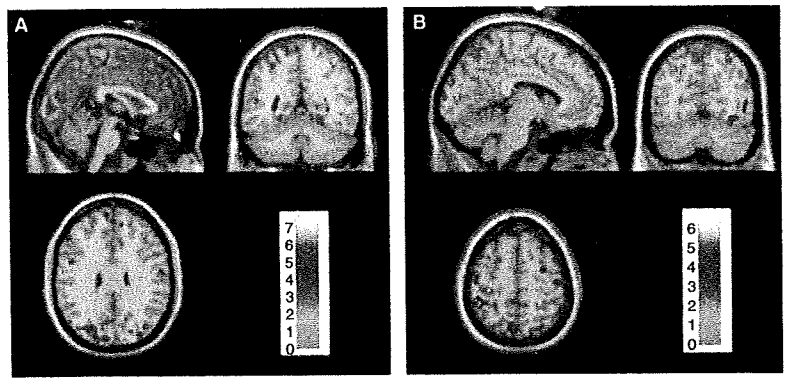

Figure 3 Regions of cerebral deactivation induced by intraluminal distention in the rectum and descending colon with a bag pressure of 40 mmHg. Brain regions deactivated during intraluminal distentions of the rectum and descending colon were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. Significant deactivations during 40-mmHg stimulus in the rectum (*x,y,z* = 2,–50,30: A) and the descending colon (*x,y,z* = –6,–66,58: B) are shown. The level of significance was set at 0.1% or less (voxel level).

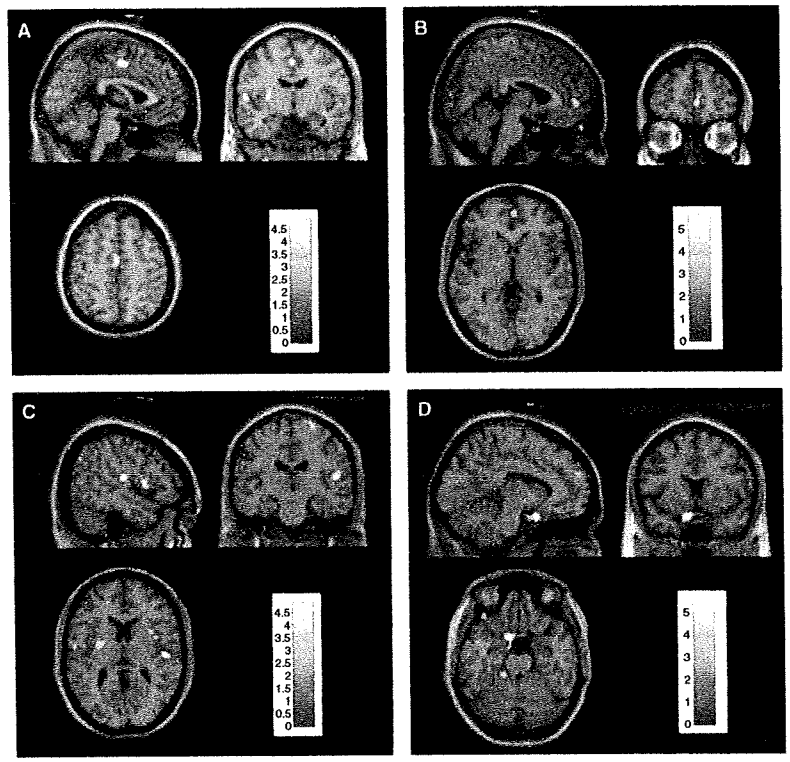

Figure 4 Comparisons of activated cerebral regions during intraluminal distention at 40 mmHg between the rectum and the descending colon. Dominant brain activations during intraluminal distentions of the rectum (*x,y,z* = 0,8,50: A and 50,–18,12: B) and the descending colon (*x,y,z* = 4,52,0: C and –8,10,–22: D) were superimposed on the Talairach–Tournoux stereotaxic atlas of the human brain. To compare regional brain activities in response to each stimulus between groups, a between-group comparison of the contrasts (distention minus baseline images) was applied. The level of significance was set at 0.1% or less (voxel level).

DISCUSSION

This is the first study to demonstrate the differences in subjective perception and central activation during intraluminal distention of the rectum and descending colon. Pain and the urge to defecate perception were more sensitive to distention in the rectum than in the descending colon, while the abdominal bloating sensation was similar. Differences in regions of brain activation, especially regions associated with affective, cognitive and/or nociceptive networks (i.e. pMCC, pACC, sACC),[22] were shown during a 40-mmHg distention of the rectum compared with the descending colon. Greater activation of the pMCC was demonstrated during the intense rectal stimulus, whereas greater activation in the more anterior part of the cingulate cortex was demonstrated during stimulation of the descending colon. There was little difference in brain activation pattern during the weak distention between the rectum and descending colon. In contrast, broad deactivation of the occipital, middle temporal (including PCC) and medial prefrontal cortices during

Table 4 Comparisons of brain regions activated during intraluminal distention

Cordinate of local maximum x,y,z (mm)	Tentative anatomical localization	t-Value (voxel level)	$P_{FWE\text{-corrected}}$ (voxel level)	$P_{FDR\text{-corrected}}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
Rectum (40-mmHg baseline) > descending colon (40-mmHg baseline)						
−32,−28,66	Left precentral gyrus (BA4)	4.88	0.206	0.078	101	0.026
50,−18,12	Right posterior insula (BA13)	4.67	0.372	0.078	64	0.154
−62,2,28	Left precentral gyrus (BA6)	4.65	0.387	0.078	36	0.583
52,8,6	Right anterior insula (BA13)	4.58	0.460	0.078	47	0.355
54,−68,36	Right angular gyrus (BA39)	4.58	0.469	0.078	31	0.706
−56,−6,6	Left superior temporal gyrus (BA22)	4.44	0.623	0.078	36	0.583
−30,−6,8	Left putamen	4.39	0.687	0.084	67	0.132
0,−8,50	Left pMCC (BA24)	4.27	0.811	0.086	99	0.028
24,−16,72	Right precentral gyrus (BA6)	4.1	0.936	0.093	45	0.391
34,10,14	Right anterior insula (BA13)	3.85	0.997	0.113	71	0.109
Rectum (20-mmHg baseline) > descending colon (20-mmHg baseline)						
54,6,6	Right anterior insula (BA13)	4.53	0.515	0.855	30	0.731
Descending colon (40-mmHg baseline) > rectum (40-mmHg baseline)						
−8,10,−22	Left rectal gyrus, sACC (BA11)	5.66	0.013	0.013	145	0.004
−58,−36,6	Left superior temporal gyrus (BA22)	5.26	0.059	0.014	43	0.429
−44,0,−14	Left superior temporal gyrus (BA38)	4.56	0.486	0.049	73	0.099
4,52,0	Right pACC (BA32)	4.26	0.817	0.076	61	0.179
−38,34,−22	Left orbitofrontal gyrus (BA47)	3.94	0.987	0.123	35	0.607
−38,−60,38	Left inferior parietal lobule (BA40)	3.90	0.993	0.127	29	0.755
Descending colon (20-mmHg baseline) > rectum (20-mmHg baseline)						
−8,8,−20	Left sACC (BA25)	4.54	0.505	0.341	44	0.409
12,−62,34	Right precuneus (BA7)	4.36	0.717	0.341	28	0.779
−40,−8,−12	Left middle temporal gyrus (BA21)	3.91	0.992	0.408	36	0.583

A between-group comparison of the contrasts (distention minus baseline images) was applied. Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level). Degree of freedom = [1, 90]. BA, Brodmann area; ACC, anterior cingulate cortex (s, subgenual; p, perigenual); MCC, midcingulate cortex (p, posterior).

the intense stimulus in the rectum and descending colon were observed respectively.

These two closely linked parts of the large bowel seem to show similar central projections with respect to visceral perception. Previous PET/fMRI studies in healthy subjects during rectal stimulation have quite consistently shown cerebral activations in the anterior insula and thalamus.[23–25] We have previously reported that stimulation of the descending colon in healthy volunteers activated similar brain regions (i.e. thalamus, pACC, inferior parietal gyrus).[13] In this study, the activated brain regions during each stimulus are almost concordant with these findings. On the other hand, the different activation patterns of the cingulate cortex to visceral stimulation of the rectum and descending colon from the present findings are intriguing.

A systematic review of previous brain imaging studies during visceral stimulation revealed that lower GI stimulus results noticeably in more effects in the anterior and ventral part of the prefrontal cortex and more anterior insula than upper GI stimulus.[26] Differences in the distribution of activated brain areas may reflect characteristics of the afferent innervations, suggesting that these findings support the concept of 'visceral homunculus' (i.e. functional anatomical distinction for visceral perception)[27] like a relative body representation in the sensorimotor cortex.[28] In this study, comparisons of the contrasts in brain activation during the intense stimulus between the rectum and descending colon revealed differential neural enhancement in the cingulate cortex. Therefore, our findings support a novel hypothesis that parts of the visceral signals from the different sites in the gut may be conveyed to the different brain regions to discriminate visceral perceptions.

This study also provides novel findings of similar and different patterns of brain deactivation to visceral stimulation of the rectum and descending colon. This is the first report to investigate in detail brain deactivation areas responding to visceral stimulation of the distal colon. Van Oudenhove *et al.*[29] found a pattern of cortical deactivation during unpleasant/painful gastric distention in healthy subjects by a PET study (i.e. the occipital and adjacent lateral parietal and temporal cortices, medial parietal cortex including PCC, medial prefrontal cortex). Occipital deactivation may be explained as attentional processes filtering out other sensory processing.[30] Medial prefrontal deactivation is thought to be an antinociceptive response for cognitive–affective evaluation of the painful sensation or the neural substrate of the coping strategy towards a predictable but unavoidable pain stimulus.[30] On the

other hand, the PCC and adjacent precuneus are thought to be tonically active regions of the brain that continuously gather information about the world around and, possibly, within us.[31] This appears to be the 'default network' brain activity, which may be especially associated with the shift from exteroceptive to interoceptive processing.[29] The results of cerebral deactivation during the stimulus to the rectum and descending colon in this study support the previous findings investigated with different methodologies,[29,30,32] suggesting that relatively constant deactivation patterns despite stimulation of different sites of the gut are more likely.

LIMITATIONS

To avoid frequent exposure to the radioisotope, an intra-personal comparison of rCBF during intraluminal distention in both the rectum and descending colon was not performed. However, the characteristics of both groups were not significantly different and the findings of activated brain regions in each group were almost in concordance with the results from previous studies.[12,13] Thus, sampling bias appears to be unlikely in this study. In addition, healthy female subjects were not investigated. Women are more likely to suffer from IBS than men, and gender differences in activated brain regions during painful rectal distention in IBS patients and healthy subjects have been reported.[33] In this PET study, a lot of clusters detected at the significant level of $P_{\text{uncorrected}}$ did not reach significance after either FDR or FWE correction at voxel level. Moreover, most of them were relatively small and therefore did not reach significance at cluster level either. This may be due to a small sample size in each group and/or methodological differences with the previous studies (e.g. stimulus intensity/duration and PET imaging analyses). Furthermore, it remains unclear whether abnormal brain activations are caused by hypersensitive nerves via mechanoreceptors within the gut, by abnormal processing of afferent inputs at the level of the dorsal horn neurons in the spinal cord, or by abnormal processing in the brain. Further investigations are therefore warranted to understand the pathophysiology of the brain–gut link in patients with functional GI disorders.

CONCLUSIONS

The findings in this study provide us with a new understanding of central discrimination during visceral perception. Despite the fact that pain perception and the urge to defecate were more sensitive in the rectum, central activations to a 20-mmHg distention of the rectum and the descending colon were alike, suggesting that assessment of brain imaging during mild to moderate stimulation of the rectum may correspond to that in other sites of the distal colon. In contrast, central projections of intense visceral stimuli from the rectum and descending colon differ to some extent in affective, cognitive, and nociceptive processing in the brain, which may result in different discriminative sensory perceptions.

ACKNOWLEDGMENTS

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan, and a Grant-in-Aid for Scientific Research from the Ministry of Health, Welfare, and Labor, Japan.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Brain regions deactivated during intraluminal distention in the rectum.

Table S2. Brain regions deactivated during intraluminal distention in the descending colon.

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Appl Psychophysiol Biofeedback
DOI 10.1007/s10484-009-9125-y

Effect of Autogenic Training on General Improvement in Patients with Irritable Bowel Syndrome: A Randomized Controlled Trial

Masae Shinozaki · Motoyori Kanazawa · Michiko Kano · Yuka Endo · Naoki Nakaya · Michio Hongo · Shin Fukudo

Abstract Autogenic training (AT) is a useful and comprehensive relaxation technique. However, no studies have investigated the effects of AT on irritable bowel syndrome (IBS). In this study we tested the hypothesis that AT improves symptoms of IBS. Twenty-one patients with IBS were randomly assigned to AT ($n = 11$, 5 male, 6 female) or control therapy ($n = 10$, 5 male, 5 female). AT patients were trained intensively, while the control therapy consisted of discussions about patients' meal habits and life styles. All patients answered a question related to adequate relief (AR) of IBS symptoms and four questionnaires: Self-induced IBS Questionnaire (SIBSQ), Self-reported Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and Medical Outcome Short Form 36 Health Survey (SF-36). The proportion of AR in the last AT session in the AT group (9/11, 81.8%) was significantly higher than that in the controls (3/10, 30.0%, Chi-square test, $p = 0.048$). Two subscales of the SF-36, i.e., social functioning and bodily pain, were significantly improved in the AT group ($p < 0.05$) as compared to the control group. Role emotional ($p = 0.051$) and general health ($p = 0.068$) showed a tendency for improvement in the AT group. AT may be useful in the treatment of IBS by enhancing self-control.

Keywords Adequate relief (AR) · Autogenic training (AT) · Irritable bowel syndrome (IBS) · Quality of life (QOL) · Randomized controlled trial (RCT)

Abbreviations

SIBSQ	Self-reported Irritable Bowel Syndrome Questionnaire
SDS	Self-reported Depression Scale
STAI	State-trait anxiety inventory
SF-36	Medical Outcome Short Form 36 Health Survey
PF	Physical functioning
RP	Role physical
BP	Bodily pain
GH	General health
VT	Vitality
SF	Social functioning
RE	Role emotional
MH	Mental health

Introduction

Irritable bowel syndrome (IBS) is a very common gastrointestinal disorder characterized by recurrent abdominal

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Published online: 08 December 2009

pain and altered bowel habits without major organic diseases as assessed by routine gastroenterological examination (Drossman 2006). The prevalence of IBS in the general population is high in western countries as well as in Japan (Thompson et al. 2002; Kanazawa et al. 2004). In addition, IBS is recognized as one of the most common diseases in primary care (Thompson et al. 2000). Rome III diagnostic criteria based on subjective gastrointestinal (GI) complaints is the current standard for IBS diagnosis (Drossman 2006; Longstreth et al. 2006a, b).

Although regarded as a digestive disease, IBS is a syndrome that fits well the definition of a biopsychosocial model, in which the relationship between physiological factors, GI symptoms, psychosocial factors, and clinical outcome reciprocally influence their expression (Drossman 2006). These phenomena are conceptualized as a "brain-gut" interaction (Fukudo et al. 1993). From the psychosocial viewpoint, IBS has a negative impact on subjects' daily activity and quality of life as it incurs substantial health-care seeking (Drossman et al. 1993). Patients with IBS frequently show exaggerated gastrointestinal motility under stress (Fukudo et al. 1993), have psychiatric comorbidities, especially depressive disorders, anxiety disorders, and somatoform disorders (Drossman 2006), and reveal psychosocial risk factors including sexual/physical abuse, economical loss, and social withdrawal (Drossman 2006). Although several new pharmacological agents for IBS have been developed (Camilleri et al. 2000; Chey et al. 2004; Chang et al. 2005; Tack et al. 2005; Reilly et al. 2005), there are still patients who do not respond to pharmacotherapy (Levy et al. 2006). For these patients, psychotherapy might be useful. Therefore, the development of a treatment for IBS based on a biopsychosocial model is indispensable.

Hypnotherapy has been shown to improve IBS-induced GI symptoms (Whorwell et al. 1984; Gonsalkorale et al. 2003; Gonsalkorale et al. 2004; Lea et al. 2003), and is now a valid alternative in the treatment of IBS (American Gastroenterological Association 2002; Drossman et al. 2002; Drossman 1999). However, hypnotherapy requires a long treatment period and its success is highly dependent on the skills of the therapist. On the other hand, autogenic training (AT), which is often used to treat different types of psychosomatic disorders (Stetter and Kupper 2002), is easier for physicians and allied health providers to perform and more accessible than hypnotherapy. Besides, after a few sessions, it is possible for patients to carry out AT by themselves. Despite these advantages, there is no evidence that AT is effective in treatment of IBS symptoms. Based on this background information, we hypothesized in this study that AT would improve GI symptoms, negative emotion, and health related quality of life (HR-QOL) in patients with IBS.

Methods

Study Sample Size

The desired sample size in this study was calculated using $\alpha = 0.05$ significance level and $\beta = 0.75$. Based on our clinical experience, we hypothesized that the improvement rate in subjects that received autogenic training would be 85% and that the improvement rate in the control subjects would be 25%. The difference (d) between the AT and control groups can therefore be calculated as $d = 0.85 - 0.25 = 0.6$. With this assumption, the sample size in this study was estimated as 10.

Study Subjects

Out of all IBS outpatients who visited the Department of Psychosomatic Medicine in Tohoku University Hospital from December 2001 to July 2005, 21 patients (10 males and 11 females) were enrolled at random in this study. Eligible patients strictly fulfilled the Rome II criteria (Thompson et al. 1999). Before the beginning of this study, the patients completed a series of tests, including blood count, C-reactive protein blood chemical analysis, thyroid hormones test, thyroid stimulating-hormone test, urinalysis, fecal occult blood test, colonoscopy and/or Ba enema. After diagnosis of IBS, patients were prescribed trimebtrine or polycalbophil calcium. Probiotics for diarrhea, anticholinergics for abdominal pain, or laxatives for constipation were prescribed depending on the dominant symptoms. The drug prescribed to each patient was not changed during this study. After treatment for 8 weeks, patients were asked whether they had adequate relief (AR) or not (Camilleri et al. 2000). Only patients who showed no adequate relief were enrolled in this study. All patients gave informed consent, and this study was approved by the Ethics Committee of Tohoku University School of Medicine (No. 2001-223).

Pharmacotherapy Outcome

Subjects were asked to answer one oral question and complete four validated questionnaires. The oral question was used as a primary endpoint, and the four validated questionnaires were used as secondary endpoints for quantification of IBS (Irvine et al. 2006).

Adequate Relief

AR is clinically useful to assess improvement of abdominal pain and/or discomfort (Camilleri et al. 2000; Chey et al. 2004). In this study, AR addressed improvement in IBS-induced GI symptoms following pharmacotherapy with a

single question ("Did you have adequate relief of IBS-related abdominal pain or discomfort?") scored on a dichotomous scale. The question was asked during the patient's medical visit, and the answer was either "Yes" or "No".

Self-reported Irritable Bowel Syndrome Questionnaire

The self-reported irritable bowel syndrome questionnaire (SIBSQ) (Endo et al. 2000) is a validated disease-specific questionnaire. SIBSQ is based on the Rome II criteria and consists of 14 GI symptoms-related questions and seven additional questions. The 14 questions are related to the following: abdominal pain, discomfort, defecation frequency, improved pain or discomfort, gas or defecation state, existence of sticky stool, feeling of residual stool, bloating, straining, defecation urgency, anticipated anxiety because of bowel symptoms, abdominal dysfunction with perceived stress, and abdominal dysfunction after meal. The 14 GI symptom-related questions are used to evaluate severity of GI symptoms on a seven-point Likert scale (1: nothing at all, 2: almost nothing, 3: slightly present 4: present, 5: moderately present 6: severely present 7: extremely present). The sum of scores for the 14 GI symptoms-related questions gives a total score for SIBSQ.

The seven additional questions are used to obtain more detailed characterization of IBS symptoms (Appendix).

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) is a well-validated 40 item self-reported questionnaire. STAI is used to measure state anxiety (20 items) and trait anxiety (20 items), wherein subjects choose one of four levels of anxiety for each item. State anxiety reflects a "transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity." State anxiety may fluctuate over time and can vary in intensity. In contrast, trait anxiety denotes "relatively stable individual differences in anxiety proneness." The Japanese version of STAI has already been validated (Nakazato and Mizuguchi 1982).

Self-Rating Depression Scale

The Self-Rating Depression Scale (SDS) consists of 20 questions scored on four-point Likert scale (Zung 1965). The Japanese version of SDS is well-validated and commonly used (Fukuda and Kobayashi 1973).

Medical Outcome Study 36-Items Short-Form Health Survey

The Medical Outcome Study 36-Items Short-Form Health Survey (SF-36) is a non-specific questionnaire for health-related quality of life (HR-QOL) (Ware and Sherbourne 1992). The SF-36 consists of eight subscales as follows: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The Japanese version of SF-36 has been validated (Fukuhara et al. 1998; Fukuhara et al. 2001).

Autogenic Training

The Autogenic Training (AT) used in this study was based on the Schultz-style (Schultz 1987). AT was performed individually for eight sessions in eight weeks (Schultz 1987; Kermani 2001). Each session consisted of 30–40 min of full exercise. Although some studies described AT session time between a few minutes (Kermani 2001) and 60 min (Mitani et al. 2006), we gave priority to patient comfortableness (Kermani 2001). The standard session of AT used in this study is shown in Table 1 (Kermani 2001; Mitani et al. 2006). In brief, traditional AT consists of 6 standard exercises after the formula "I am at peace". The first exercise aims at muscular relaxation by repetition of a verbal formula, "My right arm is heavy" emphasizing heaviness. Subsequent passive concentration is focused on feeling warm, initiated by the instruction "My right arm is warm", followed by cardiac activity using the formula "My heartbeat is calm and regular". Then follows passive concentration on the respiratory mechanism with the formula "It breathes me", then on warmth around the abdominal region with "My solar plexus is warm" and finally on coolness in the cranial region with "My forehead is cool and clear" (Kanji and Ernst 2000).

Control Session

The control session was aimed at discussing diet therapy. The session time and frequency were the same as those in

Table 1 AT standard exercise

1. My right (left) arm (leg) is heavy
2. My right (left) arm (leg) is warm
3. My heart beat is calm and regular
4. It breathes me
5. My solar plexus is warm
6. My forehead is cool and clear
7. Cancellation

the AT sessions. All control patients were given the original textbook for the session. The table of contents for the textbook used in this study is shown in Table 2.

Procedure

The study protocol is shown in Fig. 1. About 21 eligible patients were randomly assigned to the AT group ($n = 11$, 5 males, 6 females) or the control group ($n = 10$, 5 males, 5 females). Patients in the AT group completed a standard course of AT sessions eight times. The interval between AT sessions was two to four weeks, depending on the patient's social situation. A specialized psychologist (MS) performed AT in a quiet, sheltered, temperature- and humidity-controlled room. During the interval between sessions, home-exercise was recommended. AT patients were given a set of explanatory leaflets and an audiotape for home exercise. Patients in the control group had discussions about their meal habits with the psychologist and were given booklets about meal habits to prepare for the discussion. The patients were not informed which group he/she would be assigned to. However, they were not completely blinded because they could understand the contents of treatments after the beginning of the intervention (Whitehead 2004).

Table 2 Table of contents for control session textbook

1. What is IBS?
2. Treatment of IBS
3. Nutrients and dietary fibers
4. Diet therapy for IBS
5. Diet therapy for diarrhea-predominant IBS
6. Diet therapy for constipation-predominant IBS
7. Diet therapy for alternating IBS
8. Summary

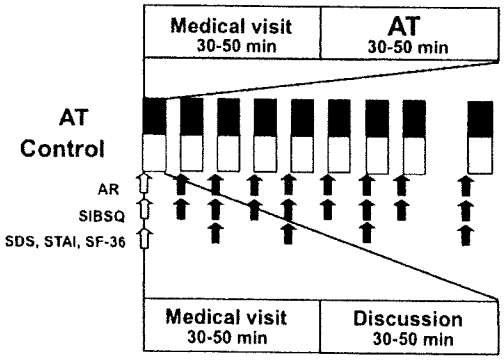

Fig. 1 Study protocol. The *white* and *black arrows* indicate points of measurement of Adequate Relief (AR), Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ), Self-reported Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and The MOS 36-item short-form health survey (SF-36). *Black square*—AT session (including details of the session). *White square*—control session (including details of the session). *White arrow*—point of measurement of baseline. *Black arrow*—point of measurement of a regular session

Statistical Analysis

The proportion of patients with AR was calculated and analyzed by Chi-square test. The difference of proportion of patients with AR, the rate ratio (RR) of AR between the AT and control groups, and the 95% confidence interval (95%CI) of these parameters were also calculated. Scores of before and after pharmacotherapy were compared using both analysis of variance (ANOVA) and Wilcoxon signed-rank test.

Results

Subjects Demographic Data

Demographic data for the patients are shown in Tables 3 and 4. No difference in age, sex, IBS subtype, SIBSQ, SDS, and STAI between the AT group and the control group was observed. In addition, SF-36 subscales were almost identical between the AT group and the control group. Only social functioning in the AT group was significantly lower than that in the control group ($p < 0.05$).

Adequate Relief

The proportion of patients with AR in the AT group (9/11, 81.8%) was significantly higher than that in the control group (3/10, 30.0%) in the last AT session as indicated by

Table 3 Subjects demographic data

Variable	AT ($N = 11$)	Control ($N = 10$)	p-Value
Demographic data			
Age	32.8 ± 2.8	30.3 ± 15.4	0.7
Sex			0.83
Male	5	5	
Female	6	5	
IBS subtype			0.58
Alternating	5	5	
Constipation	3	1	
Diarrhea	3	4	

Data are given as mean ± SD

Sex: degree of freedom = 1, p-value was calculated by a 2 × 2 Chi square

IBS subtype: degree of freedom = 2, p-value was calculated by a 2 × 3 Chi square

Table 4 IBS symptoms, negative emotion, and HR-QOL before and after treatment

	AT			Control		
	Baseline	End of treatment	*p*-Value	Baseline	End of treatment	*p*-Value
SIBSQ(Q1-14)	52.1 ± 11.6	48.9 ± 6.1	0.473	55.9 ± 13.9	36.3 ± 23.4	0.008*
SDS	46.4 ± 5.9	44.6 ± 7.4	0.315	45.9 ± 5.9	45.8 ± 9.4	0.553
STAI						
State anxiety	50.0 ± 9.1	47.2 ± 7.9	0.755	54.6 ± 11.0	51.4 ± 10.5	0.173
Trait anxiety	56.0 ± 8.1	54.5 ± 9.4	0.102	56.8 ± 11.4	52.8 ± 14.5	0.097
SF-36						
PF	47.7 ± 14.3	51.2 ± 8.3	0.600	48.9 ± 7.8	46.4 ± 13.7	0.655
RP	26.9 ± 18.9	35.6 ± 20.4	0.310	23.7 ± 19.2	33.8 ± 24.6	0.293
BP	36.8 ± 7.8	45.6 ± 11.7	0.012*	38.5 ± 9.6	41.3 ± 10.7	0.735
GH	30.9 ± 10.6	34.7 ± 9.4	0.069§	32.8 ± 10.4	33.8 ± 17.4	0.484
VT	35.4 ± 8.3	37.1 ± 6.6	0.463	36.6 ± 6.3	34.5 ± 10.7	0.097
SF	27.0 ± 12.0	41.1 ± 19.6	0.021*	43.4 ± 9.0	42.6 ± 15.7	0.866
RE	34.2 ± 14.5	46.4 ± 15.5	0.051§	33.9 ± 16.0	41.2 ± 18.2	0.575
MH	36.6 ± 9.0	42.0 ± 4.9	0.239	35.9 ± 8.5	35.6 ± 13.5	0.889

PF physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health

Data are given as mean ± SD

* $p < 0.05$, § $p < 0.1$

Chi-square test ($\chi^2 = 5.74$, $p < 0.05$, Fig. 2). The difference of proportion of patients with AR in the last AT session was 51.8% and the 95%CI ranged from 17.0 to 86.6%. The rate ratio of AR between the AT group and the control group in the last AT session was 2.73 (95%CI, 1.02–7.32).

Also, the proportion of patients with AR in the AT group was significantly higher than that in the control group in the fourth ($p < 0.05$), seventh ($p < 0.001$), and eighth ($p < 0.05$) AT session.

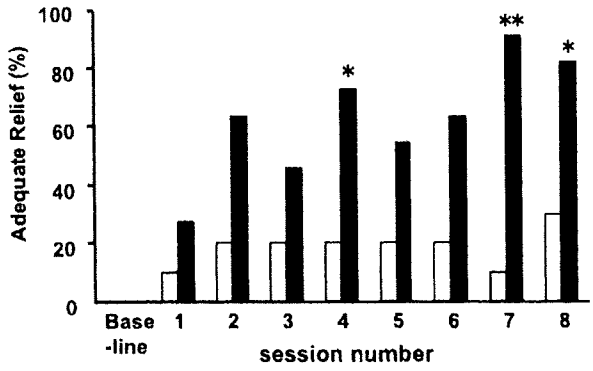

Fig. 2 AT-induced changes in adequate relief (%).*White bar*—control group ($n = 10$), *Black bar*—AT group ($n = 11$). * $p < 0.05$, ** $p < 0.001$: vs. control. Baseline means before the first session. The *white* and *black bars* indicate the proportion of adequate relief (AR) "yes". Session number is for both AT and control sessions

SIBSQ, SDS, and STAI

SIBSQ subscores, SDS, and STAI did not differ between the AT group and the control group (Table 4). ANOVA of SIBSQ total scores showed no significant difference between the AT group and the control group.

HR-QOL

No significant group effect, period effect, or group x period interaction in SF-36 subscores was detected by two-way ANOVA. However, some post-treatment SF-36 scores in the AT group significantly improved as indicated by Wilcoxon signed-rank test. Role emotional score ($p = 0.051$) and general health score ($p = 0.069$) tended to be improved only in the AT group (Table 4). Bodily pain score in the AT group significantly increased after treatment (45.6 ± 11.7) as compared with baseline (36.8 ± 7.8, $p = 0.012$, Table 4). In the control group, on the other hand, bodily pain score did not change throughout the study. Social functioning score in the AT group was significantly improved by treatment (baseline: 27.0 ± 12.0, after treatment: 41.1 ± 19.6, $p = 0.021$, Table 4). However, no change in social functioning score was detected in the control group. There were no significant changes in the other subscales of the SF-36 in both groups.

There was no difference in visiting interval between the AT group and the control group. Besides, no relationship

was noted between the length of visit interval and clinical effect.

Discussion

This is the first study to demonstrate that AT is effective in the general improvement of IBS. As shown in our results, the proportion of AR in the last AT session in the AT group was significantly higher than that in the controls. In addition, two subscales of the SF-36, i.e. social functioning and bodily pain, were significantly improved in the AT group as compared to the control group. Role emotional and general health showed a tendency for improvement in the AT group, although without statistical significance. SIBSQ, SDS, and STAI, on the other hand, did not differ between the AT group and the control group. AT has long been used as a relaxation technique (Günter and von Eye 2006), and has been reported to reduce anxiety (Kanji et al. 2006a; Jorm et al. 2004), chronic pain (Jensen and Patterson 2006), and headache (ter Kuile et al. 1994). AT has also been shown to improve some aspects of HR-QOL in patients with multiple sclerosis (Sutherland et al. 2005). However, systematic studies on headache, chronic pain, and anxiety indicate that the effects of AT on these conditions are limited (Jorm et al. 2004; Jensen and Patterson 2006; Sutherland et al. 2005). On the other hand, psychophysiological studies revealed that AT has a distinct effect on autonomic function (Kanji et al. 2006a, b; Sakakibara et al. 1994; Mishima et al. 1999). AT has been shown to increase cardiac parasympathetic tone (Sakakibara et al. 1994) and prolong the ECG R–R interval electrocardiogram (Kanji et al. 2006a, b; Mishima et al. 1999).

Emotional memory has two major forms: a conscious (explicit) memory for facts and personal events and an unconscious (implicit) memory for motor and sensory experience (Iversen et al. 2000). Autonomic function reflects typical implicit processing of emotion. Thus, grading GI symptoms, grading anxious symptoms, and grading depressive symptoms may mainly be executed by explicit brain processing, while judging AR may be based on implicit brain processing. Based on this reasoning, it is suggested that the effect of AT on general improvement of IBS is due to changes in implicit processing of emotion.

AT is one of the methods of self-induced hypnotherapy (Schultz 1987). Hypnotherapy has been used for treating refractory IBS (Whorwell et al. 1984; Whorwell 1989; Prior et al. 1990). Although the mechanism by which hypnotherapy affects IBS has not been clarified, there are several reports indicating that abdominal rectal sensitivity in IBS patients can be normalized by hypnotherapy (Lea et al. 2003; Prior et al. 1990). In addition, hypnotic suggestions are capable of changing activity of the anterior cingulate cortex as detected by positron emission tomography (Rainville et al. 1997). Therefore, the hypnotic element of AT, at least, may have changed rectal sensitivity and/or limbic brain activity in IBS patients in our study. The advantage of AT over usual hypnotherapy is that AT is easier to perform for therapists than hypnotherapy and that patients can acquire AT techniques and use them in their daily lives. Although we did not measure patients' self-efficacy in performing AT, AT might improve self-control resulting in more AR, less bodily pain, and improved social functioning. There are several protocols of hypnotherapy for IBS (Palsson 2006; Palsson et al. 2006) and gut directed hypnotherapy is one of them (Lea et al. 2003; Gonsalkorale 2006; Roberts et al. 2006; Smith 2006). In this study the AT used did not follow the gut-directed approach. However, it is of interest to search for what is the best method of inducing remission of IBS among the therapies in the hypnosis category.

In this study, socres for SIBSQ, anxiety, and depression did not change with AR. However, this is not surprising because in clinical trials of IBS, AR is not always proportional to the summation of individual GI symptoms (Irvine et al. 2006). In contrast, bodily pain score and social functioning of SF-36 were improved in the AT group. Patients with IBS in this study might regard QOL as a more important factor for AR than GI symptoms per se. This is because IBS is usually a chronic process and patients tend to have maladjusted coping style with catastrophizing (Drossman et al. 2002). In other words, most IBS patients have no adequate strategy to control their emotion and behavior before treatment. AT is one of the options that offer IBS patients a technique to control their emotion and behavior. In this study, self-efficacy may have been at the origin of improved social functioning. This notion can be examined in studies with larger sample sizes.

There are several limitations to this study. First, the degree of self-performed AT (AT home exercise) might have affected the results, although this possibility was not examined in this study. Second, longterm effects were not assessed. Although several anecdotal reports revealed effects of AT lasted for years, the long-term effects of AT clearly need to be quantified.

We believe we have shown in this study that AT may be a promising psychological treatment for IBS. Further studies with larger sample sizes and evaluation of the long-term effects of AT are warranted.

Acknowledgments This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Ministry of Health, Welfare, and Labor, Japan.

Appendix

Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ)

(Date / /)

Name (male • female) age years old
(Date of birth / /)

Please read the following questions and choose one answer from the seven choices. Mark your answer with an open circle ○.

(1) Please answer all of the following 14 questions. In the last one week, you generally had・・・.

	nothing at all	almost nothing	slightly present	present	moderately present	severely present	extremely present
① abdominal pain.	1	2	3	4	5	6	7
② abdominal discomfort.	1	2	3	4	5	6	7
③ a change in your usual number of bowel movement (either more or fewer), when the pain or discomfort started.	1	2	3	4	5	6	7
④ softer stools than usual, when the pain or discomfort started.	1	2	3	4	5	6	7
⑤ harder stools than usual, when the pain or discomfort started.	1	2	3	4	5	6	7
⑥ improvement of abdominal pain or abdominal discomfort after a bowel movement.	1	2	3	4	5	6	7
⑦ pasting mucus during a bowel movement.	1	2	3	4	5	6	7
⑧ feeling of incomplete emptying after a bowel movement.	1	2	3	4	5	6	7
⑨ feeling of abdominal distention.	1	2	3	4	5	6	7
⑩ straining anring bowel movement and/or difficulty to defecate.	1	2	3	4	5	6	7
⑪ urgency of defecation	1	2	3	4	5	6	7
⑫ anxiety about occurrence of bowel symptoms even when you have no bowel symptoms.	1	2	3	4	5	6	7
⑬ occurrence of bowel symptoms when you feel stress	1	2	3	4	5	6	7
⑭ occurrence of bowel symptoms after you take meals.	1	2	3	4	5	6	7

(2) In the last one week, what kind of stool form did you have generally?

1 separate lumpy stool
2 hard stool with aggregated lumpy stool
3 banana-like stool with cracks
4 smooth and soft stool
5 loose stool with blobs
6 mushy stool
7 watery stool

(3) In the last one week, what kind of bowel movement did you have generally?	1 no spontaneous bowel movement and used laxatives 2 no bowel movement 3 once or twice/week 4 3-4 times/week 5 5-6 times/week 6 2-3 times/day 7 over 4 times/day
(4) In the last one week, how often did you have abdominal pain or abdominal discomfort?	1 nothing 2 once/week 3 twice/week 4 3-4 times/week 5 5-6 times/week 6 once/day 7 twice/day
(5) In the last one week, how often did you visit an emergency room of the hospital because of bowel symptoms?	1 not at all 2 visited once/week 3 visited twice/week 4 visited 3-4 times/week 5 visited 5-6 times/week 6 visited once/day 7 visited over twice/day
(6) In the last one week, how often did you visit your usual outpatient clinic (except emergency room) because of bowel symptoms?	1 not at all 2 visited once/week 3 visited twice/week 4 visited 3-4 times/week 5 visited 5-6 times/week 6 visited once/day 7 visited over twice/day
(7) In the last week, how often did you feel stress?	1 not at all 2 felt once/week 3 felt twice/week 4 felt 3-4 times/week 5 felt 5-6 times/week 6 felt once/day 7 felt over twice/day
(8) In the last one week, how was your life disturbed because of bowel symptoms? (e.g. absent from job, unable to get in or on a vehicle, etc...)	1 not at all 2 no disturbance despite slight symptoms 3 no disturbance despite symptoms once 4 no disturbance with slight bearing symptoms 5 no disturbance with bearing symptoms 6 sometimes disturbed 7 disturbed

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HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2009; **24**: 540–548.
Published online 20 August 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.1051

Dose dependency of brain histamine H1 receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [^{11}C]doxepin

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Aims The strength of sedation due to antihistamines can be evaluated using positron emission tomography (PET). The purpose of the present study is to measure histamine H_1 receptor (H_1R) occupancy following oral administration of cetirizine (10 and 20 mg) in order to examine dose dependency.
Methods Fifteen healthy male volunteers (age range, 20–35 years) were divided into 3 subgroups and were studied following single oral administration of cetirizine at 10 mg ($n = 5$) and 20 mg ($n = 5$) or hydroxyzine at 30 mg ($n = 5$) using PET with ^{11}C-doxepin. Each subject was scanned also following the administration of placebo. Binding potential and H_1RO values were calculated in the prefrontal and anterior cingulate cortices. Subjective sleepiness was also measured, and the correlation to H_1RO was examined for each antihistamine.
Results The averaged H_1ROs of cetirizine 10 mg, 20 mg, and hydroxyzine 30 mg in the prefrontal and cingulate cortices was 12.6%, 25.2%, and 67.6%, respectively. The H_1RO of hydroxyzine 30 mg correlated well with subjective sleepiness ($p < 0.001$); however, those of cetirizine 10 and 20 mg showed no correlation with subjective sleepiness.
Conclusion It was demonstrated that the brain penetration of orally administered cetirizine was dose-dependent. Cetirizine 10 mg, with its low H_1RO and thus minimal sedation, could be more safely used than cetirizine 20 mg for the treatment of various allergic disorders.

KEY WORDS — cetirizine; hydroxyzine; histamine H_1 receptor (H_1R); histamine H_1 receptor occupancy (H_1RO); positron emission tomography (PET); binding potential; sedation

INTRODUCTION

Histamine H_1 receptor (H_1R) antagonists commonly known as antihistamines are often used for the treatment of allergic disorders such as seasonal rhinitis. Antihistamines act mainly on the peripheral tissues but can also induce sedation as a central side effect. This undesirable side effect is caused by blockade of nerve transmission in the histaminergic neuronal system. This system projects from the tuberomammillary nucleus in the posterior hypothalamus to almost all cortical areas (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). First-generation (sedative) antihistamines that can easily penetrate the blood-brain barrier (BBB), such as d-chlorpheniramine and hydroxyzine, tend to occupy a large proportion of post-synaptic H_1Rs (more than 50%) (Yanai et al., 1995a; Yanai et al., 1995b; Yanai et al., 1999; Okamura et al., 2000; Tagawa et al., 2001; Van Hoecke et al., 2007). Mildly-sedative antihistamines, such as cetirizine and terfenadine, slightly penetrate the BBB and mildly occupy H_1Rs in the brain (usually not more than 20% or so). Moreover, they tend to induce slight sedation at low or recommended doses, but cause dose-related cognitive impairment at higher doses. Non-sedative antihistamines (e.g., fexofenadine), which have recently been introduced as an additional subcategory, can hardly penetrate the BBB and sparingly occupy H_1Rs. Since they do not penetrate the BBB easily, they induce no sedation even at exceeded doses (Hindmarch et al., 2002; Casale et al., 2003; Holgate et al., 2003; Van Hoecke et al., 2007). We previously demonstrated the difference in BBB

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Received 14 May 2008
Accepted 17 June 2009

permeability between mildly-sedative and non-sedative antihistamines using positron emission tomography (PET) and [^{11}C]doxepin following oral administration of double doses of cetirizine (20 mg) and fexofenadine (120 mg) (Tashiro et al., 2004). Thus, variation in cerebral H_1R occupancy (H_1RO) of antihistamines can be evaluated in terms of "BBB permeability" using PET and [^{11}C]doxepin.

It is of great social importance to note that users of mildly-sedative antihistamines tend to be less cautious and might take these drugs at double or triple doses when the desired effects are not achieved by the recommended doses even while driving a car or operating potentially dangerous machinery (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). It is therefore important to examine the dose dependency of mildly-sedative antihistamines since no study has been available to date regarding the comparison of H_1ROs following treatment with these antihistamines at different doses. The primary aim of the present study is to compare the H_1ROs of cetirizine at 10 and 20 mg using PET, as well as to examine such cetirizine H_1ROs against that of hydroxyzine at 30 mg, a typical sedative antihistamine.

METHODS

The present study was approved by the Committee on Clinical Investigation of the Tohoku University Graduate School of Medicine and by the Institutional Review Committee of the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan, and was performed in accordance with the policy of the declaration of Helsinki.

Subjects and study design

Fifteen male Japanese volunteers (age range, 20–35 years), recruited through an advertisement as study subjects, were provided with a clear description of the study, and their written informed consents were obtained. All the subjects were in good health with no clinical history of major physical or mental illnesses, and were also not receiving any concomitant medication likely to interfere with the study results. There were no abusers of alcohol, caffeine, or nicotine. Alcohol, nicotine, caffeine, grapefruit, and grapefruit juice were forbidden during the study period, and food intake was controlled on the test day and the day before PET measurement. The volunteers were requested to finish a light meal at least 3 h before the start of the study.

Out of the 15 subjects, each of five subjects was administered cetirizine at 10 mg (CET10 group: mean age +/- S.D. = 21.6 +/− 1.5 y.o.; mean body weight [BW] = 60.8 +/− 7.1 kg), cetirizine at 20 mg (CET20 group: mean age +/- S.D. = 23.2 +/− 1.1 y.o.; mean BW = 60.8 +/− 5.4 kg), and hydroxyzine at 30 mg (HYD group: mean age +/- S.D. = 23.2 +/− 0.8 y.o.; mean BW = 63.6 +/− 8.6 kg). Each subject underwent PET measurements after single oral administration of one of the above antihistamines or placebo (i.e., lactobacteria preparation, 6 mg), with minimum washout intervals of 7 days between treatments. Active and placebo conditions were cross-randomized in the present study. Lactobacteria preparation has been widely used as placebo in Japan, and has shown no statistical difference between pre- and post-administration in our previous cognitive studies (Okamura et al., 2000; Tagawa et al., 2002; Tashiro et al., 2004).

Measurement of subjective sleepiness

In each subject, subjective sleepiness was measured using the line analogue rating scale (LARS) (Parkin et al., 1998; Shamsi et al., 2001) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration of each antihistamine or placebo. For each antihistamine condition, the measured subjective sleepiness was compared with that following placebo administration (Figure 1).

PET tracer and image acquisition

[^{11}C]doxepin was prepared by [^{11}C]methylation of desmethyl doxepin with [^{11}C]methyl triflate, as described previously (Iwata et al., 2001). The radiochemical purity of [^{11}C]doxepin was more than 99%, and its specific radioactivity at the time of injection was 64.9 +/− 45.3 GBq/μmol (1.75 +/− 1.23 Ci/μmol). [^{11}C]doxepin-containing saline solution was intravenously injected to each subject at 90 min after oral administration of the antihistamines, which was nearly similar to the known T_{max} of each antihistamine used: 2.1 +/−0.4 h for hydroxyzine in healthy Caucasoids, and 1.4 +/− 0.5 for CET 10 mg and 1.5 +/− 0.4 for 20 mg in Japanese volunteers (Simons et al., 1984; Lefebvre et al., 1988; Sasa et al., 1995; Tashiro et al., 2004). The injected dose and cold mass of [^{11}C]doxepin were 143.2 +/− 40.8 MBq (3.87 +/− 1.10 mCi), and 3.65 +/− 2.80 nmol, respectively.

Shortly before [^{11}C]doxepin injection, the subjects were positioned on the coach of the PET scanner so that

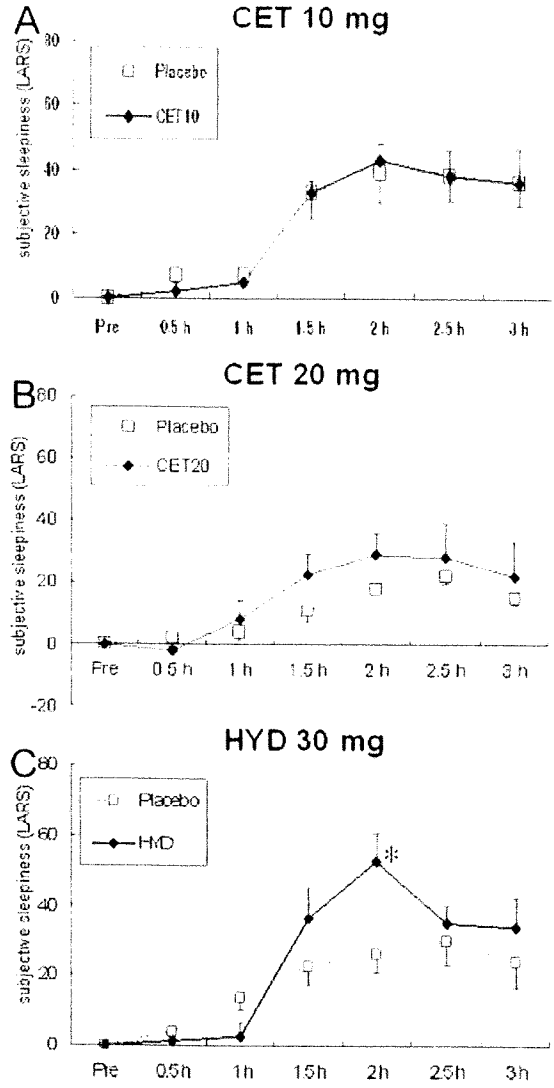

Figure 1. Results of measurements of subjective sleepiness following oral administration of cetirizine (10 and 20 mg), and hydroxyzine (30 mg). Each graph indicates the time-course of subjective sleepiness measured using the line analogue rating scale (LARS) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration. Following cetirizine (10 mg) administration, there was no significant difference compared with following placebo administration (A). Following cetirizine (20 mg) administration, there was a trend for increased sleepiness, but a significant difference was not shown relative to the placebo condition (B). Following hydroxyzine (30 mg) administration, there was a significant increase in sleepiness compared with the placebo condition (C). Abbreviations: Pre = pre-administration, CET10 = cetirizine 10 mg, CET20 = cetirizine 20 mg, HYD = hydroxyzine

the transaxial slices were parallel to the orbitomeatal line. Subjects taking cetirizine at 10 and 20 mg were scanned using SET-2400W (Shimadzu Co., Kyoto, Japan), and those taking hydroxyzine at 30 mg were scanned using ECAT PT931 (CTI, Inc., Knoxville, TN, USA). Further details regarding these scanners were described in our previous reports (Fujiwara et al., 1997; Tashiro et al., 2004). Following transmission scan using the $^{68}Ge/^{68}Ga$ line source for tissue attenuation correction, the subjects were then scanned to detect emission of high-energy photons (511 keV) (emission scan). After tissue attenuation correction and reconstruction with a filtered back-projection algorithm, the brain images were processed by applying graphical analysis to obtain binding potential (BP) images (Logan et al., 1990; Logan et al., 1996) using the time–activity curve in the cerebellum based on region of interest (ROI) analysis. This method was previously validated and described in detail (Suzuki et al., 2005). Finally, H_1RO was calculated based on the BP values of the frontal cortex and cingulate gyrus, where the H_1R density was the highest and the most suitable for H_1RO calculation. The H_1ROs of antihistamines were calculated based on the following equation: $H_1RO = [(BP \text{ with placebo} - BP \text{ with given antihistamine}) / BP \text{ with placebo}] \times 100$.

Statistical analysis. Differences in H_1ROs between cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were examined using one-way ANOVA with Bonferroni correction for multiple comparisons. The relationship between plasma drug concentration and H_1RO was examined using Pearson's correlation test. A probability of $p < 0.05$ was considered statistically significant. All statistical examinations were performed using SPSS for Windows 15.0 (Japanese version). For correlation analysis between H_1RO and subjective sleepiness, we have calculated the "LARS_AUC ratio" by taking the ratio of AUC curves of subjective sleepiness (LARS) following an antihistamine treatment to that following placebo treatment, in order to normalize inter-individual differences of subjective sleepiness. And correlation was examined between H_1RO and subjective sleepiness.

RESULTS

Subjective sleepiness

Results of subjective sleepiness measurements using LARS are shown in Figure 1. Subjective sleepiness following cetirizine 10 mg administration was not significantly different compared with that following placebo administration (Figure 1A). Following cetirizine 20 mg administration, a trend for increased sleepiness was observed, but this increase showed no

Table 1. Binding potential and histamine H_1 receptor occupancy following administration of antihistamines and placebo

Drug and Region	BP (S.E.M.)	BP_{Pla} (S.E.M.)	H_1RO [%](S.E.M.)
Hydroxyzine (30 mg)	BP_{HYD}	BP_{Pla}	H_1RO_{HYD}
frontal	0.15 (0.06)	0.53 (0.07)	64.4 (9.1)
cingulate	0.24 (0.03)	0.67 (0.02)	70.7 (5.8)
Cetirizine (20 mg)	BP_{CET20}	BP_{Pla}	H_1RO_{CET20}
frontal	0.44 (0.09)	0.62 (0.11)	25.5 (9.5)
cingulate	0.50 (0.04)	0.66 (0.05)	24.8 (6.5)
Cetirizine (10 mg)	BP_{CET10}	BP_{Pla}	H_1RO_{CET10}
frontal	0.54 (0.04)	0.62 (0.05)	11.6 (3.3)
cingulate	0.68 (0.03)	0.78 (0.02)	13.6 (3.4)

significant difference compared with the placebo condition (Figure 1B). After hydroxyzine 30 mg administration, a significant increase in sleepiness was observed compared with the placebo condition (Figure 1C).

ROI-based comparison of BP and H_1RO

BP values in H_1R-rich regions such as the frontal and cingulate cortices were evaluated based on ROI analysis (Table 1 and Figure 2). BP values following treatment with cetirizine 10 mg were only slightly lower than that following placebo treatment in the same subjects. However, BP values following treatment with hydroxyzine 30 mg were considerably low compared with those following placebo treatments. BP values after treatment with cetirizine 20 mg were between those following treatments with cetirizine 10 mg and hydroxyzine 30 mg (Table 1).

H_1ROs following treatment with cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were also calculated using the BP following antihistamine treatment in each subject and utilizing the BP data following placebo treatment in each subject as baseline (0%) (Table 1, Figure 2). The mean H_1ROs of the frontal and cingulate cortices following treatment with cetirizine 10 mg were 11.6 and 13.6%, respectively (average, 12.6%). Those following treatment with cetirizine 20 mg were 25.5 and 24.8%, respectively (average, 25.2%). Those following treatment with hydroxyzine 30 mg were 64.4 and 70.7%, respectively (average, 67.6%). These results show that H_1RO following treatment with hydroxyzine is substantially higher than that following treatment with cetirizine (Table 1, Figure 2). The differences in both the cetirizine groups to the hydroxyzine group were statistically significant (Figure 2).

As for the correlation between H_1RO and subjective sleepiness, the significant positive correlation was observed with hydroxyzine in the frontal cortex ($r=0.91$, $p=0.034$) but not in the cingulate cortex ($r=0.76$, $p=0.14$), respectively (Figure 3). A trend for positive correlation was observed with cetirizine 20 mg, although the correlation was not significant in neither the cingulate ($r=0.68$, $p=0.21$) nor frontal ($r=-0.74$, $p=0.15$) (Figure 3). As for cetirizine 10 mg, H_1RO and subjective sleepiness were inconsistent, demonstrating trends for positive correlation in the cingulate cortex ($r=0.47$, $p=0.43$) and negative

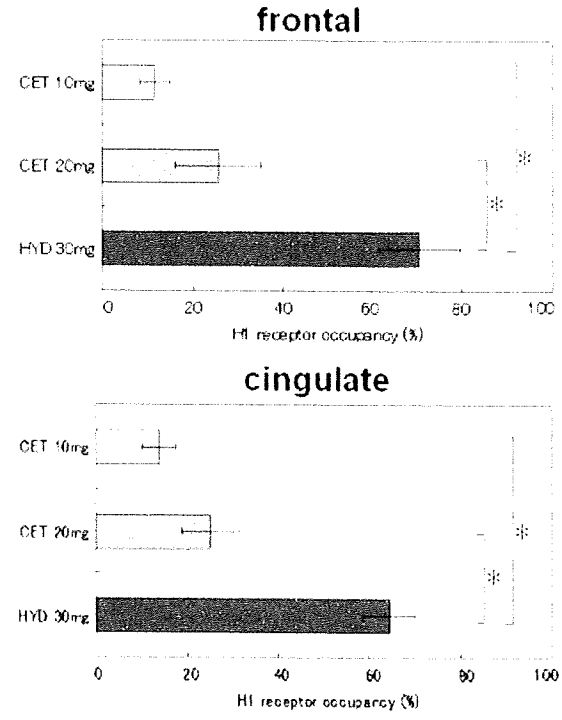

Figure 2. Histamine H_1 receptor occupancy (H_1RO) in the cingulate and frontal cortices. ROI measurements were performed in the anterior cingulate and frontal cortices following oral administration of cetirizine (10 and 20 mg) and hydroxyzine (30 mg). H_1RO due to these antihistamines are shown, taking H_1RO by those under the placebo condition as 0%. H_1RO of hydroxyzine following administration was significantly higher than those of the other antihistamines. * $p<0.001$, ANOVA followed by the Bonferroni test for multiple comparison. Error bars represent inter-individual variability (S.E.M.). Abbreviations: CET10mg = cetirizine 10 mg, CET20 mg = cetirizine 20 mg, HYD30 mg = hydroxyzine 30 mg

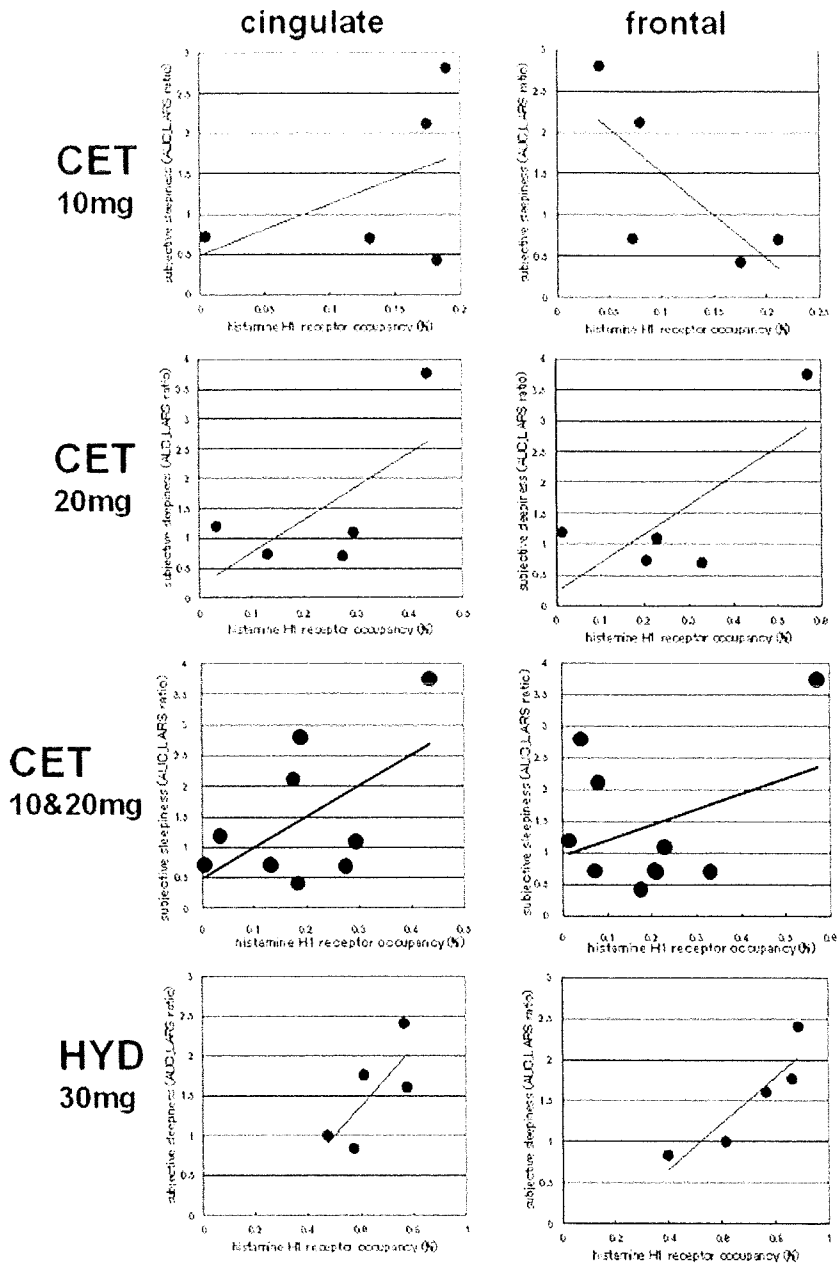

Figure 3. Correlation between histamine H1 receptor occupancy (H_1RO) and subjective sleepiness in the cingulate and frontal cortices. Subjective sleepiness is indicated as the ratio of area under the curves for the 3 h-long follow-up data of line analogue rating scale (LARS) following oral administration of each antihistamine and placebo. Abbreviations: CET10mg = cetirizine 10 mg, CET20mg = cetirizine 20 mg, CET10&20 mg = cetirizine 10 and 20 mg, HYD 30mg = hydroxyzine 30 mg

correlation in the frontal cortex ($r = -0.73$, $p = 0.16$), though both were insignificant (Figure 3). When cetirizine 10 and 20 mg data were plotted together, a trend for positive correlation was observed in the cingulate ($r = 0.58$, $p = 0.08$) but not in the frontal regions ($r = 0.36$, $p = 0.30$) (Figure 3).

DISCUSSION

In the present study, the H_1RO of cetirizine, a mildly-sedative antihistamine, was compared between two doses of 10 and 20 mg in a single-blinded placebo-controlled study design. Moreover, the H_1RO of

hydroxyzine 30 mg, a typical sedative antihistamine, was also calculated. In previous research, we calculated the H_1RO of oral cetirizine 20 mg; however, the investigation was not a placebo-controlled study. This means that the control data used for calculating H_1ROs were obtained from different subjects with the aim of reducing radiation exposure to subjects (Tashiro et al., 2004). In addition, the H_1RO of hydroxyzine was not measured in that previous study. Thus, an additional aim of the present study was to measure the H_1RO of hydroxyzine at 30 mg. The placebo-controlled study design required at least two scans for each subject and for each drug, and the use of the three-dimensional (3D) data acquisition mode enabled the reduction of radiation exposure (mean +/- S.D.: 1.98 +/− 0.57 mSv), that is, considerably smaller than that in our previous study using the 2D data acquisition mode (average, 4.31 mSv) (Tashiro et al., 2004). Therefore, the 3D data acquisition mode is suitable for conducting placebo-controlled PET clinical trials.

In the present study, we found that the baseline BP under the placebo condition showed a certain inter-individual variation (the mean values under the placebo condition for the subgroups of cetirizine 10 and 20 mg and hydroxyzine 30 mg were 0.62 +/− 0.05, 0.62 +/− 0.11, and 0.53 +/− 0.07, respectively)(Table 1). This result suggests the use of a placebo-controlled study design could minimize the effect of inter-individual variation, although the H_1RO of cetirizine 20 mg in this placebo-controlled study (mean value of frontal and cingulate cortices, 25.2%) was slightly different from that obtained in our previous study (mean value of frontal and cingulate cortices. 28.9%) (Tashiro et al., 2004).

It has been known that sedative antihistamines, such as hydroxyzine, ketotifen, diphenhydramine, and d-chlorpheniramine, occupy more than 50% of available H_1Rs, resulting in high prevalence of sleepiness and cognitive decline (Yanai et al., 1995a; Okamura et al., 2000; Tagawa et al., 2001; Tashiro et al., 2006; Van Hoecke et al., 2007; Tashiro et al., 2008). Hydroxyzine is a typical sedative antihistamine that induces psychomotor impairment even at recommended doses (20–30 mg), and it has been used as a positive control in many studies (Gengo et al., 1987; Gengo and Gabos, 1987; Walsh et al., 1992; Lee and Maibach, 2001; Van Hoecke et al., 2007). Cetirizine, also used in this study, is the main metabolite of hydroxyzine, and the conversion from hydroxyzine to cetirizine is mediated by alcohol dehydrogenase (Whomsley et al., 2005). In the present study, subjective sleepiness in the hydroxyzine group was significantly increased compared with the placebo condition, while the cetirizine subgroups did not show significant difference from the placebo conditions (Figure 1). In addition, H_1ROs following hydroxyzine treatment showed a significant difference relative to those following cetirizine treatment (Figure 2).

Mildly-sedative antihistamines, including cetirizine and loratadine, are regarded as less impairing and sedating than sedative antihistamines. For example, cetirizine at the recommended doses of 5–10 mg has been evaluated as being either non-sedating (Gengo et al., 1987; Gengo et al., 1990; Walsh et al., 1992; Patat et al., 1995; Hindmarch et al., 2001; Shamsi et al., 2001; Curran et al., 2004; Van Hoecke et al., 2007; Takahashi et al., 2008) or mildly sedating (Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002). These results from the use of cetirizine are variable; at higher than the recommended doses (20 mg), the agent has been reported to produce significant drowsiness (Gengo and Gabos, 1987) and impairment in a selected task (Gengo et al., 1990) in some studies or no cognitive impairment (Gengo et al., 1987; Gengo and Gabos, 1987) in other investigations. In a recent meta-analysis (Hindmarch and Shamsi, 1999; Shamsi and Hindmarch, 2000), the proportional impairment ratios (PIRs) based on objective measurements were 0.18 and 2.25 for cetirizine and hydroxyzine, respectively. The PIRs based on subjective measures were 0.33 and 2.57 for cetirizine and hydroxyzine, respectively (Hindmarch and Shamsi, 1999), where a smaller PIR corresponds to a weaker sedative effect.

Therefore, it has been thought that second generation antihistamines are less impairing for use in day-to-day activities (Mattila and Paakkari, 1999; Tashiro et al., 2004; Theunissen et al., 2004). However, the strength of sedation seems to vary among users and further investigations have demonstrated that not all second generation antihistamines manifest similar "non-sedative" profiles. Recently, second generation antihistamines have been further classified into the following two subgroups (Casale et al., 2003; Holgate et al., 2003): those inducing slight sedation at low doses, but causing dose-related cognitive impairment at higher doses ("mildly-sedative" antihistamines, e.g., cetirizine), and those inducing no sedation even at exceeded doses ("non-sedative" antihistamines, e.g., fexofenadine) (Tashiro et al., 2004). Based on this classification, we previously compared the BBB permeability of cetirizine 20 mg and fexofenadine 120 mg (both doses were double the standard oral doses