Attenuation of the colorectal tonic reflex in female patients with irritable bowel syndrome

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Attenuation of the colorectal tonic reflex in female patients with irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 289: G489–G494, 2005. First published May 19, 2005; doi:10.1152/ajpgi.00527.2004.—Alterations in normal intestinointestinal reflexes may be important contributors to the pathophysiology of irritable bowel syndrome (IBS). Our aims were to compare the rectal tonic responses to colonic distension in female IBS patients with predominant constipation (IBS-C) and with predominant diarrhea (IBS-D) to those in healthy females, both fasting and postprandially. Using a dual barostat assembly, 2-min colonic phasic distensions were performed during fasting and postprandially. Rectal tone was recorded before, during, and after the phasic distension. Colonic compliance and colonic sensitivity in response to the distension were also evaluated fasting and postprandially. Eight IBS-C patients, 8 IBS-D patients, and 8 age- and sex-matched healthy subjects (group N) participated. The fasting increments in rectal tone in response to colonic distension in both IBS-C (rectal balloon volume change $-4.6 \pm 6.1$ ml) and IBS-D ($-7.9 \pm 4.9$ ml) were significantly reduced compared with group N ($-34 \pm 9.7$ ml, $P = 0.01$). Similar findings were observed postprandially ($P = 0.02$). When adjusted for the colonic compliance of individual degree, the attenuation in the rectal tonic response in IBS compared with group N was maintained (fasting $P = 0.007$; postprandial $P = 0.03$). When adjusted for colonic sensitivity there was a trend for the attenuation in the rectal tonic response in IBS patients compared with group N to be maintained (fasting $P = 0.07$, postprandial $P = 0.08$). IBS patients display a definite attenuation of the normal increase in rectal tone in response to colonic distension (colorectal reflex), fasting and postprandially. Alterations in colonic compliance and sensitivity in IBS are not likely to contribute to such attenuation.

colorectum

IRRITABLE BOWEL SYNDROME (IBS), recurrent abdominal pain with diarrhea and/or constipation, is the most common chronic disorder of gastrointestinal function in most developed societies (10, 35). A variety of sensory and motor intestinal abnormalities have been documented in IBS; the most consistent finding has been that of visceral hypersensitivity to distension (4, 22). It is perhaps not surprising that sensorimotor dysfunction has been especially prominent in the fed state (17, 29) because symptoms in IBS are often precipitated by eating. Moreover, sensorimotor dysfunction appears to differ between IBS patients with predominant constipation (IBS-C) and with predominant diarrhea (IBS-D). These include a correlation between symptom severity and the overall motility index, differences in the phase 2 and phase 3 components of the migrating motor complex, and increased rectal sensitivity in IBS-D compared with IBS-C (16, 37, 25). The interactions between sensory and motor dysfunction in IBS, however, remain relatively unexplored despite the fact that dysfunction of enteric reflexes may be an important contributor to the symptoms (3, 29).

Of the long intestinal reflexes, the gastrocolonic response is the best described (31, 32, 38), and alterations in this reflex have been documented in IBS (30, 34). Conversely, the inhibitory effects of rectal distension on gastric emptying (39) and duodenjejunal motor activity (17) have also been documented in healthy subjects, whereas in IBS subjects, such rectal stimulation diminished jejunal sensitivity to a greater extent than in healthy subjects (9). Other tonic intestinal reflexes have been described in various regions of the gastrointestinal tract in healthy subjects. For example, in the jejunum, Rouillon et al. (26) reported both antegrade and retrograde tonic inhibition in response to latex balloon distension. In the colorectum, Law et al. (19) recently documented two reflex responses in the fasting state. Colonic dilatation in response to barostatic rectal distension (rectocolic reflex) was clearly apparent, whereas the corresponding antegrade reflex, namely rectal contraction in response to barostatic distension in the descending colon (colorectal reflex), was less prominent. In our own studies in healthy subjects (23), with the use of a different distension paradigm, we have recently recorded a definite enhancement of rectal tone in response to colonic distension in both the fasting and postprandial states. This colorectal reflex was modulated by colonic sensitivity, but not colonic compliance, especially in the fasting state. We therefore hypothesized that alterations in this reflex may be present in IBS patients and that such alterations may differ according to the predominant alteration of bowel habit. Moreover, we postulated that one or more of feeding, abnormal colonic sensitivity, and/or abnormal colonic compliance may be a factor(s) contributing to alterations in this reflex in IBS patients.

Our aims were therefore: 1) to evaluate the tonic response of the fasting rectum to colonic distension in female IBS patients, both IBS-C and IBS-D, and to compare these responses to those present in female healthy subjects; 2) to determine the influence of feeding on these rectal responses; and 3) to determine the influence of colonic sensitivity and colonic compliance on these rectal responses in the three groups.

METHODS

Setting and Participants

Female subjects between the ages of 18 and 55 yr were recruited by public advertisement. Eight IBS-C patients (mean ± SE age: 37 ± 3...
yr) and eight IBS-D patients (39 ± 4 yr) participated, each fulfilling the Rome II criteria for IBS and the appropriate subgroup (7). Eight asymptomatic healthy age-matched females (42 ± 5 yr) formed the control group. Exclusion criteria included previous bowel surgery, concurrent significant medical conditions, use of medications that could alter gastrointestinal sensorimotor function, and pregnancy. Subjects of childbearing capability recorded a negative urine human chorionic gonadotrophin pregnancy test, and all subjects completed the following gastrointestinal questionnaires: Rome II Integrative (7), Hospital Anxiety and Depression Scale (HAD) (40), Irritable Bowel Syndrome Quality of Life (24), and Functional Bowel Disease Severity Index (8). The study protocol was approved by the Human Research Ethics Committee of the Royal North Shore Hospital. Written informed consent was obtained from all subjects before commencement of the study.

Study Design

A dual barostat assembly (Distender Series II; G & J Electronics, Toronto, Canada) was positioned in each subject, as previously described (21), using left-sided colonoscopy without sedation after colonic lavage with 2 liters of polyethylene glycol solution (Colonlytely; Dendy Pharmaceuticals, Brighton, VIC, Australia) and an overnight fast. Polyethylene balloons (Hefty Baggies; Mobil Chemical, Pittsford, NY) with infinite compliance and a maximum volume of 600 ml tied at both ends to the barostat catheter, were positioned in the descending colon and rectum; the positions were confirmed with fluoroscopy. After a conditioning distension, the individual operating pressure (IOP) for the colon and rectum, were determined (2 mmHg above pressure at which respiratory variations were seen in the barostat recordings).

The distension sequence used in all three groups studied was identical. The experimental protocol is shown in Fig. 1. A slow-ramp colonic distension (2 mmHg/30 s) was initially performed until pain was reported or a pressure of 40 mmHg (including IOP) was reached. After a 5-min period to enable balloon volumes to return to each individual's baseline, a 2-min phasic distension 20 mmHg above the IOP was performed in the colon, whereas volume in the balloon positioned in the rectum was recorded continuously before, during, and after the distension. Subjects were provided with a 10-cm visual analog scale, as used previously, to indicate sensations of gas, urge, and pain during the phasic distension of the colon. The gastrocolonic response was defined as the change in colonic tone, measured by the change in colonic balloon volume immediately before and 30 min after the meal within each group. The appropriate generalized linear models were fitted to data from each of the fasting and postprandial phases. Models included ANOVA and analysis of covariance taking into account the paired nature of the data, including a factor for subject group covariates of colonic compliance and ASS and a term to assess the extent of the interaction between the subject group and the covariate where appropriate. Comparisons were declared significant when P ≤ 0.05. Data were summarized as means ± SE where appropriate.

RESULTS

Subject Characteristics

The IBS subgroups did not differ significantly in age, in IBS Quality of Life score (IBS-C: 59 ± 3; IBS-D: 52 ± 7), or in the Functional Bowel Disease Severity Index (46 ± 9, 67 ± 13). The HAD scores (anxiety IBS-C: 9.2 ± 1.2; IBS-D: 8.5 ± 0.7; group N: 7.7 ± 1.2; and depression 4.7 ± 1.3, 1.8 ± 0.6, 1.7 ± 0.6) were not significantly different between subject groups.

Predistension Values

Predistension barostat data (colonic and rectal IOP, colonic and rectal balloon volumes immediately before distension), colonic compliance, and colonic ASS for both the fasting and postprandial states, for each subject group, are shown in Table 1. There was a significant difference in the three-way comparison (ANOVA) between groups in the mean basal distension in the fasting state (P = 0.04). The difference was confirmed to be between IBS-C and IBS-D. This finding was not replicated in the postprandial state. There were no differences between these corresponding volumes in the colon. The fasting colonic ASS was significantly higher in IBS-C compared with group N (Table 1).

The gastrocolonic response 30 min after the meal was confirmed in each subgroup, but there was a reduced response in the IBS-C group and an enhanced response in the IBS-D group (IBS-C: −28 ± 13 ml, IBS-D: −66 ± 10 ml, group N: −46 ± 12 ml, P < 0.04 IBS-C vs. IBS-D).

Rectal Responses to Colonic Distension

Fasting state. The mean rectal volume change in response to colonic distension in the fasting state is shown in Table 2. In the healthy subjects the rectal volume change during distension and in the postdistension period was significantly different.

Data and Statistical Analysis

The colorectal reflex was defined as the rectal tonic response, measured by the change in rectal balloon volume, to the 2-min phasic colonic distension. In each subject, the rectal balloon volume was recorded each 30 s during a 2-min predistension (basal) period, the 2-min distension period, and a 2-min postdistension period. For each subject group, the mean volume during the second minute of the distension period was compared with the mean volume over the 2-min predistension period. The mean volume during the second minute of the 2-min postdistension period was similarly compared with the mean predistension volume to determine the recovery characteristics of the reflex.

Colonic compliance was determined by the slope of the pressure-volume curve obtained during the ramp distension. The aggregate sensory score (ASS) was determined from the sum of the scores for gas, urge, and pain during the phasic distension of the colon. The gastrocolonic response was defined as the change in colonic tone, measured by the change in colonic balloon volume immediately before and 30 min after the meal within each group. The appropriate generalized linear models were fitted to data from each of the fasting and postprandial phases. Models included ANOVA and analysis of covariance taking into account the paired nature of the data, including a factor for subject group covariates of colonic compliance and ASS and a term to assess the extent of the interaction between the subject group and the covariate where appropriate. Comparisons were declared significant when P ≤ 0.05. Data were summarized as means ± SE where appropriate.
The key finding of this study was that the colorectal reflex, the normal increase in rectal tone in response to phasic colonic distension (23), was significantly attenuated in both IBS-C and IBS-D patients in the fasting state compared with age and sex-matched healthy subjects. A similar, attenuation of this long intestinal reflex was present in the postprandial state. This work provides evidence for definite alterations in enteric motor function in IBS patients and is consistent with the findings of Coffin et al. (5) in the upper gut where there was a defective gastric relaxatory response to duodenal distension in patients with functional dyspepsia. Moreover, it is of interest that our finding of altered reflex function in IBS was not dependant on the differences in IBS clinical phenotype (predominant constipation or predominant diarrhea). The experiments we undertook using dual barostat methodology were technically demanding, and to our knowledge this is the first demonstration of an alteration in this reflex in patients with IBS. We used a standardized distension above the IOP, and the IOP levels were not significantly different between the groups. Our subgroups of IBS patients, as well as being age- and sex-matched, were similar in their overall symptom severity scores, quality of life indices, and levels of anxiety and depression, thus minimizing potential confounding factors that may have influenced the results. The short latency and rapid recovery characteristics of the rectal tonic response tend to support the hypothesis that rectal responses are neurally mediated, consistent with a viscerovisceral reflex. Hormonal influences, such as the sensitizing effects of cholecystokinin octapeptide on the rectum (27), are unlikely to be playing a role in this phenomenon, because results were similar in the fasting and postprandial states. We have also documented that individual differences in colonic compliance and also probably colonic sensation did not influence the attenuation of the colorectal reflex in IBS.

It is possible that the colorectal reflex appears to be attenuated in IBS-D compared with the healthy subjects because of a lower predistension rectal volume (Table 1) and a resultant “floor effect.” Our findings in the IBS-C group, however,

### Table 1. Predistension (baseline) colonic and rectal barostat data, including colonic compliance and ASS in IBS patients and healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>IBS-C</th>
<th>IBS-D</th>
<th>Group N</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>IOP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>13.5±0.7</td>
<td>12.5±0.8</td>
<td>13.5±1.1</td>
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<tr>
<td>Rectum</td>
<td>10.3±0.6</td>
<td>10.3±0.6</td>
<td>9.3±0.8</td>
<td>0.5</td>
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<td>Fasting balloon volumes, ml</td>
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<tr>
<td>Colon</td>
<td>182±24.2</td>
<td>141±27.6</td>
<td>125±12.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Rectum</td>
<td>178±25.4</td>
<td>98±10.4</td>
<td>153±23.5</td>
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<tr>
<td>Postdistension balloon volumes, ml</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>193±47.4</td>
<td>140±29</td>
<td>94±30</td>
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<tr>
<td>Rectum</td>
<td>147±66.4</td>
<td>92±13.5</td>
<td>120±28.4</td>
<td>0.6</td>
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<td>Colonic compliance, ml/mmHg</td>
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<tr>
<td>Fasting</td>
<td>5.8±0.6</td>
<td>6.3±0.9</td>
<td>5.6±0.7</td>
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<td>Postprandial</td>
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<td>Colonic ASS</td>
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<td></td>
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<td></td>
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<tr>
<td>Fasting</td>
<td>14.4±3.4</td>
<td>11.4±2</td>
<td>4.6±1.2</td>
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<tr>
<td>Postprandial</td>
<td>12.9±4.1</td>
<td>11.0±2.5</td>
<td>3.9±1</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE. ASS, aggregate sensory score; IBS, irritable bowel syndrome; IOP, individual operating pressure; group N, healthy patients; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS. *IBS-C compared with IBS-D = 80 ml, 95% CI = 19 and 142, respectively; †IBS-D compared with IBS-C = 2.7 ml/mmHg, 95% CI = 0.6 and 4.7, respectively; ‡IBS-C compared with group N = 10.8, 95% CI = 2.5 and 19.0, respectively. P values are 3-way comparisons using the ANOVA model.

The postprandial colonic compliance was lower in IBS-C compared with IBS-D subjects (Table 1). In the healthy subjects (group N), the rectal volume change during distension postprandially was again significantly different from baseline (P ≤ 0.05, Table 2). In IBS-C and IBS-D groups, as in the fasting state, the magnitude of this volume change was not significantly different from baseline and was significantly reduced compared with the healthy group during the distension period (P = 0.02).
appear robust and cannot be explained on this basis. Consistent with this phenomenon of definite reflex attenuation in IBS-C, we observed that the gastrocolonic response to feeding, another long intestinal reflex, was also reduced in IBS-C patients compared with healthy subjects. Further studies should explore these differences between IBS-C and IBS-D, because current and likely future pharmacotherapies have different efficacies in IBS-C compared with IBS-D.

Despite the current interest in visceral hypersensitivity as an important pathogenic mechanism in IBS, data on colonic sensation in IBS patients are scarce, because most attention has been directed towards the rectum (22). In the current study, colonic sensation was significantly increased in the IBS-C subgroup but not in the IBS-D subgroup, compared with healthy subjects. This enhancement was most prominent in the fasting state, although there was a strong tendency towards hypersensitivity postprandially. Such findings in IBS-C are generally consistent with other studies reporting visceral hypersensitivity in both IBS-C and IBS-D in various other intestinal regions (2). For example, Schmulson et al. (28) found that rectal sensitivity was increased in IBS patients who had hard and lumpy stools compared with those without this stool pattern, whereas Prior et al. (25) reported increased rectal sensitivity in IBS-D with rectal manometry studies. It should be noted, however, that assessment of sensitivity in this current study was based on a single 2-min phasic distension and thus may not be directly comparable to other techniques of assessing enteric sensitivity. This type of assessment was necessary because we wished to account for the effect of differences in colonic sensitivity in the three groups on rectal volumes during the actual 2-min phasic distension of the colon. Because of our findings in regard to the colorectal reflex in health (23), and based on the alterations in colonic sensitivity that we expected to be present in IBS, we adjusted the rectal response for colonic sensitivity at the site of distention. Despite this adjustment, there remained a strong tendency for an attenuated response. This finding suggests that colonic hypersensitivity is also unlikely to be a major factor influencing the rectal motor
response. Moreover, it is of interest that despite the finding of colonic hypersensitivity to distension, in the IBS-C subgroup, we observed a diminution of the rectal tonic response, as well as a delayed recovery phase, in contrast to an exaggerated and/or early rectal tonic response. Kreulen and Szurszewski (18) have previously reported that colocolonic reflexes in animal studies were demonstrable despite an absence of connection with spinal cord or other centers. It is conceivable that such reflex alterations may be entirely independent of conscious perception and further studies with lower levels of subnoxious distension or stimulation with other paradigms, such as electrical stimulation (14), are needed to explore this hypothesis.

The neural pathways involved in the colorectal reflex are poorly defined and remain speculative. As phasic distension preferentially stimulates splanchic afferents with receptive fields located in the muscle and serosa (20), rather than in the mucosa, it is possible that local dysfunction in the muscle or serosa may be responsible for the impaired rectal responses. On the other hand, dysfunction of the autonomic nervous system in IBS has been reported by a number of investigators (13, 15, 36), and the predominant symptoms in IBS have been correlated with different autonomic abnormalities. Specifically the IBS-C subgroup has been associated with lower parasympathetic tone (1, 11). It is believed that the parasympathetic nervous system is one of the major mediators of colonic motility, especially during defecation (6). It is thus conceivable that the presence of a lower cardiovagal tone may reflect unopposed sympathetic tone, which may be responsible for not only the inhibitory effects on motor function (colorectal reflex, gastrocolonic reflex) but also the increased colonic perception in the IBS (12). Further studies that simultaneously assess autonomic nervous system and colorectal reflexes are required to address this hypothesis.

Colonic compliance, a determinant of the colon’s ability to store its contents, has been reported to be either similar between IBS subgroups and healthy subjects (30) or lower in patients with IBS (20); similarly, rectal barostat studies have reported both normal (25) and reduced rectal compliance (33) in IBS-C patients. We also found decreased colonic compliance postprandially in the IBS-C subgroup, compared with the IBS-D subgroup. When the colonic distension stimulus was statistically adjusted, taking into account the differences in colonic compliance, however, there remained a significant rectal response in the healthy subjects, and the difference between the IBS subgroups and healthy subjects was preserved, implying that alterations in colonic compliance do not contribute to the blunted rectal response.

The clinical significance of the altered colorectal reflex we observed in the IBS patients and its relationship to defecation, remains somewhat uncertain. Rectal response may function as a stimulus for defecation, however, and the attenuation observed in IBS-C patients may thus conceivably be a factor contributing to maintenance of the constipated state.

In conclusion, the presence of an attenuated colorectal reflex provides further support for definitive alterations in enteric motor function in IBS patients. Impairment of such reflexes, as well as therapy directed towards alleviating visceral hypersensitivity in IBS, may represent an additional important target for pharmacotherapy and warrants further study.

**GRANT**

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**REFERENCES**


