Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome

Y Sagami, Y Shimada, J Tayama, T Nomura, M Satake, Y Endo, T Shoji, K Karahashi, M Hongo, S Fukudo

Background and aims: Corticotropin releasing hormone (CRH) is a major mediator of the stress response in the brain-gut axis. Irritable bowel syndrome (IBS) is presumed to be a disorder of the brain-gut link associated with an exaggerated response to stress. We hypothesised that peripheral administration of α-helical CRH (αhCRH), a non-selective CRH receptor antagonist, would improve gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation in IBS patients.

Methods: Ten normal healthy subjects and 10 IBS patients, diagnosed according to the Rome II criteria, were studied. The tone of the descending colon and intraluminal pressure of the sigmoid colon were measured at baseline, during rectal electrical stimulation (ES), and at recovery after administration of saline. Visceral perception after colonic distension or rectal ES was evaluated as threshold values on an ordinate scale. The same measurements were repeated after administration of αhCRH (10 μg/kg).

Results: ES induced significantly higher motility indices of the colon in IBS patients compared with controls. This response was significantly suppressed in IBS patients but not in controls after administration of αhCRH. Administration of αhCRH induced a significant increase in the barostat bag volume of controls but not in that of IBS patients. αhCRH significantly reduced the ordinate scale of abdominal pain and anxiety evoked by ES in IBS patients. Plasma adrenocorticotropic hormone and serum cortisol levels were generally not suppressed by αhCRH.

Conclusion: Peripheral administration of αhCRH improves gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation, without affecting the hypothalamo-pituitary-adrenal axis in IBS patients.
Cannulation and recording assemblies
On the evening before cannulation, each subject ingested a preparation consisting of a 125 ml solution of magnesium citrate (13.6%) and 2.5 mg of sodium picosulphate to reduce faecal effluent. Based on earlier reports and our previous studies, this bowel preparation was unlikely to affect colonic motility. At 09:00 the next day, a polyethylene catheter with a cylindrical barostat bag (Synectics Medical, Stockholm, Sweden) and three transducers (Gaelijke, Dunvegan, UK) were inserted into the proximal portion of the descending colon under colonoscopy. The catheter had a separate lumen for measuring pressure in the barostat bag which was set in the proximal portion of the descending colon approximately 65 cm from the anus. The three transducers were set in the descending, proximal sigmoid, and mid sigmoid colon, approximately 50 cm, 45 cm, and 40 cm from the anus, respectively. A bipolar electrode catheter for electrical stimulation of the mucosa was set in the rectum (15 cm from the anus) under fluoroscopic control. The position of the catheters was confirmed before and after the study session. The three transducers and the barostat bag catheter were each connected to an analogue digital converter (PC-Polygram; Synectics, Stockholm, Sweden) and a visceral stimulator (Synectics). The catheter in the rectum was connected to an electronic stimulator (NEC San-Ei Instruments Ltd, Tokyo, Japan). Using a tracking technique, the lowest pressure of any new sensation was determined for each subject's response to the previous distension. Subsequent distensions were adjusted up or down depending on the subject's response to the previous distension. The lowest pressure of any new sensation was determined as the minimal sensory threshold (ST-D), the lowest pressure that caused any definite unpleasant sensation was defined as the discomfort threshold (DT-D), and the lowest pressure that evoked a painful sensation was defined as the pain threshold (PT-D).

Rectal electrical stimulation (ES)
Rectal ES was performed using a bipolar electrode attached to a 6F catheter (Dr Osypica GMBH, Granzach-Whylen, Germany). The two poles of the electrode were situated 10 mm apart. ES was applied to the rectal mucosa at a frequency of 1.0 Hz with an intensity ranging from 0 to 50 mA. At the beginning of ES, sensory threshold was determined using a tracking technique. Subjects were asked to report any new sensation (minimal sensory threshold, ST-E), unpleasant sensation (discomfort threshold, DT-E), or painful sensation (pain threshold, PT-E). After measurement of sensory thresholds, ES was performed randomly at ST-E, DT-E, or PT-E with an intensity of 30 mA. This intensity was chosen for comparison of responses between controls and IBS patients, and is considered high enough to evoke visceral perception. The intensity of ES during the second stage of the experiment was the same as that in the first stage.

Ordinate scales for subjective symptoms
Seven subjective symptoms were evaluated on a self-rating scale from 0 (none) to 10 (maximum). They were abdominal discomfort, abdominal pain, abdominal bloating, urgency of defecation, anxiety, perceived stress, and sleepiness. Symptoms were checked at the end of B1, R1, TR1, B2, R2, and TR2 periods. During ES, subjects were asked to report symptoms immediately after stimulation at ST-E, DT-E, or PT-E with 30 mA.

Data analysis
The volume of the barostat bag was analysed for each period of the experiment. The colonic motility index was calculated by measuring the area under the pressure curve for each period using a computerised planimeter (Gastrosoft) and the following formula:

\[
\text{motility index} = 100 \times \frac{\text{area under the pressure curve (mm Hg x s)}}{\text{(duration of period} \times 60 \text{ s)}}
\]

Ordinate scales for subjective symptoms were analysed in two parts for trackings and other periods of the experiment. Stored blood samples were defrosted and levels of plasma ACTH and serum cortisol were measured by radioimmunoassay. Minimal detectable values of ACTH and cortisol were 4 pg/ml and 0.64 μg/dl, respectively, while interassay variability was 3.89% for ACTH and 2.64% for cortisol.

Statistical analysis
Data are expressed as mean (SEM) unless otherwise indicated. Differences in means between the control subjects (n = 10) and IBS patients (n = 10) were compared by repeated two way analysis of variance (ANOVA). The Mann-Whitney U test was used to compare the two groups at specific time points. The paired t test and Wilcoxon’s signed rank test were used to detect significant changes within the same group. Data for colonic motility indices from a control subject and for plasma ACTH levels from another control subject were excluded due to technical problems. A p value of less than 0.05 was regarded as significant.

RESULTS
Changes in barostat bag volume
There was a significant group (controls vs IBS patients) to period interaction in the volume of the barostat bag (two way ANOVA, F = 3.39, p = 0.0075) (fig 2). Basal bag volume in IBS patients tended to be smaller than that in controls. A significant increase in bag volume was observed in the...
second stage of the experiment among controls (from 105.8 (30.5) ml at B1 to 148.3 (37.4) ml at B2; p = 0.0038) but not among IBS patients. In IBS patients, ES during the first stage of the experiment significantly reduced bag volume from 64.9 (12.3) ml at B1 to 54.5 (13.2) ml at ES1 (p = 0.014). Even during administration of α-helical CRH, ES significantly reduced bag volume in IBS patients from 75.5 (12.0) ml at B2 to 69.6 (12.7) ml at ES2 (p = 0.0041). In contrast, ES failed to reduce bag volume among controls.

**Changes in motility indices of the colon**

There was a trend group (controls v IBS patients) effect in motility indices of the mid sigmoid colon (two way ANOVA, F = 2.97, p = 0.1). There was no significant difference at B1 between controls and IBS patients. In contrast, motility indices of the mid sigmoid colon at ES1 in IBS patients were significantly higher than those in controls (421.5 (171.6) v 124.5 (46.5); p = 0.041) (fig 3). In IBS patients, motility indices of the mid sigmoid colon at ES2 were significantly lower than those at ES1 or R1 (p<0.05, fig 3). There was no difference in motility indices of the mid sigmoid colon at ES2 between controls and IBS patients. The ES induced increase in motility indices in IBS patients was suppressed in the second stage of the experiment. In addition, motility indices of the mid sigmoid colon in controls were significantly decreased from 122.4 (19.4) at B2 to 66.6 (13.7) at R2 (p = 0.012). Motility indices of the mid sigmoid colon at R2 in IBS patients were significantly higher than those in controls (275.1 (101.9) v 66.6 (13.7); p = 0.018). In the other two sites of the colon (descending and proximal sigmoid),

![Figure 1](image1.png)

**Figure 1** Experimental design. The first stage consisted of B1 (baseline), ES1 (electrical stimulation of the rectum), and R1 (recovery). The second stage (hatched bar) consisted of B2 (baseline), ES2 (electrical stimulation of the rectum), and R2 (recovery). Response to ES consisted of measurements of thresholds following randomised stimulation at minimal sensory thresholds (S1, S2), discomfort thresholds (D1, D2), and pain thresholds (P1, P2), with an intensity of 30 mA (E30-1, E30-2). Visceral perception to colonic distension was evaluated before the first stage (tracking 0), during the first stage (tracking 1), and during the second stage (tracking 2). Ordinate scales were obtained after the period of tracking 0, B1, ES1 (S1, D1, P1, E30-1), R1, tracking 1, B2, ES2 (S2, D2, P2, E30-2), R2, and tracking 2.

![Figure 2](image2.png)

**Figure 2** Increase in bag volume of the descending colon after α-helical corticotropin releasing hormone (CRH)₉₋₄₁ (10 µg/kg) administration in control subjects but not in patients with irritable bowel syndrome (IBS). Intravenous administration of α-helical CRH₉₋₄₁ is indicated by the hatched bar. Data are expressed as mean (SEM). There was a significant group to period interaction between controls and IBS patients (two way ANOVA, p<0.05). B1: baseline, ES1: electrical stimulation of the rectum, and R1: recovery, in the first stage of the experiment. B2: baseline, ES2: electrical stimulation of the rectum, and R2: recovery in the second stage (hatched bar). *p<0.05 compared with B1 by the paired t test; †p<0.05 compared with B2 by the paired t test.

![Figure 3](image3.png)

**Figure 3** Electrical stimulation (ES) induced increase in motility indices of the mid sigmoid colon in irritable bowel syndrome (IBS) patients was blocked by administration of α-helical corticotropin releasing hormone (CRH)₉₋₄₁ (10 µg/kg). Intravenous administration of α-helical CRH₉₋₄₁ is indicated by the hatched bar. Data are expressed as mean (SEM). B1: baseline, ES1: electrical stimulation of the rectum, and R1: recovery, in the first stage of the experiment. B2: baseline, ES2: electrical stimulation of the rectum, and R2: recovery in the second stage (hatched bar). *p<0.05 compared with controls by the Mann-Whitney U test; †p<0.05 compared with ES1 or R1 by the paired t test; ‡p<0.05 compared with B2 by the paired t test.
motility indices showed a similar pattern to that of the mid sigmoid colon at all periods (data not shown).

Sensory threshold to distension or electrical stimulation
In control subjects, the minimal sensory threshold (ST-D) significantly decreased from 25.0 (2.6) mm Hg at T0 to 15.0 (1.9) mm Hg at T1 (p = 0.0035). In addition, ST-D after administration of αhCRH remained similar to that at T1 (16.2 (2.4) mm Hg at T2). Similarly, the discomfort threshold (DT-D) significantly decreased from 32.0 (3.1) mm Hg at TR0 to 23.4 (2.2) mm Hg at T1 (p = 0.03). DT-D after administration of αhCRH remained similar to that at T1 (25.0 (2.4) mm Hg at T2). In contrast, the pain threshold (PT-D) at T1 (32.8 (3.2) mm Hg; p = 0.038) was significantly lower than that at T0 (40.2 (3.0) mm Hg; p = 0.0046) or that at T1 (38.8 (2.5) mm Hg; p = 0.015). In summary, there was no significant difference in ST-D, DT-D, or PT-D between controls and IBS patients.

In the first and second stages, there was no significant difference for any of the threshold values (ST-E, DT-E, and PT-E) to ES between controls and IBS patients, although all three thresholds tended to be higher during the second stage among both controls and IBS patients (table 1).

Ordinate scale and subjective symptoms
The ordinate scale of abdominal pain in control subjects was significantly different from that in IBS patients (two way ANOVA, F = 5.18, p = 0.035) (fig 4). In IBS patients, the ordinate scale of abdominal pain at ES2 during administration of αhCRH was significantly lower than that at ES1 during administration of saline (ANOVA, F = 6.84, p = 0.018) (fig 4). However, in controls, the abdominal pain scale at ES2 did not differ from that at ES1. The ordinate scale of abdominal discomfort, abdominal bloating, or urgency for defecation showed a similar pattern to that of abdominal pain (data not shown).

The ordinate scale of anxiety showed a similar pattern to that of abdominal pain (fig 5). Two way ANOVA of the anxiety ordinate scale revealed a significant period effect (F = 6.57, p<0.0001) and a group to period interaction.

| Table 1 Sensory thresholds to electrical stimulation (ES) of the rectum |
|------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Control                                | First stage (saline) | Second stage (αhCRH) | P Value |                   |
| First sensation (E)                    | 18.3 (3.2)        | 19.5 (3.5)        | 0.66    |                   |
| Discomfort (E)                         | 24.4 (3.9)        | 29.6 (3.8)        | 0.059   |                   |
| Pain (E)                               | 30.4 (3.9)        | 36.3 (4.1)        | 0.065   |                   |
| IBS                                    | First sensation (E) | 17.9 (2.8)        | 20.7 (3.0)        | 0.46    |                   |
| Discomfort (E)                         | 23.7 (3.6)        | 29.0 (3.6)        | 0.13    |                   |
| Pain (E)                               | 31.8 (3.8)        | 37.8 (4.0)        | 0.13    |                   |

Data are expressed as mean (SEM) (mA). There was no significant change between the two stages of the experiment by the paired t test. However, all thresholds in the antagonist stage (second stage) showed higher mean values than those in the saline stage (first stage).

IBS, irritable bowel syndrome; αhCRH, α-helical corticotropin releasing hormone.

In IBS patients, there was no significant difference in the minimal sensory threshold (ST-D) at T0 (23.4 (2.9) mm Hg) and at T1 (20.4 (3.3) mm Hg). ST-D at T2 (15.2 (2.2) mm Hg) was significantly lower than at T0 (p = 0.0002). The discomfort threshold (DT-D) showed a similar pattern to that of ST-D with values of 32.0 (2.5) mm Hg at T0, 30.6 (2.8) mm Hg at T1, and 24.0 (3.5) mm Hg at T2 (p = 0.0031). In contrast, the pain threshold (PT-D) at T2 (33.6 (2.8) mm Hg) was significantly lower than that at T0 (40.2 (3.0) mm Hg; p = 0.0046) or that at T1 (38.8 (2.5) mm Hg; p = 0.015). In summary, there was no significant difference in ST-D, DT-D, or PT-D between controls and IBS patients.

In the first and second stages, there was no significant difference for any of the threshold values (ST-E, DT-E, and PT-E) to ES between controls and IBS patients, although all three thresholds tended to be higher during the second stage among both controls and IBS patients (table 1).

Figure 4 Changes in the ordinate scale of abdominal pain. B1: baseline, ES1: electrical stimulation of the rectum (S1: sensory threshold, D1: discomfort threshold, P1: pain threshold, E30-1: 30 mA), and R1: recovery, in the first stage of the experiment. B2: baseline, ES2: electrical stimulation of the rectum (S2: sensory threshold, D2: discomfort threshold, P2: pain threshold, E30-2: 30 mA), and R2: recovery, in the second stage (hatched bar). Data are expressed as mean (SEM). There was a significant group to period interaction between controls and irritable bowel syndrome (IBS) patients (two way ANOVA, p<0.05). In IBS patients, the ordinate scale of abdominal pain at ES2 was significantly lower than that at ES1 (ANOVA, p<0.05).
In IBS patients, the ordinate scale of anxiety at P2 (period of pain threshold to ES during administration of a_hCRH) was significantly lower than that at P1 (period of pain threshold to ES during administration of saline; p = 0.042) (fig 5). In contrast, the ordinate scale of anxiety in controls did not change in the second stage of the experiment. The ordinate scale of stress showed a similar pattern to that of anxiety (data not shown).

Although the ordinate scale of sleepiness did not change significantly just after administration of a_hCRH, 14 subjects (nine controls, five IBS patients) reported mild sleepiness and relaxed sensations (data not shown).

**Neuroendocrine data**

Administration of a_hCRH failed to reduce ACTH levels in plasma as ACTH increased time dependently (two way ANOVA, period effect, p < 0.0001). However, plasma ACTH in IBS patients tended to be higher than that in controls (fig 6). No significant group to period interaction was indicated.

Two way ANOVA of serum cortisol revealed a significant period effect (F = 3.16, p = 0.012). However, there was no significant difference in levels of serum cortisol between the two groups.

**DISCUSSION**

This is the first study to demonstrate that colonic function and visceral perception in IBS patients can be modified by peripheral administration of a_hCRH, a non-selective CRH receptor antagonist. Earlier studies reported that CRH receptor antagonists inhibit gut motor alterations induced by stress.7 9 10 In addition, exogenous CRH is known to exaggerate colonic motility and abdominal pain in IBS patients.18 Therefore, the present study provides strong support for the hypothesis that CRH signalling pathways play a key role in the pathophysiology of IBS.

In this study, a_hCRH administration decreased colonic tone in control subjects but not in IBS patients. In fact, colonic tone in IBS patients increased throughout our experiment and was even exaggerated by electrical stimulation of the rectum. These phenomena may be explained by the physiological effect of CRH. Indeed, it has been reported that direct administration of CRH increases colonic intraluminal pressure and ejects fluid from colonic segments in vitro and that a_hCRH blocks these effects in rats.29 Therefore,
increased sensitivity of the gut to CRH in IBS patients may account for the above phenomena. Our result showing increased colonic tone after transmucosal electrical stimulation of the gut in IBS patients is a partial replication of that of a previous report from our laboratory indicating that electrical stimulation produces different colonic responses in normal subjects and IBS patients. These findings may be explained by accommodative dysfunction of the colon or increased CRH tone in the brain of IBS patients. However, in this study, the dose of zCRH (10 μg/kg) may not have been high enough to antagonise increased CRH action in the gut, brain, or both, in IBS patients. Experimental stressors, or CRH administration have been reported to increase the reactivity of the colon in IBS patients. In this study, the same phenomenon was replicated and administration of zCRH blocked this response. It is therefore assumed that the CRH pathway is involved in the mechanism of increased phasic contractions of the colon in response to various stimuli in IBS patients. In this study, basal motility indices were influenced by prior mechanical distention. Mechanical distention of the gut is known to induce the peristaltic reflex and/or colo-colonic inhibitory reflex, and intense stimulation of the gut induces visceral sensation. Colonic distention has also been reported to produce exaggerated colonic motility among IBS patients. Therefore, the decrease in motility indices of the colon in IBS patients after administration of zCRH in this study may partially reflect inhibition of exaggerated phasic contractions of the colon by luminal distention.

The precise site of action of intravenously administered CRH antagonists on gastrointestinal function is unknown. Several subtypes of the CRH receptor have been reported. Among them, CRH1 is predominantly expressed in the brain and CRH2 in peripheral sites. It has been reported that peripheral administration of CRH stimulates colonic motility, and that blockage of peripheral CRH receptors inhibits accelerated colonic motility. Blockage of the enteric nervous system (ENS) by tetrodotoxin or lidocaine also inhibits activation of colonic segments induced by CRH in vitro. Therefore, the decrease in motility indices of the colon in IBS patients after administration of zCRH in this study might be due to CRH1 antagonism of the ENS.

An earlier study reported decreased sensory thresholds (allodynia) and increased subjective sensation (hyperalgesia) to rectosigmoid distention in IBS patients. In this study, no overt allodynia was detected but hyperalgesia was replicated in IBS patients. Stimulation induced by gut distension is transmitted via unmyelinated C fibres, and gut ES is presumably transmitted via myelinated Aβ fibres. In this study, zCRH suppressed ES induced visceral sensation and normalised visceral hyperalgesia in IBS patients. Therefore, it is suggested that the CRH pathway might be involved, at least partially, in visceral hyperalgesia, which could be mediated via Aβ fibres.

Administration of zCRH reduced anxiety induced by gut stimuli in IBS patients but not in control subjects. Moreover, zCRH induced sleepiness in 70% of all subjects. It is thus plausible that peripheral administration of zCRH influences the central nervous system either by decreased visceral input through blockage of peripheral CRH receptors or by a direct action of zCRH on the brain. There is a specific unidirectional blood to brain transporter system for CRH, and like CRH, zCRH may not penetrate the brain. Therefore, intravenously administered zCRH may affect the brain through CRH receptors at circumventricular organs that are relatively unprotected by the blood-brain barrier. This notion is supported by earlier reports indicating that intravenous administration of CRH influences sleep electroencephalograms in humans and that blockage of central CRH receptors reduces spontaneous waking.

In this study, levels of plasma ACTH and serum cortisol were not suppressed by zCRH (10 μg/kg). There are two possibilities for this result. One is that zCRH has lower affinity for CRH1 receptors than for CRH2 receptors. The other is that the dose of zCRH used in this study, although it improved visceral hyperalgesia in IBS patients, was not high enough to completely block CRH receptors in the pituitary gland.

In conclusion, intravenous administration of zCRH alters colonic function and reduces symptoms induced by rectal electrical stimulation in IBS patients, with no inhibitory effects on the hypothalamo-pituitary-adrenal axis. These data suggest that CRH may play an important role in the pathophysiology of IBS.

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REFERENCES
A healthy 81 year old man was referred to us for acute bowel obstruction. The patient did not have a history of chronic illness and was not taking any medication.

On admission, the patient had diffuse abdominal pain, vomiting, and no bowel movements for 24 hours. There was no fever. Clinical examination showed abdominal distension without any contracture or palpable mass. Laboratory data were as follows: leucocyte count 11000/mm$^3$ and haemoglobin level 15 g/dl. C reactive protein concentration was normal.

**Question**

What does this x-ray show?

See page 979 for answer

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**Image 1** Abdominal x-ray showing small bowel distension with hydroaeric levels.
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