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Visceral sensation and irritable bowel syndrome; with special reference to comparison with functional abdominal pain syndrome

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Abstract

Objective and background:

Stress-induced visceral hypersensitivity may play an important role in the pathogenesis of irritable bowel syndrome (IBS) but not in functional abdominal pain syndrome (FAPS). We examined rectal sensation in those patients.

Methodology:

Experiment 1: Rectal thresholds of pain (PT) and maximum tolerance were assessed by barostat with ramp distention before and after repetitive rectal painful distention (RRD). Experiment 2, PT was measured in basal state and after intravenous CRF (100 μg) or vehicle, together with or without RRD. Experiment 3: Three phasic distentions at physiological range were randomly loaded. The subjects were asked to mark the visual analogue scale (VAS) in reference to subjective intensity of sensation.

Results:

Experiment 1: Majority of IBS patients showed rectal hypersensitivity before RRD in contrast to FAPS. All IBS patients developed hypersensitivity after RRD, however, none of the FAPS patients did. RRD significantly reduced both thresholds in IBS (n=7) but did not change in controls (n=14) and FAPS (n=6). Experiment 2: PT was not modified by RRD in placebo group (n=6), while it was significantly reduced in CRF-treated group (n=5). On the other hand, CRF (n=5) or vehicle (n=5) without RRD did not alter PT. Experiment 3: The VAS ratings were increased in IBS (n=7) but significantly decreased in FAPS (n=6) as compared to controls (n=14).

Conclusions:

RRD-induced rectal hypersensitivity seems to be reliable marker for IBS, and CRF may contribute to this response. FAPS patients may have hyposensitivity to non-noxious

physiological distention, suggesting FAPS has different pathogenesis from IBS.

Kew words

barostat, CRF, FAPS, IBS, stress

Short title

Visceral sensation of IBS and FAPS

Introduction

Functional gastrointestinal disorders (FGIDs) are characterized as chronic or recurrent gastrointestinal (GI) symptoms, which are not explained by structural or biochemical abnormalities.[1] Irritable bowel syndrome (IBS) is one of the FGIDs, and recently several reports suggested that visceral hypersensitivity plays an important role in the pathogenesis of this disorder.[2-6] On the other hand, visceral stimulation such as repetitive sigmoid distention was reported to induce rectal hyperalgesia in all examined IBS patients, but in none of the healthy subjects.[4] Since visceral stimulation can be interpreted as stress to IBS,[2] these lines of evidence suggest that stress-induced altered visceral sensation may be specific visceral response to this disorder. However, these altered visceral sensation in IBS patients may result from response bias,[7] which is possibly induced by comorbid psychological state such as anxiety or somatization.[8] Functional abdominal pain syndrome (FAPS), which is also one of the FGIDs, is similar to the psychiatric diagnosis of Somatoform Pain Disorder in the DSM-IV.[1] Although IBS and FAPS have common clinical feature, such as chronic unexplained abdominal pain, their pathogenesis is thought to be different according to their disease concepts defined in Rome II criteria.[1]

In this study, we examined rectal perceptual thresholds before and after visceral stimulation in patients with IBS, FAPS and healthy controls in order to test our hypothesis that stress-induced altered visceral sensation is an important underlying mechanism in IBS in contrast to FAPS. Moreover, we also examined the subjective intensity of sensation assessed by visual analogue scale (VAS). On the other hand, since corticotropin-releasing factor (CRF) is considered to be a major mediator of stress responses in the brain-gut axis, we evaluated the effect of CRF in rectal sensation in

order to know the mechanisms of stress-induced altered visceral sensation.

Methods

All these following studies were approved by the Hokkaido University Ethical Committee on Human Studies. Verbal and written informed consent was obtained from each subject.

Experiment 1: Rectal perceptual thresholds and the effect of repetitive rectal painful distention (RRD).

Subjects

Controls. Fourteen healthy subjects were recruited by advertisement to serve as controls.

Patients. Seven patients with IBS and six patients with FAPS were recruited from the Department of Comprehensive Medicine, Hokkaido University Hospital. Selection criteria included a positive diagnosis by the Rome II criteria.[1]

Psychological status checklist

All subjects completed the hospital anxiety and depression scale (HADS) questionnaire, which assesses current psychological status such as anxiety and depression.[9, 10]

Visceral stimulation device

The computer-driven barostat device (Synectics Visceral Stimulator; Synectics, Stockholm, Sweden) was used for the evaluation of rectal sensation.

Thresholds

Rectal perceptual thresholds such as pain (PT) and maximum tolerance (MT) were determined during rectal distention.

Experimental protocol

All medications known to affect the GI tract were discontinued 48 hours before the procedure. After 15-hour fast, bowel cleansing was performed by warm water enema (250 ml). Subjects were placed in left lateral decubitus position on the bed, and the barostat bag catheter which was lubricated by olive oil was inserted into the rectum. Experimental rectal distention protocol started after 30-min resting period.

The first, subjects were given ramp distention. The barostat device was programmed to inflate the bag with inflation rate at 40 ml/min. During the ramp distention, we determined PT and MT. When the subjects felt intolerable for distention and pressed the pushbutton (i.e., threshold of MT was obtained), the bag was instantaneously deflated and finished this first session. Ten min later, phasic distention with sensory tracking (RRD as conditioning) was started. The barostat was programmed to deliver intermittent phasic distention (60-second duration) separated by 30-sec intervals. Inflation and deflation rate of phasic distention was 14 ml/sec. The distended pressure was programmed as follows; 5, 10, 5, 15, 20, 25, 10, 30, 35, 40, 45, 50 mmHg. This protocol was maintained until the subject complained of pain. When the subject indicated pain, then distention device changed the mode to the sensory tracking, i.e., the following pressure of distention was randomized to stay the same or to be decreased by 3 mmHg. And then, if subject did not feel pain in the tracking mode, the following distention was randomized to stay the same or to be increased by 3 mmHg. The distention of tracking mode was lasted until the subject reported pain 6 times. Ten min later, ramp distention was performed and thresholds were determined again.

Experiment 2: The effect of CRF on rectal sensation in healthy humans.

Subjects

Twenty one healthy male subjects (mean age 26.5) weighing about 50 Kg were recruited by advertisement.

Experimental protocol

A double-blind placebo-controlled study design (CRF or vehicle) was used. In the first experiment, subjects were given ramp distention and PT was determined. Then vehicle (1 ml of saline, n=6) or CRF [hCRH "Mitsubishi" Injection; Mitsubishi Pharma, Osaka, Japan, 100 μg (2 μg/kg) in 1 ml saline, n=5] was injected intravenously (iv). Ten min later, RRD was loaded. After 10 minutes from the completion of RRD, then the ramp distention was given again and PT was measured. Another series of experiment was to determine the effect of CRF without RRD on rectal sensation. Subjects were given ramp distention to determine PT. Then vehicle (1 ml of saline, n=5) or CRF (100 μg in 1 ml saline, n=5) was injected iv, and 45 min later, ramp distention was induced again to determine PT.

Experiment 3: Subjective intensity of sensation in response to phasic distention.

Subjects

All subjects recruited in Experiment 1 were employed again.

Intensity

Subjective intensity of sensation in response to rectal distention was determined by VAS ranging from no sensation (0) to severe (100) arrayed along a 100-mm bar.

Experimental protocol

Three phasic distentions of 10, 15 and 20 mmHg for 60 sec separated by 30-sec intervals at a resting pressure of 0 mmHg, were randomly loaded. The subjects were asked to mark the VAS in reference to subjective intensity of sensation immediately

after each distention. Our pilot study revealed that the threshold for discomfort in response to rectal ramp distention was 12.1 ± 1.0, 16.9 ± 2.0 and 20.8 ± 2.0 mmHg for IBS, control and FAPS, respectively, which was not statistically different but tended to be higher in FAPS and lower in IBS group in contrast to other perceptual thresholds. Then, the loaded pressure in this experiment was set around discomfort threshold of controls, in order to detect the possible difference of visceral response among groups. This distention was thought to be non-painful, physiological level of distention.

Statistical analysis

All data were expressed as means ± SE. For multiple group comparison, an analysis of variance (ANOVA) or Kruskal-Wallis one-way ANOVA followed by the least significant difference test or the Mann-Whitney rank sum test was performed. Fisher's exact test was used to compare proportional differences (male and female ratio) among groups. For two group comparison, Student's t test or Student's t test for paired comparison was used.

Statistica (StatSoft Inc. Tulsa, Okla., USA) was used for all statistical computations. An α cutoff of $P < 0.05$ was used throughout the study.

Results

Experiment 1:

Clinical Characteristics

Table 1 summarizes the clinical characteristics with IBS, FAPS and control. HADS anxiety and depression score were significantly greater in the both patients as compared to control [Kruskal-Wallis one way ANOVA: $\chi^2 = 19.8$, $P < 0.05$ for anxiety, $\chi^2 = 17.2$,

$P < 0.05$ for depression, IBS or FAPS vs. control, $P < 0.05$ for both scores].

Perceptual thresholds

Basal condition

There was a significant main effect of group (control, IBS, FAPS) for the thresholds [ANOVA; $F = 6.52$; $P < 0.05$]. Both thresholds were significantly lower in IBS as compared to control [PT: 31.2 ± 3.5 for control vs. 19.8 ± 2.5 for IBS, $P < 0.05$, MT: 42.9 ± 3.0 for control vs. 24.8 ± 3.6 for IBS, $P < 0.05$]. However, these parameters were not significantly different between FAPS and control (PT: 33.8 ± 3.0, MT: 43.6 ± 6.3 for FAPS vs. control, $P > 0.05$).

The effect of RRD on rectal sensation

There was a significant interaction (group×RRD) for the thresholds [ANOVA $F = 7.73$, $P < 0.05$]. RRD significantly reduced both thresholds in IBS ($P < 0.05$), while it did not modify them in control and FAPS (Figure 1).

Figure 2 also showed the distribution of rectal perceptual thresholds before and after RRD for each subject in IBS and FAPS. We calculated the 95% confidence intervals of controls, and defined it as normal value. In the baseline, 5 (PT) or 6 (MT) of the 7 IBS patients and only one FAPS patient (PT) showed rectal hypersensitivity. On the other hand, all the patients with IBS developed rectal hypersensitivity after RRD load, while none of the FAPS patients did. Then we set the cut off pain threshold after RRD as 20 mmHg, high efficiency (96.3%) with very good sensitivity (100%) and specificity (95%) to discriminate IBS patients from other subjects was obtained.

Experiment 2:

PT was not changed by RRD in vehicle group, but it was significantly reduced after

RRD in CRF-treated group ($P < 0.05$, Figure 3). In the second experiment, either CRF or vehicle did not alter PT.

Experiment 3:

There was a significant main effect of group (ANOVA: $F = 7.53$, $P < 0.05$, Figure 4). FAPS had significantly lower VAS ratings across the three loaded pressures as compared to control or IBS ($P < 0.05$), and IBS had significantly higher VAS ratings as compared to control ($P < 0.05$). The VAS ratings at 10 and 15 mmHg were not significantly different between FAPS and control, but the value was significantly reduced in FAPS at 20 mmHg ($P < 0.05$). Although ANOVA demonstrated IBS had significantly higher VAS ratings, each value tended to be higher, but not significantly different from control. Moreover, there was a significant interaction (group×loaded pressure, ANOVA: $F = 3.53$, $P < 0.05$).

Discussion

Experiment 1: the effect of RRD on PT

The most important point of the experiment is that RRD induced rectal hypersensitivity in all IBS patients, but none of the patients with FAPS did, indicating conditioning (stress)-induced rectal hypersensitivity may be sensitive marker for IBS. Our result may also explain the fact that various type of stress influence the onset or exacerbation of IBS.[11] On the other hand, we recently reported that CRF plays an important role on visceral hypersensitivity induced by repetitive colorectal distention in rats.[12] CRF is released in both central and periphery in response to stress,[13] and reported to stimulate mast cell to degranulate, and facilitate release of serotonin in rat colon,[14] which is well

known stimulator of visceral afferents. These lines of evidence suggest the possibility that CRF may induce rectal hypersensitivity through activating visceral afferents in IBS.

Experiment 2: CRF and PT

To test this above hypothesis, we conducted next experiment. We showed that iv-CRF together with RRD reduced PT, indicating CRF can modify visceral sensory function in healthy humans and mimicked the stress response specifically observed in IBS patients. These results suggest that CRF may play an important role in stress-induced visceral hypersensitivity and this neuropeptide may relate to the pathogenesis of IBS. Recent report demonstrated that peripheral administration of CRF antagonist improves GI motility, visceral perception, and negative mood in response to gut stimulation in IBS patients,[15] which also supports our hypothesis. Present study also revealed that RRD without iv-CRF did not alter rectal sensation and moreover, iv-CRF alone did not induce it either, suggesting that both exogenous (iv) and endogenously released CRF in brain induced by RRD may be required to achieve rectal hypersensitivity in healthy humans. The reasons why RRD-induced rectal hypersensitivity is exclusively observed in IBS patients but not in healthy controls, and exogenous CRF is needed to induce rectal hypersensitivity in healthy controls remain to be shown. Since IBS patients were reported to have exaggerated endocrinological and GI motility response to iv-CRF as compared with healthy controls,[16] we would speculate that physiological level of CRF under stress may enough to modify visceral sensation in IBS patients, while iv-CRF in addition to endogenously released CRF may be needed to mimic this response in healthy humans. Further study is warranted to support this speculation.

Experiment 3: Subjective intensity of sensation assessed by VAS

IBS patients had significantly higher perceived intensity, which is consistent with

previous reports. [2, 4] On the other hand, FAPS patients demonstrated reduced intensity of sensation in response to non-painful physiological distention, but it was not induced by painful distention.

The rectum is innervated by both pelvic and lumbar splanchnic nerves. The pelvic nerve afferents are activated at lower stimulation intensities and they mediate non-noxious physiological sensations such as the presence of stool or gas. On the other hand, lumbar splanchnic afferents would be better tuned to signal the onset of higher-intensity mechanical events.[17] These lines of evidence suggest that hyposensitivity at lower pressure of distention might result from altered pelvic nerve function in FAPS.

No definitive neurophysiological study in FAPS has been published to date, but neuropathic pain induced by central sensitization is thought to be the most probable pathogenesis.[18] Peripheral neuropathic conditions resulting from various types of nerve injury could provide ongoing afferent input to the spinal cord, keeping it in a constant state of central sensitization.[19] Such nerve injury could result from abdominal surgeries or injuries to pelvic nerves during pregnancy or delivery. In fact, some FAPS patients were reported to undergo several abdominal surgical interventions in order to disclose the origin of chronic abdominal pain.[20] However, once central sensitization is established, symptoms can persist in the absence of ongoing abnormal peripheral stimulation. In the present study, only two patients had borne children and none of the patients had a history of abdominal surgery. However, other factors such as viral infection etc. are also well known to be related to nerve injuries, moreover, an important role of genetic factors in the predisposition to develop peripheral neuropathic pain is suggested by animal models, indicating that preexisting factors separate from the degree

of neural injury may influence these processes.[21] In this context, our result, i.e. suggestive dysfunction of pelvic nerve may support this pathophysiological hypothesis. In any event, inconsistency of visceral sensitivity between lower and higher pressure of distention might be a key feature to understanding the pathogenesis of FAPS.

In conclusion, RRD-induced rectal hypersensitivity seems to be reliable marker for IBS, and CRF may contribute to this response. FAPS patients may have hyposensitivity to non-noxious physiological distention, suggesting FAPS has different pathogenesis from IBS.

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Table 1. Clinical characteristics of the subjects

Clinical parameters	IBS	FAPS	Control
No. of subjects	7	6	14
Mean age (yr)	25.3 ± 3.2	45.0 ± 7.4	33.8 ± 4.9
Age range	17-34	28-61	22-62
Sex (M/F %)	29/71	33/67	43/57
HADS			
Anxiety	7.4 ± 1.2*	12.5 ± 1.8*	2.1 ± 0.10
Depression	5.9 ± 1.5*	6.5 ± 1.8*	1.9 ± 0.16

Hospital anxiety and depression scale (HADS). *: P vs. control < 0.05, Kruskal-Wallis one way ANOVA followed by Mann-Whitney Rank Sum Test.

Figure legends

Figure 1.

The effect of repetitive rectal painful distention (RRD) on rectal perceptual thresholds in response to ramp distention. Values are shown as mean ± SE. * P vs. before RRD < 0.05, analysis of variance followed by least significant difference test. Max; maximum tolerance.

Figure 2.

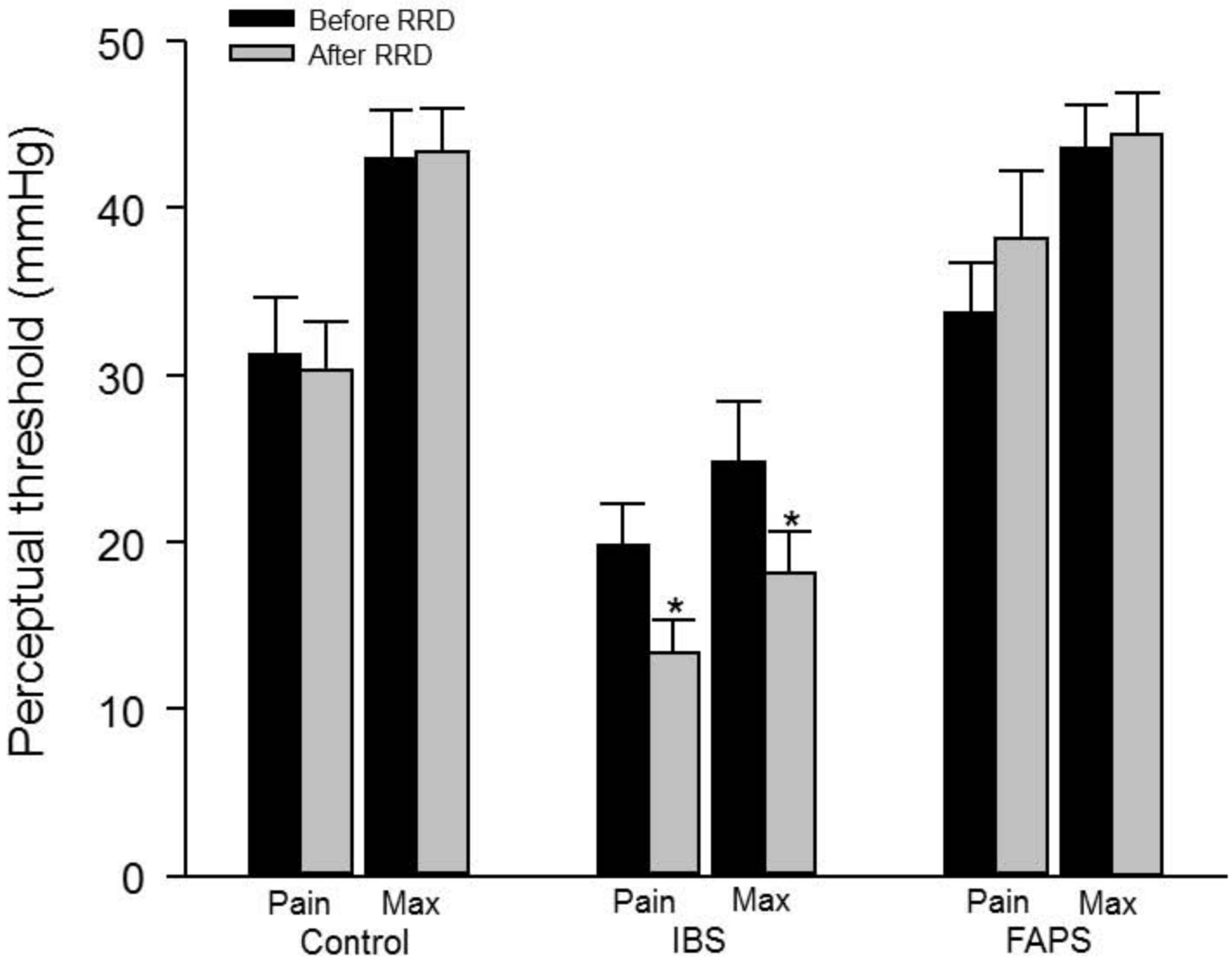
The threshold of each patient with IBS and FAPS is shown as symbol. The values before and after conditioning of same subject are connected by a line. Boxes represent the 95% confidence interval of control subjects.

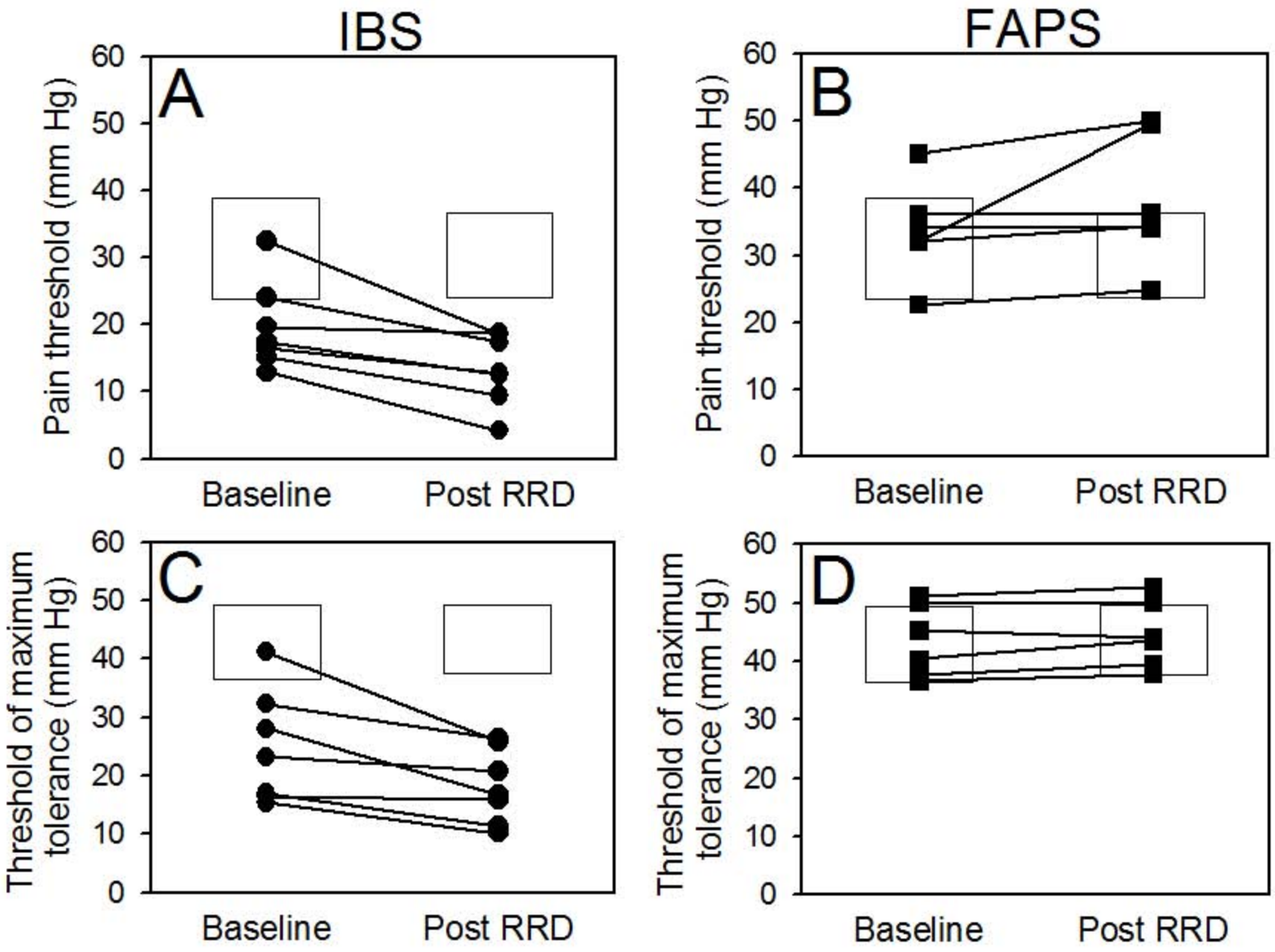
Figure 3.

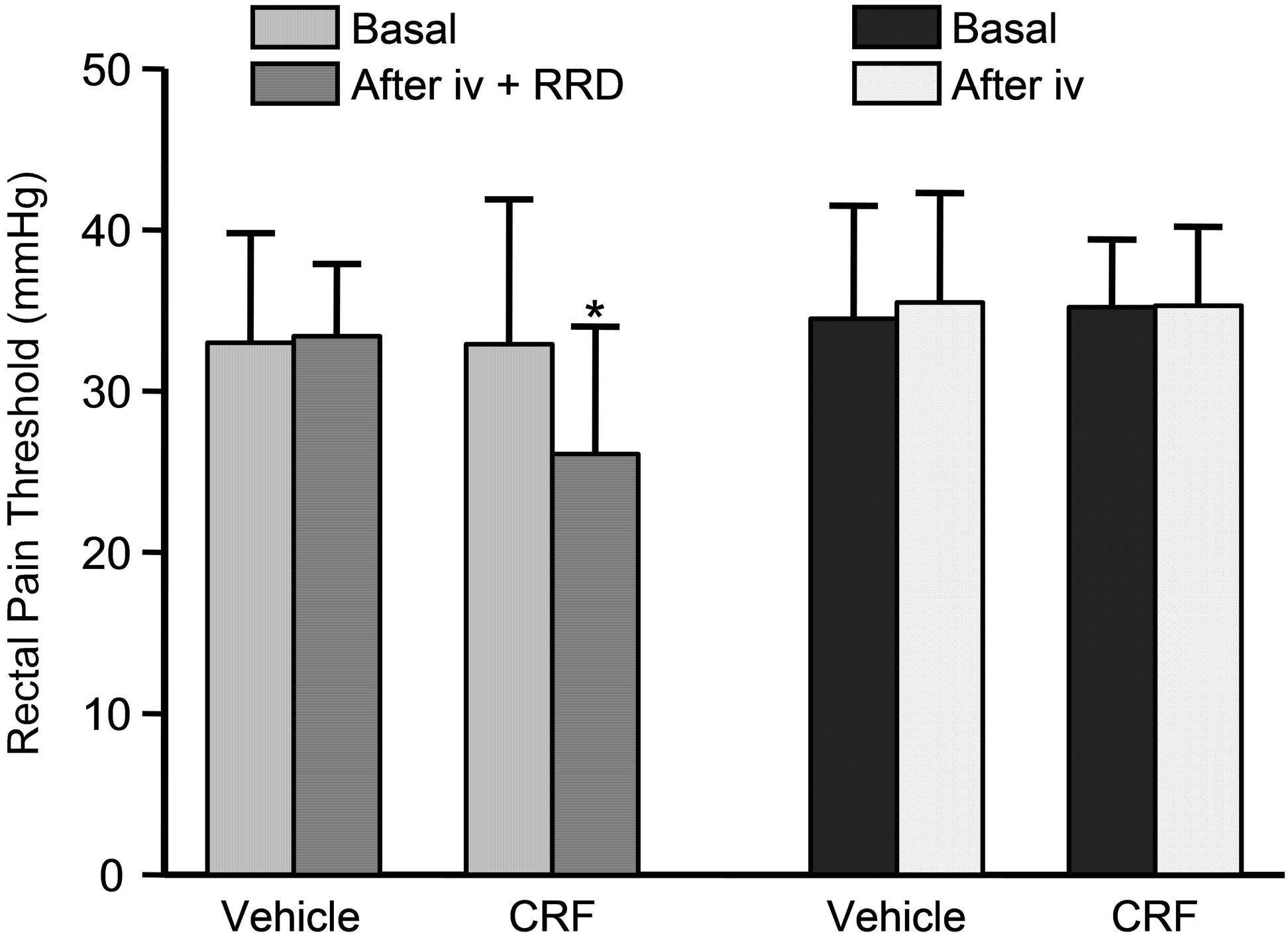
Effect of intravenous (iv) CRF on rectal pain thresholds with (left column) or without (right column) repetitive rectal painful distention (RRD) in healthy humans. Values are shown as means ± SE. * P < 0.05; significant decrease in pain threshold from before RRD to after RRD.

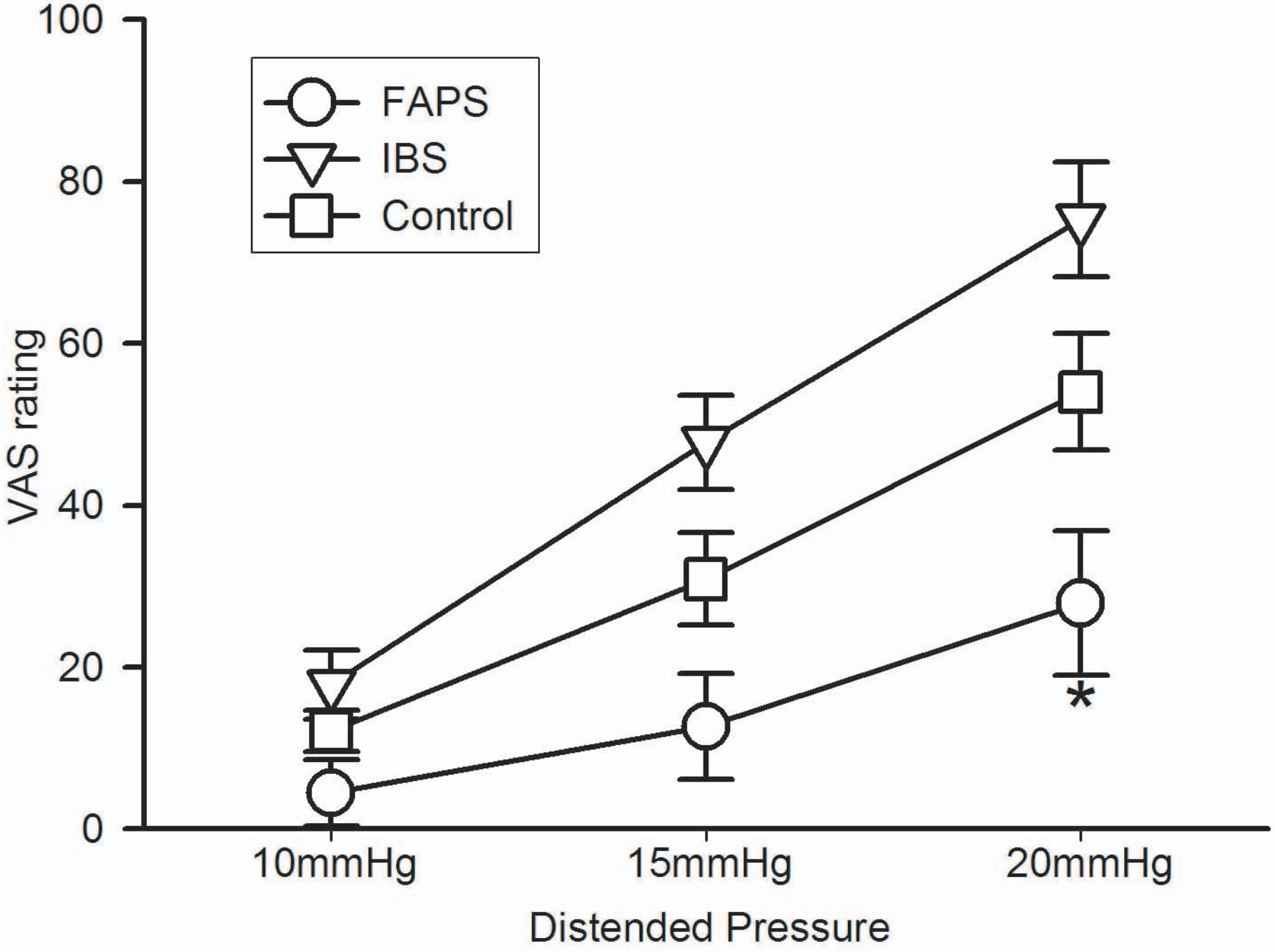
Figure 4.

Intensity of sensation assessed by visual analogue scale (VAS) at three different phasic distentions. Values are shown as mean ± SE. * P vs. control < 0.05, analysis of variance followed by the least significant difference test.


Before RRD
After RRD
Perceptual threshold (mmHg)
50
40
30
20
10
0
Pain
Max
Control
Pain
Max
IBS
Pain
Max
FAPS
*
*


IBS
FAPS
A
B
C
D
Pain threshold (mm Hg)
Threshold of maximum tolerance (mm Hg)
0
10
20
30
40
50
60
Baseline
Post RRD


Basal
After iv + RRD
Basal
After iv
Rectal Pain Threshold (mmHg)
50
40
30
20
10
0
*
Vehicle
CRF
Vehicle
CRF


100
80
60
40
20
0
VAS rating
FAPS
IBS
Control
*
10mmHg
15mmHg
20mmHg
Distended Pressure