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Effect of alpha-helical CRH on quantitative electroencephalogram in patients with irritable bowel syndrome

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Abstract *Patients with irritable bowel syndrome (IBS) may have a higher tone of corticotropin-releasing hormone (CRH) in the brain. We tested our hypothesis that peripheral administration of CRH antagonist, α-helical CRH_{9-41} (αhCRH), improves decreased alpha power spectra and increased beta power spectra of electroencephalogram (EEG) in IBS patients. A barostat bag was inserted to the descending colon of 10 normal controls and 10 IBS patients. The EEG power spectra and topography were measured during baseline period and colonic distention period with the administration of saline followed by the administration of 10 μg kg^{-1} of αhCRH. IBS patients showed a significantly lower alpha power percentage and a higher beta power percentage than normal controls during baseline. Colonic distention induced a decrease in the alpha power percentage and an increase in the beta power percentage in both groups without difference between groups. After the administration of αhCRH, changes in the EEG power spectra in response to colonic distention were blunted and the differences in the EEG power spectra between IBS patients and controls vanished. Peripheral administration of αhCRH almost normalized EEG activities in IBS patients. Our data strongly suggest that CRH plays an important role in IBS.*

Keywords *corticotropin-releasing hormone, irritable bowel syndrome, electroencephalogram, CRH antagonist, brain gut interactions, visceral perception.*

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder indicating a remarkable aberration of brain–gut interactions.[1] The symptoms are characterized by sustained abdominal pain and altered bowel habits with no detectable organic disorder in routine clinical examinations.[2,3] Patients with IBS have several pathophysiological conditions: dysmotility of the lower gastrointestinal tract,[4] visceral hypersensitivity,[5] and psychological abnormalities.[2] Among them, visceral hypersensitivity which is typically demonstrated by an increased sensitivity to balloon distention of the rectum has recently been considered as a biological marker for IBS.[6,7] Neuroimaging studies using positron emission tomography (PET)[8] or functional magnetic resonance imaging (fMRI)[9,10] indicate exaggerated or aberrant cortical responses to visceral stimulation in IBS patients. Moreover, prolongation of duration of rapid eye movement (REM) sleep in IBS patients was reported.[11] These data suggest a possible involvement of the central nervous system (CNS) in the pathophysiology of IBS.

We previously reported abnormal electroencephalogram (EEG) in IBS patients.[12,13] Major findings of quantitative EEG in IBS patients were a low alpha power percentage and a high beta power percentage.[12,13] Besides, indices of less alpha power and more beta power correlated with colonic motility in IBS patients when exposed to laboratory stressors.[12,13] We also reported that administration of a corticotropin-releasing hormone (CRH) induced exaggerated colonic motility and secretion of adrenocorticotropic hormone (ACTH) in IBS patients.[14] Intravenous administration of CRH decreases perceptual thresholds of rectal distention in humans.[15] Moreover, peripheral administration of CRH reduces slow wave sleep in man[16] and

increases fast wave EEG in rats.[17] From these reports, it is feasible to assume that upregulated CRH receptors in the nervous system may contribute to the pathophysiological features of IBS.

We aimed to investigate differences in EEG power spectra between IBS patients and healthy controls after the administration of saline or CRH antagonist. We hypothesized that low alpha power percentage and high beta power percentage would be normalized in IBS patients after administration of CRH antagonist. Because CRH is a key mediator of stress,[18] subjects were exposed to visceral stimulation. We predicted that differential responses in EEG power before and after the administration of CRH antagonist between IBS patients and controls would be enhanced by visceral stimuli.

METHODS

Subjects

Subjects were 10 IBS patients (five male and five female) with a mean age of 31.3 years (range, 20–54 years) and 10 healthy controls (five male and five female) with a mean age of 20.7 years (range, 20–27 years). Control subjects were paid volunteers recruited from the Tohoku University campus. They had no symptoms nor history of major diseases. All of the IBS patients were diagnosed by the Rome II criteria[19] and their bowel pattern was diarrhoea-predominant.[19] In animal experiments, CRH increases fecal pellet output and exaggerated colonic motility.[20] Therefore, we enrolled diarrhoea-predominant IBS patients. No patients had a history of abdominal surgery or evidence of organic diseases by diagnostic studies including blood tests, urinalysis, stool analyses, abdominal X-rays, barium enema and colonoscopy. Medication for IBS patients was ceased from 7 days before the commencement of the experiment. Three IBS patients were medicated with trimebutine, scopolamine or loperamide and 7 days (168 h) are enough to eliminate these drugs from the body. Patients with IBS did not have a history of abdominal surgery nor any evidence of organic diseases by colonoscopy. Informed consent was obtained from all subjects. This study was approved by the Tohoku University Ethics Committee.

Canulation and recording assemblies

On the evening before colonoscopy, subjects ingested a 125 mL solution of magnesium citrate (13.6%) and 2.5 mg of sodium picosulphate to lessen the fecal effluent. A polyethylene catheter with a barostat bag (Synectics Medical, Stockholm, Sweden) were inserted into the descending colon using colonoscopy at 09:00 a.m. The bag was set in the descending colon and the distance of the bag from the anus was approximately 65 cm. The shape of the bag was cylindrical, 10 cm in length, 15 cm in diameter and 700 mL in capacity. The catheter had a separate lumen for measuring intrabag pressure. The position of catheters was certained before and after the study. The barostat bag catheter was connected to an analogue to a digital converter (PC-Polygram; Synectics, Stockholm, Sweden) and a visceral stimulator (Synectics), which was operated through commands to a computer (GX 1, DELL and USA). A plastic cannula was inserted into the right arm vein for infusion.

Electroencephalography

Electroencephalography electrodes were put on the scalp of the subjects at 10:00 a.m. EEG was recorded with silver/silver chloride electrodes on 13 sites (Fp1, Fp2, F7, F8, C3, C4, T5, T6, O1, O2, Cz, Fz and Pz) in accordance with the international 10–20 system for EEG electrode placement.[21] The reference electrodes were put on bilateral earlobes. Electrode impedance was set <10 kohm. Analogue EEG was recorded on a data recorder (XR-510, TEAC, Tokyo, Japan) with an EEG filter setting at 1–100 Hz. Analogue data was converted into digital data by using the analogue to digital translation board [AD16-16 (PCI) E; Contec, Tokyo, Japan] in a computer (NEC PC-9821 Ra333, Tokyo, Japan). The subjects were instructed to keep their eyes closed but remain conscious during the study. For artefact control, the EOG was recorded between supra- and side-orbital electrode using the same bandpass. Subjects' muscle movements were monitored by video tape to reject the motion artefact. The EEG was monitored throughout the study to confirm that the patients were awake. The examiners gave the subjects adequate warning if necessary.

Experimental protocols

The subjects lay quietly in a supine position on a comfortable bed at 11:00 a.m. after setting up the equipment. The experiment was performed in a quiet room to facilitate relaxation. The subjects rested for 60 min. The experiment consisted of two sessions; an initial session for the administration of saline and a second session for the administration of CRH antagonist, αhCRH (Bachem, Bubendorf, Switzerland). Saline or αhCRH was infused at a speed of 1.3 mL min^{-1}. Saline was injected at the beginning of the saline stage

and was infused during the saline session. Before the CRH antagonist session, 10 $\mu g\ kg^{-1}$ of αhCRH was dissolved in 100 mL of saline. Saline which contained 2 $\mu g\ kg^{-1}$ of antagonist was intravenously injected for 3 min at the beginning of the CRH antagonist session. The remaining 8 $\mu g\ kg^{-1}$ of CRH antagonist was continuously infused after the bolus injection. In the previous study,[22] this dosage (10 $\mu g\ kg^{-1}$) of αhCRH has been shown to influence on subjective aspects of brain function; reducing anxiety and perceived stress induced by visceral stimulation. In saline session, EEG were recorded with a 20-min period for baseline-1/1, a 20-min period for baseline-1/2 and a 10-min period for balloon distention (distention-1). In the CRH antagonist session, the same measurements were repeated with a 20-min period for baseline-2/1, a 20-min period for baseline-2/2 and a 10-min period for balloon distention (distention-2). The pressure of the bag was set at 10 mmHg except a period for stress by visceral stimulation.[22] Using a tracking technique,[22] the bag was stepwisely distended with 2 mmHg, starting from 0 up to 60 mmHg. Each step of distention lasted 10 s.

The quantitative EEG analysis

After certification of no artefacts or no paroxysmal EEG abnormality by visual observation of EEG, 60-s segments of EEG were collected from the last several minutes of each period. The EEG was recorded in the same point of period in both groups. These data were analysed with a fast Fourier transform technique using a computer (7T-18; NEC San-Ei, Tokyo, Japan) and software (Atamap II; Kissei Comtec, Nagano, Japan).[12,13] The total power was obtained by adding the powers from 2.0 to 29.8 Hz. The total potency was expressed as the percentage of the total power for each subject. The relative power spectra in delta (2.0–3.8 Hz), theta (4.0–7.8 Hz), alpha (8.0–12.8 Hz), and beta (13.0–29.8 Hz) bands were expressed as the percentage to the total power spectra.

Statistical analysis

Two-way analysis of variance (ANOVA) was performed on the group effect (IBS patients *vs* controls), period effect (saline: baseline-1/1, baseline-1/2, and distention-1, and αhCRH: baseline-2/1, baseline-2/2, and distention-2) and group × period interaction. *Post hoc* analyses were done with Tukey's test. EEG topography[13] using data from the 13 scalp sites was constructed by power % between groups. Statistical data were expressed as mean ± standard error of the mean and *P*-values of <0.05 were considered as significant.

RESULTS

The drug was found to have no harmful effects on the subjects. No epileptogenic activity on EEG was observed during the study. Fig. 1 showed an example of EEG in an IBS patient (male, aged 20) before (baseline 1/1) and after (baseline 2/1) the administration of αhCRH without visceral stimulation. Alpha wave increased in many locus after the administration of αhCRH.

Alpha power percentage

ANOVA of alpha power percentage disclosed significant group effects, period effect, group × period interaction in many regions (Fig. 2). The significant group × period interaction was found at Fp1 ($F = 3.18$, d.f. = 5, $P < 0.05$) and Fp2 ($F = 3.56$, d.f. = 5, $P < 0.01$). The significant group effect was detected at F7 ($F = 5.17$, d.f. = 1, $P < 0.05$), F8 ($F = 5.55$, d.f. = 1, $P < 0.05$), Fp1 ($F = 7.23$, d.f. = 1, $P < 0.05$), Fp2 ($F = 7.50$, d.f. = 1, $P < 0.05$), Fz ($F = 5.54$, d.f. = 1, $P < 0.05$), O1 ($F = 6.78$, d.f. = 1, $P < 0.05$) and O2 ($F = 4.63$, d.f. = 1, $P < 0.05$). The significant period effect was disclosed in all regions; C3 ($F = 18.97$, d.f. = 5, $P < 0.001$), C4 ($F = 16.90$, d.f. = 5, $P < 0.001$), Cz ($F = 16.50$, d.f. = 5, $P < 0.001$), F7 ($F = 26.67$, d.f. = 5, $P < 0.001$), F8 ($F = 23.11$, d.f. = 5, $P < 0.001$), Fp1 ($F = 17.89$, d.f. = 5, $P < 0.001$); Fp2 ($F = 17.25$, d.f. = 5, $P < 0.001$), Fz ($F = 25.45$, d.f. = 5, $P < 0.001$), O1 ($F = 6.83$, d.f. = 5, $P < 0.001$), O2 ($F = 9.28$, d.f. = 5, $P < 0.001$), Pz ($F = 13.15$, d.f. = 5, $P < 0.001$), T5 ($F = 8.43$, d.f. = 5, $P < 0.001$) and T6 ($F = 11.45$, d.f. = 5, $P < 0.001$).

Post hoc analysis revealed significant differential effects of distention and differential effects of αhCRH between groups. As detected significant group × period interactions, IBS patients showed a significantly lower alpha power percentage than normal controls during baseline-1/1 at Fp1 (IBS: 13.8 ± 3.0% *vs* normal: 29.4 ± 4.0%, $P < 0.05$) and Fp2 (IBS: 14.2 ± 2.9% *vs* normal: 31.0 ± 4.4%, $P < 0.05$). During baseline-1/2, IBS patients again showed a significantly lower alpha power percentage at Fp1 (IBS: 15.2 ± 3.0% *vs* normal: 30.8 ± 3.7%, $P < 0.05$) and Fp2 (IBS: 16.3 ± 3.1% *vs* 32.5 ± 3.9%, $P < 0.05$). Distention-1 significantly reduced the alpha power percentage in controls at Fp1 ($P < 0.05$) and Fp2 ($P < 0.05$), resulting in similar values for both groups. In the αhCRH session, in contrast to the saline session, no differences in alpha power

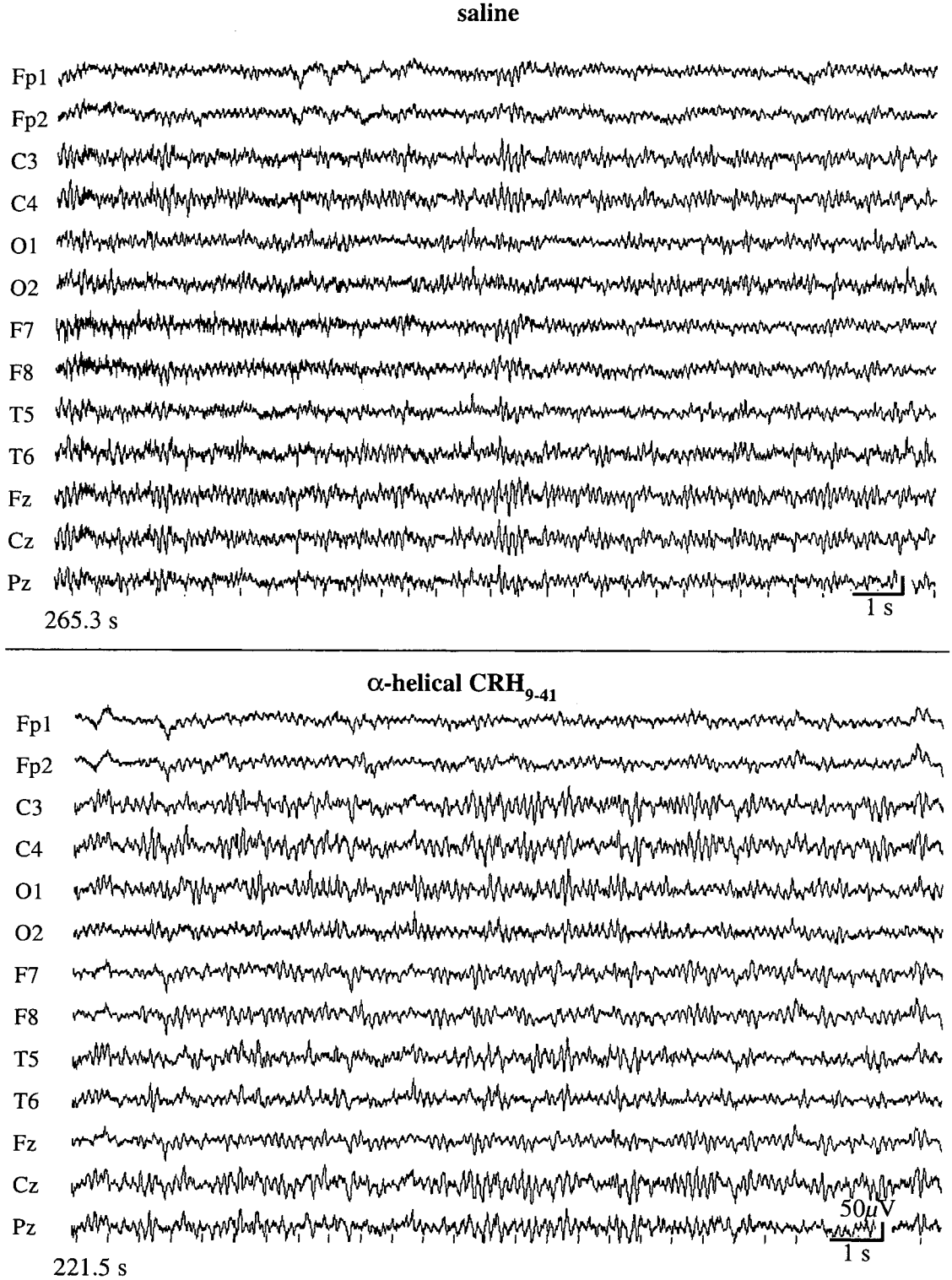

Figure 1 An example of electroencephalogram in a patient with irritable bowel syndrome (IBS) (male, aged 20 years). Upper panel indicated the baseline 1/1 (saline) and lower panel indicated the baseline 2/1 (αhCRH). Note increase in alpha wave in many locus after the administration of αhCRH.

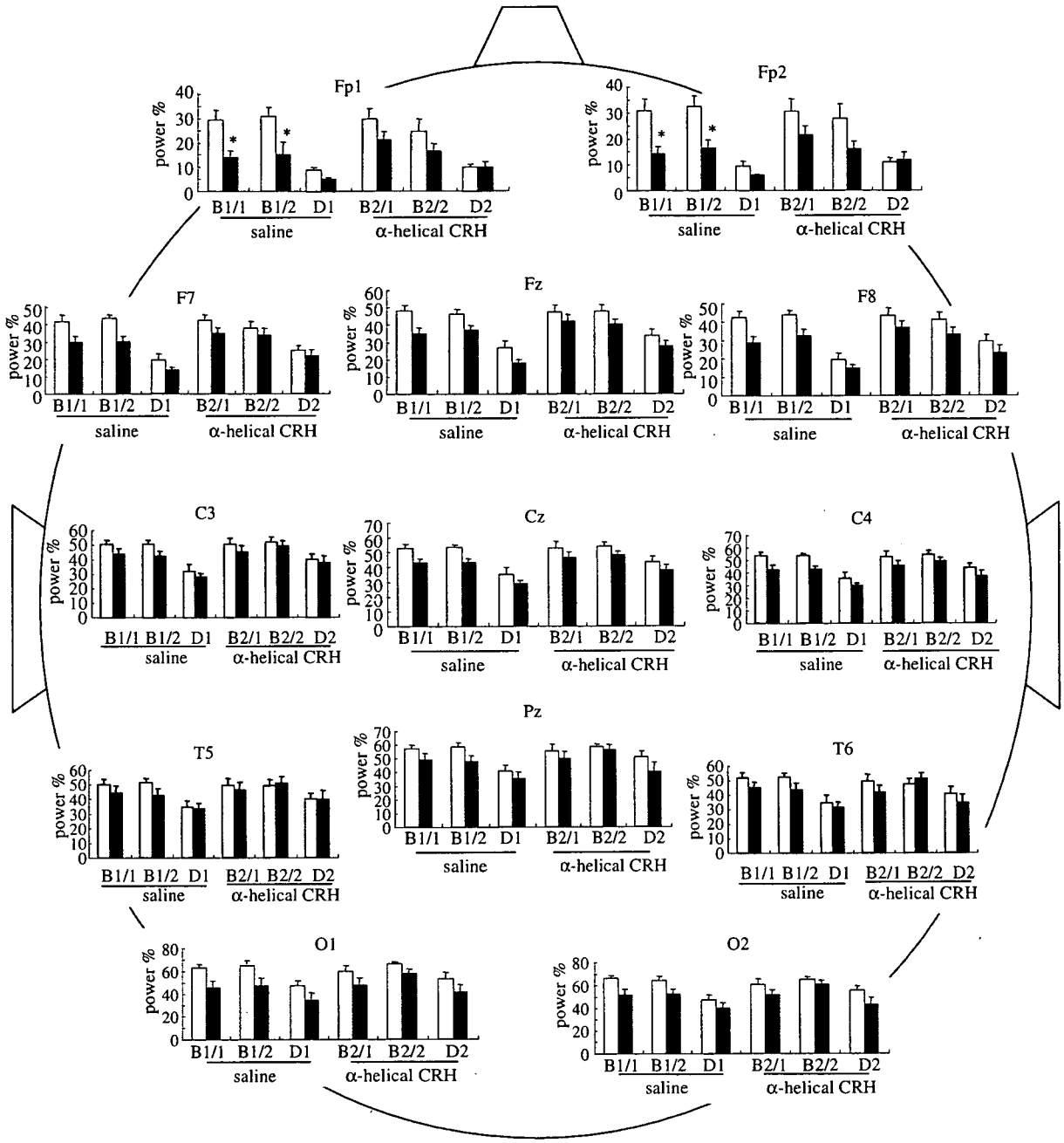

Figure 2 Change in the electroencephalographic alpha power percentage. Data are expressed as mean ± standard error of the mean. Black bars indicate patients with irritable bowel syndrome (IBS) ($n = 10$), and white bars indicate normal controls ($n = 10$). *Significant group difference between IBS patients and controls (*$P < 0.05$, Tukey). There were significant interactions in Fp1 and Fp2 and significant group effects in F7, F8, O1 and O2.

percentage between IBS patients and controls were found during baseline-2/1 and baseline-2/2 at Fp1 and Fp2. Significant reduction in alpha power percentage by distention at Fp1 ($P < 0.05$), F7 ($P < 0.05$), F8 ($P < 0.05$), Fz ($P < 0.05$), O1 ($P < 0.05$), Pz ($P < 0.05$) was diminished during administration of αhCRH in controls. In IBS patients, significant reduction in alpha power percentage by distention at F7 ($P < 0.05$), F8 ($P < 0.05$), Fz ($P < 0.05$) was diminished during administration of αhCRH.

Beta power percentage

ANOVA of beta power percentage disclosed significant group effects, period effect, group × period interactions in many regions (Fig. 3). The significant group × period interaction was found at F7 ($F = 4.02$, d.f. = 5, $P < 0.01$) and Fp2 ($F = 2.82$, d.f. = 5, $P < 0.05$). The significant group effect was disclosed in occipital site; O1 ($F = 7.67$, d.f. = 1, $P < 0.05$) and O2 ($F = 11.45$, d.f. = 1, $P < 0.01$). The significant period effect was disclosed at C4 ($F = 2.69$, d.f. = 5, $P < 0.05$), F8 ($F = 2.57$, d.f. = 5, $P < 0.05$), Fp1 ($F = 8.06$, d.f. = 5,

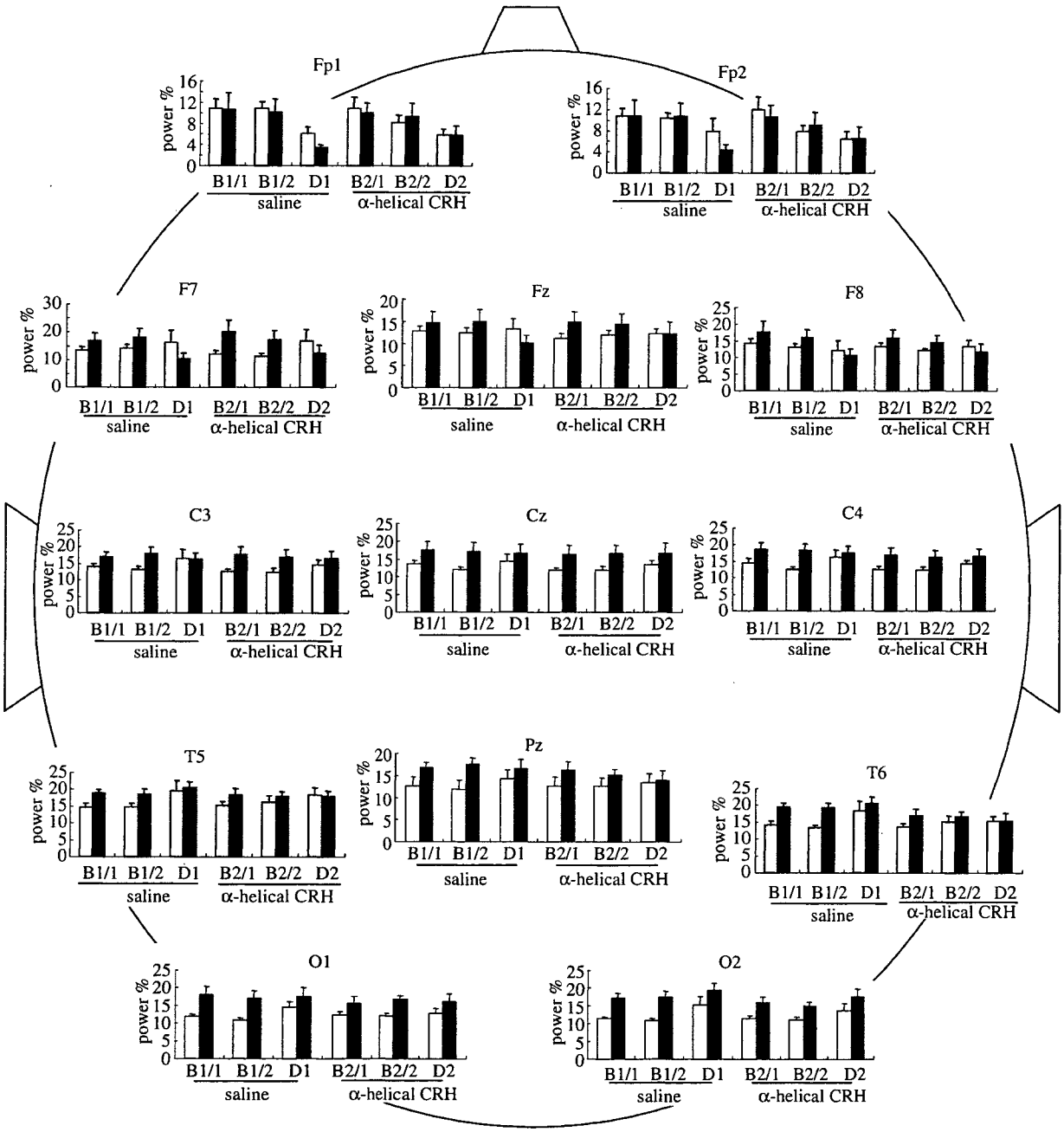

Figure 3 Change in the electroencephalographic beta power percentage. Data are expressed as mean ± standard error of the mean. Black bars indicate patients with irritable bowel syndrome (IBS) ($n = 10$), and white bars indicate normal controls ($n = 10$). There were significant group effects in O1 and O2.

$P < 0.001$), Fp2 ($F = 5.52$, d.f. = 5, $P < 0.001$) and O1 ($F = 3.41$, d.f. = 5, $P < 0.01$). In many regions, IBS patients showed a higher beta power percentage than normal controls during baseline-1/1. During baseline-1/2, IBS patients again showed a higher beta power percentage. Distention-1 increased the beta power percentage in controls, resulting in similar values for both groups. In the αhCRH session, in contrast to saline session, no differences in the beta power percentage between IBS patients and controls were found during baseline-2/1 at most of regions. No differences in beta power percentage between IBS patients and controls continued during baseline-2/2. Increase in beta power percentage by distention was not remarkable during administration of αhCRH in both groups.

Delta power percentage

ANOVA of delta power percentage disclosed significant group effects and period effect in some regions (Fig. 4). However, there was no significant group × period interaction. The significant group effect was disclosed at Fp1 ($F = 4.77$, d.f. = 1, $P < 0.05$), Fz ($F = 4.66$, d.f. = 1, $P < 0.05$) and O1 ($F = 4.75$, d.f. = 1, $P < 0.05$). The significant period effect was disclosed in all regions; C3 ($F = 19.70$, d.f. = 5, $P < 0.001$), C4 ($F = 15.85$, d.f. = 5, $P < 0.001$), Cz ($F = 15.93$, d.f. = 5, $P < 0.001$), F7 ($F = 19.14$, d.f. = 5, $P < 0.001$), F8 ($F = 20.60$, d.f. = 5, $P < 0.001$), Fp1 ($F = 11.90$, d.f. = 5, $P < 0.001$), Fp2 ($F = 10.46$, d.f. = 5, $P < 0.001$), Fz ($F = 21.79$, d.f. = 5, $P < 0.001$), O1 ($F = 3.68$, d.f. = 5, $P < 0.01$), O2 ($F = 5.11$, d.f. = 5, $P < 0.001$), Pz ($F = 13.34$, d.f. = 5, $P < 0.001$), T5 ($F = 9.60$, d.f. = 5, $P < 0.001$) and T6 ($F = 6.95$, d.f. = 5, $P < 0.001$). *Post hoc* analysis revealed a striking difference between IBS patients and controls in the frontal midline region (Fz). IBS patients showed a significantly higher delta power percentage than normal controls during baseline-1/1 (IBS: 30.2 ± 4.7% *vs* controls: 18.8 ± 2.4%, $P < 0.05$), baseline-1/2 (IBS: 28.3 ± 4.0% *vs* controls: 16.8 ± 1.6%, $P < 0.05$) and distention-1 (IBS: 49.5 ± 3.2% *vs* controls: 38.7 ± 4.8%, $P < 0.05$). In the αhCRH session, no differences between IBS patients and controls were detected in baseline-2/1, baseline-2/2 and distention-2 in the Fz region.

Theta power percentage

ANOVA of theta power percentage disclosed no significant group effect, period effect or group × period interaction (Fig. 5).

Electroencephalographic topography

In the saline session, alpha power percentage during baseline-1/1 was higher in the occipital region and lower in the frontal region in both groups (Fig. 6). IBS patients had a significantly lower alpha power percentage at Fp1 ($t = 3.11$, $P < 0.01$), Fp2 ($t = 3.20$, $P < 0.01$), C4 ($t = 2.54$, $P < 0.05$), O1 ($t = 2.54$, $P < 0.05$), O2 ($t = 2.68$, $P < 0.05$), F7 ($t = 2.24$, $P < 0.05$), F8 ($t = 2.67$, $P < 0.05$), Fz ($t = 2.72$, $P < 0.05$) and Cz ($t = 2.42$, $P < 0.05$) sites than controls during baseline-1/1. During baseline-1/2, IBS patients showed a significantly lower alpha power percentage at Fp1 ($t = 3.32$, $P < 0.01$), Fp2 ($t = 3.25$, $P < 0.01$), C4 ($t = 3.17$, $P < 0.01$), O1 ($t = 2.43$, $P < 0.05$), O2 ($t = 2.10$, $P < 0.05$), F7 ($t = 3.38$, $P < 0.01$), F8 ($t = 2.87$, $P < 0.05$), Fz ($t = 2.43$, $P < 0.05$), Cz ($t = 3.22$, $P < 0.01$) and Pz ($t = 2.22$, $P < 0.05$) electrodes than controls. During distention-1, IBS patients had a significantly lower alpha power percentage at Fp1 ($t = 2.47$, $P < 0.05$) electrodes than controls. In the αhCRH session, there was no significantly different region in the alpha power percentage between IBS patients and controls (Fig. 6).

In the saline session, IBS patients had a significantly higher beta power percentage at O1 ($t = 2.65$, $P < 0.05$), O2 ($t = 4.13$, $P < 0.01$), T5 ($t = 2.69$, $P < 0.05$), T6 ($t = 3.12$, $P < 0.01$) and Pz ($t = 2.58$, $P < 0.05$) regions than controls during baseline-1/1 (Fig. 7). During baseline-1/2, the IBS patients had a significantly higher beta power percentage at C3 ($t = 2.13$, $P < 0.05$), C4 ($t = 2.72$, $P < 0.05$), O1 ($t = 2.76$, $P < 0.05$), O2 ($t = 3.39$, $P < 0.01$), T6 ($t = 3.50$, $P < 0.01$) and Pz ($t = 3.08$, $P < 0.01$) regions than normal controls. During distention-1, no significant difference between IBS patients and controls was found in the beta power percentage. In the αhCRH session, the IBS patients had a significantly higher beta power percentage at the O2 ($t = 2.58$, $P < 0.05$) electrodes than normal controls during baseline-2/1. During baseline-2/2, IBS patients had a significantly higher beta power percentage at the O1 ($t = 3.67$, $P < 0.01$) and O2 ($t = 3.10$, $P < 0.01$) electrodes than controls (Fig. 7). During distention-2, no significant difference between the groups was found in the beta power percentage.

DISCUSSION

This is the first study which demonstrates the effect of peripheral infusion of CRH antagonist, αhCRH, on quantitative EEG in humans. Quantitative EEG findings in IBS patients in our previous reports were replicated. Colonic distention in healthy controls

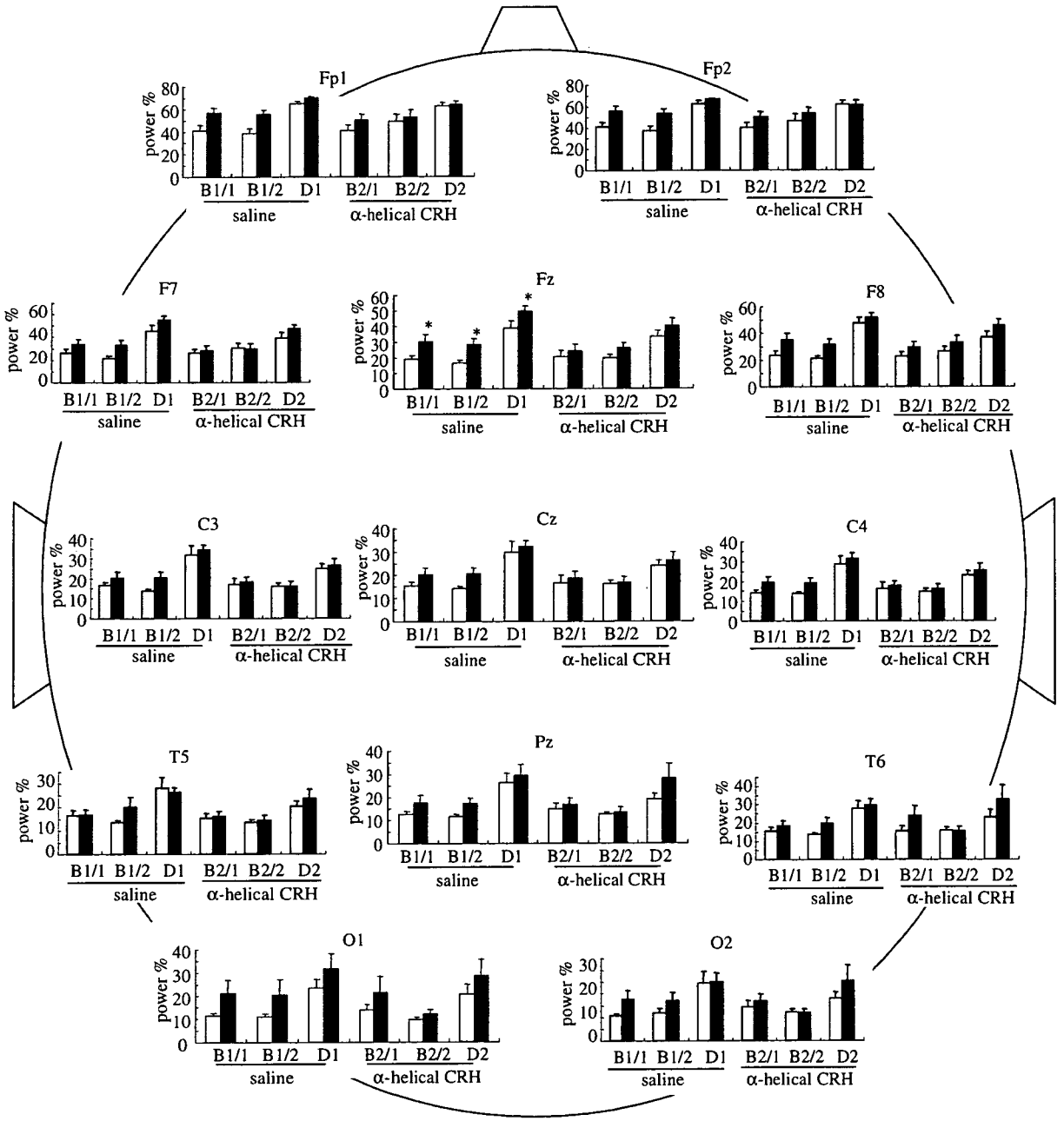

Figure 4 Change in the electroencephalographic delta power percentage. Data are expressed as mean ± standard error of the mean. Black bars indicate patients with irritable bowel syndrome (IBS) (n = 10), and white bars indicate normal controls (n = 10). *Significant group differences between IBS patients and controls (*P < 0.05, Tukey). There were significant group effects in Fp1 and O1.

induced quantitative EEG which resembled IBS patients. Because administration of CRH antagonist made low alpha power percentage and high beta power percentage of EEG in IBS patients improved, our hypothesis was supported.

We previously reported that quantitative EEG in IBS patients showed a low alpha power percentage during the resting state.[13] In this study, the same EEG patterns of IBS patients were replicated from independent samples. Although the characters of stimuli were

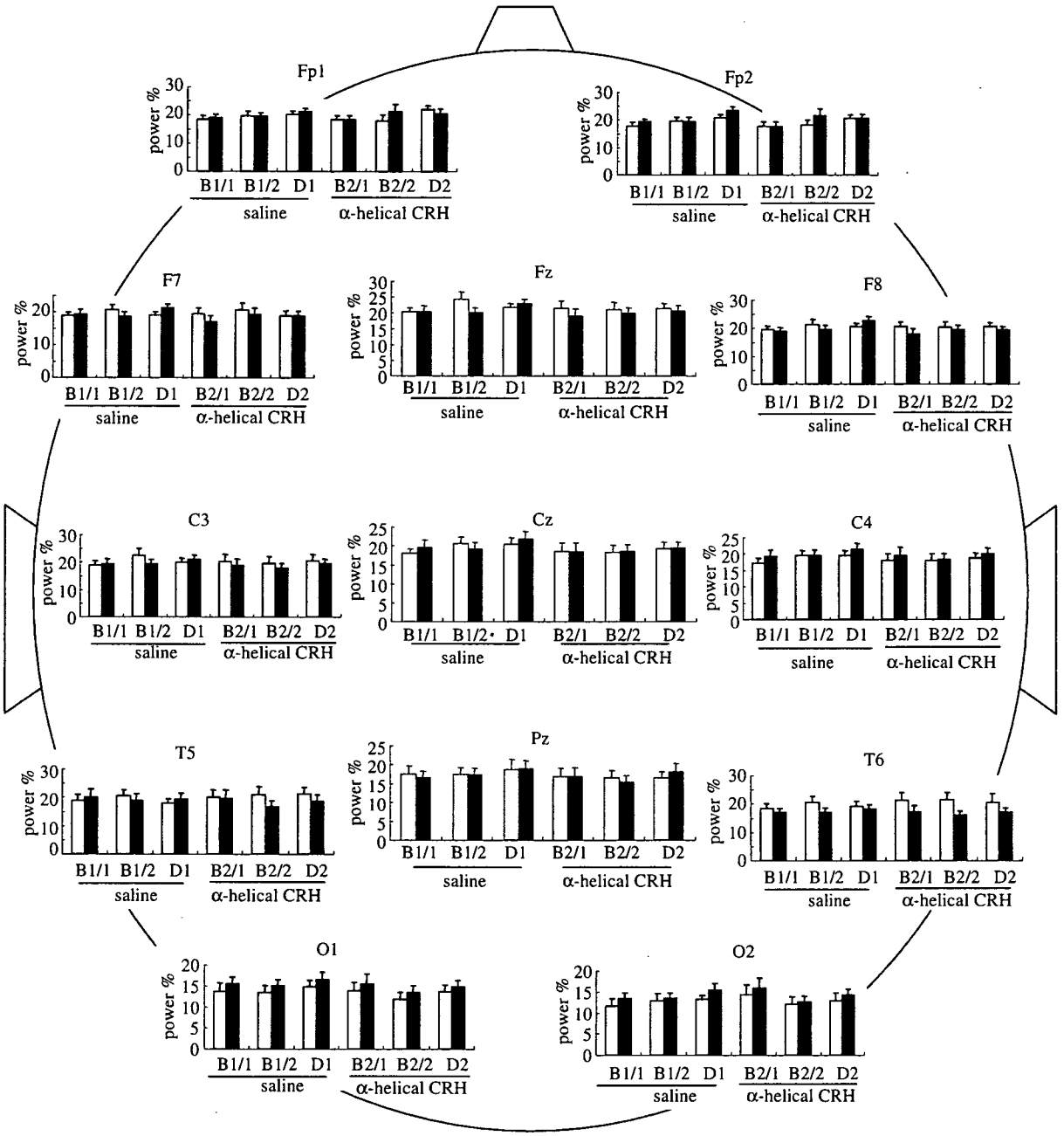

Figure 5 Change in the electroencephalographic theta power percentage. Data are expressed as mean ± standard error of the mean. Black bars indicate patients with irritable bowel syndrome (IBS) (n = 10), and white bars indicate normal controls (n = 10).

different between the present report (colonic distention) and the previous report (mental arithmetic),[12,13] both stimuli caused a decrease in the alpha power percentage, without regard to the pathway of the input of the stimuli; i.e. via auditory pathway or via visceral afferent pathway. The conscious, relaxed EEG recordings among normal subjects is usually predominated by alpha rhythm, which is replaced by fast (beta) and/or slow (delta, theta) EEG activity in a variety of physiological and pathological conditions including anxiety,[23] emotional tension,[24] and physical pain.[25–30] Alpha power percentage decreases,[27–29] beta power percentage increases[26,29] and delta power percentage increases[25,29,30] during physical pain. In this study,

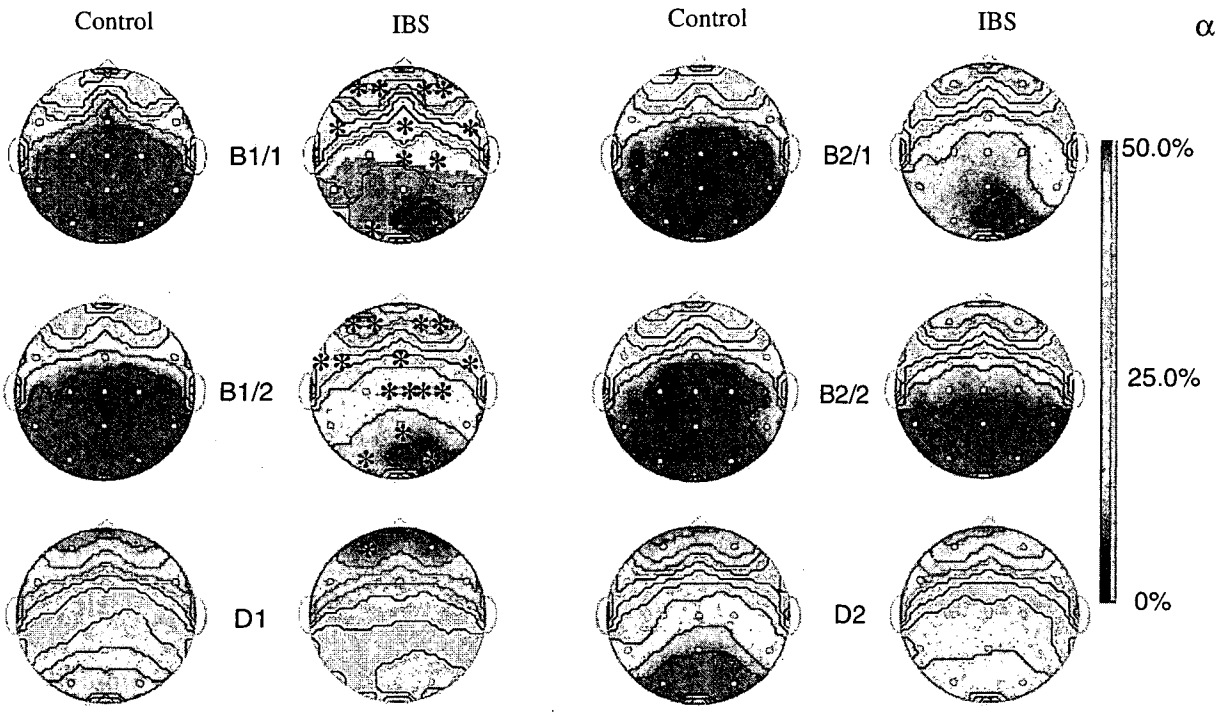

Figure 6 Topogram of the alpha power percentage of electroencephalogram (EEG) in patients with irritable bowel syndrome (IBS) and normal controls (upper panel). The top is the frontal and the bottom is the occipital region. *Significant group differences between IBS patients and controls (*$P < 0.05$; **$P < 0.01$, Student's *t*-test).

delta power % increased >50% in the forehead electrodes at distention. There is a report of pain-induced eye blink reflex.[31] However, we carefully excluded artefact. Moreover, during controlling eye movements, capsaicin administration[28] and cold pressor test[29] produced the similar results to this study. While EEG responses in both groups in this study may reflect the increased level of arousal during visceral perception, basal EEG power percentage in IBS patients may reflect an increased level of arousal even in the resting state. Somatosensory stimuli are known to activate the temporal and parietal area.[27,29] Ischaemic arm stress reduces alpha power % in the temporal and parietal area.[27] Cold pressor to the arm increases beta power % in the temporal area.[29] In this experiment, beta power % in temporal and parietal area was significantly higher during resting state in IBS patients than in controls. This may reflect hypersensitivity of the colon to the cannulation *per se* in IBS patients. Silverman *et al.*[8] presented abnormal activation of left dorsolateral prefrontal cortex to rectal distention in IBS patients. Distention-induced attenuation of alpha power % at Fp1 in IBS patients of this study may reflect activation of the prefrontal cortex. The prefrontal cortex is related to interpretation of stimulation.[32–34] Therefore, our data also provide evidence of regionally different activation of the brain in response to visceral stimulation in IBS patients.

The most striking findings of this study are that the differences in the EEG power spectra between IBS patients and controls almost vanished after the intravenous administration of αhCRH. Moreover, changes in EEG in response to colonic distention were blunted by the administration of the CRH antagonist. Visceral stimulation is reported to induce release of excitatory neurotransmitters in the brain.[35–37] Visceral stimulation activates locus coeruleus (LC), a nucleus containing approximately 50% of brain noradrenaline neurons.[35,36] We previously proved that colorectal distention induces visceral perception and hippocampal noradrenaline release in rats.[37] During acute stress, LC activates the hypothalamo–pituitary–adrenal axis and behavioural responses to stressors, via a multisynaptic mechanism involving noradrenergic activation of paraventricular nucleus (PVN)-excitatory neural pathways.[36] A number of reports have indicated that CRH receptors located in, or close to the LC are involved in the induction of stress responses.[38] CRH in the locus coeruleus mediates EEG activation associated with stress due to the altered state of proprioception (hypotension).[39] The blockade of

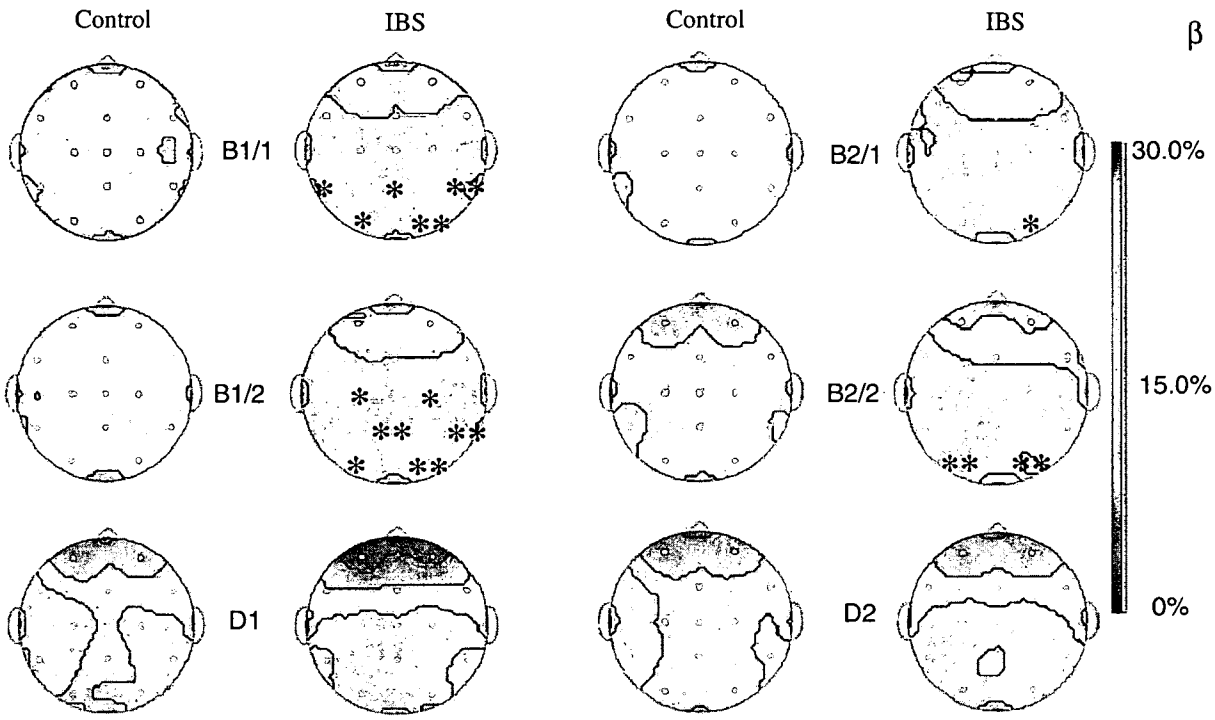

Figure 7 Topogram of the beta power percentage of electroencephalogram (EEG) in patients with irritable bowel syndrome (IBS) and normal controls (lower panel). The top is the frontal and the bottom is the occipital region. *Significant group differences between IBS patients and controls (*$P < 0.05$; **$P < 0.01$, Student's t-test).

central CRH receptors reduces spontaneous waking in rats.[40] A specific CRH-R1 antagonist inhibits stimulatory effects of exogenous CRH on neuronal firing of LC and the startle response amplitude in rats.[41] IBS patients are hypersensitive to visceral stimulation.[42] Moreover, neuroimaging studies using fMRI[9,10] indicate an exaggerated cortical response to visceral stimulation among IBS patients. Therefore, together with these earlier findings, the present data suggest the feasibility of our hypothesis that visceral stimulation activates CRH nerve conduction in humans and that IBS patients have upregulated CRH receptors in the brain.

The precise pathway of antagonistic action of intravenous administration of αhCRH on EEG in this study is still unknown. An earlier study[43] reported that intravenous administration of αhCRH did not induce any effects on cognitive or emotional state in normal subjects. However, structured interviews, psychometric tests and EEGs were not performed in that study.[43] There is a specific unidirectional brain-to-blood transporter system for CRH.[44] Therefore, αhCRH may not directly penetrate into the brain through the blood-brain barrier. A more plausible possibility is that the intravenous administration of CRH antagonists affects the CNS through CRH receptors at the circumventricular organs that are relatively unprotected by the blood-brain barrier.[40] As the CRH-R_2 receptor mRNA is expressed in the area postrema which is one of the circumventricular organs,[45] 41-amino acids peptide CRH or 33-amino acids peptide αhCRH may act in circumventricular organs at first and then affect most of the CNS. This notion is supported by earlier reports that intravenous CRH influences sleep EEG[16] and auditory evoked potentials in humans.[46] Moreover, urocortin, a peptide of the CRH family, is known to penetrate into the brain with a certain concentration of leptin.[45] There are abundant CRH receptors in the gut.[47] Intravenous administration of CRH decreases perceptual thresholds to the rectal distention in humans.[15] Therefore, we cannot completely rule out the possibility of penetration of αhCRH into the brain or the effect of αhCRH on EEG via blockade of afferent signals from the gut. Further study is necessary to determine the precise site of action of αhCRH.

There are several limitations in this study. Firstly, IBS patients were slightly older than controls. It is known that EEG is influenced by age[48] and sex.[49] In this study, the male and female rate was the same in both groups. We have already showed the difference in EEG power spectra between IBS patients and age-matched

controls.[12,13] Therefore, the difference in age cannot explain the differences in the specific EEG power spectra in this study. Secondly, our findings may be limited to the diarrhoea-predominant IBS patients. Thirdly, we could not compare EEG responses between the postsaline administration state with those after the administration of CRH_{9-41} on a different day with randomized order with double-blinded fashion. That was because performing colonoscopy on the subjects twice was difficult. However, together with a study by Sagami *et al.*,[22] this study now clarifies that this peptide blocks or weakens action of CRH even by peripheral administration. Therefore, more precise research using this peptide with IBS patients is now capable. Examination of CRH antagonist as a therapeutic drug or IBS is also warranted.

In conclusion, peripheral administration of αhCRH almost normalized EEG activities in IBS patients. Our data strongly suggest that CRH plays an important role in pathophysiology of IBS and electrophysiological property of the brain during visceral perception.

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REFERENCES

1 Mayer EA, Raybould HE. Role of visceral afferent mechanism in functional bowel disorders. *Gastroenterology* 1990; **99**: 1688–704.
2 Whitehead WE, Schuster MM. Irritable bowel syndrome: definition of the syndrome and relation to other disorder. In: Whitehead WE, Schuster MM, ed. *Gastrointestinal Disorders: Behavioral and Physiological Basis for Treatment*. New York: Academic Press, **1985**: 155–77.
3 Read NW. Irritable bowel syndrome (IBS) – definition and pathophysiology. *Scand J Gastroenterol* 1987; **22**(Suppl. 130): 7–13.
4 Drossman DA, Sandler RS, McKee DC, Levity AJ. Bowel Patterns among subjects not seeking health care. *Gastroenterology* 1982; **83**: 529–32.
5 Richie J. Pain from distension of the pervic colon by inflating a balloon in the irritable bowel syndrome. *Gut* 1973; **6**: 105–12.
6 Whitehead WE, Holtkotter B, Enck P *et al.* Tolerance for rectsigmoid distension in irritable bowel syndrome. *Gastroenterology* 1990; **98**: 1187–92.
7 Bouin M, Plourde V, Boivin M *et al.* Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology* 2002; **122**: 1771–1777.
8 Silverman D, Munakata J, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 1997; **112**: 64–72.
9 Mertz H, Morgan V, Tanner G *et al.* Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000; **118**: 842–8.
10 Drossman DA, Ringel Y, Vogt BA *et al.* Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. *Gastroenterology* 2003; **124**: 754–61.
11 Kumar D, Thompson PD, Wingate DL, Vesselinova-Jenkins CK, Libby G. Abnormal REM sleep in irritable bowel syndrome. *Gastroenterology* 1992; **103**: 12–7.
12 Fukudo S, Nomura T, Muranaka M, Taguchi F. Brain-gut response to stress and cholinergic stimulation in irritable bowel syndrome. *J Clin Gastroenterol* 1993; **17**: 133–41.
13 Nomura T, Fukudo S, Matsuoka H, Hongo M. Abnormal electroencephalogram in irritable bowel syndrome. *Scand J Gastroenterol* 1999; **5**: 25–31.
14 Fukudo S, Nomura T, Hongo M. Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotropic hormone in normal controls and patient with irritable bowel syndrome. *Gut* 1998; **42**: 845–9.
15 Lembo T, Plourde V, Shui Z *et al.* Effect of the corticotropin-releasing factor (CRF) on rectal afferent nerves in humans. *Neurogastroenterol Mot* 1996; **8**: 9–18.
16 Holsboer F, von Bardeleben U, Steiger A. Effects of intravenous corticotropin-releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. *Neuroendocrinology* 1988; **48**: 32–8.
17 Bradbury MJ, Dement WC, Edgar DM. Effects of adrenalectomy and subsequent corticosterone replacement on rat sleep state and EEG power spectra. *Am J Physiol* 1998; **275**: R555–65.
18 Maillot C, Million M, Wei Jy, Gauthier A, Tache Y. Peripheral corticotropin-releasing factor and stress-stimulated colonic motor activity involve type 1 receptor in rats. *Gastroenterology* 2000; **119**: 1569–79.
19 Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45**(Suppl. II): 43–7.
20 Mönnikes H, Schmidt BG, Taché Y. Psychological stress-induced accelerated colonic transit in rats involves hypothalamic corticotrophin-releasing factor. *Gastroenterology* 1993; **104**: 716–23.
21 Jasper HH. The 10–20 electrode system of the international federation. *Electroencephalogr Clin Neurophysiol* 1958; **10**: 371–5.
22 Sagami Y, Shimada Y, Tayama J *et al.* Effect of a corticotropin-releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut* 2004; **53**: 958–64.

23 Cohn R. The influence of emotion on the human electroencephalogram. *J Nerv Ment Dis* 1946; **104**: 351–7.
24 Freedman NL, Hafer BM, Daniel RS. EEG arousal decrement during paired-associate learning. *J Comp Physiol Psychol* 1966; **61**: 15–9.
25 Pera DL, Svensson P, Valeriani M, Watanabe I, Arendt-Nielsen L, Chen ACN. Long-lasting effect evoked by tonic muscle pain on parietal EEG activity in humans. *Clin Neurophysiol* 2000; **111**: 2130–7.
26 Reinert A, Treede R, Bromm B. The pain inhibiting pain effect: an electrophysiological study in humans. *Brain Res* 2000; **862**: 103–10.
27 Rainero I, Amanzoi M, Vighetti S, Bergamasco B, Pinessi L, BenedettiF. Quantitative EEG responses to ischaemic arm stress in migraine. *Cephalalgia* 2001; **21**: 224–9.
28 Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Chen ACN. Different EEG topographic effects of painful and non-painful intramuscular stimulation in man. *Exp Brain Res* 2001; **141**: 195–203.
29 Chang PF, Arendt-Nielsen L, Chen ACN. Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. *Brain Res Bull* 2002; **57**: 667–75.
30 Thomaides T, Tagaris G, Karageorgiou C. EEG and topographic frequency analysis in migraine attack before and after sumatriptan infusion. *Headache* 1996; **36**: 111–4.
31 Ellrich J, Bromm B, Hopf HC. Pain – evoked blink reflex. *Muscle Nerve* 1997; **20**: 265–70.
32 Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain* 1995; **118**: 279–306.
33 Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 1988; **331**: 585–9.
34 Rainville P, Hofbauer RK, Paus T, Duncan GH, Bushnell MC, Price DD. Cerebral mechanisms of hypnotic induction and suggestion. *J Cogn Neurosci* 1999; **11**: 110–25.
35 Elam M, Thorén P, Svensson TH. Locus coeruleus neurons and sympathetic nerves: activation by visceral afferents. *Brain Res* 1986; **375**: 117–25.
36 Lechner SM, Curtis AL, Brons R, Valentino RJ. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. *Brain Res* 1997; **756**: 114–24.
37 Saito K, Kanazawa M, Fukudo S. Colorectal distention induces hippocampal noradrenalinee release in rats. *Brain Res* 2002; **947**: 146–9.
38 Foote SL, Bloom FE, Aston-Jones G. Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. *Physiol Rev* 1983; **63**: 844–914.
39 Page ME, Berridge CW, Foote SL, Valentino RJ. Corticotropin-releasing factor in the locus coeruleus mediates EEG activation associated with hypotensive stress. *Neurosci Lett* 1993; **164**: 81–4.
40 Chang FC, Opp MR. Blockade of corticotropin-releasing hormone receptors reduces spontaneous waking in the rat. *Am J Physiol* 1998; **275**: R793–802.
41 Schulz DW, Mansbach RS, Sprous J *et al.* CP-154,526: A potent and selective nonpeptide antagonist of corticotropin releasing factor receptors. *Proc Natl Acad Sci USA* 1996; **93**: 10477–10482.
42 Munakata J, Nailboff B, Harraf F *et al.* Repetitive sigmoid stimulation induces rectal hyperalgesia is patients with irritable bowel syndrome. *Gastroenterology* 1997; **112**: 55–63.
43 Baram TZ, Mitchell WG, Haden E. Inhibition of pituitary-adrenal secretion by a corticotropin releasing hormone antagonist in humans. *Mol Psychiatry* 1996; **1**: 320–4.
44 Martins JM, Kastin AJ, Banks WA. Unidirectional specific and modulated brain to blood transport of corticotropin-releasing hormone. *Neuroendocrinology* 1996; **63**: 338–48.
45 Kastin AJ, Akerstorm V, Pan W. Activation of urocortin transport into brain by leptin. *Peptides* 2000; **21**: 1811–7.
46 Fehm HL, Born J. Effects of corticotropin releasing hormone on human brain function: an analysis based on auditory evoked potentials. *Horm Metab Res Suppl* 1987; **16**: 75–9.
47 Muramatsu Y, Fukushima K Iino K *et al.* Urocortin and corticotropin-releasing factor receptor expression in the human colonic mucosa. *Peptide* 2000; **21**: 1799–809.
48 Yordanova J, Kolev V, Basar E. EEG theta and frontal alpha oscillations during auditory processing change with aging. *Electroencephalogr Clin Neurophysiol* 1998; **108**: 497–505.
49 Volf NV, Razumnikova OM. Sex differences in EEG coherence during a verbal memory task in normal adults. *Int J Psychophysiol* 1999; **34**: 113–22.

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Translation and validation of a Japanese version of the irritable bowel syndrome-quality of life measure (IBS-QOL-J)

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Abstract

Aims: To compare quality of life (QOL) for patients with irritable bowel syndrome (IBS) between the U.S. and Japan, it is indispensable to develop common instruments. The IBS-QOL, which is widely used in Western countries, was translated into Japanese as there has been a lack of Japanese disease-specific QOL measures for IBS.

Methods: The original 34 items of the IBS-QOL were translated from English into Japanese through two independent forward translations, resolution, back translation, and resolution of differences. Forty nine patients who had GI symptoms but did not have any organic diseases (including 30 IBS patients diagnosed by Rome II criteria) were recruited from Tohoku University Hospital in Sendai, Japan and completed a Japanese version of the IBS-QOL (IBS-QOL-J) concomitant with a Japanese version of the IBS severity index (IBSSI-J) twice within 7–14 days.

Results: The IBS-QOL-J demonstrated high internal consistency (Cronbach's alpha; 0.96) and high reproducibility (intraclass correlation coefficient; 0.92, $p < 0.001$). Convergent analyses confirmed that the overall score of IBS-QOL-J was significantly correlated with overall severity of IBS symptoms on the IBSSI-J ($r = -0.36$, $p = 0.01$) and with the individual items on the IBSSI-J that assess interference with life in general ($r = -0.47$, $p = 0.001$) and dissatisfaction with bowel habits ($r = -0.32$, $p < 0.05$). Eight patients who reported continuous abdominal pain in the past 6 months had significantly lower scores in the IBS-QOL-J than those who did not (53.7 +- 12.7 vs. 73.6 +- 19.5, $p < 0.01$). Age, sex, education or marital status did not affect scores on the measure.

Conclusion: The IBS-QOL-J is a reliable instrument to assess the disease-specific QOL for IBS. Considering cross-cultural comparison, this measure is likely to be a valuable tool to investigate the QOL in Japanese patients with IBS.

Background

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder and is often associated with psychological distress [1,2]. People with IBS have a significantly diminished quality of life (QOL) [3,4]. Even though a large percentage of subjects with IBS do not seek medical care (approximately 75%) [5], IBS is associated with significantly more absences from work and school and with impaired QOL [3,4]. The impact on QOL in patients with IBS is often underestimated by friends and family members, and even by the patient's doctors because they are not disabled in any obvious way and there is no apparent impact on life expectancy.

How much of a burden illness is on an individual's life depends on several factors. It is becoming recognized that assessment of QOL associated with a person's illness should be taken into account in order to understand the burden illness on several medical conditions. We have demonstrated that both IBS patients and IBS non-consulters report not only more severe gastrointestinal symptoms and psychological distress but also more impaired health-related QOL than people who do not have IBS, as has been reported in other countries [6]. In contrast to reports form the United States [7], IBS patients were not different from IBS non-consulters for physical and psychological QOL scores on the SF-36 [8].

Although generic instruments like the SF-36 offer the opportunity to compare the impacts of different conditions on health status [9,10], disease-specific measures are more sensitive than generic measures of QOL to the effects of illness and the impact of treatment [9]. Within the gastroenterology field, disease-specific quality-of-life measures have been developed primarily for inflammatory bowel disease [11].

Patrick and Drossman developed and validated a specific QOL measure, the IBS-QOL, to assess the impairment of QOL in IBS [12]. The instrument defines "perceived quality of life" according to a needs-based model that considers QOL as the degree to which all or most needs are met [13]. It reveals patients' predominant concerns with high degree of specificity and attribution to the bowel symptoms associated with the condition [12]. Furthermore, they confirmed that this instrument is responsive to treatment in a clinical population of patients with FBD [14]. This instrument has been translated into several languages (i.e. Dutch, Spanish, French, Chinese and Korean) and is widely used [15-21].

There have been no studies on the cross-cultural differences in IBS between the U.S. and Japan due to the lack of common disease-related instruments. To compare QOL in patients with IBS between these countries, it is indispensable to develop disease-specific QOL measurements like the IBS-QOL in Japanese. The aim of this study was to test the reliability and validity of a Japanese version of the IBS-QOL (IBS-QOL-J).

Methods

Forty-nine consecutive patients (27 female and 22 male) who suffered with chronic or recurrent abdominal pain, abdominal discomfort and/or altered bowel habit in Tohoku University Hospital, Sendai, Japan were invited to participate. All the participants completed the IBS-QOL-J (see Additional file 1) concomitant with a Japanese version of the IBSSI (IBSSI-J) [22] twice between 7–14 days interval to confirm the test-retest reproducibility. The Japanese version of the Rome II modular questionnaire, in conjunction with medical evaluation to exclude alternative diagnosis, was used to diagnose IBS [22]. None of the participants had any organic GI diseases or any other severe physical and/or psychological disorders. Age, sex, marital status, education, race, number of visits to physicians due to GI symptoms, and existence of continuous or nearly continuous abdominal pain in the past 6 months were also investigated (Table 1). This study was approved by the Tohoku University Ethics Committee (No. 2004-061). All the participants gave written informed consent.

The Rome II modular questionnaire (RMIIQ) has been used as a diagnostic instrument for functional GI disorders according to Rome II diagnostic criteria [23]. This instrument includes 4 key questions used to define IBS plus 11 supportive items that address bowel habits. IBS is defined by abdominal discomfort or pain that was present during at least 3 weeks in the last 3 months and that has two of three features: (1) Relieved with defecation; and/or (2) onset associated with a change in frequency of stool; and/or (3) onset associated with a change in form (appearance) of stool [22,23]. Subtypes of IBS were assessed by predominant stool pattern; hard or lumpy stools >25% and loose (mushy) or watery stools <25% of bowel movements as IBS with constipation (IBS-C), and loose (mushy) or watery stools >25% and hard or lumpy stools <25% of bowel movements as IBS with diarrhea (IBS-D) [24].

The IBS Severity Index (IBSSI) was developed and validated in the U.K. to assess the major GI symptoms in IBS [25]. This scoring system is simple and consists of only 5 items each with 100-point scale (0, none; 100, worst). These items are severity and duration of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits (bowel score) and interference with life in general (QOL). The maximum total score is 500 points [22,25]. Recently, these two instruments have been translated into Japanese and validated for Japanese patients

Table 1: Characteristics of the sample (n = 49)

Sex	
Male	22
Female	27
Age (yrs, mean ± SD)	38 ±15
Race	
Japanese	49
Others	0
Marital status	
Single living alone	10
Single living with a partner	14
Married	24
Divorced	1
Education	
8th grade or less	3
Some high school	1
High school graduate	19
Some college or technical school	8
College graduate	18
Diagnosis by Rome II criteria	
Irritable bowel syndrome (IBS)	30
IBS subtypes of bowel habit	
IBS with constipation (IBS-C)	6
IBS with diarrhea (IBS-D)	14
Mixed or unspecified IBS	10
Other functional bowel disorders (FBD)	19
Classification of symptom severity by IBSSI	
Mild	15
Moderate	22
Severe	12

IBSSI: IBS severity index. Data were expressed as number of subjects except for age.

with functional bowel disorders (FBD) by our research group [22].

The IBS-QOL consists of 34 items with 5-point response scales (0 to 4). The IBS-QOL is scored for 8 subscales; dysphoria (8 items), interference with activity (7 items), body image (4 items), health worry (3 items), food avoidance (3 items), social reaction (4 items), sexual concerns (2 items) and relationships (3 items) [12]. Higher values indicate better QOL after converting the raw score on the IBS-QOL into 0 to 100 points. The process for the validation study of the IBS-QOL-J was as follows: The original 34 items of the IBS-QOL were translated from English into Japanese through two independent forward translations (by M.K. and S.F.), resolution, back translation by a native speaker of English, and resolution of differences. As a result of the discussion among the translators and the authors of the original version (D.A.D. and W.E.W.), no obvious difference of contents was found between the original and the back-translated versions.

Cronbach's alpha was calculated to assess the internal consistency reliability. A high internal consistency suggests that the scale is measuring a single construct. Reproducibility was assessed by comparing the total IBS-QOL-J score at baseline to a second one later. Convergent and discriminant validity involve comparing logically related measures to see if they are correlated more strongly (convergent) or more weakly (discriminant). The overall score for the IBSSI-J and the scores for the 5 components at baseline were used to assess convergent validity of the IBS-QOL-J. Strengths of association as the test-retest reliability or the convergent/construct validity were tested by a simple regression analysis, Pearson's correlation coefficient. Multiple regression analysis was used to confirm the relationships among the IBS-QOL-J score, age, gender, education and marital status.

Results

Characteristics of the participants are shown in Table 1. The mean age with standard deviation (SD) of participants was 38 +- 15 years (19–79 years old). Thirty patients were diagnosed as IBS by the Japanese version of Rome II modular questionnaire, and the rest of them were considered to have other FBD. Six patients diagnosed as IBS were constipation predominant (IBS-C), 14 were diarrhea predominant (IBS-D) and 10 were not classifiable as either. Overall score of the IBS-QOL-J demonstrated high reproducibility (intraclass correlation coefficient, 0.92, $p < 0.001$) and high internal consistency (Cronbach's alpha,

0.96). Each individual score on the IBS-QOL-J also showed high reproducibility and relatively high internal consistency (Table 2). Response to the individual items significantly correlated with overall score of the IBS-QOL-J except for Q5 from the body image domain and Q32 from the health worry domain (Table 3).

Validity of the IBS-QOL-J was confirmed by the significant correlations with measures of disease severity. The overall score of IBS-QOL-J was significantly correlated with overall severity of IBS symptoms on the IBSSI-J ($r = -0.36$, $p = 0.01$) and with the individual questions on the IBSSI-J that assess interference with life in general ($r = -0.47$, $p = 0.001$) and dissatisfaction with bowel habits ($r = -0.32$, $p = 0.03$, Table 4). The correlations between the overall score of the IBS-QOL-J and individual scores of abdominal pain (severity and duration) were weaker and were not statistically significant. Abdominal distension (severity) on the IBSSI-J was correlated to quality of life was as measured by the IBS-QOL-J.

Linear regression analyses revealed that the number of physician visits in the past 6 months was significantly associated with the overall score of IBS-QOL-J ($r = -0.33$, $p < 0.05$) but not with the overall severity score ($r = 0.19$, $p > 0.1$). Eight patients who reported continuous or nearly continuous abdominal pain in the past 6 months had significantly lower scores in the IBS-QOL-J than those who did not (53.7 +- 12.7 vs. 73.6 +- 19.5, $p < 0.01$, Fig. 1). There was no significant difference in the overall score or each of individual score on the IBS-QOL-J between patients who were diagnosed as IBS by the RIIMQ and those who were not (namely, the other FBD) in the participants (Table 5). Age, sex, education or marital status did not affect scores on the measure as a predictor variable. Most of the IBS-QOL-J scores in Japanese patients with IBS were quite comparable to those in the English version of the IBS-QOL in IBS patients in the U.S. There was no significant difference in the overall or each individual score on the IBS-QOL-J between subtypes of bowel movement in 30 patients diagnosed as IBS.

Discussion

The Japanese version of the IBS-QOL (IBS-QOL-J) instrument was confirmed to be reliable and valid. This disease-specific QOL measurement shows high internal consistency for the overall score. The reproducibility over the two-week study period was excellent. The original version of the IBS-QOL has previously been shown to have high internal consistency and reproducibility [12]. On this original instrument, discriminant and convergent validity [12] and responsiveness [14] were also demonstrated. Not only severity of symptoms but also psychological well-being predicted this score [26]. Although Cronbach's alpha scores for most of the individual domains also resulted high (Table 2), the factor analysis revealed that a couple of individual items affected rather low alpha scores for the specific domains (Table 3). Further larger studies should be needed to confirm whether cross-cultural differences in patients' concerns might be associated with the inconsistencies in the present study.

Disease-specific quality of life instruments are sensitive and responsive to measuring treatment response over time; thus, they are especially useful in clinical research trials in which health status is analyzed [9]. Several disease-specific QOL measures for IBS or functional GI disorders have been developed (e.g. IBSQOL developed by Hahn et al. [27]). However, in most instruments, their responsiveness has not been demonstrated except for the IBS-QOL. In a systematic review by Bijkerk et al, it was shown that the IBS-QOL is the best of the five IBS-specific QOL scores to establish changes in health-related QOL [28]. On the other hands, the IBS severity index (IBSSI) is considered to be the best choice for a detailed IBS symptom assessment [28].

Table 2: Reliability and validity for the overall and individual scores on the IBS-QOL-J

IBS-QOL	Score (mean ± SD) (Time 1)	Cronbach's alpha (Time 1)	Intraclass correlation coefficient (ICC)
Overall scale	70.3 ± 19.9	0.96	0.92[a]
Subscales (number of items)			
Dysphoria (8)	61.5 ± 27.1	0.94	0.88[a]
Interference with activity (7)	66.4 ± 24.7	0.86	0.94[a]
Body image (4)	82.9 ± 18.0	0.56	0.90[a]
Health worry (3)	76.0 ± 18.6	0.48	0.81[a]
Food avoidance (3)	59.5 ± 28.2	0.83	0.92[a]
Social reaction (4)	78.2 ± 19.2	0.76	0.85[a]
Sexual concerns (2)	84.7 ± 19.6	0.61	0.80[a]
Relationships (3)	71.3 ± 25.6	0.74	0.87[a]

[a] $p < 0.001$; Pearson's correlation coefficient.

Table 3: Evaluation of the utility of individual items on the IBS-QOL-J

Domain	Item	Correlation	Domain	Item	Correlation
Dysphoria	Q1	-0.83**	*Health worry*	Q4	-0.56**
	Q6	-0.86**		Q15	-0.74**
	Q7	-0.82**		Q32	-0.19
	Q9	-0.76**	*Food avoidance*	Q11	-0.45**
	Q10	-0.75**		Q23	-0.55**
	Q13	-0.72**		Q28	-0.59**
	Q16	-0.80**	*Social reaction*	Q2	-0.60**
	Q30	-0.89**		Q14	-0.54**
Interference with activity	Q3	-0.60**		Q17	-0.60**
	Q18	-0.78**		Q34	-0.79**
	Q19	-0.60**	*Relationships*	Q8	-0.66**
	Q22	-0.70**		Q24	-0.70**
	Q27	-0.75**		Q33	-0.70**
	Q29	-0.73**	*Body image*	Q5	-0.10
	Q31	-0.53**		Q21	-0.76**
Sexual	Q12	-0.30*		Q25	-0.61**
	Q20	-0.47**		Q26	-0.68**

*$p < 0.05$, **$p < 0.01$; Pearson's correlation coefficient between individual items and overall score of the IBS-QOL-J.

Recently, we have translated the Rome II modular questionnaire for IBS and the IBSSI into Japanese and have confirmed reliability and reproducibility in patients with functional bowel disorders (FBD) [22]. Our results in the present study show that the IBS-QOL-J is strongly correlated with the self-rating scales for the overall severity measure. Besides, patients who reported continuous or nearly continuous abdominal pain showed a lower overall score on the IBS-QOL-J than those who did not. On the other hand, our study did not confirm that there are significant differences in the QOL score among subtypes of bowel movement in patients with IBS. These results suggest that IBS patients who have abdominal pain continuously may have more impaired QOL despite predominant stool patterns. Furthermore, patients considered as frequent consulters according to a previous systemic review [29] show lower scores in the IBS-QOL-J. Previous reports on the original IBS-QOL show a significant association between the IBS-QOL and number of visit to physicians for IBS problems [14]. Thus, the findings of the present study are consistent with those of the original version of the disease-specific QOL measure for IBS.

The mean overall score of the IBS-QOL-J in patients with IBS was similar with that of original version [12] measured in the U.S. (68.2 vs. 63.2 points) despite different diagnostic criteria (Rome II vs. Rome I) and subject population (tertiary care vs. GI clinic plus advertisement). The mean overall score of the IBS-QOL-J in patients with IBS also showed a similar result with that measured by the Korean version of the IBS-QOL in South Korea [21]. Nevertheless, the mean individual scores of body image (80.0 vs. 62.5), health worry (73.1 vs. 59.2), food avoidance (55.3 vs. 43.4) and sexual concerns (89.2 vs. 73.5) on the Japanese version were over 10-point higher [12] (see Table 5).

Our results failed to confirm that the overall IBS-QOL-J score is significantly associated with the individual scores of the abdominal pain severity or pain duration in the

Table 4: Correlations between overall score of the IBS-QOL-J and overall and individual scores of the IBSSI-J

	IBS-QOL-J	
	Correlation	Significance
IBSSI-J		
Overall	-0.36	0.01
Abdominal pain (severity)	-0.21	N.S.
Abdominal pain (duration)	-0.23	N.S.
Abdominal distension	-0.00	N.S.
Bowel movement	-0.32	0.03
Quality of life	-0.47	0.001

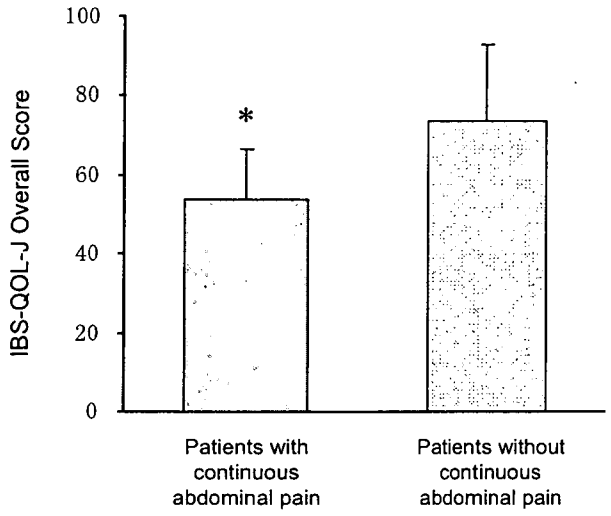

Figure 1
Comparison of the IBS-QOL-J scores between patients who reported continuous or nearly continuous abdominal pain and those who did not. Results were expressed as mean with standard deviation of the overall scores on the IBS-QOL-J. Patients who reported continuous abdominal pain showed a significant lower score than those who did not (*$p < 0.01$, Mann-Whitney U test).

IBSSI-J. We do not believe that gastrointestinal (GI) symptoms of the patients in this study were less severe because more than two-thirds demonstrated moderate to severe symptoms on the IBSSI-J according to the severity classification system on the original version [25] (see Table 1). Despite 41 of 49 patients had taken medical treatment for their GI symptoms including antispasmodic agents and antidepressants, they did not report lower abdominal pain scores compared with the rest of the patients who had not in the present study.

It has been demonstrated that the Japanese subjects are less prone to be accepting of pain behaviors [30] and express their sexual activities to someone [31] compared with people in the Western countries. There was no difference in the individual score of sexual concerns between married and unmarried patients in this study, in fact. When the sexual concerns are assessed in the Japanese patients, it should be taken into account that they may hesitate or avoid expression of such topics even if they have any sexual problems. Although we could not compare differences in these scores directly, cross-cultural difference between the countries (e.g. race, food, belief, social milieu and health-care system) might affect some dimensions of perception for the health-related QOL in patients with IBS.

The IBS-QOL-J appears to be a reliable instrument to assess the disease-specific QOL for IBS in Japanese patients. However, this validation study was cross-sectional, and thus could not investigate responsiveness. Moreover, our sample was relatively small and recruited from only the referred FBD patients. Further validation studies are warranted to investigate reliability and validity on the Japanese version of the IBS-QOL. It is important to assess not only severity of symptoms but also disease-specific QOL when considering the strategy for treatment for IBS since no biological measure is available for assessing IBS. Considering cross-cultural comparisons, these instru-

Table 5: Comparison of the IBS-QOL between Japan and the U.S

	Score (mean ± SD)		
	IBS (Japan)	**Other FBD** (Japan)	**IBS*** (U.S.)
Number	30	19	155
Female (%)	18 (60)	9 (47)	138 (89)
Age (yrs)	39 ± 17	37 ± 12	39 ± 12
IBSSI (Overall)	250 ± 95.5[a]	172 ± 89.8	-[b]
IBS-QOL			
Overall	68.2 ± 19.7	73.6 ± 20.2	63.2 ± 18.5
Dysphoria	61.0 ± 26.8	62.2 ± 28.4	63.1 ± 23.9
Interference with activity	62.3 ± 25.8	72.9 ± 21.9	63.1 ± 22.3
Body image	80.0 ± 18.0	87.5 ± 17.4	62.5 ± 24.3
Health worry	73.1 ± 19.4	80.7 ± 16.7	59.2 ± 24.6
Food avoidance	55.3 ± 27.2	66.2 ± 29.1	43.4 ± 26.7
Social reaction	77.1 ± 18.9	79.9 ± 21.4	69.4 ± 22.9
Sexual concerns	89.2 ± 22.9	87.5 ± 13.2	73.5 ± 27.6
Relationships	72.2 ± 23.0	67.7 ± 29.8	72.3 ± 21.7

*IBS was diagnosed by Rome I criteria, data from Patrick, et al, 1998 (with permission, ref. 12). [a]$p < 0.01$ vs other FBD. [b]IBSSI was not investigated. Higher values indicate better QOL score for the IBS-QOL.

ments are likely to be a valuable tool to investigate the QOL in Japanese patients with IBS.

Additional material

Additional File 1
Japanese version of irritable bowel syndrome quality of life (IBS-QOL-J) instrument.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1751-0759-1-6-S1.pdf]

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References
1. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E, Richter JE, Koch GG: **U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact.** *Dig Dis Sci* 1993, **38**:1569-1580.
2. Locke GR 3rd, Weaver AL, Melton LJ 3rd, Talley NJ: **Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study.** *Am J Gastroenterol* 2004, **99**:350-357.
3. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA: **The impact of irritable bowel syndrome on health-related quality of life.** *Gastroenterology* 2000, **119**:654-660.
4. Frank L, Kleinman L, Rentz A, Ciesla G, Kim JJ, Zacker C: **Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases.** *Clin Ther* 2002, **24**:675-689.
5. Drossman DA, Sandler RS, McKee DC, Lovitz AJ: **Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction.** *Gastroenterology* 1982, **83**:529-534.
6. Kanazawa M, Endo Y, Whitehead WE, Kano M, Hongo M, Fukudo S: **Patients and nonconsulters with irritable bowel syndrome reporting a parental history of bowel problems have more impaired psychological distress.** *Dig Dis Sci* 2004, **49**:1046-1053.
7. Whitehead WE, Burnett CK, Cook EW 3rd, Taub E: **Impact of irritable bowel syndrome on quality of life.** *Dig Dis Sci* 1996, **41**:2248-2253.
8. Ware JE, Sherbourne CD: **The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.** *Med Care* 1992, **30**:473-483.
9. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE: **Psychosocial aspects of the functional gastrointestinal disorders.** In *Rome II The Functional Gastrointestinal Disorders* 2nd edition. Edited by: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE. McLean, VA: Degnon Associates; 2000:157-245.
10. Guyatt GH, Feeny DH, Patrick DL: **Measuring health-related quality of life.** *Ann Intern Med* 1993, **118**:622-629.
11. Drossman DA: **Inflammatory bowel disease.** In *Quality of life and pharmacoeconomics in clinical trials* 2nd edition. Edited by: Spilker B. New York: Raven Press; 1966:925-935.
12. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL: **Quality of life in persons with irritable bowel syndrome: development and validation of a new measure.** *Dig Dis Sci* 1998, **43**:400-411.
13. McKenna SP: **A new theoretical approach to the measurement of quality of life.** *Drug Inf J* 1994, **28**:13-18.
14. Drossman DA, Patrick DL, Whitehead WE, Toner BB, Diamant NE, Hu Y, Jia H, Bangdiwala SI: **Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire.** *Am J Gastroenterol* 2000, **95**:999-1007.
15. Drossman DA, Whitehead WE, Toner BB, Diamant N, Hu YJ, Bangdiwala SI, Jia H: **What determines severity among patients with painful functional bowel disorders?** *Am J Gastroenterol* 2000, **95**:974-980.
16. Akehurst RL, Brazier JE, Mathers N, O'Keefe C, Kaltenthaler E, Morgan A, Platts M, Walters SJ: **Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting.** *Pharmacoeconomics* 2002, **20**:455-462.
17. Wang W, Pan G, Qian J: **Cognitive therapy for patients with refractory irritable bowel syndrome [in Chinese with English abstract].** *Zhonghua Nei Ke Za Zhi* 2002, **41**:156-159.
18. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, Emmot S, Proffitt V, Akman D, Frusciante K, Le T, Meyer K, Bradshaw B, Mikula K, Morris CB, Blackman CJ, Hu Y, Jia H, Li JZ, Koch GG, Bangdiwala SI: **Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders.** *Gastroenterology* 2003, **125**:19-31.
19. Whitehead WE, Levy RL, Von Korff M, Whitehead WE, Levy RL, Von Korff M, Feld AD, Palsson OS, Turner M, Drossman DA: **The usual medical care for irritable bowel syndrome.** *Aliment Pharmacol Ther* 2004, **20**:1305-1315.
20. Blanchard EB, Lackner JM, Gusmano R, Gudleski GD, Sanders K, Keefer L, Krasner S: **Prediction of treatment outcome among patients with irritable bowel syndrome treated with group cognitive therapy.** *Behav Res Ther* 2006, **44**:317-337.
21. Park JM, Choi MG, Oh JH, Cho YK, Lee IS, Kim SW, Choi KY, Chung IS: **Cross-cultural validation of irritable bowel syndrome quality of life in Korea.** *Dig Dis Sci* 2006, **51**:1478-1484.
22. Shinozaki M, Kanazawa M, Sagami Y, Endo Y, Hongo M, Drossman DA, Whitehead WE, Fukudo S: **Validation of the Japanese version of the Rome II modular questionnaire and irritable bowel syndrome severity index.** *J Gastroenterol* 2006, **41**:491-494.
23. Drossman DA, Talley NJ, Whitehead WE, Thompson WG, Corazziari E: **Research diagnostic questions for functional gastrointestinal disorders: Rome II Modular Questionnaire: Investigations and Respondent Forms.** In *Rome II The Functional Gastrointestinal Disorders* 2nd edition. Edited by: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE. McLean, VA: Degnon Associates; 2000:669-714.
24. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC: **Functional bowel disorders.** *Gastroenterology* 2006, **130**:1480-1491.
25. Francis CY, Morris J, Whorwell PJ: **The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress.** *Aliment Pharmacol Ther* 1997, **11**:395-402.
26. Lembo A, Ameen VZ, Drossman DA: **Irritable bowel syndrome: toward an understanding of severity.** *Clin Gastroenterol Hepatol* 2005, **3**:717-725.
27. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E: **Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome.** *Aliment Pharmacol Ther* 1997, **11**:547-552.
28. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW: **Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics.** *Am J Gastroenterol* 2003, **98**:122-127.
29. Gill D, Sharpe M: **Frequent consulters in general practice: a systematic review of studies of prevalence, associations and outcome.** *J Psychosom Res* 1999, **47**:115-130.
30. Hobara M: **Beliefs about appropriate pain behavior: cross-cultural and sex differences between Japanese and Euro-Americans.** *Eur J Pain* 2005, **9**:389-393.
31. Ide M, Fugl-Meyer AR: **Life satisfaction in persons with spinal cord injury: a comparative investigation between Sweden and Japan.** *Spinal Cord* 2001, **39**:387-393.