomfort at a pressure ≤ 24 mm Hg ($p < 0.001$). The curves obtained with oxytocin (20 mU/min) displayed a significant shift towards higher distension pressures when compared with placebo. Furthermore, barostat bag distension up to the pressure of 28 mm Hg without inducing an abdominal sensation was possible in three patients after oxytocin (20 mU/min), compared with none after placebo ($p < 0.001$).

Pain threshold

During isobaric distensions, the mean distending pressure inducing a sensation of pain was 24.8 (6.3) mm Hg with placebo. After the infusion of oxytocin (10 mU/min), the mean distension pressure to induce a sensation of pain was 26.8 (2.8) mm Hg (NS versus placebo) (Fig 4). With oxytocin, at the dose of 20, 30, and 50 mU/min, there was a significant increase in the mean distending pressure required to induce a sensation of pain up to 33.3 (7.8) mm Hg (20 mU/min) ($p < 0.01$), 34.2 (7.6) mm Hg (30 mU/min) ($p < 0.01$), and 34.3 (7.9) mm Hg (50 mU/min) ($p < 0.01$) respectively.

Figure 3 shows the cumulative number of patients experiencing a sensation of abdominal pain, with either placebo or oxytocin at the dose of 20 mU/min, for a given distending pressure. With placebo, nine of 20 patients experienced pain at a pressure ≤ 28 mm Hg compared with only seven of 16 patients after oxytocin (20 mU/min) ($p < 0.001$). The curves obtained with oxytocin at the dose of 20 mU/min displayed a significant shift towards higher distension pressures when compared with placebo. Furthermore, barostat bag distension up to the pressure of 32 mm Hg was possible without inducing a pain sensation in six IBS patients after oxytocin (20 mU/min) compared with none after placebo ($p < 0.001$).

from 10 to 30 mU/min. However, during intravenous infusion of oxytocin at the dose of 50 mU/min, four patients experienced moderate headache. This is the reason why this group of patients was limited to four.

Results of the fully factorial (M) ANOVA of the effects of treatment by oxytocin at the various doses or placebo and order of distension session on the pain threshold

	Sum of squares	DF	Mean squares	F ratio	p Value
Order	2.849	2	1.425	0.323	0.572
Treatment	311.239	4	103.746	11.752	0.001
Interaction	50.147	7	7.164	0.811	0.582

DF=degrees of freedom.

Exclusion of a carry over effect of repeated distension tests

To exclude a carry over effect of repeated distension tests, we analysed the influence of the order of distension tests and treatment on the sensory thresholds in a general linear model (Table). No influence of the order was observed, nor any interaction between treatment and order.

EFFECT OF NALOXONE ON MODIFICATIONS OF VISCERAL PERCEPTION INDUCED BY OXYTOCIN (20 M_U/MIN)

During isobaric distensions, the mean distending pressure inducing a first sensation was 22.7 (6.6) mm Hg with oxytocin at the dose of 30 mU/min. When naloxone was injected, the mean distending pressure within the barostat bag inducing a first sensation was 22.5 (7.1) mm Hg (NS versus oxytocin 30 mU/min alone).

Likewise, the mean distending pressure inducing a sensation of pain was 33.1 (7.2) mm Hg with oxytocin at the dose of 20 mU/min and was not affected by injection of naloxone (33.3 (6.9) mm Hg) (NS versus oxytocin 30 mU/min alone).

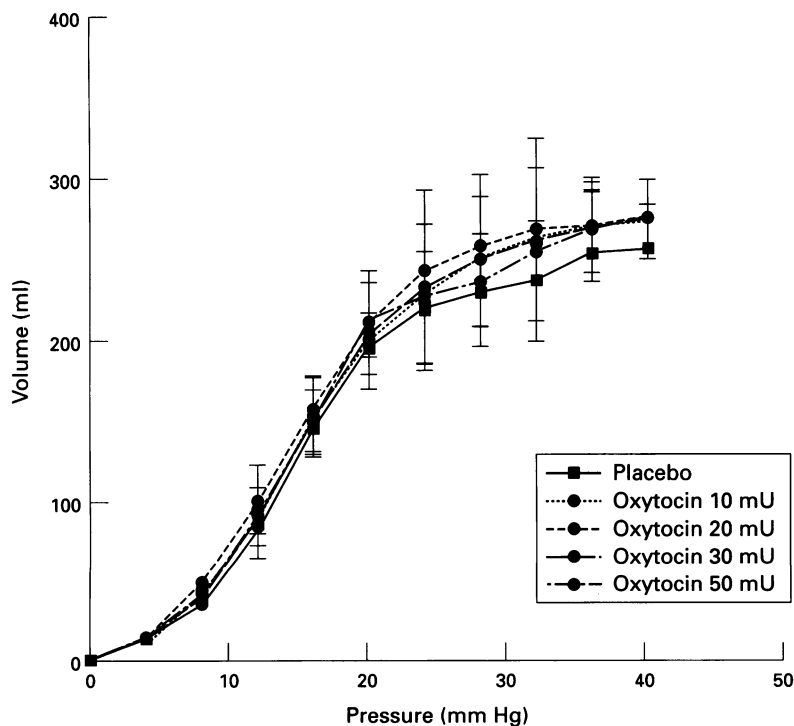


Figure 5: Colonic pressure-volume curves obtained during isobaric distension in IBS patients taking either placebo or oxytocin injection (10, 20, 30, and 50 mU/min). Curves do not differ significantly (analysis of variance). The slope of these curves was also not different.

PRESSURE-VOLUME RELATION DURING ISOBARIC DISTENSIONS (PLACEBO AND OXYTOCIN)

Pressure-volume curves (compliance curves) were obtained during isobaric distensions after placebo and the different doses of oxytocin. There was no significant difference in the bag volume for a given pressure when comparing distensions with placebo and the different doses of oxytocin (Fig 5).

EFFECT OF OXYTOCIN ON THE SOMATIC PERCEPTION CHARACTERISED BY THE RIII REFLEX

When electrical stimulation was applied on the skin of the leg behind the lateral malleolus, a RIII reflex was recorded at the level of the biceps femoris, for a stimulation of 10.4 (1.5) mA, with placebo and 11.8 (1.7) mA, with oxytocin 30 mU/min (NS). The intensity of the response was also not changed by oxytocin.

Discussion

In this study, we observed that a continuous infusion of oxytocin could increase the sensory thresholds of first perception and pain triggered by a luminal distension of the left colon. This study has been conducted in IBS patients with a characterised visceral hypersensitivity to colonic distension, their sensory thresholds ranging in the pressures previously recorded in another group of IBS patients²⁰ and those were significantly lowered compared with controls. IBS patients have also been characterised as hypersensitive in volume scaled distension experiments, using a similar protocol and in comparison with healthy controls.¹⁸ In these patients with a pronounced hypersensitivity, oxytocin was able to increase the first sensation and the pain thresholds up to those observed in the control group of our previous study.¹⁸ Similar results have been obtained previously with the somatostatin analogue octreotide on colonic²⁰ and rectal³¹ sensory thresholds or with the κ agonist fedotozine on colonic sensory thresholds.³²

This effect of oxytocin is not the consequence of a modification of the compliance of the colonic wall, as shown by the pressure-volume curves. At all tested doses of oxytocin, these curves were closely similar and their slope was not different. Similarly, octreotide and fedotozine did not change the elastic properties of the rectocolonic wall.^{18 20 31 32} This finding leads to the conclusion that oxytocin could act directly on the nerve afferent pathways to modulate sensory thresholds. In contrast, changes in compliance have been observed with granisetron, a 5HT-3 antagonist acting on sensory thresholds and also on gut compliance and colonic transit.^{33 34} The effects of oxytocin on gut motility have been poorly investigated so far. In rats, oxytocin does not delay gastric emptying during the lactation period.³⁵ In another study, oxytocin injected in the vagus dorsal motor nucleus decreased gastric motility and tone, thereby mimicking the action of the paraventricular nucleus on gastric motility.³⁶ The

actions are mediated through the central nervous system.

Oxytocin could thus also act as an analgesic at either the central or peripheral levels to modulate perception of nociceptive sensations. Systemic or intracerebral injection of vasopressin has been reported to produce antinociception in rodents.³⁷⁻³⁸ Oxytocin given intraperitoneally²² as well as intracisternally²²⁻²³ has an antinociceptive effect in rodents and could be a potential analgesic agent. The antinociceptive effect of oxytocin occurs through the activation of oxytocin receptors because the intracerebroventricular injection of the oxytocin antagonist d(CH₂)₅-Tyr(Me)-[Orn⁸]-vasotocin, while having no influence in itself on nociception, completely prevented the antinociceptive effect of an equal dose of oxytocin.³⁹ Moreover, intraperitoneal effective doses to obtain an effect on nociception are about 200 times higher in rats than intracerebroventricular ones, indicating that antinociceptive effects of oxytocin could be centrally mediated.³⁹ This assumption is reinforced by the finding that in the mouse, an intracerebral injection of the oxytocin receptor antagonist blocks the effect of subcutaneous oxytocin, arguing in favour of the possibility for oxytocin to cross the blood-brain barrier.⁴⁰ In humans, an injection of oxytocin (300 µg) into the third ventricle of a patient with intractable pain caused by opiate resistant cancer pain was reported to result in effective analgesia lasting 75 minutes.²⁴⁻²⁵

The analgesic effect of oxytocin on nociceptive perception at a central level is supported by detailed observations on the location of oxytocin in various areas of the brain. It has been established that oxytocin is not confined to the hypothalamic-neurohypophyseal tract but is widely distributed in neuronal networks in the central nervous system.²¹ Several authors have located oxytocin and various kinds of neuropeptides in the nucleus tractus solitarii, which is involved in the regulation of afferents of cardiovascular, respiratory, gustatory, and gastrointestinal systems.⁴¹ Oxytocinergic neurons project from the hypothalamic paraventricular nucleus to many regions in the brain, including areas involved in pain transmission – such as, the periaqueductal gray and the raphe nuclei.²²

Few studies have, in contrast, evaluated the peripheral role of oxytocin. It is present in neural pathways in the spinal cord, concentrated in superficial layers of the spinal dorsal horns, in particular in the substantia gelatinosa (which is involved in the primary processing nociceptive information), and the intermediolateral column (site of origin of preganglionic sympathetic neurones).³⁷ However oxytocin does not seem to have a major role in the nociceptive processes in the lumbosacral spinal cord in the rat.³⁷

Oxytocin may thus play the part of a general analgesic. Therefore, we evaluated the effects of an infusion of oxytocin on the somatic perception of a cutaneous electrical stimulation. The level of perception was characterised by the RIII reflex of the biceps femori.

We did not observe any effect of oxytocin in these experimental conditions on somatic perception in IBS patients. Somatic perception is known to be normal in patients with IBS.⁴² This finding allows us to assume that oxytocin does not act through a global analgesic effect and that it could even act only on hypersensitive sensory pathways.

Finally we considered the question of the relation between the endogenous opioid system and oxytocin. This relation has been studied in rats: the antinociceptive effect of oxytocin is prevented by naltrexone and oxytocin causes a small but significant increase in the intensity and duration of the antinociceptive effect of morphine.³⁹ However, a minor but still significant part of the antinociceptive effect of oxytocin may be naloxone insensitive.²² In mice, the development of acute morphine tolerance and naloxone-precipitated morphine withdrawal symptoms were inhibited by oxytocin after subcutaneous and intracerebroventricular injection.⁴³ The same effects were seen after central administration of a specific antioxytocin serum.⁴⁴ In this study, we could not inhibit the effect of oxytocin on colonic sensory thresholds by naloxone, indicating that in IBS patients, oxytocin modulates visceral hypersensitivity without interacting with enkephalinergic nerves.

In conclusion, oxytocin increases thresholds of visceral sensory perception in IBS patients, through a modulation of the activity of afferent nerve pathways. The exact level of action of oxytocin is not known so far but its action is not related to a global analgesic effect. Oxytocin also does not change colonic compliance and adaptation of the colon to distension. Although a clinical use of oxytocin to treat abdominal pain related to IBS cannot be envisaged, a better understanding of the relation between visceral sensitivity and the hormones acting on the female genital tract could lead to the development of new treatments for IBS patients as shown recently with the report of some clinical benefit of leuprolide in this disorder.⁴⁵⁻⁴⁶

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