Differential Activation in Amygdala and Plasma Noradrenaline during Colorectal Distention by Administration of Corticotropin-reporteleasing Hormone between Healthy Individuals and Patients with Irritable Bowel Syndrome

VII. 6. Differential Activation in Amygdala and Plasma Noradrenaline during Colorectal Distention by Administration of Corticotropin-reporteleasing Hormone between Healthy Individuals and Patients with Irritable Bowel Syndrome

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Corticotropin-releasing hormone (CRH) is a major mediator of stress responses in the brain-gut axis. Hypothalamic CRH secretion results in secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which stimulates the adrenal gland to release cortisol. CRH receptors are widely distributed in the intestine as well as throughout the central nervous system[1)]. Functional brain imaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) during visceral stimulation in IBS patients[2)] showed more activation in the insula, cingulate cortex, prefrontal cortices, amygdala, and hippocampus[3)] compared to healthy controls. In this study, we investigated the influence of CRH on HPA-axis and brain responses to visceral stimuli in IBS patients and healthy controls. Here, we hypothesized that exogenous administration of CRH in IBS patients is associated with increased responses in both the “visceral pain matrix”, especially the emotional-arousal network, and the ACTH-cortisol axes compared to healthy controls.

We enrolled 16 male IBS patients and 16 male healthy subjects, and randomly divided them between CRH and saline injection groups. All of the IBS patients were diagnosed based on the Rome lll criteria[4)]. The State-Trait Anxiety Inventory and

Self-Rating Depression Scale were used to assess their anxiety and depression levels and showed no significant differences between IBS and HC groups. This study was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine, Japan. We used the barostat protocol. A bag was inserted into the colorectum. The catheter was then connected to computerized barostat equipment (Synectics Visceral Stimulator; Medtronics Synectics; Shoreview, MN). The patients randomly underwent no (0 mmHg), mild (20 mmHg), or strong (40 mmHg) colorectal distension. CRH (2 μg/kg) or saline was then administered via injection, and the distention protocol was repeated. Blood samples were obtained from an intravenous cannula after each period, and subjective symptoms were evaluated using an ordinate scale[2)]. rCBF in each subject was measured using a PET scanner in three-dimension sampling mode (HEADTOME V SET-2400W; Shimadzu, Kyoto, Japan). The scanner produced 63 transaxial slices with a thickness of 3.125 mm, an axial field of view of 200 mm, an in-plane resolution of 5.9 mm, full width at half maximum (FWHM), and an axial resolution of 3.9 mm FWHM. For each scan, 30 seconds after receiving injection of approximately 185 MBq of $H_2{}^{15}O$ intravenously through the right cubital vein, colorectal bag inflation was started. Data acquisition (70 s) began after barostat bag inflation. Plasma noradrenaline, adrenaline, ACTH, and cortisol levels were measured at the time of each distention. Data were analyzed using SPM8. ROIs were defined using the Wake Forest University (Winston-Salem, North Carolina) PickAtlas toolbox in SPM8 as follows: amygdala, hippocampus, insula, secondary/primary somatosensory cortex, anterior cingulate cortex, midcingulate cortex, thalamus, posterior cingulate cortex, medial prefrontal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, midbrain and pons. Active voxels for each ROI were considered statistically significant at a threshold of Family-Wise Error (FWE) corrected $P < .05$. An overall generalized estimating equation (GEE) analysis (SPSS 21.0, IBM Corp.) was performed during the random distention.

The comparison between IBS patients and controls at baseline after CRH injection showed significantly higher activity in the right amygdala in IBS patients compared to controls in a regions of interest (ROI) analysis ($t = 3.63$, cluster [k] = 42, ROI PFWE-corr = .017; local maximum—x: 34, y: 2, z: -22) (Figure). There was no significant difference between IBS patients and controls for the contrast baseline after saline injection – baseline before saline injection. The controls receiving CRH injection showed significantly stronger activation in the amygdala, hippocampus and middle cingulate cortex at intense distention

compared to baseline compared to those receiving saline injection in a ROI analysis (Fig. 1). However, there were no differences in brain responses between IBS patients receiving CRH injection compared to patients receiving saline injection.

The neuroendocrine changes after CRH or saline injection during random distention was analyzed using GEE. Plasma ACTH showed a significant drug effect ($P < .001$) and drug × distention interaction ($P = .027$) (Fig. 1). However, there was no significant difference between the two groups (IBS, controls). Serum cortisol levels showed a significant drug effect ($P < .001$), drug × distention interaction ($P < .001$) and drug × distention × group interaction ($P = .001$) (Fig. 1).

During random distention after drug injection, ordinate scale showed a significant group effect in the abdominal pain scale ($P < .001$). All ordinate scales showed significant distention effects.

We showed that exogenous administration of CRH modulates the increases in colorectal distention-induced activation of visceral sensation-related brain regions and neuroendocrine changes in both IBS patients and healthy controls. IBS patients had higher baseline activities in the amygdala, a key emotional-arousal area within the visceral pain networks, after CRH injection than controls. Rather, CRH increases colorectal distention-induced activity in the amygdala in healthy subjects but not IBS patients. Our findings suggest a ceiling response in the amygdala during CRH administration and colorectal distention in IBS patients and its synergetic activation of neuroendocrine function may be an important factor to trigger gastrointestinal symptoms in IBS patients[5)].

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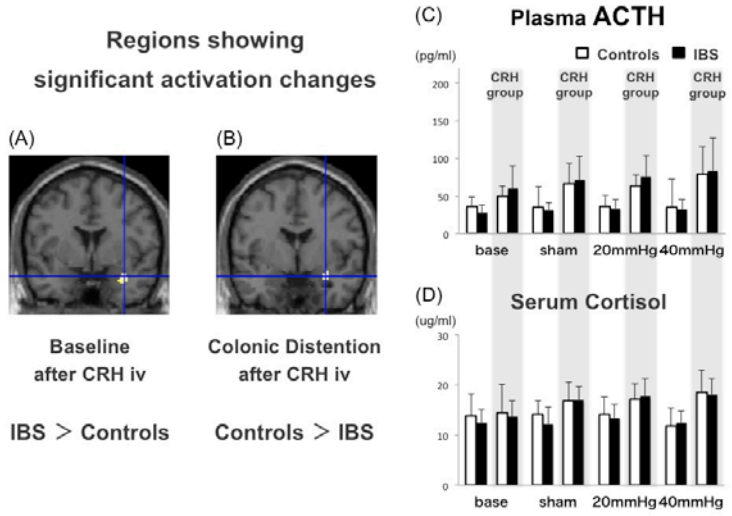

Figure 1. Regional brain and neuroendocrine responses. (A) IBS patients showed significantly more activity than controls in the right amygdala at baseline after CRH injection compared with that at baseline before CRH injection. (B) Controls showed significantly greater activation than IBS patients in the right amygdala at intense distention after CRH injection compared with saline injection than IBS patients. (C) A significant drug effect and drug × distention interaction in plasma ACTH (pg/ml) and (D) a significant drug effect, drug × distention interaction and drug × distention × group interaction in serum cortisol during random distention after drug injection was noted between controls with saline (n = 8), IBS patients with saline (n= 8), controls with CRH (n = 8) and IBS patients with CRH (n = 8), analyzed by GEE.