Abdominal pain is a major symptom of both functional and organic gastroenterological disorders. Irritable bowel syndrome (IBS), the most common gut functional syndrome, is characterised by abdominal pain or discomfort in association with bloating and/or defecation disorders and/or altered bowel habits. Hypersensitivity to physiological or experimental visceral stimuli (that is, reduction of pain or discomfort thresholds) has been repetitively demonstrated in these patients and is considered a major clinical feature of IBS. The pathophysiology of such visceral hypersensitivity is probably multifactorial, involving both peripheral and central neural mechanisms, but still remains poorly understood. This concept has been challenged as it is mainly based on indirect evidence provided by measurements of subjective pain thresholds evoked by experimental visceral stimuli. There are still few objective data demonstrating hyperexcitability of pain systems in IBS patients although alteration of the processing of visceral sensory information in humans has been suggested in electrophysiological and functional neuroimaging studies.

The aim of the present study was to investigate modulation of spinal transmission of nociceptive signals in IBS patients. We used an electrophysiological approach based on recordings of the somatic nociceptive cutaneous muscular flexion (RIII) reflex. The threshold and amplitude of this polymodal spinal reflex, elicited by electrical stimulation of a cutaneous sensory nerve and recorded from a flexor muscle on the ipsilateral lower limb, suggests activation of two functionally distinct populations of mechanoreceptors by these two modes of stimulation. In the present study, we used a similar approach to compare the effects of rectal distensions on electrophysiological recordings of the RIII reflex in IBS patients and in healthy volunteers.

METHODS

Participants
Seventeen IBS patients (14 women; age range 31–76 years; mean 51 (13) years) recruited in a tertiary referral centre and 10 healthy volunteers (seven women; age range 30–46 years; mean 37 (6) years) participated in the study.

IBS patients were eligible if they met the Rome I criteria for IBS, including recurrent abdominal pain and bowel dysfunction for at least three months during the previous year. Each patient underwent a complete evaluation to exclude organic disease, including a detailed medical history and physical examination and a normal total colonoscopy within the five years preceding inclusion. None of these patients had past abdominal surgery, except for appendectomy. Antispasmodics, laxatives, and/or antidiarrhoeal agents were stopped at least 15 days before the experimental protocol. Seven patients were classified as constipation predominant IBS, five as diarrhoea predominant IBS, two had alternating bowel disorders while three had normal bowel movements. During the week before the experimental study, IBS patients were asked to report prospectively the mean daily intensity of abdominal pain and bloating on visual analogue scales.

Abbreviations: IBS, irritable bowel syndrome; RIII reflex, somatic nociceptive cutaneous muscular flexion reflex
Inflation rate while at the end of slow ramp distension the deflation rate of the balloon until 0 ml was similar to the distension periods of each experimental sequence.

The sural nerve was then adjusted to 20% above the threshold average minimal current that elicited the reflex response. The RIII reflex threshold was defined as the minimal current that was sufficient to elicit a response. The responses were recorded from the ipsilateral biceps femoris muscle. The RIII response was measured via a pair of surface electrodes placed 2 cm apart on the degreased skin overlaying the nerve within its retromalleolar path. Each electrical stimulation consisted of a train of five constant current pulses of 1 ms duration. Electromyographic responses were recorded from the ipsilateral biceps femoris via a pair of surface electrodes placed 2 cm apart on the degreased skin over the muscle. The RIII response was digitised, full wave rectified, and expressed as a percentage of the mean control value. Mean volume was calculated for each distension step. The period of increasing volume is followed by 1 minute of constant volume rate of 40 ml/min (slow ramp distension). At the end of each phasic distension, the RIII responses were averaged at one minute intervals and expressed as a percentage of the mean control value. Mean volume was calculated for each distension step. Slow ramp distensions were performed up to the pain threshold (score 5) or the maximal volume of the balloon.

Experimental design
Experiments were performed after a 12 hour fast in a quiet room where patients were relaxed. Experimental sessions began with determination of the RIII reflex response; thereafter slow ramp and rapid phasic distensions were performed in a randomised manner.

Rapid distensions were performed at four levels (10, 20, 30, and 40 mm Hg). Each level was applied once and the order of application was randomised. Each distension was maintained for three minutes, and 10 minutes elapsed between application of each distension to avoid sensitisation phenomena. The RIII reflex responses were measured during the three minutes before distension (control period), during the three min distension period, and during the three minutes following distension (post-distension period). For each level of distension, the RIII reflex was strongly facilitated during distension with a progressive return to baseline in the post-distension period. In IBS patients the reflex was strongly facilitated during distension with a progressive return to baseline during the post-distension period.

Perception of rectal distensions
Before the experiments, participants were informed of the visceral sensation they might experience. The sensation elicited by rectal distension was graded from 0 to 6 using a verbal questionnaire previously validated: 0, no perception; 1, initial perception; 2, sensation of gas; 3, sensation of stool; 4 urge to defecate or onset of discomfort; 5, moderate pain; and 6, intense or unbearable pain. In the case of rapid distension, participants reported their sensations at the end of each distension period, and during slow ramp distension they reported their sensations at fixed intervals (every 50 ml of distension). Distensions were performed until the threshold of moderate pain (score 5). Whenever intense or unbearable painful sensations (score 6) were experienced during any level of distension, the experiment was immediately suspended.

Rectal distension
An oversized spherical polyvinyl bag (10 cm diameter, infinite compliance until maximal volume of 600 ml) was mounted on the tip of a double lumen polyvinyl tube (12 Fr) and inserted into the rectum. The proximal opening of the tube was linked to an electronic barostat (INRA, Toulouse, France) that allowed controlled inflation and deflation of the balloon with air and continuous monitoring and recording of the volume and pressure inside the balloon. When in place, the balloon was unfolded by slowly injecting air under controlled pressure (<20 mm Hg) and then completely deflated. After a 20 minute period of rest, the barostat was used to inflate the balloon either rapidly (900 ml/min) to a constant pressure plateau (rapid phasic distension) or continuously at a constant volume rate of 40 ml/min (slow ramp distension). At the end of each phasic distension, the deflation rate of the balloon until 0 ml was similar to the inflation rate while at the end of slow ramp distension the balloon was rapidly deflated (900 ml/min) until 0 ml.

Figure 1 Individual examples showing the differential effects of slow ramp distension on the somatic nociceptive cutaneomuscular flexion (RIII) reflex recorded from the lower limb in healthy volunteers (A) and patients with irritable bowel syndrome (IBS) (B). Each bar represents a single reflex response expressed as a percentage of the mean value for the three minute pre-distension period. The period of increasing volume is indicated by arrows. (A) In healthy volunteers the reflex responses were progressively inhibited during distension, with a progressive return to baseline in the post-distension period. (B) In contrast, volunteers, in IBS patients the reflex was strongly facilitated during distension with a progressive return to baseline during the post-distension period.
Pain modulation in IBS

Fourteen IBS patients and 10 healthy volunteers completed the study. Three IBS patients were excluded because they could not tolerate the electrical stimuli (n = 2) or because of a lack of stability of the reflex responses (n = 1).

In IBS patients, the mean daily intensity of abdominal pain during the week before the experiment was 29.9 (24.7) and the intensity of abdominal bloating was 48.5 (26.3). The intensity of abdominal pain and bloating on the experimental day were not significantly different from those reported during the pretest period.

The RIII reflex threshold was not different between IBS patients (6.3 (0.3) mA) and healthy volunteers (7.6 (0.4) mA) (p = 0.3).

Figure 2  Cumulative results showing the effects of slow ramp distension on the somatic nociceptive cutaneomuscular flexion (RIII) reflex in healthy volunteers and irritable bowel syndrome (IBS) patients. The mean RIII reflex response recorded during each minute was expressed as a percentage of the mean value recorded during the three minute pre-distension control period (means (SEM)) and during the three minute post-distension period (P1, P2, P3). (A) In healthy volunteers, slow ramp distension induced a progressive decrease in the RIII with a progressive return to baseline after the end of distension. (B) In IBS patients, the effect of slow ramp distension were significantly different to those observed in volunteers as it induced progressive facilitation of the RIII reflex. Data are mean (SEM); **p<0.01; ***p<0.001.

Figure 3  Curves showing the volume-pressure relationship during slow ramp distensions in healthy volunteers and irritable bowel syndrome (IBS) patients. No significant difference was observed between the groups. Data are mean (SEM).

Figure 4  Curves showing the volume-sensation relationship during slow ramp distension. (A) Group comparisons did not show significant differences between healthy volunteers and irritable bowel syndrome (IBS) patients. (B) A significant increase in visceral sensation (that is, visceral hypersensitivity) was observed only in the subgroup of IBS patients (n = 10) showing facilitation of the somatic nociceptive cutaneomuscular flexion (RIII) reflex. *p<0.05; **p<0.01.

RESULTS

Individual examples of the effects of slow ramp distensions on the RIII reflex in healthy volunteers and IBS patients are shown in fig 1 and cumulative data observed in the two groups are shown in fig 2. In healthy volunteers, slow ramp distension induced a progressive inhibition of the reflex...
healthy volunteers were different according to the level of duration of symptoms, and bowel frequency).

Individual analysis revealed that clear facilitatory effects were not significantly different from healthy volunteers (fig 4B). In this subgroup of patients, the RIII reflex threshold and compliance curves were similar to those observed in healthy volunteers.

Compliance curves were similar in the two groups (fig 3) as well as maximal volume of distension: 338 (92) ml in IBS patients versus 377 (118) ml in healthy volunteers.

The volume-sensation relationship was similar in the two groups (fig 4A). However, in the subgroup of 10 IBS patients demonstrating facilitation of the RIII reflex, sensations evoked by distension were significantly more pronounced in IBS patients versus 377 (118) ml in healthy volunteers.

which peaked at the maximal volume of distension (61 (13)% of control values). In contrast, progressive facilitation of the RIII reflex (139 (15)% of pre-distension control values at the maximal volume of distension; \( p<0.01 \) healthy volunteers) was observed during slow ramp distension in IBS patients.

Figure 5 Cumulative data showing the effects of graded rapid rectal distensions ranging from 10 to 40 mm Hg (A–D) on the somatic nociceptive cutaneomuscular flexion (RIII) reflex recorded from the lower limb in healthy volunteers and irritable bowel syndrome (IBS) patients. For each distension level, the mean RIII reflex response during each minute was expressed as a percentage of the mean value recorded during the three minute pre-distension control period. The three minute distension period is indicated by arrows. Data are mean (SEM); \( **p<0.01 \).

Effects of rapid distensions
The effects of rapid distensions on the reflex responses in healthy volunteers were different according to the level of distension. No significant change in the reflex was observed during the 10 mmHg distension (fig 5A). An increase in the RIII responses was observed during the first minute of distension of the 20 and 30 mm Hg distensions (fig 5B, 5C). The 40 mm Hg stepwise distension induced biphasic effects: facilitation of the RIII response during the first minute followed by inhibition during the third minute (fig 5D).

In IBS patients, the effects of the 10, 20, and 30 mm Hg distension steps on the RIII responses were not significantly different from those observed in healthy volunteers. However, in contrast with healthy volunteers, no inhibition but facilitation of the RIII reflex was observed during the second and third minutes of the 40 mm Hg distension \( (p<0.01) \) (fig 5D).
Volumes of distension during the 10, 20, 30, and 40 mm Hg distention steps (fig 6), compliance curves (results not shown), and sensations evoked by rapid distensions (fig 7) were not significantly different between the two groups. The effects of rapid distensions on the RIII reflex were not related to the clinical presentation of IBS patients (that is, pain intensity or abdominal bloating recorded the week before the experimental session as well as on the experimental day, duration of symptoms, and bowel frequency).

DISCUSSION
In the present study, we found that rectal distensions induced facilitations of the RIII spinal nociceptive flexion reflex in a large subgroup of IBS patients. These results provide direct and objective arguments favouring the idea that visceral hyperalgesia/hyperalgesia reported in IBS patients is associated with hyperexcitability of spinal nociceptive neurones.

The role of visceral hyperalgesia as a major pathophysiological determinant of functional bowel disorders was proposed some 30 years ago. This concept was initially based on the observation of a reduction in painful or discomfort thresholds during balloon distensions of the rectosigmoid in IBS patients and was expanded further to other functional gastrointestinal disorders. However, there is still very little objective evidence demonstrating alteration of visceral pain processing in IBS patients observed during slow ramp distensions while the effects of rapid distensions were similar to those observed in volunteers (except for the highest level of distension). Such differential effects depending on the mode of distension argue against sensitisation of spinal neurones which, on the contrary, would have resulted in facilitatory effects during both types of distension. The fact that the RIII reflex threshold was different between healthy volunteers and IBS patients also tends to rule out the hypothesis of direct and permanent changes in the excitability of spinal neurones. Therefore, the hypothesis of failure of central inhibition in IBS patients appears more likely. Segmental and/or heterosegmental (that is, descending) systems that tonically or phasically modulate spinal transmission of somatic and visceral nociceptive signals have been described in both animals and humans. Tonic modulatory systems of pain transmission were probably not altered in IBS patients as the RIII reflex thresholds were not different between patients and healthy volunteers. In contrast, facilitation of the reflex responses may be explained by a reduction in segmental and/or descending inhibitory controls, which are phasically triggered by visceral stimuli. In conclusion, the present results suggest that our methodology may help to identify a subgroup of IBS patients with spinal hyperexcitability. This might be of particular interest as IBS is probably a heterogeneous and multifactorial condition, and clinical criteria, such as the Rome II criteria, do not allow discrimination between the relevant subgroups of patients. Further pathophysiological or pharmacological studies should aim at verifying whether the different subgroups of patients respond differently to new compounds acting on gut sensitivity.
ACKNOWLEDGEMENTS

B Coffin and D Bouhassira were responsible for the design of the study, conduct of the experiments, analysis and interpretation of the data, and writing of the paper. J-M Sabaté and L Barbe contributed to the experiments. R Jian contributed to the design of the study and writing of the paper. This study was supported by an unrestricted grant funded by L’institut UPSA de la douleur and la Société d’Etude et de Traitement de la Douleur.

Authors’ affiliations


REFERENCES