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Effect of sex on perception of rectosigmoid stimuli in irritable bowel syndrome

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[1]*Center for Neurovisceral Sciences & Women's Health, Departments of Medicine,* [2]*Physiology,* [3]*Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at University of California, Los Angeles; and* [4]*Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California;* [5]*Department of Experimental Medicine, School of Medicine, Universidad Nacional Autónoma de Mexico, Mexico City, Mexico; and* [6]*Department of Internal Medicine, College of Medicine, Hanyang University, Seoul, Korea*

Chang, Lin, Emeran A. Mayer, Jennifer S. Labus, Max Schmulson, Oh Young Lee, Teresa I. Olivas, Jean Stains, and Bruce D. Naliboff. Effect of sex on perception of rectosigmoid stimuli in irritable bowel syndrome. *Am J Physiol Regul Integr Comp Physiol* 291: R277–R284, 2006. First published March 30, 2006; doi:10.1152/ajpregu.00729.2005.—In irritable bowel syndrome (IBS) patients, the relationship between sex and sensitivity to visceral stimuli is incompletely understood. Our aim was to evaluate the effect of sex on perceptual responses to visceral stimulation in IBS. Fifty-eight IBS patients (mean age 42 ± 1 yr; 34 men, 24 women) and 26 healthy controls (mean age 38 ± 3 yr; 9 men, 17 women) underwent barostat-assisted distensions of the rectum and sigmoid colon. Rectal discomfort thresholds were measured using a randomized, phasic distension paradigm before and after repeated noxious sigmoid stimulation (SIG, 60-mmHg pulses). Sex had a significant effect on rectal discomfort thresholds. Women with IBS were the most sensitive (lower thresholds [27 ± 2.7 mmHg] and higher ratings), with significantly lower rectal discomfort thresholds compared with men with IBS (38 ± 2.3 mmHg) and healthy women who were the least sensitive (41.9 ± 3.2 mmHg; both $P < 0.01$). There were no significant differences in rectal discomfort thresholds between healthy men (34 ± 4.3 mmHg) and men with IBS. Across both IBS and control groups, women demonstrated a significant lowering of discomfort thresholds after noxious sigmoid stimulation ($P < 0.01$), while men did not. Sex significantly influences perceptual sensitivity to rectosigmoid distension. Women show greater perceptual responses to this paradigm.

visceral perception; gender

IRRITABLE BOWEL SYNDROME (IBS) is one of the most common gastrointestinal (GI) disorders seen by primary care physicians and gastroenterologists (12). Enhanced perception of certain visceral stimuli ("visceral hypersensitivity"), either as a result of increased sensitivity of visceral afferent pathways or as a central amplification of visceral afferent input, has emerged as a principal mechanism underlying IBS and other functional bowel disorders (4, 26, 29, 32, 58). In regard to their response to controlled rectal balloon distension, IBS patients appear to be a heterogeneous group, with hypersensitive and normosen-

sitive groups. Using randomized rectal distension paradigms only, 47–64% of patients with IBS have been found to have lowered rectal discomfort thresholds (26, 29, 32). The clinical and biological factors associated with hypersensitive or normosensitive rectal thresholds remain poorly understood.

There is increasing evidence to suggest that sex is an important factor in symptom patterns, physiological responses, and possibly treatment responses in IBS (6, 12, 20). Several pieces of evidence suggest that the female sex is associated with a higher prevalence of chronic pain disorders, including IBS, and that female experimental animals and healthy women may be more sensitive to experimental pain. For example, two-thirds of individuals with IBS are women, with an estimated prevalence in women ranging from 14–24% (12). Sex-related differences are also thought to play a role in GI motility (19, 25, 27, 40, 50, 54), brain responses to visceral stimuli (31), symptom presentation (20, 45, 48, 49), and possibly symptomatic responses to treatment in IBS (5, 28). Furthermore, there is a significant clinical overlap of IBS with other functional pain syndromes which have a female predominance such as fibromyalgia, interstitial cystitis, and migraine headaches with aura (59). Suggested reasons for the high female prevalence in chronic pain disorders include psychological, sociocultural, and biological factors. In general, females appear to be more sensitive to pain, as indexed by enhanced sensitivity and decreased tolerance to painful stimuli (2). A particularly well-characterized phenomenon is the greater propensity of healthy women and women with chronic musculoskeletal pain to develop temporal summation of repeated noxious somatic stimuli (37, 43). This finding has been implicated as a possible mechanism underlying the greater susceptibility of women to develop central sensitization and hyperalgesic states (43).

The aim of the current study was to characterize the effects of sex on viscerosensory responses in IBS patients. We wanted to test the general hypothesis that women (with and without IBS) are more sensitive than men to rectosigmoid distension, and show a greater sensitizing response to a repetitive noxious visceral stimulus. By evaluating perceptual responses to a

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sufficiently large number of men and women with and without IBS, we specifically asked the following questions: *1)* Are there sex-related differences in the perception of aversive rectal stimuli? and *2)* Are there sex-related differences in the perceptual response to repeated noxious sigmoid stimuli, analogous to reported sex differences in temporal summation of somatic stimuli?

METHODS

Study Subjects

Healthy controls. Twenty-six healthy control subjects (17 women, 9 men) without evidence of acute or chronic illness were recruited by newspaper advertisement. In particular, there was no evidence in any of the subjects of an acute or chronic pain syndrome or abdominal symptoms either by bowel symptom questionnaire, personal history, or physical examination. There was no significant difference in the mean ages of healthy women (41 yrs, range 21–63 yrs) and men (33 yrs, range 21–67 yrs).

IBS patients. Fifty-eight IBS patients (24 women, 34 men) were recruited from the UCLA Functional Bowel Disease Clinic and by newspaper advertisement. The mean ages of women with IBS (41 yrs, range 26–60 yrs) and men with IBS (42 yrs, range 26–68 yrs) were similar. In addition, the mean age of IBS patients was not significantly different from that of healthy individuals (42 yrs vs. 38 yrs, NS). Selection criteria included a positive diagnosis by the Rome I criteria (51), a clinical diagnosis of IBS made by a gastroenterologist experienced in the diagnosis of functional bowel disorders, and the exclusion of organic disease. Diarrhea-predominant IBS (IBS-D) was defined as >3 bowel movements per day and/or loose or watery stools and no hard or lumpy stools ($n = 22$). Constipation-predominant IBS (IBS-C) was defined as <3 bowel movements per week and/or hard or lumpy stools and no loose or watery stools ($n = 13$). IBS alternating bowel habit (IBS-A) was defined as alternating bowel habits that did not meet IBS-D or IBS-C criteria ($n = 23$). Some of these subjects were enrolled before the establishment of Rome II criteria for IBS and subclassification for bowel habit subtype, and therefore these criteria were not used.

None of the patients were withdrawn from the study voluntarily or by the investigators. Data from a small subgroup of these study subjects were previously presented (29); however, sex differences were not analyzed because of inadequate sample size. Verbal and written consent was obtained from each subject. This study's protocols were approved by the VA Greater Los Angeles Healthcare System Research and Development Committee and Committee on Human Studies.

Materials and Apparatus

Bowel symptom questionnaire. All subjects completed a UCLA bowel symptom questionnaire with validated GI symptoms based on the Rome criteria (51) on encounter with the center. In addition to abdominal symptoms and bowel habits, additional measures included assessment of acute and chronic symptom severity and evaluation of current GI symptom intensity by 20-cm validated intensity and unpleasantness graphic verbal descriptor scales (15).

Psychological symptom checklist. All subjects completed the SCL-90R symptom checklist (10), which assesses current psychological symptom severity in the following areas: anxiety, depression, hostility, interpersonal sensitivity, obsessive-compulsive behavior, paranoia, phobic behavior, psychosis, and somatization. Raw scores were normalized based on a nonpsychiatric patient standard by calculating an area t score (0–100 scale) for each domain and for the global symptom index (GSI). Subjects with a GSI t score >63 or any two subscales with t scores >63 were considered to represent a case at risk for a psychiatric disturbance.

Visceral stimulation device. Distension of the sigmoid colon and rectum was effected by air inflation of a double-balloon, as previously described in detail (29). The use of a computer-driven volume displacement device allowed for controlled inflation of the balloons (26, 29, 32). The distension device was programmed to deliver distension at a volume rate (870 ml/min) to constant pressure plateaus, to simultaneously record pressures and volumes (sampling rate = 1/s) and to log the sensations (i.e., no sensation, moderate sensation, discomfort, and pain) from a hand-held, push-button marker device on a data file. We have previously validated the response characteristics of the distension device (21).

The double-balloon catheter consisted of two identical latex balloons (external diameter, 5 cm; length of each, 9 cm) attached to a Silastic elastomer tube (external diameter, 18 French) at both proximal and distal ends (MAK-LA, Los Angeles). The distance between the two balloons was 9 cm. Before and after completion of every procedure, each balloon was inflated three times to rule out any leak and measure intrinsic compliance (during the third distension) as previously described (21, 26). The intrinsic compliance of the latex balloons was electronically subtracted from the rectal and sigmoid compliance values obtained in vivo (21, 26). A flexible sigmoidoscopy (Olympus CF-100S) to 40 cm from the anal verge was performed without premedication on each subject for placement of the balloons (1 rectum; 1 sigmoid). After insertion of the proximal tip of a Teflon guidewire through the channel of the sigmoidoscope, the sigmoidoscope was withdrawn with evacuation of air. The lubricated double-balloon catheter was then passed over the guidewire such that the distal balloon was 4 cm from the anal verge. The catheter was secured with tape, and the wire was withdrawn. Fluoroscopy studies have confirmed the proper positioning of the rectosigmoid balloons using this technique (unpublished observations).

Experimental Protocol

All medications known to affect the GI tract were discontinued 48 h before the procedure. None of the study subjects were taking antidepressant medication. Information about the use of oral contraceptive agents and hormone replacement therapy was not obtained for the majority of female subjects. A 12-h fast and application of 2 Fleet enemas (C. B. Fleet, Lynchburg, VA) preceded the sigmoidoscopy for balloon placement. All experimental rectosigmoid stimulation studies were performed 30 min after balloon placement. Subjects were placed in the left lateral decubitus position on a padded table.

Although the examiner was always present, interaction with the subjects ceased after initial explanation of the respective task. Subjects had no visual or auditory cues to anticipate the location or time courses of the distensions, nor were they instructed about the nature of the distension protocols. The sensory tracking paradigm was employed to evaluate rectal perception during baseline and was repeated after sigmoid stimulation (29). Baseline does not refer to true resting conditions, since perceptual responses may be influenced by autonomic responses to the presence of the rectosigmoid balloon.

Threshold tracking paradigm (rectum). To obtain a measure of rectal sensitivity, rectal perception was assessed by measuring discomfort thresholds in response to a rectal phasic distension paradigm that minimized response bias (rectal sensory tracking). The electronic distension device was programmed to deliver intermittent phasic stimuli (30-s duration; 5-mmHg increments) separated by an interpulse interval (30-s duration; 5-mmHg increments) within a nonbiased stimulus-tracking paradigm, as previously reported by Whitehead et al. (57). Total duration of the sensory tracking paradigm was 600 s. All of the patients and controls completed the entire number of distension trials. During each stimulus and rest, subjects were prompted by the distension device to report the intensity of their sensations by triggering the push-button marker device. If the subject indicated a sensation below the discomfort level (i.e., no sensation or moderate sensation), the following stimulus was increased by 5

mmHg. If the subject indicated discomfort, the following stimulus was randomized to remain the same or decreased by 5 mmHg. If the subject reported the onset of pain, the following stimulus was always decreased by 5 mmHg.

Noxious distension (sigmoid colon, SIG). To determine the effect of a noxious mechanical sigmoid colon stimulus on perception of rectal distension, study subjects received repetitive distensions of the sigmoid colon over a period of 600 s. During this period, the sigmoid colon received intermittent rapid phasic distensions (30-s duration; 60 mmHg) with an interpulse rest (30-s duration; 5 mmHg).

Evaluation of Outcome Parameters

Discomfort thresholds. Perception thresholds for rectal discomfort and the onset of pain were determined from the tracking protocol and expressed in reference to intrarectal pressure and estimated wall tension. Discomfort thresholds were quantified by averaging the last six stimulus pressures of the tracking protocol. The length of the task was 600 s, which is sufficient to give stable discomfort thresholds (32). Individual discomfort thresholds (mmHg) were compared before (PRE-SIG) and after noxious sigmoid stimulation (POST-SIG).

Affective and sensory intensity ratings of distensions. Subjective sensory intensity and unpleasantness of the rectal sensory tracking and the sigmoid stimulation tasks were assessed by validated graphic descriptor scales (15). The intensity scale consisted of descriptors of increasing intensity ranging from "no sensation" to "extremely intense" arrayed along a 20-cm vertical bar. Similarly, the unpleasantness scale consisted of descriptors of increasing unpleasantness ranging from "none" to "very intolerable." Ratings were assessed immediately after each task.

Stress symptom ratings. Emotional responses (stress symptom rating scales) were measured at baseline, at PRE-SIG, and POST-SIG (30).

Mechanoelastic properties of rectosigmoid. To determine whether differences in the perceptual responses may be secondary to changes in the mechanoelastic properties of the rectosigmoid colon, we used several previously reported techniques to assess tone and compliance. Changes in resting volume (at the baseline pressure) were used as an estimate of rectal and sigmoid colon tone in response to repetitive distension. The method of determining resting volume has been described previously (29). Dynamic rectal compliance was calculated as ΔVolume $\div$ ΔPressure, corresponding to the slope of the compliance curve, as previously reported (21).

Statistical Analysis

Mixed model approach for repeated measurements provides greater statistical power, flexibility, and parsimony; handles missing data more effectively; and is less prone to false positives than ANOVA and MANOVA (1, 22, 53). Therefore, mixed-effects models for repeated measures specifying an autoregressive covariance structure were applied to test the hypotheses regarding the effects of group (IBS, Control), sex (men, women), noxious sigmoid stimulation (PRE-SIG, POST-SIG), and condition (baseline, PRE-SIG, POST-SIG), and their potential interactions on the dependent variables of interest. Given a significant omnibus test or evidence of a trend $P < 0.08$, pairwise least squared difference tests of the estimated marginal means from the model were performed. For measures assessed during only 1 time point, standard ANOVA was performed. On the basis of a three-factor (group $\times$ sigmoid stimulation $\times$ condition) repeated-measure ANOVA design, post hoc power analysis indicated that a sample size of $n = 79$ provided a >80% chance to detect a medium-effect size difference ($d = 0.56$) at $\alpha = 0.05$ for the between-group tests. The repeated measurement design of the study increased statistical power for the within-group comparisons. With a sample size of $n = 79$, the power for the within-subjects test for the group condition and the interaction (group $\times$ sex) was >90%. Furthermore, the difference in rectal discomfort threshold detected in women with IBS vs. healthy

women corresponded to a large effect size, Cohen's $d = 0.90$. Post hoc power analysis applying an independent t-test one wave of data (one assessment period, e.g., PRE-SIG condition) yielded 76% power to detect $d = 0.90$ for the healthy men vs. men with IBS and vs. healthy women comparisons. Arguably, the addition of two waves of data (e.g., PRE-SIG and POST-SIG conditions) increased the statistical power of this test to an adequate level. The bivariate relationship between the discomfort threshold and the demographic and disease severity were evaluated using Spearman's correlation coefficient. Mean values $\pm$ SE are shown throughout the text and in the tables and figures.

RESULTS

The clinical characteristics of the IBS patients are shown in Table 1. There were no significant differences in mean age between men and women with IBS and healthy control subjects. There was also no significant sex difference in bowel habit predominance within the IBS group. Women with IBS rated their abdominal pain over the past 6 mo as significantly more unpleasant than men with IBS ($P < 0.05$). SCL-90R scores suggestive of psychological distress were seen in 41.2% of IBS patients compared with 11.1% of healthy controls (χ^2 $P < 0.03$). There was no significant difference in rectal thresholds between those with elevated SCL-90R scores and those without elevated scores in the study subjects as a whole, as well as within the individual IBS and control groups.

Perceptual and Mechanoelastic Responses to Rectosigmoid Distension in IBS and Control Patients

Rectal discomfort thresholds. A mixed-effects model examined the effects of sex, group, and noxious sigmoid stimulation (PRE-SIG, POST-SIG) and their interactions on rectal discomfort thresholds. As shown in Fig. 1, when examining rectal discomfort thresholds, there was a significant interaction between sex and group ($F_{1,79} = 8.48$, $P < 0.01$) and sex and condition ($F_{1,102.78} = 4.83$, $P < 0.05$). Specifically, for IBS patients, discomfort thresholds were higher for men (38.0 $\pm$ 2.2 mmHg) compared with women (27.0 $\pm$ 2.7; $P < 0.01$). Furthermore, women with IBS had significantly lower discomfort thresholds compared with healthy women (41.9 $\pm$ 3.2 mmHg; $P < 0.001$). However, there were no significant differences between healthy men and women or between men with IBS and controls. With regard to changes in rectal dis-

Table 1. *Clinical characteristics of the men and women with IBS*

	Men With IBS (n = 34)	Women With IBS (n = 24)
Mean age, yr	41.9±2.0	41.0±1.8
Bowel habit predominance, *n*		
IBS-D	14	8
IBS-C	6	7
IBS-A	14	9
Abdominal pain ratings, cm		
Present sensory intensity	7.0±0.8	7.7±1.4
Present unpleasantness	6.0±0.7	6.2±1.2
Chronic sensory intensity	12.9±0.7	13.7±1.0
Chronic unpleasantness	10.4±0.6	12.9±0.6*

Values are presented as means $\pm$ SE. Verbal descriptor scales of pain ratings range from 0 to 20 cm. *Significant sex difference. IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-C, constipation-predominant IBS; IBS-A, IBS with alternating bowel habit.
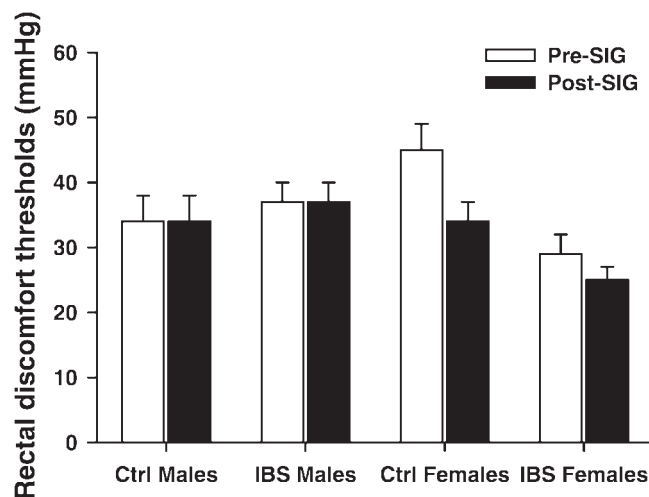
Fig. 1. Sex differences in rectal thresholds at baseline and after noxious sigmoid distension in irritable bowel syndrome (IBS) patients and healthy controls (Ctrl) are shown. There was a significant interaction between sex and disease group ($P < 0.01$), and sex and condition ($P < 0.05$).

comfort thresholds before and after sigmoid stimulation, on average, across both IBS and control groups, women demonstrated higher discomfort thresholds PRE-SIG (37.0 ± 2.2 mmHg) compared with POST-SIG (31.9 ± 2.2 mmHg; $P < 0.01$); that is, they showed a decrease in rectal perception after noxious sigmoid stimulation, while the male groups did not.

Perceptual Ratings of Rectosigmoid Stimuli.

Rectal distension. A mixed-effects model examined the influence of group, sex, and noxious sigmoid stimulation on unpleasantness and intensity ratings of the rectal stimuli. There was a highly significant group difference for the unpleasantness, but not intensity, ratings ($F_{1,75} = 13.28$, $P < 0.001$). Specifically, IBS patients had significantly higher unpleasantness ratings in response to rectal distension (10.2 ± 0.34 cm) compared with controls (7.9 ± 0.53 cm) before and after sigmoid stimulation. Sensory intensity ratings reported by the IBS (12.2 ± 0.43 cm) and control groups (11.0 ± 0.66 cm) were similar. There were no sex-related differences in perceptual ratings in either subject group (Table 2).

Sigmoid distension. A mixed-effects model examined the influence of group, sex, and noxious sigmoid stimulation on

Table 2. *Perceptual ratings following rectal distensions PRE- and POST-SIG in male and female IBS patients and healthy controls*

Time	Group	Sex	Unpleasantness	Intensity
PRE-SIG	IBS	Men	9.7 ± 0.50	12.5 ± 0.61
		Women	10.8 ± 0.60	12.4 ± 0.73
	Controls	Men	8.5 ± 1.00	11.9 ± 1.2
		Women	7.3 ± 0.69	10.7 ± 0.83
POST-SIG	IBS	Men	9.7 ± 0.50	11.9 ± 0.61
		Women	10.6 ± 0.63	12.0 ± 0.76
	Controls	Men	8.3 ± 1.0	11.1 ± 1.2
		Women	7.7 ± 0.69	10.3 ± 0.83

Values are presented as means $\pm$ SE. PRE-SIG, before noxious sigmoid conditioning stimulus; POST-SIG, after noxious sigmoid conditioning stimulus.

Table 3. *Perceptual ratings following sigmoid distensions in male and female IBS patients and healthy controls*

Group	Sex	Unpleasantness, cm	Intensity, cm
IBS	Men	12.1 ± 0.81	13.6 ± 0.91
	Women	12.9 ± 0.96	13.7 ± 1.10
Controls	Men	10.6 ± 1.71	12.6 ± 1.96
	Women	8.2 ± 1.13	10.1 ± 1.29

Values are presented as means $\pm$ SE.

unpleasantness and intensity ratings of the noxious sigmoid stimuli. The analysis of unpleasantness ratings revealed a significant main effect for group ($F_{1,132.34} = 6.51$, $P < 0.05$). Specifically, IBS patients (12.5 ± 0.6 cm) rated the unpleasantness of the noxious sigmoid stimulation higher than did control subjects (9.4 ± 1.02 cm). Neither group nor sex significantly influenced intensity ratings of the noxious sigmoid stimulation (IBS: 13.6 ± 0.72 vs. Controls: 11.4 ± 1.17; Table 3).

Stress symptom ratings. Mixed-effects models were applied to examine the potential influence of group, sex, and condition (baseline, PRE-SIG, and POST-SIG) on the stress symptom ratings: arousal, anger, stress, fatigue, attention, and anxiety. In general, there were significant main effects for group (IBS vs. controls) and condition (baseline vs. PRE-SIG vs. POST-SIG) for these ratings except for attention and anxiety. These results are summarized in Table 4.

It is noteworthy that for *arousal* ratings, there was a main effect for group ($F_{1,62.98} = 7.01$, $P < 0.05$) and condition ($F_{2,92.34} = 3.46$, $P < 0.05$). On average, controls reported significantly higher arousal ratings than their IBS counterparts. Arousal ratings were highest during the baseline conditions compared with PRE-SIG and POST-SIG conditions. Healthy women had higher arousal scores than women with IBS during the PRE-SIG (control = 7.4 ± 0.6, IBS = 4.8 ± 0.5, $P < 0.001$) and POST-SIG conditions (control = 7.1 ± 0.6, IBS = 4.8 ± 0.5, $P < 0.001$). Furthermore, for men (both $P < 0.05$) and women ($P < 0.01$ and $P < 0.001$) with IBS, arousal scores were significantly lower during the PRE-SIG (male IBS = 5.9 ± 0.4 and female IBS = 4.8 ± 0.5) and POST-SIG (male IBS = 5.6 ± 0.4 and female IBS = 4.8 ± 0.5) distension conditions compared with baseline (male IBS = 6.4 ± 0.4 and female IBS = 6.2 ± 0.5).

There was a significant interaction effect on anger ratings for sex, group, and condition ($F_{2,127.64} = 5.05$, $P < 0.01$), as well as a main effect for condition ($F_{2,127.64} = 9.41$, $P < 0.001$), and a trend for a group main effect ($F_{2,67.21} = 3.71$, $P = 0.058$). Specifically, women with IBS had higher anger ratings than men with IBS at PRE-SIG (female IBS = 5.44 ± 0.52, male IBS = 3.65 ± 0.38, $P < 0.01$) and POST-SIG (female IBS = 5.60 ± 0.52, male IBS = 4.27 ± 0.38, $P < 0.05$) distensions. Compared with baseline (female IBS = 3.10 ± 0.52, male IBS = 3.09 ± 0.38), men ($P < 0.05$) and women ($P < 0.001$) with IBS had significantly higher anger ratings during POST-SIG distensions. In addition, women with IBS demonstrated significantly higher anger ratings during PRE-SIG distensions compared with baseline ($P < 0.001$). Finally, women with IBS had higher anger ratings than healthy women at both PRE-SIG (female control = 3.2 ± 0.6, $P < 0.01$) and POST-SIG time points (female control = 3.2 ± 0.6, $P < 0.01$).

Table 4. *Stress Symptom Ratings (SSR) after rectal distensions PRE- and POST-SIG in IBS and healthy controls*

SSR	Group	Baseline	PRE-SIG	POST-SIG	Group Effect (P value)	Condition Effect (P value)
Arousal	IBS	6.3±0.3	5.4±0.3	5.3±0.3	<0.05	< 0.05
	Controls	7.3±0.6	7.0±0.6	7.2±0.6		
Anger	IBS	3.1±0.3	4.5±0.3	4.9±0.3	<0.01	<0.001
	Controls	2.4±0.6	3.7±0.6	3.4±0.6		
Stress	IBS	4.9±0.4	5.3±0.4	5.4±0.4	<0.05	<0.05
	Controls	3.0±0.7	4.4±0.7	3.9±0.7		
Fatigue	IBS	4.9±0.3	5.7±0.3	5.8±0.3	0.054	<0.05
	Controls	3.9±0.6	4.6±0.6	4.2±0.6		
Anxiety	IBS	4.5±0.3	4.3±0.3	4.6±0.3	NS	NS
	Controls	3.2±0.6	4.1±0.6	3.5±0.6		
Attention	IBS	7.6±0.3	6.5±0.3	6.3±0.3	NS	NS
	Controls	7.9±0.6	7.6±0.6	7.9±0.6		

Values are presented as means ± SE.

Rectosigmoid Mechanoelastic Properties

Rectal distension. No differences were seen for the influence of group, sex, or condition for static or dynamic compliance. For the measure of rectal tone, a main effect was found for condition ($F_{1,124.56} = 6.22$, $P < 0.05$). Specifically, rectal tone was greater in the overall subject group during the POST-SIG condition (35.4 ± 4.0 ml) compared with the PRE-SIG condition (25.5 ± 4.0 ml).

Sigmoid distension. ANOVA examined the influence of group and sex on static and dynamic sigmoid rectal compliance, as well as sigmoid tone. There were no significant differences in static or dynamic compliance of the sigmoid colon in IBS patients and control subjects. No differences were observed in sigmoid tone related to group or sex.

DISCUSSION

The main findings of this study support a significant independent effect of sex on the perception of aversive rectal and sigmoid stimuli: *1)* Women with IBS showed evidence for increased perceptual responses (i.e., visceral hypersensitivity) to rectosigmoid stimuli, whereas healthy women showed reduced perceptual responses. *2)* Women as a group, regardless of a diagnosis of IBS, showed evidence of sensitization after repeated noxious sigmoid stimulation. *3)* Healthy men and men with IBS did not differ in their responses to the rectosigmoid stimuli and showed no significant evidence for sensitization after sigmoid stimulation. Even though our findings confirm previous reports in the literature (4, 9, 26, 29, 32, 58) about visceral hypersensitivity in IBS patients, the observed group difference in discomfort thresholds between patients and controls, was mainly due to a significant difference between the female IBS patients and controls. In contrast, no significant differences were observed between male patients and controls.

Are There Sex-Related Differences in the Perception of Aversive Rectal Stimuli?

We demonstrate that women with IBS showed heightened perceptual responses to aversive rectal stimuli with lower discomfort thresholds compared to men with IBS and healthy women. The observed differences in perception thresholds taken together with the lack of sex differences in mechanoelastic properties strongly suggests that the observed differ-

ences are related to the transmission and/or modulation of visceral afferent information from the gut.

Sex-related differences in responses to experimental pain have been studied in both humans and animals, and in general, a greater sensitivity of women and female animals to noxious stimuli has been found (reviewed in Refs. 2, 14, and 42). Although our findings show that healthy women had decreased rectal perception compared to women with IBS, there was not a statistically significant difference compared with healthy men. Our findings are similar to those reported by others using visceral distension paradigms in the upper GI tract, specifically the esophagus in healthy subjects (35, 39) and the duodenum in healthy subjects and functional GI patients (16), which did not show significant sex-related differences in terms of pressure thresholds. In the only other study that compared colonic perception in healthy men and women, Soffer et al. (46) measured perceptual ratings to intermittent, randomized distensions of the descending colon during fasting and postprandial conditions in nine healthy men and nine healthy women. There were no significant sex differences in sensory ratings or colonic compliance before or after the meal.

Despite large numbers of published studies comparing visceral perception in IBS and controls, our study is only one of two that has evaluated sex differences in IBS. In contrast to the findings in healthy women, we demonstrate that women with IBS had lower rectal discomfort thresholds than men with or without IBS. In support of a greater visceral sensitivity in women with IBS, compared with men, are the findings from Ragnarsson and colleagues (38) who compared rectal sensitivity in men and women with IBS before and after a meal. In their study of 52 IBS patients (39 women and 13 men), women showed a significant decrease in postprandial rectal pressure thresholds of maximal tolerated distension compared with men.

The current finding of greater perceptual responses of women with IBS is consistent with two recent reports by our group using ^{15}O-water PET to study differences in regional brain activation between men and women with IBS (3, 31). Even though both groups of patients showed activation of the expected pain regions, men with IBS showed greater activation of brain regions, including the dorsal pons/periaqueductal gray, which may be involved in endogenous pain inhibition. In contrast, women with IBS showed greater activation of limbic

and paralimbic regions, which may be part of a pain facilitation circuit (31). On the basis of the current findings and the preliminary results from brain imaging studies, one may speculate that the more effective endogenous pain inhibition system, which is activated in healthy women in response to a potentially noxious pelvic stimulus, is specifically compromised in women with IBS, making them more sensitive to rectosigmoid (and possibly other pelvic visceral) stimuli (4, 26, 29, 32, 58).

Our finding of greater visceral sensitivity in women with IBS compared to men with IBS is supported by clinical reports of increased symptom severity in women compared with men (8, 52). In particular, one study found that the intensity of abdominal pain and bloating was more severe in women than in men (8). However, it needs to be emphasized that many factors (including peripheral sex-related differences, as well as other-than-biologic differences) may influence pain responses, including type of stimulus, clinical setting, and other conditions [e.g., menstrual phase (18), reproductive status, and pregnancy], willingness to report, and attitudes toward pain. Although the type of stimulus, methodology of the stimulus application, and clinical setting were standardized in this study, information about menstrual and reproductive status was only obtained in a minority of subjects, and therefore, their association with visceral perception could not be assessed. While this is a limitation of the study, Houghton and colleagues (18) did not demonstrate differences in rectal perceptual thresholds between the different menstrual cycle phases in healthy women but did show that women with IBS had lowered rectal pain thresholds (i.e., visceral hypersensitivity) during menses compared with the other phases of the menstrual cycle. We avoided studying women during menstruation and, therefore, menstrual cycle phase is unlikely a significant factor to explain the differences in rectal perceptual thresholds in this study.

Are There Sex-Related Differences in the Perceptual Response to Repeated Noxious Sigmoid Stimuli, Analogous to Reported Sex Differences in Temporal Summation of Somatic Stimuli?

One of our study's most dramatic findings is that healthy women have significantly higher thresholds to rectosigmoid distension, but are just as likely to develop visceral sensitization as women with IBS. In contrast, healthy men and men with IBS did not demonstrate evidence of a significant change in visceral perception following repetitive noxious distension. Therefore, it appears that women with or without a diagnosis of IBS are more likely to consistently demonstrate enhanced perceptual responses after a repeated noxious stimulus to the sigmoid colon. Several studies have been reported as demonstrating the sensitizing effect of repeated noxious distension of pelvic viscera on perception (29, 33, 34, 44). However, in none of these studies were sex-related differences evaluated.

Several studies have been reported showing a greater probability of women to show sensitization to repeated thermal (13) or repeated mechanical noxious stimulation (43) in the form of temporal summation. Temporal summation refers to the progressive augmentation of pain perception in response to repetitive noxious stimulation at a particular frequency (37) and is thought to be a centrally mediated event, involving an increase in the excitability of dorsal horn nociceptive neurons (41, 43).

This hyperexcitability of nociceptive processing has been postulated to be a key pathophysiological mechanism underlying chronic visceral and somatic pain conditions, such as IBS and fibromyalgia (43, 47, 56). Even though the experimental paradigm used in the current study does not test for temporal summation, the repeated sigmoid stimulus did result in a sensitization response. The fact that repeated stimulation of the sigmoid colon resulted in enhanced perceptual responses not only to sigmoid distension, but also to distension of a distant site (e.g., the rectum), strongly supports a spinal or supraspinal mechanism underlying the observed differences in sensitization. It has been postulated that an inadequate activation of endogenous pain inhibitory systems, which in the healthy organism counter-regulates the development of central sensitization, may be an important mechanism contributing to the enhanced visceral perception seen in different functional disorders (7, 24, 60). Even though the repeated visceral stimulation paradigms applied in the current study and in previously published studies of the rectosigmoid and the urinary bladder (29, 33, 34, 44) were not properly designed to assess temporal summation as in the somatic pain studies, the fact that women showed a greater sensitization in several of these studies, suggests that a greater development of spinal sensitization may play a role in the greater vulnerability for overlapping syndromes such as IBS, interstitial cystitis, and fibromyalgia, which occur more commonly in women.

Relationship of Subjective Emotional Responses With Visceral Perception

In general, arousal and attention ratings decreased, and anger and fatigue ratings increased during rectosigmoid stimulation in IBS but not in healthy controls. IBS patients showed lower arousal ratings and higher anger, stress, and fatigue ratings compared with healthy controls. Anger and stress ratings were significantly higher in women with IBS than men with IBS. Relationships between subjective emotions, visceral motor responses (55), and visceral perception (17) have previously been reported, and these relationships have been discussed in detail in the framework of bidirectional brain-gut interactions (23). For example, several studies have demonstrated that experimental stress conditions cannot only increase colonic motility (55), but also increase emotional (55) and perceptual (11, 36) responses to visceral stimuli. Both visceral and central nervous system responses in these studies were greater in IBS patients.

In conclusion, the findings in this study support the significant effect of sex on the perception of aversive rectal and sigmoid stimuli. Specific novel findings contribute to an increase in the pathophysiological understanding of IBS. Healthy women did not show increased visceral sensitivity to rectosigmoid distension, which may result from effective endogenous antinociceptive mechanisms activated specifically in response to pelvic stimuli (e.g., intercourse, menstrual cramps, urinary tract infections, pregnancy, labor). The significantly lower rectal thresholds in women with IBS compared to men with IBS suggest that these endogenous pain modulation systems may be compromised in women with IBS, making them more sensitive to rectosigmoid stimuli. The greater susceptibility of women to the induction of visceral sensitization may explain the increased prevalence of women with chronic visceral pain

disorders such as IBS. The presence of both enhanced visceral perception and increased emotional responses, in particular anger and stress ratings, is consistent with a greater responsiveness of the emotional motor system in women with IBS. These findings also have implications in the design and interpretation of barostat studies of visceral sensitivity. The use of women rather than men with IBS may be more suitable given the lack of differences between men with IBS and healthy men.

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