Effects of rectal distensions on nociceptive flexion reflexes in humans

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Bouhassira, Didier, Jean-Marc Sabaté, Benoît Coffin, Daniel Le Bars, Jean-Claude Willer, and Raymond Jian. Effects of rectal distensions on nociceptive flexion reflexes in humans. Am. J. Physiol. 275 (Gastrointest. Liver Physiol. 38): G410–G417, 1998.—We previously showed that gastric distension inhibits the somatic nociceptive flexion RIII reflex. To explore further the visceral-somatic interactions, we tested in the present study the effects of rectal distensions on RIII reflexes. Rapid and slow-ramp rectal distensions were performed in 10 healthy volunteers with an electronic barostat. The RIII reflex was continuously recorded from the lower limb during both types of distension and from the upper limb during rapid distensions. The visceral sensations were scored on a graded questionnaire. Rapid distensions facilitated the RIII reflex recorded from the lower limb, but at the highest distension level, facilitation was followed by inhibition. Slow-ramp distension induced gradual inhibition of the RIII reflex, which correlated with both distension volume and visceral sensation. RIII reflex recorded from the upper limb was also inhibited by rapid rectal distensions. Reflex inhibitions were probably related to the activation of pain modulation systems. One plausible explanation for the facilitatory effects, observed only at the lower limb, is the convergence of rectal and reflex afferents at the same levels of the spinal cord. The differential effects of rapid and slow-ramp distensions suggest the activation of two distinct populations of mechanoreceptors by these two modes of distension.

pain; nociception; visceral perception; sensory pathways

THE OBSERVATION THAT patients with functional intestinal disorders, such as nonulcer dyspepsia, noncardiac chest pain, or irritable bowel syndrome, have a lowered threshold for discomfort during balloon distension (2, 8, 9, 24, 29, 36, 37) has led to the suggestion that these disorders are related to alterations in visceral sensitivity (26–28). This new pathophysiological concept has highlighted the need for standardized reproducible methods of evaluating visceral sensitivity in humans. In most studies, the evaluation of sensory perception has been based on subjective reports. Several approaches have been proposed for more objective evaluation of visceral sensitivity. They include measurement of intestinointestinal reflexes, recording of cortical potentials evoked by visceral stimuli (1), and very recently, brain function imaging (38). We developed a different approach based on the counterirritation process, i.e., the inhibition of a pain by a different pain. In a previous study in healthy volunteers (6), we showed that gastric distensions induced stable reproducible inhibitions of a somatic nociceptive flexion reflex, the RIII reflex. This reflex is a polysynaptic spinal reflex elicited by electrical stimulation of a sensory nerve and recorded from a flexor muscle in the ipsilateral limb. The threshold and amplitude of the RIII reflex are closely related to those of the concomitant cutaneous sensations evoked by electrical stimulation (40). As inhibitions of this reflex by gastric distensions were closely correlated to both the volume of distension and the resulting visceral sensation, we proposed that the RIII reflex technique could be used to evaluate visceral sensations and somatovisceral interactions more objectively in humans. In this connection, we recently showed that this method could be used to test the pharmacological effects of fedotozine, a compound that acts on visceral sensitivity (13).

Using a similar approach in the present study, we tested the effects of rectal distensions on the RIII reflex. To differentiate between segmental and heterosegmental effects, we compared the effects of distensions on the RIII reflex recorded from the lower and upper limbs, respectively. We also compared the effects of two distension modes, rapid and slow ramp, which are supposed to stimulate different rectal mechanoreceptors (25, 30, 35).

METHODS

After the protocol was approved by a local Ethics Committee, the experiments were performed on 10 healthy volunteers (5 men and 5 women, aged 20–40 yr) with no evidence of chronic or acute illness, gastrointestinal symptoms, or altered bowel habits. Volunteers were carefully briefed about the experimental procedure and gave informed written consent to participate in the study.

Noceceptive Flexion Reflex (RIII Reflex)

The RIII reflex was elicited and recorded from both the lower and upper limbs, according to previously described and validated techniques (6, 7, 40). Briefly, subjects were placed in a lateral decubitus position, and the RIII reflex was elicited and recorded by an entirely computerized system (Physio Labo system, Notocord, Igny, France). To elicit the lower limb reflex, the sural nerve was electrically stimulated at a frequency of 0.17 Hz (10 stimulations/min), via a pair of surface electrodes placed 2 cm apart on the degreased skin overlying the nerve within its retromalleolar path. To elicit the upper limb reflex, the same stimuli were applied to cutaneous branches of the ulnar nerve on the fourth and fifth fingers, by means of ring electrodes. Each electrical stimulation consisted of a train of five constant current pulses of 1 ms each. Electromyographic responses were recorded via surface electrodes fixed on the degreased skin overlying ipsilateral...
Rectal Distension

A polyvinyl overshine spherical bag with a maximal diameter of 10 cm and infinite compliance up to a maximal volume of 600 ml was mounted on the tip of a double-lumen polyvinyl tube (12 Fr), tightly folded, lubricated, and inserted into the rectum. The distal attachment site was 4 cm from the anal verge. The tube was secured in the correct position with tape. Its proximal opening 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 mmHg). The balloon was then completely deflated. After a 15- to 20-min period of rest, the barostat was used to inflate the balloon, either rapidly at 900 ml/min to a constant pressure plateau (rapid distension) or continuously at a constant volume rate of 40 ml/min (ramp distension).

Perception of Rectal Distensions

Before the experiments, volunteers were informed of the visceral sensations they might experience. They were asked to grade the sensation elicited by the rectal distension from 0 to 6 on a verbal questionnaire, as follows: 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. For rapid distensions, subjects reported their sensation at the end of each postdistension period. For slow-ramp distension, they reported their sensation at the following fixed intervals: after every 100 ml of distension up to 300 ml, and then after every 50 ml up to the

Fig. 1. Individual example showing effects of rapid rectal distensions from 10 to 40 mmHg (A–D) on RIII reflex recorded from the lower limb. Arrows delimit 3-min period of distension. Each bar represents a single reflex response, expressed as a % of the mean value for the 3-min predistension control period.

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10 mm Hg

20 mm Hg

30 mm Hg

40 mm Hg

%
pain threshold (score 5). Whenever a sensation of intense or unbearable pain (score 6) was experienced during any level of distension, the distension was immediately suspended.

Experimental Design and Data Analysis

The 10 volunteers underwent experiments on 2 different days, separated by an interval of 10–14 days. All experiments were performed after a 12-h fast.

Day 1. The respective effects of rapid phasic and continuous slow ramp were tested on the RIII reflex recorded from the lower limb. The two types of distension were performed in randomized order and separated by 1 h of rest. Rapid distensions were performed at four levels (10, 20, 30, and 40 mmHg). Each level was applied once, and the order of application was randomized. Each distension was maintained for 3 min, and 10–15 min elapsed between the application of each level of distension to avoid sensitization phenomena. The RIII reflex responses were measured during the 3 min before distension (control period), during the 3-min distension period, and during the 3 min after distension (postdistension period). For each level of distension, the RIII responses were averaged at 1-min intervals and expressed as a percentage of the mean control value. Slow-ramp rectal distension was performed up to either the pain threshold or the maximum volume of the balloon (600 ml). The RIII reflex responses were measured during the 4 min before distension (control period), during the continuous rectal distension period, and during the 4 min after distension (postdistension period). The sensations elicited by the distensions were scored as described above.

Day 2. The effects of four levels of rapid distensions (10–40 mmHg) were tested on the RIII reflex recorded from the upper limb, using the same experimental design as that used on day 1. Slow-ramp distensions were not performed, because of a lack of stability of the reflex recorded from the upper limb (see below).

Statistical Analysis

Results were expressed as means ± SE. Statistical analysis of RIII inhibition was performed by two-way ANOVA, with the Fishers post hoc least-significant difference test. Relationships between two variables were tested by the Kendall rank correlation ($\tau$). $P < 0.05$ was considered significant.

RESULTS

Effects of Rectal Distensions on RIII Reflex Recorded From Lower Limb

The mean threshold of sural nerve stimulation required to evoke the RIII reflex from the lower limb was 9.4 ± 0.2 mA. Stimulation at 1.2 times the threshold

Fig. 2. Cumulative data showing effects of graded rapid rectal distensions ranging from 10 to 40 mmHg (A–D) on RIII reflex recorded from the lower limb. For each distension level, the mean RIII reflex response during each minute was expressed as a % of the mean value recorded during the 3-min predistension control period. The 3-min distension period (solid bars) is indicated by arrows. Data are means ± SE. *$P < 0.05$, ***$P < 0.001$ vs. control values.
level elicited a fairly stable RIII reflex response during the predistension period (see control period in Fig. 1) and evoked a moderate painful sensation of the pin-prick type. Subjects reported that this sensation originated from the level of the stimulating electrodes and was projected up to the distal cutaneous receptive field of the sural nerve on the external side of the foot. The sensation fluctuated minimally and was well tolerated throughout the experiments (70–80 min).

Rapid distensions. The four levels of distension could be completed in all the subjects except one who interrupted the 40-mmHg distension after 2 min. An example of the effects of the four levels of rectal distension on the RIII reflex is shown in Fig. 1, and the cumulative results observed in the 10 volunteers are shown in Fig. 2. The 10-mmHg distension did not significantly modify the RIII reflex during the 3 min of distension. The 20- and 30-mmHg distensions induced a significant increase in the reflex (i.e., facilitation) during the first minute of distension (129 ± 5% and 159 ± 7% of mean control values, respectively; P < 0.001). The 40-mmHg distension facilitated the RIII reflex during the first minute (127 ± 7% of mean control values; P < 0.001) and inhibited it during the second and third minute (72 ± 8% and 66 ± 5% of mean control values, respectively; P < 0.001). The 10-, 20-, 30-, and 40-mmHg distensions elicited mean sensation scores of 1.2 ± 0.3, 2.9 ± 0.3, 3.6 ± 0.1, and 4.8 ± 0.1, respectively.

Slow-ramp distension. An example of the effect of slow-ramp distension on the RIII reflex recorded from the lower limb is shown in Fig. 3A. Cumulative results are given in Fig. 3B, which also shows the evolution of intrabag pressure during distension. Progressive inhibition of the reflex was observed and reached its maximum (68±9% inhibition of mean control value) at the maximal level of distension (pressure, 38 ± 4 mmHg; volume, 398 ± 35 ml). As shown in Fig. 4, the inhibition of the RIII reflex correlated with both the volume and the sensation scores.

Effects of Rectal Distensions on RIII Reflex Recorded From Upper Limb

The mean threshold required to evoke the RIII reflex from the upper limb was 8.5 ± 1.2 mA. In four subjects,
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The present results indicate that, in humans, rectal distensions induce different effects on the RIII nociceptive flexion reflex, depending on the site of recording (i.e., upper or lower limb) and the mode of distension (i.e., rapid or slow ramp). The inhibitory effects were probably due to the activation of pain modulation systems. Reflex facilitation, which was only observed for the reflex recorded from the lower limb, may well have been due to the convergence of somatic and visceral inputs at the same levels of the spinal cord. The different effects of rapid and slow-ramp distensions suggest that two functionally distinct types of rectal mechanoreceptor were activated by these different modes of distension.

Rapid rectal distensions induced inhibitions of the reflex recorded from the upper limb that correlated with both the level of distension and visceral sensation. These inhibitions were similar to those observed for the RIII reflex recorded from the lower limb during gastric distension (6). In both cases, a conditioning visceral heterotopic stimulus was applied in an area far from the response tested (i.e., the RIII reflex). These heterossegmental effects were similar to those observed in animals. Thus, in the cat and rat, the activities of nociceptive spinal dorsal horn neurons and somatic nociceptive reflexes were indeed found to be strongly inhibited by somatic or visceral heterotopic noxious conditioning stimuli (10, 15, 16, 21–23, 31, 34). Such inhibitory effects probably involved systems that modulate the spinal transmission of nociceptive signals. One such system, initially described in the rat (22, 23), is called diffuse noxious inhibitory controls (DNIC). DNIC are triggered exclusively by heterotopic nociceptive stimuli and are sustained by an anatomic loop involving supraspinal structures located in the caudal medulla (3–5). Using the RIII nociceptive flexion reflex as a test response, it has been demonstrated that a supraspinally mediated system analogous to DNIC and similarly organized also exists in humans (7, 14, 41, 42). Such a system probably constitutes one of the neurophysiological bases for the counterirritation phenomenon (i.e., the inhibition of a pain by a different pain). However, in contrast to heterotopic somatic stimuli, the present study and our previous one (6) indicate that inhibition of the RIII reflex is induced, not only by nociceptive visceral stimuli, but also by nonpainful visceral stimuli. Similar results have been observed in animals (10, 34). The differences between the effects of heterotopic visceral stimuli and somatic stimuli on the RIII reflex might be related to the specific organization of the sensory receptors involved in visceral pain. Indeed, the presence of specific nociceptors, well established in the skin, is still controversial in the viscera, although high-threshold receptors have been described in several regions of the gastrointestinal tract (11, 12, 33).

**Fig. 4.** A: relationship between volume of rectal distension and sensation perceived, as assessed by verbal questionnaire ($r = 0.49; P < 0.0001$). B: relationship between volume of rectal distension and RIII reflex responses, expressed as % of control values ($r = -0.47; P < 0.0001$). C: relationship between sensation score and RIII reflex responses, expressed as % of control values ($r = -0.49; P < 0.0001$).

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Correlated significantly with the levels of distension ($r = 0.87; P < 0.001$). In addition, a significant correlation was observed between RIII reflex inhibition and sensation scores ($r = 0.55; P < 0.001$).

**DISCUSSION**

The stimulation of the cutaneous branches of the cubital nerve was not well tolerated, and/or the reflex responses were not stable enough during the control period. In the remaining six subjects, stimulation at 1.2 times the threshold level elicited a RIII reflex response during the predistension period that was judged stable enough. An example of the effects of the four levels of rectal distension on the RIII reflex recorded from the upper limb is shown in Fig. 5, and the cumulative results are indicated in Fig. 6. Distension of 10 mmHg did not significantly modify the RIII reflex, but the 20-, 30-, and 40-mmHg distensions caused significant inhibition ($72 \pm 10\%, 60 \pm 6\%,$ and $54 \pm 7\%$ of mean control values, respectively; $P < 0.01$). Inhibitions were maximal during the second and third minute of distension. For the 30- and 40-mmHg distensions, inhibitions outlasted the distension period by 1 and 2 min, respectively. The 10-, 20-, 30-, and 40-mmHg distensions elicited mean sensation scores of $0.7 \pm 0.2, 2.8 \pm 0.4, 4 \pm 0.2$, and $4.9 \pm 0.1$, respectively. Perception scores
Alternatively, one cannot exclude the possibility that other modulating systems, such as those entirely organized in the spinal cord (17) or those mediated by vagal afferents, are also involved in the inhibition of the RIII reflex.

More surprisingly, rapid rectal distensions had both facilitating and inhibitory effects on the RIII reflex recorded from the lower limb. Facilitation was observed during the initial period of low levels of rectal distension and to a lesser extent, during the highest level of distension. Because such facilitation was not observed when RIII reflex was recorded from the upper limb, one plausible explanation is that it was due to the convergence of rectal and RIII reflex afferents at the same levels of the spinal cord. Other central mechanisms, such as a general arousal induced preferentially by rapid distensions or the activation of extrarectal pelvic receptors by abrupt visceral displacements, are less likely, because they would have induced similar effects for the reflexes recorded from the upper and lower limbs. The viscerosomatic convergence of nociceptive information is a process that is often observed in animals during the recording of neuronal activity in many regions of the central nervous system and is considered to be the mechanism underlying referred pain (11, 12, 33). In particular, it has been observed that some nociceptive lumbar neurons with a cutaneous excitatory receptive field located on the lower limb, are activated also by colorectal distension (32). The spinal projections of rectal afferents are not completely understood in humans. Both sacral (parasympathetic) afferents running in the pelvic nerve and lumbar (sympathetic) afferents running in the splanchnic nerve have been described (11, 12, 26, 33). The convergence of some of these afferents with those of the RIII reflex, which is integrated in the lumbar and sacral levels of the spinal cord, is therefore possible. Because facilitations were observed only during the initial phase of the rapid distensions, one can propose that convergence involved rectal afferent pathways connected with functionally distinct mechanoreceptors selectively activated by this type of distension (see below). In the present study, it was interesting to observe that the highest level of rapid rectal distension induced brief facilitation of the reflex, followed by its inhibition. This biphasic effect suggests competition between the two processes (i.e., facilitation due to convergence and inhibition due to inhibitory controls).

Unlike rapid distensions, slow-ramp rectal distensions only inhibited RIII reflex recorded from the lower limb. These inhibitory effects, which correlated with both the distension level and the visceral sensation perceived, probably involved spinal and/or supraspinal mechanisms similar to those discussed above. In this respect, it would have been interesting to compare the
effects of slow-ramp distension on the upper and lower limb reflexes. However, the effects of slow-ramp distensions were not tested on the upper limb reflex, since electrical stimuli were less well tolerated and the RIII reflex was much less stable in the upper limb.

Several lines of evidence suggest that different types of mechanoreceptors are activated during rapid and slow-ramp rectal distension in humans: 1) in normal volunteers, perception thresholds are higher for rapid than for slow-ramp distension (30, 39), 2) in patients with irritable bowel syndrome, sensory thresholds are reduced for rapid distension but normal for slow-ramp distension (30), and 3) intrarectal lidocaine induced a rise in perception thresholds during slow-ramp distension but not during rapid distension, in both normal control subjects and patients with irritable bowel syndrome (25). The results of electrophysiological and anatomic studies in animals suggest that thoracolumbar afferents have receptive fields located in the muscle layer, serosa, and mesentery, whereas for sacral afferents the receptive fields are mucosal (12, 18–20). In humans, it has been proposed that mucosal mechanoreceptors are preferentially stimulated during slow rectal distensions, whereas splanchnic afferents, whose receptive fields are in the serosa and mesentery and project into the lumbar spinal cord, are preferentially activated during rapid distensions (25, 30). In accordance with this hypothesis, it has been reported that patients with sacral spinal cord lesions experienced residual perception during rapid phasic rectal distensions but no sensation during slow-ramp distensions (25). The opposite effects of rapid and slow-ramp distensions on the RIII reflex recorded on the lower limb might be due to the selective activation of these different populations of rectal mechanoreceptors by the two modes of distension. However, one cannot exclude the possibility that the facilitating effects observed here were due to the greater synchronization of afferent activities induced by rapid rather than slow-ramp distensions. One way of eliminating this possibility would be to study the effects of both types of rectal distension on the RIII reflex after intrarectal administration of xylocaine to reduce the response of the superficial mucosal receptors.

In conclusion, the present results confirm the advantages of RIII nociceptive reflex recording to evaluate visceral sensitivity in humans. This approach might constitute an interesting tool for studying both the changes in somatovisceral convergence and pain modulation systems in various pathological states.

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