Pain 132 (2007) 252–263

PAIN

www.elsevier.com/locate/pain

Research papers

Correlation between alexithymia and hypersensitivity to visceral stimulation in human

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Received 11 March 2006; received in revised form 23 January 2007; accepted 23 January 2007

Abstract

Empirical studies indicate that alexithymia exacerbates physical illness. However, direct evidence to explain the mechanism of this exacerbation has not been provided. One hypothesis is that alexithymics amplify unpleasant internal signals. In the present study, we investigated how alexithymia influences sensitivity to visceral stimulation in human. In 45 non-clinical healthy subjects (34 males and 11 females), brain processing of visceral sensation induced by colonic distension was examined using $H_2{}^{15}O$ positron emission tomography (PET). Subjective feeling evaluated on an ordinate scale and neuroendocrine response to stimuli were also measured. The degree of alexithymia was determined using the 20-item of Toronto alexithymia scale (TAS-20), and the correlation between reaction to stimuli and the scores of TAS-20 and its three subscales [difficulty to identify feelings (DIF), difficulty to describe feelings (DDF) and external oriented thinking (EOT)] was evaluated. Greater activation was observed during colonic distension in the pregenual anterior cingulate cortex, right insula and midbrain in the 10 (out of 45) subjects that were identified as alexithymic by TAS-20 scores larger than 61. TAS-20 scores positively correlated with both activity in the right insula and orbital gyrus and adrenaline levels in the blood in response to stimulation. Subjects with high scores of DIF perceived strong pain, urgency for defecation, stress, anxiety, and slight sleepiness. The present study demonstrates that alexithymia is associated with hypersensitivity to visceral stimulation. This finding supports the somatosensory amplification hypothesized in alexithymics and is important to elucidate the influence of alexithymia on brain-gut function, particularly to understand the pathophysiology of FGIDs (functional gastrointestinal disorders).

Keywords: Visceral pain; Alexithymia; Hypersensitivity; PET; Emotional perception

1. Introduction

Alexithymia is a personality construct derived from clinical observations of patients with psychosomatic illness (Sifneos, 1973), and is characterized by the following: reduced ability to identify and describe one's feelings, difficulty in distinguishing feelings from the bodily sensations of emotional arousal, impaired symbolization, and a tendency to focus on external events rather than inner experiences (Taylor et al., 1997). High rates of alexithymia have been reported in patients with essential hypertension, myocardial infarction, inflammatory bowel disease (IBD), functional gastrointestinal disorders (FGIDs), chronic pain, somatization, panic

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0304-3959/$32.00
doi:10.1016/j.pain.2007.01.032

disorder, eating disorders, and post-traumatic stress disorders (Taylor, 2000). These findings suggest that alexithymia has aversive effects not only on mental health but also on physical health.

Several pathways linking alexithymia to physical illness have been hypothesized at the physiological, behavioral, and cognitive levels (Lumley et al., 1996). One is that affect regulation and elaboration are impaired in alexithymics. In that case, arousal, which can continuously remain active, potentially disturbs the autonomic, pituitary–adrenal, and/or immune systems leading to tissue damage. Alexithymia may also indirectly lead individuals to physical illness by prompting unhealthy behavior, such as smoking, drug abuse, disordered eating, or a sedentary lifestyle. Another hypothesis is that alexithymics amplify unpleasant proprioceptive or external stimulation. Previous studies have shown that the degree of alexithymia correlates with the score of somatosensory amplification and that alexithymics exhibit significantly low tolerance to painful electric stimulation (Nyklicek and Vingerhoets, 2000; Nakao et al., 2002). However, no direct evidence on how alexithymia relates to somatic symptoms or physical illnesses has been provided.

FGIDs are characterized by chronic gastrointestinal symptoms with no biochemical or structural abnormalities detected by routine clinical examination and are therefore distinguished from IBD, which involves discrete inflammation of the gastrointestinal tract (Drossman, 2006). FGIDs highly associated with alexithymia as 66% of patients with FGIDs have been reported to have high alexithymic scores even after the influence of anxiety and depression has been controlled (Porcelli et al., 1999). Patients with FGIDs who do not respond to treatment are more likely to have alexithymia than those who do, making alexithymia a potential predictor of treatment outcome in FGID patients (Porcelli et al., 2003; Porcelli et al., 2004b). FGID symptoms result from deregulation of both intestinal motor and sensory functions, and central nervous system activity, which is mediated by bi-directional circuits between the central and enteric nervous systems; the so-called "brain-gut" axis (Drossman, 2006). Brain-gut function has been investigated using neuroimaging techniques that measure brain response during gut stimulation (Derbyshire, 2003). Using this method to understand the mechanism by which alexithymia may affect brain-gut function would help clarify the pathways that link alexithymia to FGIDs.

The primary aim of the present study was to examine how alexithymia associates with sensitivity to visceral stimulation. In our experiments, brain activity, blood neuroendocrine levels, and subjective perception in response to visceral stimulation induced by a barostat bag inserted into the colon were measured in healthy volunteers.

2. Methods

2.1. Subjects

Forty-five healthy volunteers (34 males and 11 females) participated in this study. All subjects were right-handed and aged 22 ± 2 (mean $\pm$ SD). Each subject underwent a basic evaluation including a medical history review to exclude individuals with organic diseases and was given a physical examination and colonoscopy. None of the subjects had a history of psychiatric or neurological disorders, and none had gastrointestinal symptoms or signs. Subjects were given a description of the study protocol, and their written informed consents were obtained. This study was approved by the Ethics Committee of Tohoku University School of Medicine and was performed in accordance with the policy of the Declaration of Helsinki.

2.2. Assessment of alexithymia

Alexithymia was assessed in each subject using the 20-item of Toronto alexithymia scale (TAS-20), which is the most psychometrically valid measurement of alexithymia (Bagby et al., 1994a,b; Parker et al., 2003; Taylor et al., 2003). TAS-20, which comprises three subscales, i.e. difficulty to identify feelings (DIF), difficulty to describe ones' feelings (DDF), and presence of externally oriented thinking (EOT), is a self-report questionnaire with maximum score of 100 that measures participants' ability to describe and identify feelings, and their tendency to exhibit externally oriented thinking. Participants answer questions on a 5-point scale indicating 'strongly disagree' to 'strongly agree.' Individuals with a TAS-20 total score of more than 61 are considered alexithymic and those with a score of less than 51 are considered non-alexithymic (Taylor et al., 1997). The Japanese version of the TAS-20 has already been found to be psychometrically valid (Komaki et al., 2003).

2.3. Protocol

On the day before the experiment, subjects were given low residue meals and their colons were cleansed as previously described (Hamaguchi et al., 2004). In the morning of the experiment day, colonoscopy was performed on each subject under X-ray monitoring. A splinting device was inserted into the descending colon and the colonoscope was removed. A catheter with a barostat bag (700 ml in volume) was then inserted into the upper part of the descending colon and the splinting device was removed. Colonic distension stimuli were provided with a computerized barostat pump (Mdetronics Synectics, Shoreview, MN, USA), which inflated the bag at a rate of 38 ml/s. First each subject underwent a baseline PET scan without bag stimulation. Thereafter, the colon was stimulated with a bag pressure of 0, 20, and 40 mmHg for 80 s. The intensity of each stimulus was randomly chosen to avoid stimulation order effect, and the time interval between two stimuli was 15 min.

2.4. PET scan acquisition

Scans of the distribution of $H_2{}^{15}O$ were obtained using an SET-2400W PET scanner (Shimadzu, Japan) operated at high sensitivity three-dimensional mode with average axial

resolution of 4.5 mm at maximum strength and sensitivity for a 20-cm cylindrical phantom of 48.6 kcps/kBq/ml (Fujiwara et al., 1997). For each scan, the subject received approximately 5 mCi (185 MBq) of $H_2{}^{15}O$ intravenously through the antecubital vein and underwent colonic distension during measurement of rCBF. Scans were started about 10 s after the beginning of colonic distension, at which both radioactivity peak and peak pressure of the bag reached simultaneously a plateau. PET scanning room was darkened and the subjects, while awake, were instructed to keep their eyes closed for the whole period of the scan (70 s).

2.5. Subjective perception of stimulation

After each visceral stimulation, the subjects were asked to report the following seven items of visceral sensation or emotion: abdominal discomfort, abdominal distension, abdominal pain, urgency for defecation, perceived stress, sleepiness, and anxiety. Each sensation was evaluated on an ordinate scale from 0 (no sensation) to 10 (maximal sensation) as previously described (Hamaguchi et al., 2004). Abdominal distension was characterized by a swollen abdomen due to colon pressure, while abdominal discomfort was characterized as any other uncomfortable feeling in the abdomen. Abdominal pain was defined as any soreness in the abdomen and urgency for defecation was defined as a sudden compelling urge to defecate. To evaluate responses to stimulation, differences in the value of each ordinate scale between baseline and stimulation with 40, 20, and 0 mmHg were used for analysis.

2.6. Biochemical assays

A plastic catheter was inserted into the left forearm vein of each subject and saline was infused at a speed of 1.6 ml/min. Blood samples were taken through the catheter after each PET scan (baseline, 0, 20, and 40 mmHg) and immediately centrifuged at 3000 rpm at 4 °C for 5 min. The supernatant was aspirated and stored at −20 °C until assay. Levels of plasma ACTH and serum cortisol were measured by standard radio-immunoassay. Levels of noradrenaline and adrenaline in the plasma were determined with high-performance liquid chromatography and electrochemical detection after batch alumina extraction. To evaluate responses to stimulation, the ratio of value after stimulation with 40, 20, and 0 mmHg/value at baseline in each blood sample was used for analysis.

2.7. Statistical analysis

Statistical parametric mapping software (SPM2, Wellcome department of Cognitive Neurology, London, UK) was used for PET images realignment, normalization, smoothing, and to create statistical maps of significant rCBF changes (Friston et al., 1995a; Friston et al., 1995b). All rCBF images were stereotaxically normalized into the standard space defined by Talairach and Tournoux (1988) using an rCBF template image supplied with SPM2. The normalized images were smoothed using a $12 \times 12 \times 12$-mm Gaussian filter, and the values of rCBF were expressed in ml dl^{-1} min^{-1}, adjusted for individual global CBF values using the ANCOVA, and scaled to the mean of 50. Contribution of each parameter of interest to changes in rCBF was estimated by SPM2 according to the general linear model at voxel level. Estimates were made using linear compounds of contrasts, and the resulting set of voxel values constituted a parametric map for each contrast. To examine whether specific brain regions correlate with alexithymia, we performed a correlation analysis between rCBF changes at stimulation with the pressure of 40, 20, 0 mmHg and individual TAS-20 scores for all 45 subjects. Additionally, a conjunction analysis was performed to assess differences between alexithymic and non-alexithymic subjects in cerebral regional activation at stimulation with the pressure of 40 mmHg as compared no stimulation (baseline). Conjunction analysis can reveal brain areas with significant main effect of two contrasts (Price and Friston, 1997). In our analysis, alexithymia$_{40mmHg\text{-}baseline}$ and non-alexithymia$_{40mmHg\text{-}baseline}$ were subtracted. Voxels were considered statistically significant at a threshold of $p < 0.001$ (uncorrected). Correlation between the difference in the value of each ordinate scale, TAS-20 score, and TAS-20 subscale values was evaluated by the Pearson's correlation method for all 45 subjects. Similarly, correlation between the difference in the ratio value in each blood sample, TAS-20 score, and TAS-20 subscale value was evaluated by the Pearson's correlation method for all 45 subjects.

3. Results

3.1. TAS-20 score

The averaged TAS-20 score of the 45 volunteers was 47.8 ± 11 (mean ± SD), while the averaged scores for DIF, DDF, and EOT subscales were 14.0 ± 7.2, 14.0 ± 5.0, and 19.5 ± 3.6 (mean ± SD), respectively. Among the 45 subjects, 10 individuals (5 males and 5 females) with TAS-20 scores of more than 61 (61–67) were considered alexithymic and 28 individuals (22 males and 6 females) with TAS-20 scores of less than 51 (26–50) were considered non-alexithymic according to cut-off criteria (Taylor et al., 1997). For reference, an approximate 8–10% alexithymia prevalence has been reported in normal population (Taylor, 2000). Actually, in our previous study, the averaged TAS-20 score of 247 student volunteers was 46.5 ± 8.5 (mean ± SD) (Kano et al., 2003). In addition, in a sample of Finish general population ($n = 2018$) between the age of 25 and 64 years, the prevalence of alexithymia was 12.8% in men and 8.2% in women and the averaged TAS-20 score was 44.1 ± 11.8 (mean ± SD) (Honkalampi et al., 2000).

3.2. Correlation between alexithymia and subjective perception following visceral stimulation

The correlation between individual TAS-20 and TAS-20 subscale scores, and subjective perception of colonic stimulation is shown in Table 1 and Fig. 1. At stimulation with the pressure of 40 mmHg, TAS-20 score significantly correlated with abdominal distension ($r = 0.3$, $p < 0.05$) and anxiety ($r = 0.3$, $p < 0.05$), while the score of DIF (difficulty to identify feelings) correlated with abdominal distension ($r = 0.27$, $p < 0.05$), abdominal pain ($r = 0.34$,

Table 1
Correlation (r) between individual TAS-20 and TAS-20 subscale scores and subjective visceral perception (abdominal discomfort, abdominal distension, abdominal pain, urgency for defecation, perceived stress, sleepiness, and anxiety) to colonic stimulation with (a) 40, (b) 20, and (c) 0 mmHg

	Discomfort	Distension	Pain	Urgency	Stress	Sleepiness	Anxiety
(a) 40 mmHg							
TAS20	0.05	0.3*	0.21	0.15	0.20	−0.10	0.3*
DIF	0.20	0.27*	0.34*	0.31*	0.3*	−0.3*	0.42**
DDF	−0.13	0.08	0.03	−0.02	0.06	0.18	0.14
EOT	−0.06	0.11	−0.03	−0.05	0.03	−0.04	−0.05
(b) 20 mmHg							
TAS20	0.01	0.11	−0.03	−0.19	0.02	−0.04	0.13
DIF	0.14	0.24	0.13	−0.13	0.24	−0.29	0.27
DDF	−0.04	0.02	−0.16	−0.13	−0.01	0.00	0.03
EOT	−0.21	−0.17	−0.16	−0.11	−0.26	0.39**	−0.15
(c) 0 mmHg							
TAS20	0.04	−0.01	−0.06	−0.18	−0.14	0.06	0.09
DIF	0.12	0.15	−0.02	−0.20	−0.10	−0.11	0.09
DDF	0.16	0.74	0.02	−0.08	−0.08	−0.07	0.03
EOT	−0.30*	−0.38**	−0.2	−0.09	−0.1	0.47**	0.05

Significance, $^{*}p < 0.05$; $^{**}p < 0.01$.

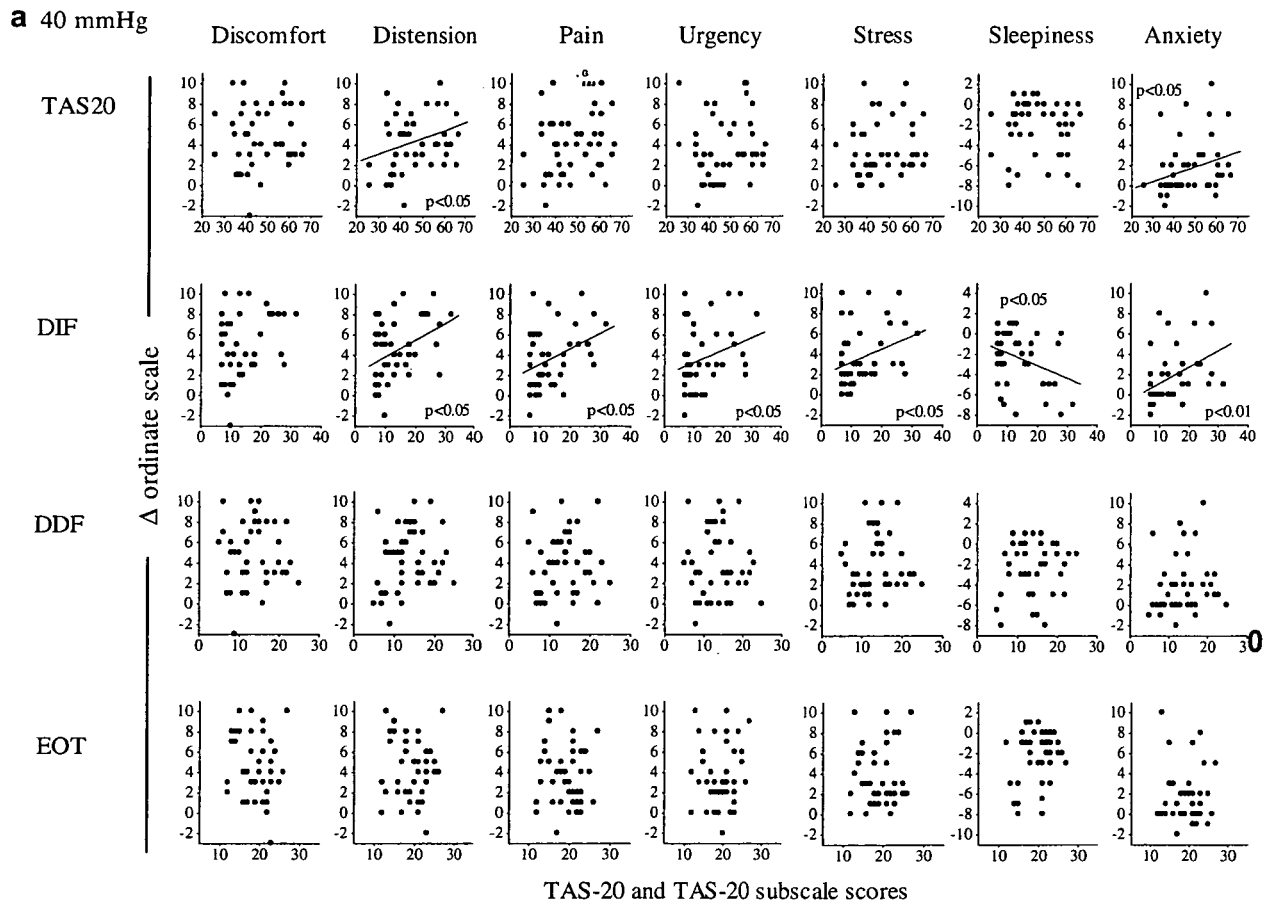

Fig. 1. Plot of the relationship between individual TAS-20 and TAS-20 subscale scores, and subjective visceral perception (abdominal discomfort, abdominal distension, abdominal pain, urgency for defecation, perceived stress, sleepiness, and anxiety) to colonic stimulation with (a) 40, (b) 20, and (c) 0 mmHg.

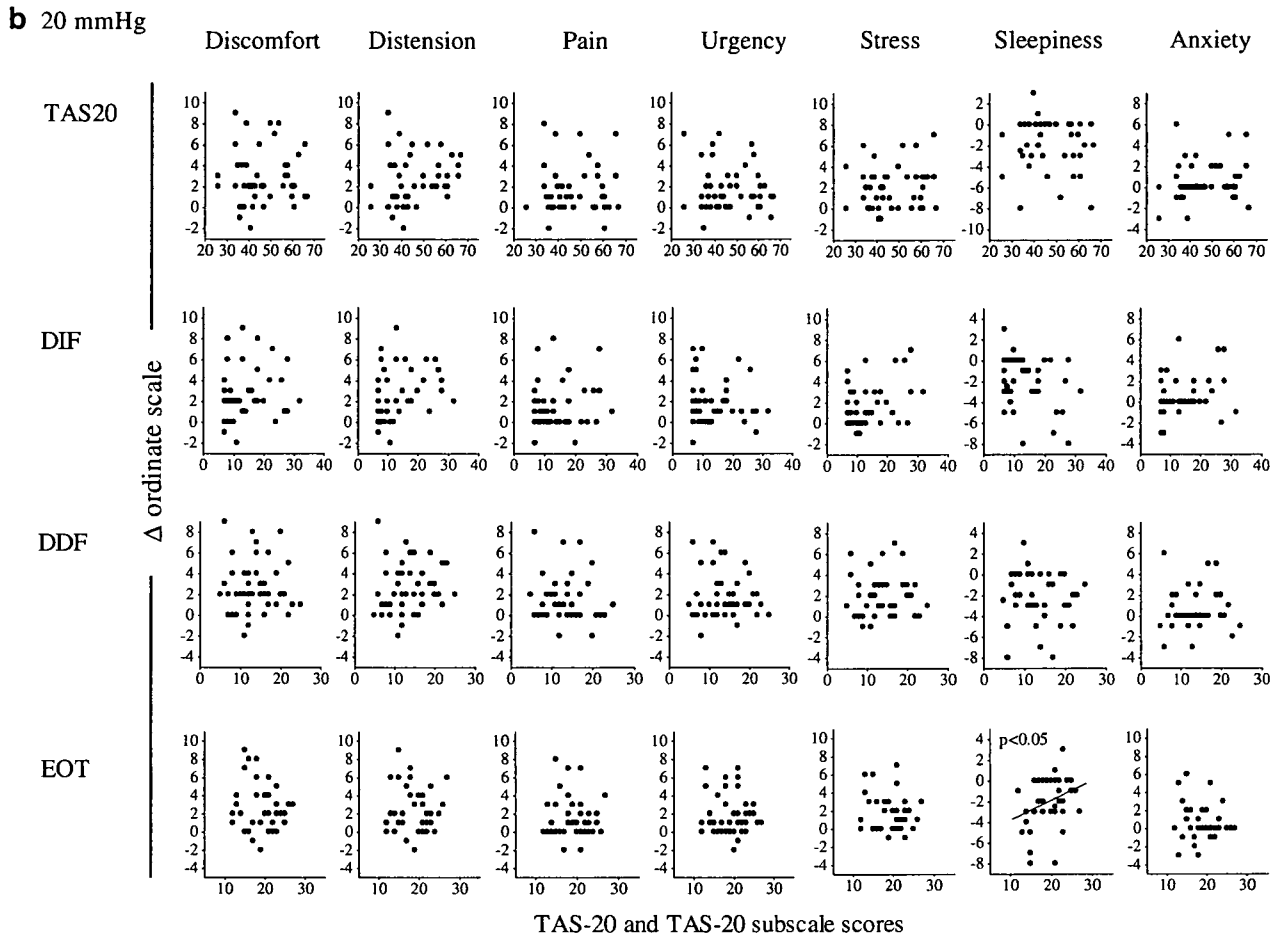

Fig. 1 (*continued*)

$p < 0.05$), urgency for defecation ($r = 0.31, p < 0.05$), perceived stress ($r = 0.3$, $p < 0.05$), sleepiness ($r = -0.3$, $p < 0.05$), and anxiety ($r = 0.28$, $p < 0.005$). The scores of DDF (difficulty to describe feelings) and EOT (externally oriented thinking) did not correlate with any subjective perception. At stimulation with the pressure of 20 mmHg, the scores of TAS-20, DIF, and DDF did not correlate with any visceral perception. However, the score of EOT correlated with sleepiness ($r = 0.39$, $p < 0.01$). At sham stimulation (0 mmHg), the scores of TAS-20, DIF, and DDF did not correlate with any subjective feeling, while the score of EOT correlated with abdominal discomfort ($r = -0.3$, $p < 0.05$), abdominal distension ($r = -0.38$, $p < 0.01$), and sleepiness ($r = 0.47, p < 0.01$).

3.3. Correlation between alexithymia and changes in blood neuroendocrine levels in response to visceral stimulation

The correlation between the degree of alexithymia and changes in blood neuroendocrine levels in response to colonic stimulation with the pressure of 40 mmHg is shown in Table 2. TAS-20 score positively correlated with blood level of adrenaline ($r = 0.29$, $p < 0.05$), while the score of DIF positively correlated with blood levels of ACTH ($r = 0.33$, $p < 0.05$) and adrenaline ($r = 0.39$, $p < 0.01$). In contrast, the score of EOT negatively correlated with blood levels of ACTH ($r = -0.31$, $p < 0.05$) and adrenaline ($r = -0.27$, $p < 0.05$). There was no correlation between the score of TAS-20, DIF, DDF, or EOT and change in blood neuroendocrine levels in response to colonic stimulation with the pressure of 0 and 20 mmHg.

3.4. Correlation between alexithymia and rCBF following visceral stimulation

At stimulation with the pressure of 40 mmHg, TAS-20 score positively correlated with rCBF in the orbital gyrus, insula, frontal gyrus, superior temporal gyrus, precentral gyrus, and cerebellum (Fig. 2 and Table 3). On the other hand, TAS-20 score negatively correlated with rCBF in the superior parietal lobe, cuneus, precuneus, middle frontal gyrus, and cerebellum (Fig. 3). The score of DIF positively correlated with rCBF in

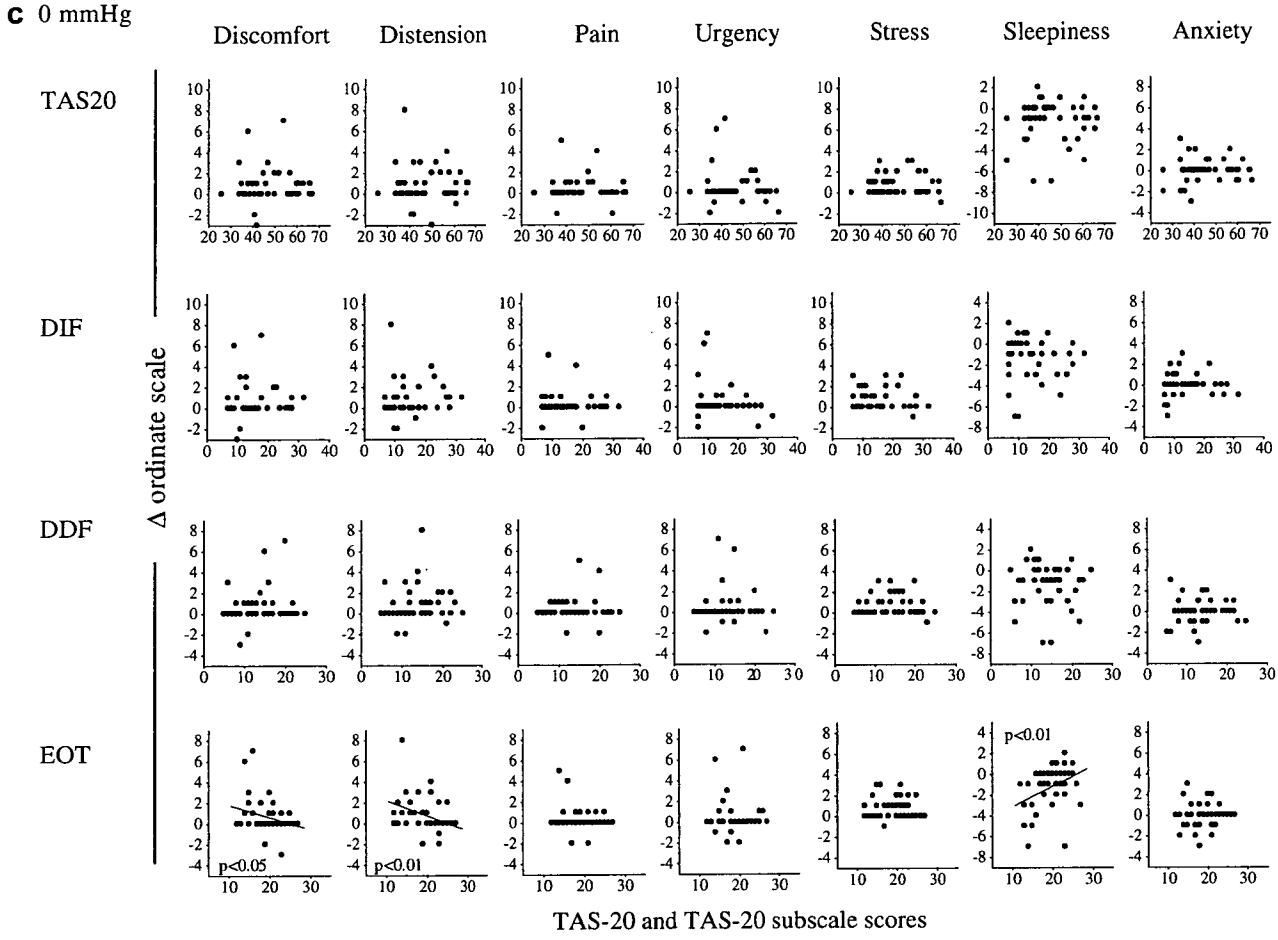

Fig. 1 (*continued*)

the orbital gyrus, insula, frontal gyrus, and cerebellum. Brain areas that negatively correlated with the score of DIF were: the precuneus, cuneus, and cerebellum. The score of DDF positively correlated with rCBF in the orbital gyrus, inferior parietal gyrus, frontal gyrus, and insula, and negatively correlated with the parietal and occipital gyrus and precuneus. Although TAS-20 score, the score of DIF, and the score of DDF correlated either positively or negatively with rCBF in similar brain areas (e.g. orbital gyrus and insula) areas that correlated with the score of EOT were distinct. The score of EOT positively correlated with rCBF in the middle and temporal gyrus, precuneus, inferior temporal gyrus, postcentral gyrus, and supramarginal gyrus, and negatively corre-

Table 2
Correlation between individual TAS-20 and TAS-20 subscale scores and changes in blood neuroendocrine levels in response to colonic stimulation with 40 mmHg

	Cortisol	ACTH	Adrenaline	Noradrenaline
TAS20	0.11	0.14	0.29*	0.09
DIF	0.06	0.33*	0.39**	0.16
DDF	0.11	0.14	0.29	0.09
EOT	−0.07	−0.31*	−0.27*	−0.11

ACTH, adrenocorticotropic hormone; Significance, $^{*}p < 0.05$; $^{**}p < 0.01$.

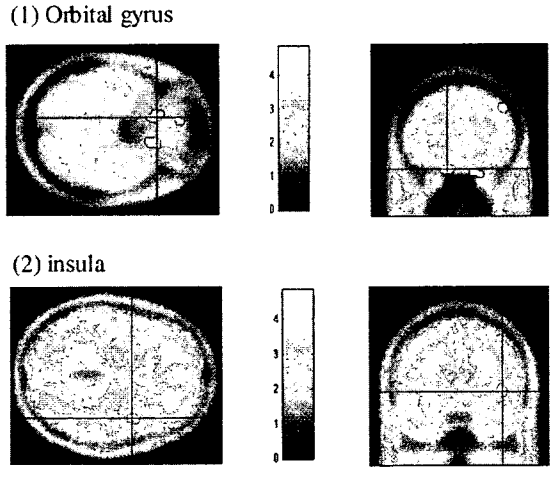

Fig. 2. A statistical parametric map (SPM) showing the bilateral orbital gyrus and the right insula where rCBF positively correlated with TAS-20 score during colonic stimulation with a bag pressure of 40 mmHg ($p < 0.001$, uncorrected).

Table 3
Coordinates and Z-scores for brain areas that positively or correlated with TAS-20 score and the scores of DIF, DDF and EOT during colonic stimulation with 40 mmHg ($p < 0.001$, uncorrected)

Region (putative Brodmann's area)	Cluster size	Z-score	Talairach coordinates		
			x	*y*	*z*
TAS 20 positive correlation					
Orbital gyrus (47)	99	4.29	−12	26	−22
Insula (13)	73	4.26	44	0	4
Middle frontal gyrus (8)	50	4.19	44	28	40
Middle frontal gyrus (46)	78	3.83	54	36	26
Orbital gyrus (11/47)	168	3.66	20	30	−28
Cerebellum	99	3.62	−28	−70	−50
Superior temporal gyrus	26	3.61	−62	−26	14
Precentral gyrus (6)	24	3.56	62	−14	38
Cerebellum	31	3.48	28	−76	−50
Superior frontal gyrus (11)	41	3.46	−10	50	−24
TAS 20 negative correlation					
Cerebellum	233	4.52	−40	−78	−16
Cerebellum	403	4.19	42	−74	−2
Superior parietal lobe (7)	33	3.87	32	−50	62
Cuneus (7)	65	3.71	−16	−74	32
Precuneus (7)	68	3.65	−2	−68	58
Middle frontal gyrus (6)	41	3.45	−28	−6	56
Precuneus (7)	28	3.42	−8	−48	46
DIF positive correlation					
Orbital gyrus (11/47)	52	4.06	16	38	−24
Cerebellum	66	4.04	14	−82	−40
Insula (13)	235	4.00	44	−4	6
Cerebellum	64	3.71	−22	−76	−50
Superior frontal gyrus (10)	57	3.64	−28	44	20
Insula (13)	26	3.52	−54	2	4
DIF negative correlation					
Precuneus (7)	97	3.72	0	−70	60
Cuneus (7)	51	3.65	−16	−72	32
Cerebellum	27	3.47	−36	−78	−16
DDF positive correlation					
Orbital gyrus (47)	168	4.37	−12	28	−24
Inferior parietal gyrus (39)	80	3.83	−53	−60	42
Frontal lobe sub-gyrus	37	3.79	−28	42	0
Middle frontal gyrus (8)	42	3.72	46	26	42
Supramarginal gyrus (39/40)	79	3.66	−62	−50	28
Middle frontal gyrus (46)	29	3.53	56	36	28
Insula (13)	22	3.40	30	12	6
DDF negative correlation					
Superior parietal lobe (7)	75	4.25	32	−48	62
Middle temporal gyrus (39)	145	3.84	50	−60	6
Inferior occipital gyrus (18)	73	3.81	−38	−80	−14
Precuneus (7)	48	3.64	−16	−56	52
Middle occipital gyrus (19)	48	3.54	24	−92	16
Inferior temporal gyrus (19)	31	3.54	42	−72	−2
Superior parietal lobe (7)	39	3.41	−6	−66	56
Middle occipital gyrus (19)	3.4	3.4	−18	−100	8
EOT positive correlation					
Middle temporal gyrus (22)	592	3.99	54	−38	4
Cerebellum	213	3.98	36	−86	−30
Inferior temporal gyrus (20)	80	3.91	−60	−16	−28
Precuneus (7)	37	3.74	12	−76	42
Cerebellum declive	30	3.62	−52	−52	−20
Inferior temporal gyrus (21)	43	3.51	−54	−54	−4
Inferior temporal gyrus (21)	131	3.51	60	−4	−14

Table 3 (*continued*)

Region (putative Brodmann's area)	Cluster size	Z-score	Talairach coordinates		
			x	y	z
Postcentral gyrus (43)	75	3.43	53	−12	18
Supramarginal gyrus (40)	66	3.31	−58	−54	24
EOT negative correlation					
Middle frontal gyrus (6)	67	3.35	−2	−26	58

lated with rCBF in the middle frontal gyrus. At stimulation with 20 and 0 mmHg, no correlation between the score of TAS-20 and rCBF was observed in any brain area.

3.5. Differences in response to visceral stimulation between alexithymics and non-alexithymics

Differences between alexithymics and non-alexithymics in response to visceral stimulation with the pressure of 40 mmHg are listed in Table 4. Areas of the brain where rCBF was higher in the alexithymics than in the non-alexithymics were: the right insula, middle frontal gyrus, midbrain, pregenual anterior cingulate gyrus, superior temporal gyrus, and postcentral gyrus (Fig. 4). In contrast, areas of the brain where the alexithymics had lower rCBF than the non-alexithymics were: the inferior frontal lobe, occipital lobe, inferior parietal lobe, cerebellum, and cuneus.

4. Discussion

The present study demonstrates that alexithymia is associated with hypersensitivity to visceral stimulation induced by colonic distension. The salient results were as follows: (1) TAS-20 score positively correlated with activation of brain areas, such as the insula and orbital gyrus. Also, visceral stimulation induced more activation in the insula, pregenual anterior cingulate cortex, and brainstem of the alexithymics than in those of the non-alexithymics. (2) Blood levels of adrenaline in response to colonic stimulation with 40 mmHg positively correlated with TAS-20 score. (3) The more alexithymic subjects were, the more anxiety for visceral stimulation they expressed. Especially, subjects with high score of DIF reported strong pain, urgency for defecation and stress, and less sleepiness than the other subjects. Although these observations may suggest an association between alexithymia and hypersensitivity to visceral stimulation, they need to be interpreted conservatively as it is unclear whether alexithymia causes or results from these effects.

Visceral stimulation, especially by colonic distension, has been reported to elicit activation of various brain areas including, the anterior prefrontal, primary and secondary sensory, perigenual and ventral cingulate, supplementary motor areas, orbitofrontal and insular cortices, thalamus, midbrain, and/or anterior cerebellum (Silverman et al., 1997; Berman et al., 2000; Naliboff et al., 2001; Derbyshire, 2003). In addition, it has been shown that a specialized spinothalamocortical tract conveys interoceptive sensory information to the cortex, enabling a detailed dynamic representation of particular internal bodily states and that mapping of each interoceptive state occurs within

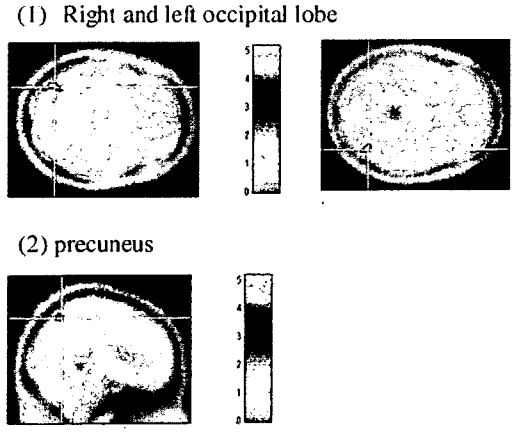

Fig. 3. A statistical parametric map (SPM) showing the bilateral occipital lobe and the precuneus where rCBF negatively correlated with TAS-20 score during colonic stimulation with a bag pressure of 40 mmHg ($p < 0.001$, uncorrected).

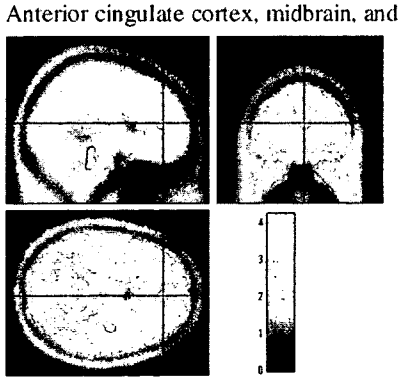

Fig. 4. A statistical parametric map (SPM) showing the pregenual anterior cingulate cortex, midbrain, and right insula where rCBF was higher in the alexithymic subjects than in the non-alexithymics during colonic distension with a bag pressure of 40 mmHg ($p < 0.001$, uncorrected).

Table 4
Coordinates and Z-scores for areas where rCBF was higher or lower in the alexithymics than in the non-alexithymics in response to colonic distension with a bag pressure of 40 mmHg ($p < 0.001$, uncorrected)

Region (putative Brodmann's area)	Cluster size	Z-score	Talairach coordinates		
			x	y	z
Alexithymics > non-alexithymics (0 < 40 mmHg)					
Insula (13)	78	4.05	38	−16	16
Middle frontal gyrus (6)	50	3.93	22	28	60
Midbrain	157	3.83	2	−34	−16
Cingulate gyrus (32)	40	3.69	4	42	14
Superior temporal gyrus (22)	36	3.62	44	−40	18
Postcentral gyrus (3)	22	3.47	56	−16	20
Alexithymics < non-alexithymics (0 < 40 mmHg)					
Inferior frontal lobe (45)	130	4.07	−40	−78	−16
Occipital lobe (18)	83	3.96	−36	−92	−16
Inferior parietal lobe (40)	52	3.86	36	−42	44
Parietal lobe (40)	40	3.57	−56	−28	44
Cerebellum	25	3.50	36	−52	−34
Cuneus (18)	23	3.32	−8	−84	14

the orbitofrontal and right insula cortices, which represent the neuroanatomical endpoint of the lamina I interoceptive system (Craig, 2002; Critchley, 2004; Critchley et al., 2004). A recent study has shown that in the large cingulate cortex, the pregenual ACC responded to visceral stimulation and was associated with perception of secondary pain, which is characterized by greater unpleasantness (Vogt, 2005). Electrical stimulation of the insula has been reported to elicit changes in blood pressure, heart rate, respiration, gastric motility, peristaltic activity, salivation, and adrenaline secretion (Neafsey et al., 1993). Moreover, the orbitofrontal cortex has been shown to receive robust sensory input and to act as an internal environmental integrator that coordinates behavioral, autonomic, and endocrine responses (Barbas, 2000). The brainstem, on the other hand, is known to control ascending nociceptive input and nuclei such as the rostral ventromedial medulla and periaqueductal gray (PAG), which are able to both inhibit and facilitate nociceptive responses. Particularly, activation of the right PAG has been reported to correlate with anxiety during visceral stimulation but not somatic stimulation (Dunckley et al., 2005). Therefore, it may be assumed that activation of brain areas associated with alexithymia supports afferent representation of bodily states, and efferent autonomic and endocrine responses that accompany it. In this respect, our results indicate that alexithymics may be more aroused by interoception of unpleasant feeling than non-alexithymics thereby displaying more autonomic responses. The results of this study also support the somatosensory amplification hypothesis on alexithymia and could be used to confirm not only the results of clinical reports showing that alexithymia is associated with pain sensitivity in several chronic pain samples (Lumley et al., 1996; Lumley et al., 2002; Glaros and Lumley, 2005; Lumley et al., 2005), but also the occurrence of gastrointestinal symptoms in patients with no reasonable organic abnormalities (Porcelli et al., 1999; Porcelli et al., 2003; Porcelli et al., 2004a,b; van Kerkhoven et al., 2006).

Prior brain studies on alexithymia have focused on its disturbance of emotional processing, based on the hypothesis that people with alexithymia have a deficit in the conscious awareness of emotion (Lane et al., 1997). Anatomically, a significant positive correlation has been reported between the size of the right anterior cingulate gyrus and alexithymia (Gündel et al., 2004). In addition, fMRI studies have shown different activity in the anterior cingulate and the mediofrontal during emotional stimuli processing (Berthoz et al., 2002) and reduced activation of the posterior cingulate cortex during imagination of happy events (Mantani et al., 2005). Accordingly, our previous PET study has revealed reduced activation of the right hemisphere when viewing facial expressions, particularly, low activation of the right dorsal ACC and insula was observed in response to angry faces than to neutral faces (Kano et al., 2003). These findings, which are based on emotion-inducing pictures or recall of emotional events, correspond to features of alexithymia that indicate deficit in cognitive processing of emotion. On the other hand, the present study demonstrates that individuals with high alexithymia were more emotionally distressed and displayed excessive arousal to visceral sensation. Therefore, subjects with alexithymia might be less aware of affective stimuli at the cognitive level but highly aroused by affective stimuli at the physiological level.

From the point of view of cognitive-developmental model of emotional awareness (Lane and Schwartz, 1987), the problem of alexithymia has been posited as deficient development in the cognitive mature stage, which allows some rudimentary form of emotional experiences like awareness of bodily sensations (Lane et al.,

1997; Taylor et al., 1997; Lane et al., 2000; Lane, 2000). Our results may represent intensive responses in an undeveloped form of alexithymia, probably associated with deficit in cognitive emotional processing. Further research is needed to clarify this aspect of alexithymia. Nevertheless in this study, the scores of TAS-20 negatively correlated with rCBF changes in the cuneus and precuneus. The cuneus and precuneus are principal areas involved in conscious recall of memory-related imagery (Fletcher et al., 1995) and may participate in representation of polymodal imagery associated with successful memory retrieval (Maddock et al., 2001), namely these brain areas play a specific role in higher-order cognitive functions (Cavanna and Trimble, 2006). Therefore, deactivation in the cuneus and precuneus in alexithymic subjects during visceral stimulation might be associated with deficits in cognitive processing of emotion. Although contradictive data as to the association between somatosensory amplification and alexithymia have been reported (de Zwaan et al., 1996; Jackson et al., 2002), analysis using TAS-20 subscales indicates that the scores of DIF and DDF, but not that of EOT, are associated with the score of somatosensory amplification scale (SSAS) (Nakao et al., 2002). High scores of DIF were particularly effective in predicting "somatization" scales in 254 psychiatric patients, whereas the scores of DDF and EOT gave no specific indication (Grabe et al., 2004). In several pain studies, DIF and/or DDF scores but not EOT score were associated with sensitivity to pain (Lumley et al., 2002; Glaros and Lumley, 2005; Lumley et al., 2005). Our results are in line with these findings, indicating that among the alexithymic features measured by TAS-20, DIF may be associated with the increased responses.

From the results of previous studies showing that alexithymia was associated with gastrointestinal symptoms with no relation to endoscopic findings in 1141 patients (van Kerkhoven et al., 2006) and that even after controlling the influence of co-morbidity of psychiatric disorders, high rate of alexithymia remained in FGID patients (Porcelli et al., 1999; Porcelli et al., 2004a), the alexithymia construct itself is not something that can be ignored to study FGIDs. Our results revealed the connection between alexithymia and hypersensitivity to visceral stimulation using brain activation, neuroendocrine response, and subjective perception, which are regarded as primary mechanisms of symptom development in FGIDs (Delvaux, 2002; Mertz, 2002; Chang, 2005). We believe that understanding the influence of alexithymia and cognitive emotional processing on brain-gut function would be useful to elucidate the pathophysiology of FGIDs.

This study shed light on the correlation between alexithymia and hypersensitivity to visceral stimulation, however, it has some limitations. Although TAS-20 is the most psychometrically valid measurement of alexithymia, it has been pointed out that there is an overlap between the TAS-20, measures of negative affect, and limitation as a self-report questionnaire (Lane et al., 1997; Subic-Wrana et al., 2005). Future study will be necessary to determine alexithymia tendency by multimethods including a structured interview, which has been proposed recently (Bagby et al., 2006). Previous studies demonstrated that TAS-20 score in men, but not in women, is associated with the size of ACC (Gündel et al., 2004) and neuroendocrine response (Spitzer et al., 2005), and that there are gender differences for FGID patients in brain activation to rectal distension (Berman et al., 2000; Naliboff et al., 2003; Mayer et al., 2004). The sample size in this study was too small to elucidate the gender differences. Moreover, we adapted a bag pressure of 40 mmHg as a painful visceral stimulation based on previous evidence (Bouin et al., 2002; Hamaguchi et al., 2004), although there are objections that distension with 45–60 mmHg is necessary to produce pain (Naliboff et al., 2003). These discrepancies need to be addressed in future studies with larger sample size.

In conclusion, the present study demonstrates that alexithymia is associated with hypersensitivity to visceral colonic stimulation. Our results show a positive correlation between TAS-20, and (1) activation of specific brain areas; (2) changes in blood neuroendocrine levels; and (3) subjective perception. These results support the somatosensory amplification hypothesis on alexithymia and could be one of the key mechanisms to explain the link between alexithymia and physical illness, especially FGIDs.

Acknowledgements

This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, and the Ministry of Health, Welfare, and Labor, Japan. The authors appreciate the technical assistance of Mr. Miyake, Y. Ishikawa, and S. Watanuki in PET studies.

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Neurogastroenterol Motil (2007) **19**, 831–838 doi: 10.1111/j.1365-2982.2007.00959.x

Role of histaminergic neurons in hypnotic modulation of brain processing of visceral perception

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Abstract *Modulating visceral sensation of the body is important to the understanding of emotion formation. Molecules that act during hypnosis and modify visceral pain perception are not known. We tested our hypothesis that hypnotic suggestion changes electrophysiological processing of visceroafferent signals in the human brain and that these conditions are in part dependent on histaminergic neurons. Twelve healthy male subjects were studied on two separate days: a day of treatment with histamine H_1 receptor antagonist (d-chlorpheniramine 100 $\mu g\ kg^{-1}$, intravenously) and another day of that with placebo (saline, the same amount) in a randomized order. We recorded cortical evoked potentials to 100 rectal electrical stimuli after neutral, hyperalgesic or analgesic hypnotic suggestions as given to modulate the visceral perception. Analgesic suggestion reduced the amplitude of the deepest positive peak of viscerosensory evoked potential. Administration of histamine H_1 antagonist diminished the attenuation of viscerosensory evoked potential by analgesic suggestion. Our results suggest that central pain modulatory system in the brain is activated by hypnotic suggestion and that brain histamine is a mediator in the hypnotic modulation of visceral sensory pathway as well as in the control of consciousness level. These findings lead us to possible new treatment for control of visceral perception.*

Keywords *central pain modulatory system, cerebral evoked potential, histamine H_1 receptor, hypnotic suggestion, visceral hypersensitivity, visceral perception.*

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Received: 27 February 2007
Accepted for publication: 25 April 2007

Abbreviations ACC, anterior cingulate cortex; ANOVA, analysis of variance; CEP, cerebral evoked potential; CNS, central nervous system; EEG, electroencephalogram; H_1R, histamine H_1 receptor; HGSHS-A, the Harvard Group Scale of Hypnotic Susceptibility, Form A; N1, the first negative peak; N2, the second negative peak; P1, the first positive peak; PAG, periaqueductal grey.

INTRODUCTION

Interoception and emotion are known to play a crucial role in a number of pathophysiological conditions, including irritable bowel syndrome, a functional gastrointestinal disorder characterized by chronic abdominal pain and discomfort.[1] The neurophysiological mechanisms that underlies the modulation of visceral hypersensitivity remains unclear.[2]

Hypnosis and placebo have been reported to induce certain expectation of pain modulation.[3] Studies examining brain activity have reported that hypnosis[4] and placebo[5,6] trigger descending opioidergic and non-opioidergic pain modulatory systems. In addition, hypnotic suggestion has been shown to reduce pain by activation of an endogenous pain inhibitory signal, which descends to the spinal cord and prevents the transmission of pain-related information.[7] On the other hand, Rainville *et al.*[4] have found significantly increased activity of the anterior cingulated cortex (ACC) during hypnotic suggestion of increasing pain. In the pain modulatory system, not only endogenous opioid peptides but also other non-opioid mediators are known to be involved.[8]

Neuronal histamine is one of the important mediators of both peripheral and central pain sensitization. The descending histaminergic neurons originate from the hypothalamus and terminate at the periaqueductal grey (PAG) and the dorsal horn of the spinal cord.[9] In earlier studies, highly selective histamine H_1 receptor (H_1R) agonists have been shown to induce hypernociceptive response,[10], whereas H_1R antagonists have been demonstrated to reduce histamine-induced pain

in experimental models.[11,12] In addition, it has been reported that H_1 receptor knockout mice display lower sensitivity to pain than normal mice.[13] These findings suggest that histamine in the central nervous system (CNS) is a dominantly pronociceptive neurotransmitter via the H_1 receptor.

Recording of the cerebral evoked potentials (CEP) is a non-invasive technique, commonly used to investigate the CNS processing of information during activation of peripheral nerves.[14] Cerebral evoked potential has been used to investigate CNS processing of visceral sensation and a highly reproducible recording has been established.[15,16] This is critically important because exogenous (stimuli-dependent) and endogenous (stimuli-independent) components of pain processing occur in different time windows.[17] Therefore, CEP is an appropriate method for detection of fine changes in the time-dependent domain of central processing of visceral perception.

To investigate the role of neuronal histamine in brain processing of visceral perception during hypnotic analgesia or hyperalgesia, we examined in this study the following hypotheses:

1 Hypnotic suggestion modulates brain processing of visceroafferent signals recorded by CEP.
2 Blockage of the H_1R enhances the analgesic effects and attenuates the hyperalgesic effects of visceral perception by hypnotic suggestion.

MATERIALS AND METHODS

Subjects

Twelve healthy subjects were enrolled in this study. Subjects consisted of men with a mean age of 21.3 ± 0.6 years. All subjects' healthcare status were checked before enrolment, who had no symptoms or history of major diseases. This study was approved by the Ethics Committee of Tohoku University School of Medicine, and all subjects in the study gave their written informed consent.

Cannulation and recording assemblies

At 9:00 on the experimental day, each subject ingested a preparation consisting of 2000 mL solution of sodium chloride (2.93 g), potassium chloride (1.485 g), sodium carbohydrate (3.37 g), sodium sulphate (11.37 g) and polyethylene glycol 4000. At 12:00, a bipolar electrode catheter (6F, Dr Osypica GMBH, Granzach-Wyhlen, Germany) connected to an electronic stimulator (NEC San-Ei Instruments Ltd, Tokyo, Japan) was inserted 15 cm into the rectum from the anal verge. The two poles of the electrode were situated 10 mm apart. A polytetra-fluoroethylene cannula was inserted into the left arm vein and saline or *d*-chlorpheniramine was infused at a speed of 1 mL min^{-1}.

Electrical stimulation of the rectum and CEP

The methods for taking viscerosensory CEP were already described elsewhere.[18,19] In brief, electrical stimulation was applied to the rectal mucosa with a square of 200 μs duration at a frequency of approximately 1.0 Hz and an intensity ranging from 0 to 50 mA. After measurement of sensory thresholds, each electrical stimulation was performed randomly 100 times with an intensity of either 0 mA (sham stimulation) or 30 mA. The intensity of 30 mA was chosen high enough to evoke visceral perception in most subjects.[19]

Silver–silver chloride surface electrodes were applied to the scalp with electrode paste (Elefix, Nihon Kohden, Tokyo, Japan). The active electrode was positioned at Cz (vertex), using the international 10-20 system of electroencephalogram (EEG) electrode placement.[20] Cz was chosen because previous topographic mapping studies have shown this to be the site where all components of CEP are adequately recorded.[21] A reference electrode was positioned on the left ear lobe, and a ground electrode was placed on the neck. Scalp electrodes impedance was <5 kiro-ohm throughout the study. Signal of EEG and electrical stimulation of the rectum were simultaneously recorded with an amplifier and on a data recorder (XR-510; TEAC, Tokyo, Japan). The recordings were performed in a temperature-controlled (25 °C) quiet room on subjects in the supine position, who were asked to open their eyes and minimize eye blinks and movements.

A signal processor (7T18, NEC Sanei Instruments Ltd) and a computer program (EPLYZER version 2.0; Kissei Comtec Co., Matsumoto, Japan) were used for data analysis. The amplifier gain was set at 100 000, and the recording sensitivity was 50 μV. The bandpass filter settings were 1–100 Hz, and a 50 Hz notch filter was used to reduce interference from the main electrical supply. The sampling rate was 2500 Hz, and the recording epoch was 800 ms in duration. The first 100 ms of the epoch was the prestimulation time. An automatic artefact reject was used to prevent contamination from eye blinks and movements. After each stimulus, individual epochs of data were saved, and the average of the run could be viewed during acquisition. The CEP peaks were evaluated by visual inspection and were designated as a first negative peak (N1), first positive peak (P1), second negative peak (N2), etc.,

numbered in order of occurrence. Criteria for the existence of a particular peak were that the response was reproducible and consistently present in most of the subjects. Classification of a particular peak depended on the proximity to the mean latency. Besides, in this study we focused on the hypnotic modulation of pain affect processing (endogenous components), so the early components of CEP (exogenous components) were omitted in this report.[4]

Hypnotic induction and suggestions

The instructions for hypnotic induction were taken from the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS-A).[22] This standardized measure has excellent test–retest reliability after long intervals.[22] Indirect suggestions for modulation of pain affect (increase: hyperalgesic; decrease: analgesic) were adapted from Rainville *et al.*[23] The neutral suggestion consisted of the same syllables as the hyperalgesic or the analgesic suggestion but with meaningless words.

Experimental design

Following cannulation, the subjects were allowed 30 min for adaptation. Next, either 100 $\mu g\ kg^{-1}$ of *d*-chlorpheniramine or the same amount of saline was then administered to each subject. All subjects were studied for 2 days with at least 1 month between visits, and received during each visit either *d*-chlorpheniramine or saline in a randomized order. Subjects were not informed of the timing of administration of *d*-chlorpheniramine.

The experiment consisted of three stages: baseline, hypnotic induction and electrical stimulation with hypnotic suggestion. After baseline measurement, subjects received hypnotic induction according to a standard method.[23] Subjects received electrical stimulation with 30 mA and sham stimulation with 0 mA under three hypnotic conditions (neutral, hyperalgesic, or analgesic) at random. Before each CEP recording, subjects were given the neutral, hyperalgesic, or analgesic suggestion for neutralizing, increasing, or decreasing abdominal pain affect respectively.

Subjects rated both intensity of abdominal pain and unpleasantness of abdominal pain using the ordinate scale from 0 (none) to 10 (maximum) immediately after each condition.[24]

Data analysis

For CEP data and visceral perception data acquired under each condition, a multivariate repeated measures analysis of variance [ANOVA: stimulation (0 mA *vs* 30 mA) × suggestion (neutral *vs* hyperalgesic *vs* analgesic) × drug (saline *vs* *d*-chlorpheniraqmine) as within subject] was conducted. *Post hoc* test was performed when the significant main effect or interaction were detected in ANOVAS. Furthermore, to test the strength of the relation between subjective visceral sensation and electrophysiological properties of the CEP components, regression analyses of the unpleasantness ratings and the CEP components across all participants were performed. After removing effects due to interpersonal variability, the residual variance in CEP components and unpleasantness rating were analysed for correlation analyses.[4] Values in the text were expressed as mean ± standard error. The level of significance was set at a P-value <0.05.

RESULTS

Effect of hypnotic suggestion on visceral perception

Hypnotic suggestion dramatically changed the form of CEP in healthy subjects (Fig. 1A). Compared with neutral suggestion, analgesic suggestion dampened CEP amplitude, whereas hyperalgesic suggestion did not change it (Fig. 1A). Cerebral evoked potential was triphasic and consisted of N1, P1 and N2. Analgesic suggestion induced a significant decrease in CEP amplitude of the P1–N2 component [$F(2,20) = 3.71$, $P = 0.043$] (Fig. 2B) but not in that of the N1–P1 component (Fig. 2A). On the other hand, hyperalgesic suggestion resulted no significant change in CEP amplitude in both the N1–P1 and P1–N2 components. The latency of the N1, P1 and N2 components was not different amongst the three hypnotic suggestions (Fig. 3A,B).

The subjects rated sham stimulation with 0 mA as no or weak sensation and showed no significant difference in visceral perception to the sham stimulation amongst the three hypnotic suggestions (neutral: 0.5 ± 1.0; hyperalgesic: 0.8 ± 1.2; analgesic: 0.2 ± 0.4). On the other hand, the stimulus with 30 mA induced moderate sensation and unpleasantness in the subjects. More importantly, both unpleasantness of pain [$F(2,44) = 17.91$, $P < 0.0001$] and its intensity [$F(2,44) = 10.00$, $P < 0.001$] were significantly enhanced by the hyperalgesic suggestion, but attenuated by the analgesic suggestion (Fig. 4A,B).

For hyperalgesic effects, we found that the N1–P1 and P1–N2 amplitude was positively correlated (N1–P1: Pearson's correlation coefficient, $r = 0.687$, $P = 0.001$; P1–N2: $r = 0.650$, $P = 0.001$), and the N1

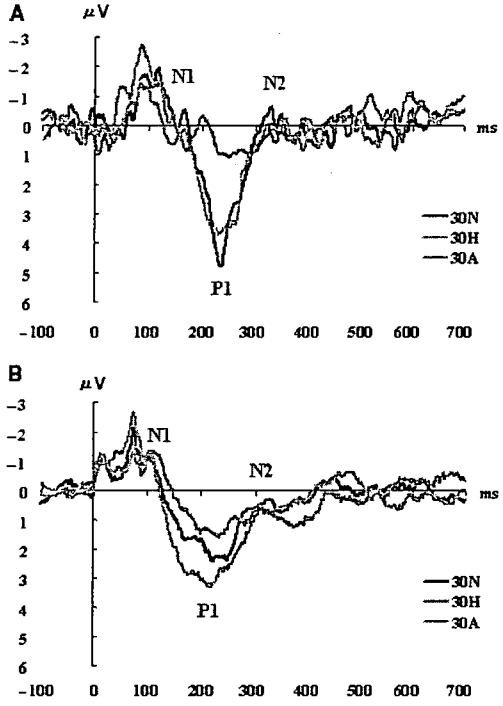

Figure 1 The grand mean averaged cerebral evoked potential responses to electrical stimulation of the rectum with 30 mA from (A) 12 healthy subjects treated with placebo and (B) 12 healthy subjects treated with *d*-chlorpheniramine. Each line indicates the effects of a suggestion under hypnosis (black line, neutral suggestion; red line, hyperalgesic suggestion; and green line, analgesic suggestion).

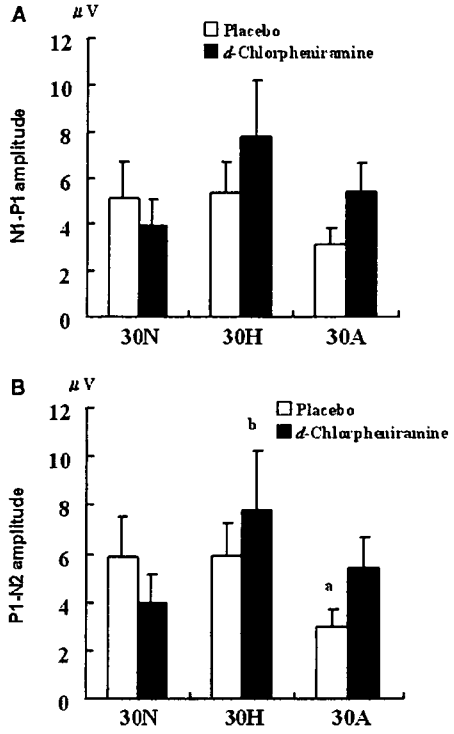

Figure 2 The amplitude (μV) of cerebral evoked potential (CEP) components after electrical stimulation of the rectum with 30 mA. (A) The N1–P1 amplitude nd (B) P1–N2 amplitude of rectal CEP in placebo condition and *d*-chlorpheniramine condition. [a]Denotes a significant decrease in amplitude compared with neutral suggestion ($P = 0.043$). [b]Denotes a significant increase in amplitude compared with neutral suggestion ($P = 0.007$). 30N: neutral, 30H: hyperalgesic, 30A: analgesic, suggestion with 30 mA. Values are expressed as mean ± SE.

latency was negatively correlated with the unpleasantness rating ($r = -0.514$, $P = 0.012$). For analgesic effects, we also found that the N1–P1 and P1–N2 amplitude was positively correlated (N1–P1: Pearson's correlation coefficient, $r = 0.828$, $P < 0.001$; P1–N2: $r = 0.850$, $P < 0.001$), and the N1 latency was negatively correlated with the unpleasantness rating ($r = -0.608$, $P = 0.002$).

Effect of histamine H_1R blockage on hypnotic modulation of visceral perception

Blockage of the H_1R remarkably changed the morphology of CEP in the healthy subjects (Fig. 1B). The reduction in CEP amplitude induced by analgesic suggestion after treatment with placebo was reversed when *d*-chlorpheniramine was administered. The P1–N2 component of CEP amplitude (Fig. 2B) showed significant effect of drug × suggestion interaction as indicated by ANOVA [$F(2,22) = 3.40$, $P = 0.033$]. In H_1R blockage condition, analgesic suggestion failed to reduce the P1–N2 amplitude ($P = 0.302$) but hyperalgesic suggestion induced a significant increase in the P1–N2 amplitude ($P = 0.007$). ANOVA of the N1–P1 amplitude showed no significant effect of *d*-chlorpheniramine (Fig. 2A). A significant main effect of drug on the P1 latency was observed by ANOVA, indicating a shorter latency with *d*-chlorpheniramine than with placebo [$F(1,11) = 7.74$, $P = 0.018$] (Fig. 3B). ANOVA showed tendency of shorter N1 latency as the marginal main effect of drug [$F(1,11) = 4.58$, $P = 0.056$] (Fig. 3A). ANOVA of the N2 latency showed no significant effect of *d*-chlorpheniramine (Fig. 3C).

For subjective visceral perception, no significant effect of drug or drug × suggestion interaction on unpleasantness of pain or intensity of pain was observed (Fig. 4A,B). However, compared with the placebo condition, the H_1R blockage condition attenuated the analgesic effect in subjective unpleasantness. Indeed, independent *t*-analysis showed significant difference between the neutral and analgesic suggestion

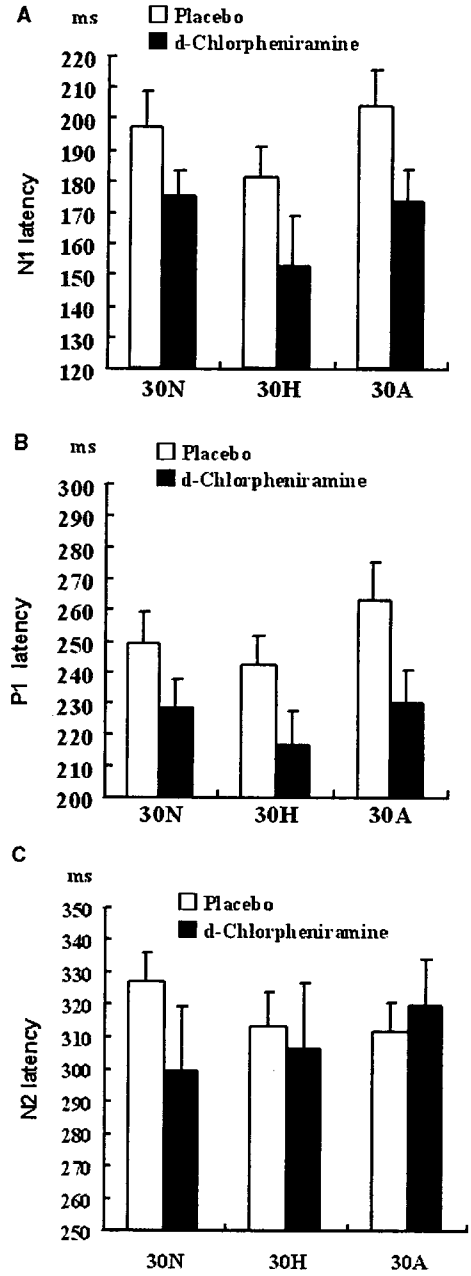

Figure 3 The latency (ms) of cerebral evoked potential (CEP) components after electrical stimulation of the rectum with 30 mA. (A) The N1 latency, (B) P1 latency and (C) N2 latency of rectal CEP in placebo condition and *d*-chlorpheniramine condition. 30N: neutral, 30H: hyperalgesic, 30A: analgesic, suggestion with 30 mA. Values are expressed as mean ± SE.

with the placebo condition [$t(44) = 2.17$, $P = 0.036$] but not the H_1R blockage condition [$t(44) = 0.48$, $P = 0.634$] (Fig. 4B).

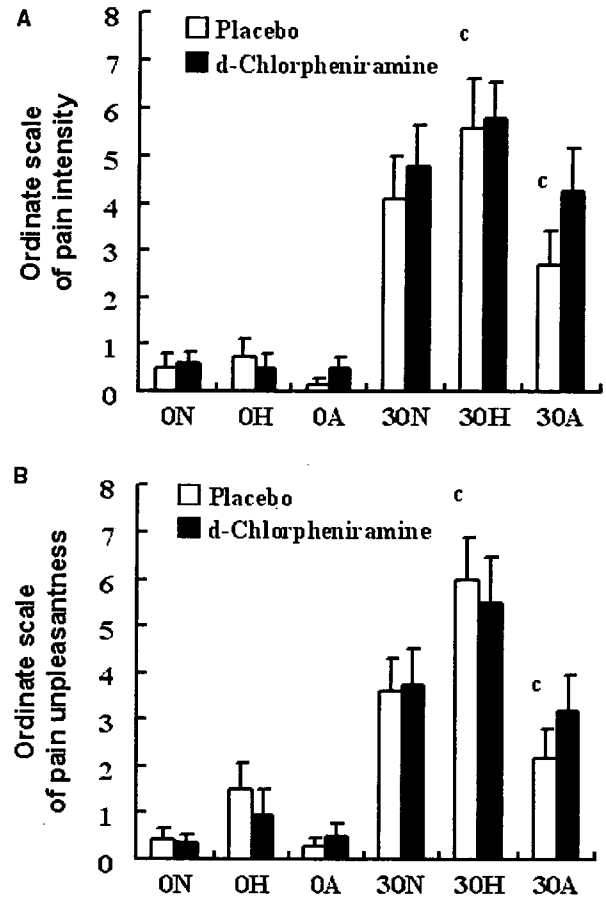

Figure 4 The ordinate scale (0–10) of visceral perception to electrical stimulation of the rectum with 0 mA or 30 mA. (A) The pain intensity, (B) pain unpleasantness in ordinate scales in placebo condition and *d*-chlorpheniramine condition. [c]Denotes significant changes compared with neutral suggestion ($P < 0.001$). 0N: neutral, 0H: hyperalgesic, 0A: analgesic, suggestion with 0 mA (sham stimulation), 30N: neutral, 30H: hyperalgesic, 30A: analgesic, suggestion with 30 mA. Values are expressed as mean ± SE.

Threshold of electrical stimulation of the rectum

Threshold of the electrical stimulation of the rectum indicated as follows; sensation: 16.8 ± 1.9 mA, discomfort: 28.7 ± 2.5 mA and pain: 37.4 ± 2.0 mA.

DISCUSSION

This study is the first to show that hypnotic suggestion changes electrophysiological processing of visceral perception in the human brain under normal visceral states and that this change is at least in part dependent on neuronal histamine. Visceral perception has long been believed to be a consciously uncontrollable

phenomenon. However, this study opens a new door to explore brain neurocircuit in the processing and control of visceral perception.

In this study, reasonable pain reduction was associated with a decrease in CEP amplitude. In many studies, great care is taken to prevent subjective factors from causing bias. However, for visceral perception during hypnotic modulation only few objective measures have been reported. Previous studies on CEP following gastrointestinal stimulation have showed that recording of CEP is a reliable and reproducible method for studying gastrointestinal sensory pathways.[15,16] In addition, Our previous studies have shown that as stimulation intensity and sensory perception increase, the latency of CEP components shortens and their amplitude increases.[17–19] This phenomenon is common across all evoked potential modalities and reflects the recruitment of an increasing number of afferents with faster conduction velocity.[25] The fact that analgesic suggestion reduced CEP amplitude with a concomitant decrease in subjective sensations to rectal stimulation provides evidence of the high inducibility of adaptive modulation of visceral perception via a functional module of the brain. On the other hand, hyperalgesic suggestion induced changes in subjective ratings of perception which well correlated with CEP changes. However, all CEP components did not always change significantly. These results suggest that the hyperalgesic effect on verbal responses was more dependent on the cortico-cortical modulation rather than the activations of afferent pathways.[26]

Previous studies of evoked potentials in other sensory systems have shown that an increase in evoked potential amplitude can occur either due to an increase in excitability of the afferent pathways or via an inhibition of the descending pain inhibitory system.[27,28] Previous studies examining brain activity during pain modulation by suggestion-induced expectation confirm that increased activity were found in brain areas controlling descending inhibitory systems, but may not in brain areas receiving ascending nociceptive input.[3] The descending pain modulatory system is well characterized as anatomical network that enables us to regulate nociceptive processing (largely within the dorsal horn) in various circumstances and produce either facilitation (pronociception) or inhibition (antinociception).[25] Signals of EEG can well document this type of inhibitory control in humans.[29–31] In our study, analgesic suggestion may have induced a certain expectation of decreased pain and probably induced increased activity of the inhibition components of the descending pain modulatory system, as well as top–down pain control. Such change would allow reduction in CEP P1–N2 amplitude but not delay in CEP latencies. Our findings provide the first evidence that hypnotic modulation can alter visceral perception by changing electrophysiological properties in time-window of 200–300 ms following visceral stimulation in the human brain.

In this study, the modulatory effects of analgesic suggestion on brain processing of visceral perception were proved to be at least in part dependent on histaminergic neurons. This is a great advantage of this study because identification of the controlling molecule of suggestion and pain will produce further understanding of the central control of pain. Peripheral histamine is involved in stimulation of nociceptive fibres.[10–13] Clinically, antihistamines are empirically administered to expect augmented antinociception in para-anaesthetic medication. On the other hands, central histamine has both analgesic[12,32–34] and algesic[11,13,35,36] effects. It has emerged that central histamine plays an important role in antinociception.[37] The evidence supporting antinociceptive (but not pronociceptive) action of central histamine can be summarized as follows: (i) histamine, when applied into the cerebral ventricles or PAG, has an analgesic effect in several paradigms including the tail-flic and hot-plate tests;[12,32–33] and (ii) H_1 and/or H_2 receptor antagonists block central histamine-mediated antinociception. Both H_1 and H_2 receptor antagonists when applied intracerebrovenricularly or into the PAG, have been shown to block central histamine-induced antinociception.[32–34] The descending histaminergic neurons originate from the hypothalamus and terminate at the PAG and the dorsal horn of the spinal cord.[9] In addition, in human brain, the highest H_1R binding sites are in the limbic system and the cerebral cortex (especially prefrontal, temporal and cingulate regions).[38] The descending influences from prefrontal cortex that elicit inhibition of nociceptive transmission are being identified in different behavioural circumstances; such as during hypnotic or placebo suggestions. In this study, administration of H_1R antagonist to the healthy subjects clearly reversed analgesic suggestion-induced reduction in P1 amplitude and subjective visceral pain. Therefore, during hypnotic suggestion in human, the H_1R blockage might inhibit the descending inhibitory control via deactivation of histamine neurons in fronto-cingulate regions.

In this study, the H_1R blockage resulted in the overall shortening of CEP latencies. Attenuation of the endogenous components of CEP results in the overall shortening of CEP latencies.[31] The highest histamine H_1 binding sites are in the limbic system and the

cerebral cortex.[38] Therefore, in human brain, the H_1R blockage might attenuate the endogenous components of CEP via deactivation of histamine neurons in cerebral cortical regions.

In conclusion, we could prove the hypothesis that hypnotic suggestion modulates brain processing of visceroafferent signals recorded by CEP. We have also shown in this study that blockage of the H_1 reduces analgesic effects of hypnotic suggestion in healthy normal subjects.

ACKNOWLEDGMENTS

We would like to thank Prof. Kazuhiko Yanai and Prof. Masatoshi Itou for their advice throughout this study. This research was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan, by Grant-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan, and by Grant-in-Aid for Research from IBS Club. This manuscript is a part of the doctorial dissertation at Tohoku University.

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