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Introduction

Psychological stress induces symptoms in the lower digestive tract of humans such as abdominal pain, diarrhea or constipation[1)]. These phenomena are explained by stress-induced colonic motility[2)] and visceral perception abhorred by the stress[3)]. Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized with chronic abdominal pain and abdominal bowel habituation. Recently, research of IBS has been given much attention because of high prevalence and the great influence on the medical economy. However, the cause and the pathophysiology are uncertain. The functional relation between the central nervous system and the gastrointestinal tract is beginning to be clarified[2)] and the brain-gut interaction is considered to be a major pathophysiology of IBS.

The functional module of the brain in response to colorectal distention has not been completely determined yet. Whether the visceral perception is actually projected to the somatosensory area is doubtful. Silverman et al., reported that rectal distention induced activation of the anterior cingulate cortex in healthy persons but not in IBS patients[4)]. In contrast, Mertz et al., reported that in IBS patients, but not in healthy persons, painful stimuli to the rectum led to greater activation of the anterior cingulate cortex than did non-painful stimuli[5)]. Therefore, greater detailed information about the gastrointestinal tract to the brain is needed. Moreover, the stimulated part in earlier studies was the rectum but the pain-producing part in IBS patients is thought to be the colon. In addition, there are a lot of uncertain points in the brain area which relate to emotion provoked by visceral perception.

This study aims to verify the following hypotheses: there are regions of the brain which relate to visceral perception and emotion provoked by visceral stimulation.

Method

Subjects

Fifteen volunteers participated in this study. They were all male, right-handed, and aged 22±1 (mean±SE). All subjects were free from gastrointestinal symptoms or signs. Each underwent a basic evaluation to exclude organic diseases including medical history and were given a physical examination and colonoscopy. All subjects gave informed consent as approved by the Ethics Committee in Tohoku University School of Medicine.

Distention Protocol

On the day before examination, the subjects took a low residue diet. At 21: 00 before the examination, they ingested 17g (13.6%) of magnesium citrate, 75mg of sodium picosulfate, and 24mg of sennoside A & B to cleanse the colon. Subjects were tested in the fasted state at 8: 15. A colonoscope was inserted into the splenic flexure and a splinting device was inserted along the scope. After the removal of the scope, a plastic tube with a thin polyethylene bag (Synectics Medical, Stockholm) was inserted into the descending colon. The maximal volume of the bag was 700 ml and the maximal diameter of the bag at full inflation was 10 cm. The location of the bag was confirmed with X-ray fluoroscopy. The splinting device was removed and the bag was taped in place. Subjects rested in bed from 9: 15.

The colonic distention stimuli were provided with a computerized barostat pump (Medtronics Synectics, Shoreview, MN). The sham stimulation with 0 mmHg was given at first. The colon was then stimulated with the bag pressure of 0 mmHg, 20 mmHg, and 40 mmHg for 80 seconds. The intensity of stimulus was randomly given to avoid the order effect of the stimulation.

After the stimulation, subjects were asked the following 7 items of visceral sensation or emotion: abdominal discomfort, abdominal distention, abdominal pain, urgency, perceived stress, sleepiness, and anxiety. They judged the sensation from 0 ("not sensed") to 10 ("maximally sensed") on the ordinate scale, which was previously validated [6)].

Positron emission tomography (PET) scanning

[^{15}O] labeled water which was synthesized by the cyclotron was injected into the right arm vein at the beginning of colonic distention. Ten seconds later, both radioactivity and peak pressure of the bag reached plateau. The PET scan was then started and continued for 70 seconds. We measured rCBF during 4 scans (70 seconds each) using a PET scanner in three-dimension sampling mode (HEADTOME V SET-2400W, Shimadzu, Japan). To ensure that the radioactivity levels in the subjects returned to background before starting a new scan, a 10 min interval was given between successive scans.

Analysis

The PET image analyzed for brain image analysis software (Statistical Parametric Mapping；SPM99, The Wellcome Department of Cognitive Neurology, London) according to the Friston method[7-9)]. The PET images were realigned, spatially normalized and transformed into an approximate Talairach-Tournoux stereotactic space[10)], 3D Gaussian filtered (FWHM = 13 mm), and proportionally scaled to account for global confounders. The size of each voxel was set at 2×2×2 mm. The individual specificity of the whole brain blood flow between subjects was corrected in analysis of covariance (ANCOVA).

The multiple regression analysis was done on each voxel of each ordinate scale and the whole brain in each stimulation in order to clarify the region where the rCBF fluctuated by correlating with visceral perception and emotion. We set 0.1 % level of significance or less (uncorrected, $Z > 3.60$) at the region of significant correlation.

Results

Numerous brain regions correlate significantly and positively to visceral perception and emotion in results of multiple regression analysis of threshold set at Z value > 3.60, uncorrected $p < 0.001$. They were the cortical and limbic area, e.g., superior frontal gyrus (BA 10), middle frontal gyrus (BA 9 and 10), inferior frontal gyrus (BA 39, 40, and 44), precentral gyrus (BA 6), postcentral gyrus (BA40), cingulate gyrus (BA 24 and 32), hippocampal gyrus (BA35), parahippocampal gyrus (BA 20), insula, and thalamus.

Abdominal discomfort showed a significant positive correlation to rCBF in the right inferior parietal lobe (BA 40) contained in the inferior frontal gyrus (BA 44)(Fig. 1-a). Abdominal distention showed a significant positive correlation to rCBF in the right inferior frontal gyrus (BA 44) and the inferior parietal lobe (BA 40) (Fig. 1-b).

Abdominal pain showed a significant positive correlation to rCBF in the right inferior parietal lobe (BA40) and the left cerebellum. Perceived stress showed a significant positive correlation to rCBF in the right inferior parietal lobe (BA40). Urgency, anxiety and sleepiness showed no significant positive or negative relation to rCBF at analysis with the corrected p value.

Discussion

Our data revealed a positive relation between abdominal distention and rCBF of the left inferior parietal somatosensory cortex, which is consistent with an earlier report[11)]. Hobday et al., reported that rectal balloon distention induced activation of the inferior comatosensory (S1) cortex[11)]. The signal from the visceral organ is projected to the prefrontal cortex from the lateral thalamic nucleus group[12)]. This might be related to recognition of orientation of the stimulated body. The earlier reports[4),5),11)] stimulated the rectum, which integrates visceral information. However, in this study, pure visceral viscas were stimulated. Therefore, the results of this study strongly suggest co-activation of the somatosensory cortex with the prefrontal cortex and the anterior cingulate cortex.

Several reports have indicated that the anterior cingulate cortex is activated with the stimulation of the colorectum[4),5),13)]. The results of this study are consistent with those earlier reports. Moreover, increased rCBF in the anterior cingulate cortex is proportional to visceral perception, suggesting that this limbic cortex plays a major role in gastrointestinal symptoms in humans. The supplementary motor cortex which between the limbic cortex and the primary motor cortex was also activated in this study. The supplementary motor area is mutually being coupled with the anterior cingulate cortex, the primary motor cortex, and the prefrontal cortex[14)]. Goldberg et al., has advocated the idea of an intermediary role of the supplementary motor cortex[15)]. The supplementary motor area may choose order and strategy of dealing with motion for a realization of the stimuli to humans. The relation between perceived stress and rCBF of the right prefrontal cortex in this study may indicate the preparation of motion against stress and avoidant behavior at the sensation of unease.

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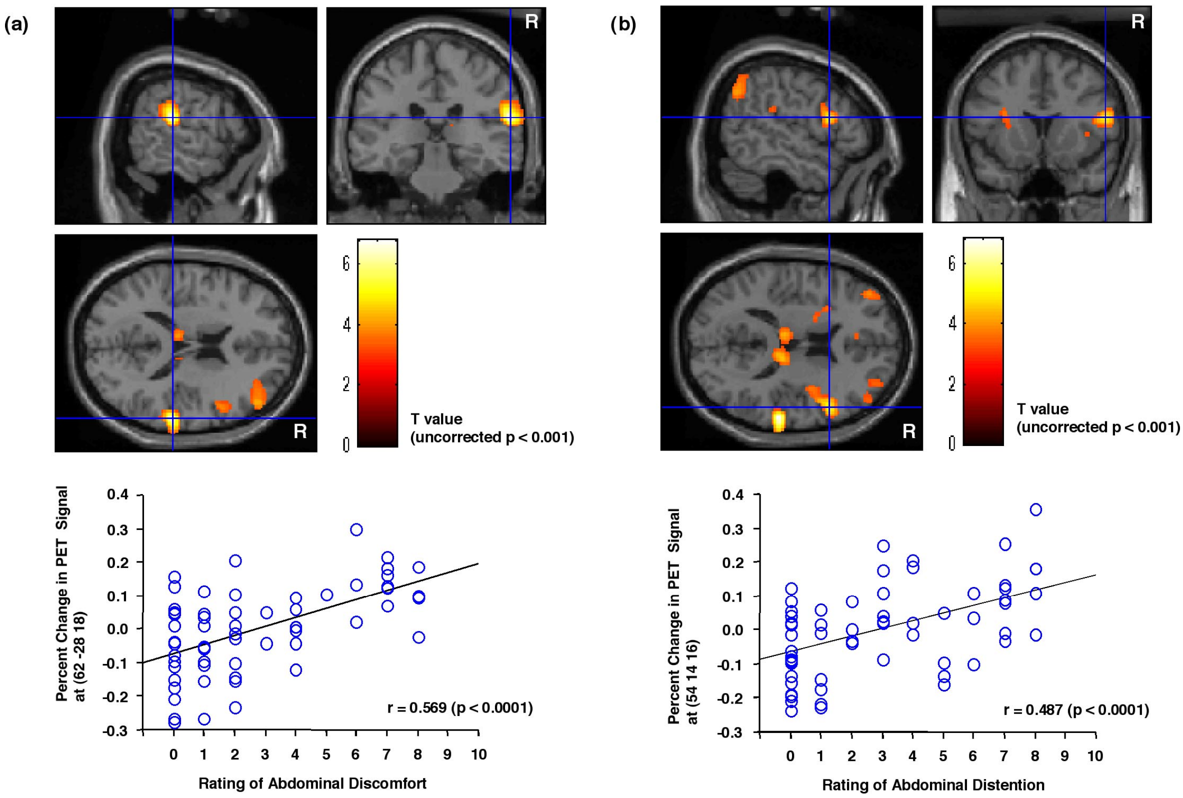

Fig. 1. Brain regions of positive correlation to visceral perception and emotion. Results from the multiple regression analysis. (a) shows demonstrating voxels in the right inferior parietal lobule, (x y z), (62 -28 18), contained the postcentral gyrus and the inferior frontal gyrus that correlated significantly to abdominal discomfort. There were superimposed on the structural MRI scan of a single subject. (b) shows demonstrating voxels in the right inferior frontal gyrus, (x y z), (54 14 16) that correlated significantly to abdominal distention. The bottom shows the median percent change in PET signal from baseline across subjects (with the value for each subject in the ordinate scale) for rating of visceral perception and emotion. Results are from the single regression analysis.