Increased Brain Histamine H1 receptor Binding in Patients with Anorexia Nervosa

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Introduction

Anorexia nervosa (AN) is a behavioral disorder characterized by fear of becoming obese, refusal to maintain a minimally normal body weight, disturbance of body image, and denial of the seriousness of the current low body weight[1)]. AN occurs mainly in adolescent or young adult females[1)]. AN patients start a self-imposed diet with chronic starvation featuring continuous strengthening symptoms and AN signs. The cause and progression of AN may involve biological vulnerability with dysfunction in the central neuron system being one of the most important causation factors.

The central histaminergic neuron system modulates various physiological functions such as wakefulness, sleep-awake cycle, fluid balance, body temperature, cardiovascular control, appetite control, stress-related hormone release, learning, memory, aggressive behavior, and emotion[2)]. Central histaminergic activity is increased by food intake after starvation[3)]. Also, dehydration has been reported to increase the synthesis and release of histamine in the hypothalamus[4)]. Moreover, H_1R concentration has been shown to be inversely correlated with food intake, particularly low protein diets[5)]. In addition, the central histaminergic neuron system is affected by various stressors[6-9)]. These findings suggest the alteration of central histaminergic activity in AN patients. However, there has been no report on AN.

We tested the following hypotheses in this study: females have higher H_1R density in the limbic system than males, and the density of central H_1R is increased in AN patients.

Methods and materials

Twelve female AN patients (BMI=14.1±1.7), 11 healthy age-matched male volunteers (BMI=20.4±1.3), and 12 healthy age-matched female volunteers (BMI=20.3±1.1) were enrolled in this study. All subjects gave a written informed consent.

Doxepin, a tricyclic antidepressant, was C-11 labeled and used as a PET tracer. The injected dose and cold mass of [^{11}C]doxepin were 117.0 ± 23.0 MBq (3.16 ± 0.62 mCi) and 1.86 ± 1.64 nmol, respectively.

The scanner collected 63 simultaneous transverse slices with a spatial resolution of 4 mm (transaxial) and 4.5 mm (axial) full-width at half-maximum in the center of the field of view. The sensitivity for a 20-cm cylindrical phantom was 48.6 kcps $kBq^{-1}mL^{-1}$ (1.8 Mcps $\mu Ci^{-1}mL^{-1}$) in the three-dimensional mode[10)]. Dynamic PET images were obtained for 90 min (22 sequential scans; 6 scans×90s, 7 scans×180s, 6 scans x 300s and 3 scans×600s) after [^{11}C]doxepin injection.

PET dynamic images, after being corrected for tissue attenuation, were reconstructed using a filtered back projection algorithm. The reconstructed PET images were co-registered to the identical stereotaxic brain coordinate system using its own MRI-T1 image as a reference. Regions of interest (ROIs) were first placed on the cerebellum. Information from the ROIs was automatically copied onto the co-registered PET images to obtain time activity curves (TACs). Cerebellar TAC was used as input function to calculate parametric brain images of the binding potential (BP) of [^{11}C]doxepin based on the graphical analysis method introduced by Logan and colleagues[11)]. The applicability of this method to a human study with [^{11}C]doxepin has been confirmed[12)]. Finally, brain BP images were created.

Results (Figs. 1-a, 1-b)

BP of [^{11}C]doxepin in control females was significantly higher than that in control males in the left (L)-Medial prefrontal cortex, right (R)-Orbitofrontal cortex, L-Orbitofrontal cortex, R-Temporal cortex, R-Amygdala, L-Amygdala, R-Hippocampas, and L-Hippocampas. On the other hand, there was no area where BP of [^{11}C]doxepin was significantly lower in control females than in males.

BP of [^{11}C]doxepin in AN patients was significantly higher than that in control females in L-Lentiform nucleus, and R-Amygdala. On the other hand, there was no area where BP of [^{11}C]doxepin was significantly lower in AN patients than in control females .

Discussion

The first point that can be drawn from our results is that the histaminergic neuron system in the human brain is different between males and females. In support of this finding, a human CSF study has shown that females have higher levels of histamine metabolites than males[13]. In addition, animal studies have also shown sex differences in the central histaminergic neuron system. These differences include H_1R densities (male<female)[14], suppressive effect of histidine on food intake (male<female)[15], stress related hypothalamic histamine release[16] in rat. These findings suggest that central histaminergic activity is higher in females than in males in both animals and humans. Thus, females may adapt better to starvation through the central histaminergic neuron system than males. The risk of developing AN may be increased by not only the social background that women want to be thin because people tend to admire a thin figure, but also biological vulnerability associated with central histaminergic activity.

The second point is that AN patients showed significantly higher BP of [^{11}C]doxepin in the amygdala and lentiform nucleus than healthy females. In our previous study, chronic food-deprivation-induced stress in rats, which can be an AN model, reduces central H_1R density[9]. In addition, a human PET study in patients with depressive disorder, which is one of the representative stress-related disorders, has shown lower BP of [^{11}C]doxepin in several brain areas in these patients than in healthy controls[17]. The decreased H_1R density and BP of [^{11}C]doxepin in these studies have been explained by the sustained release of endogenous histamine and the down-regulation of H_1R as a consequence of endogenous ligands. However, the present results show the opposite. If the increased BP of [^{11}C]doxepin in the amygdala is the cause of AN, females with higher H_1R in the amygdala may be more susceptible to AN. The increased BP of [^{11}C]doxepin in the amygdala of AN patients may also be a result of AN. Central histaminergic activity is increased by food intake after starvation (3) and H_1R concentration is increased by feeding low-protein diets (5). Starvation and feeding in AN patients may facilitate the increase in H_1R concentration in the amygdala.

BP of [^{11}C]doxepin in the orbitofrontal cortex, amygdala and hippocampus was higher in females and AN patients than in males. These brain areas may play important roles in the central modulation of eating behavior because they are parts of the limbic system controlling emotion, cognition, and decision making[18]. These are very interesting results associated with the characteristics observed in AN patients, such as distorted cognition and emotional changes to food and body image. Therefore, the central histaminergic neuron system may play a role in AN, not only through stimulation of the satiety center, but also through activation of advanced psychological systems.

In conclusion, the present study demonstrates that females have higher BP of $[^{11}C]$doxepin in the limbic system than males, and that AN patients have higher BP of $[^{11}C]$doxepin in the amygdala and lentiform nucleus than normal females. These findings suggest that the central histaminergic neuron system may play an important role in the pathophysiology of AN.

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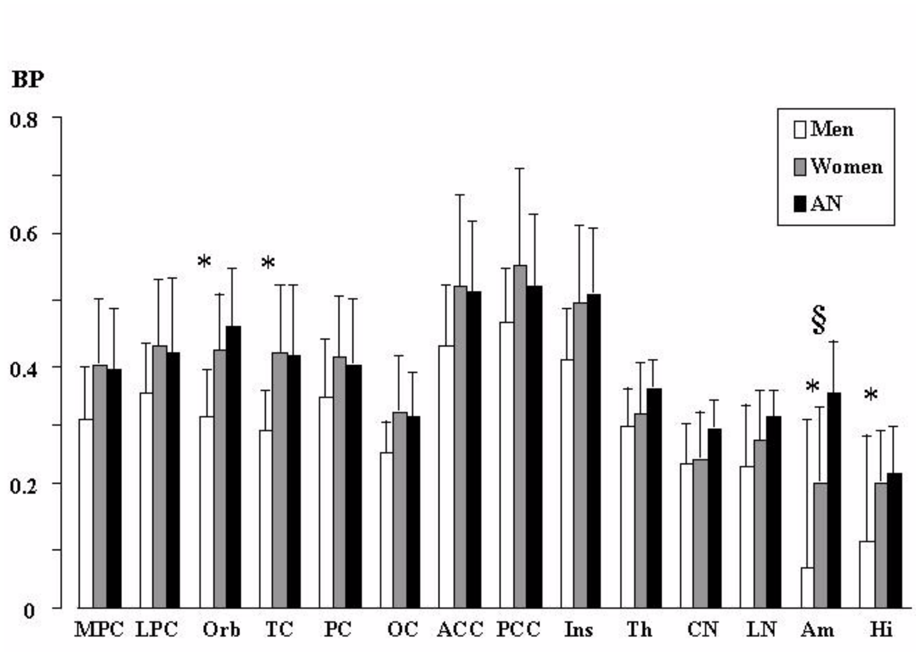

Figure 1 **(a)** ROI-based comparisons of BP of [^{11}C]doxepin in the right cerebral hemisphere MPC, medial prefrontal cortex; LPC, lateral prefrontal cortex; Orb, orbitofrontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Ins, insula; Th, thalamus; CN, caudate nucleus; LN, lentiform nucleus; Am, amygdala; Hi, hippocampus.
* Men vs. Women ($p<0.05$), § Women vs. AN ($p<0.05$).

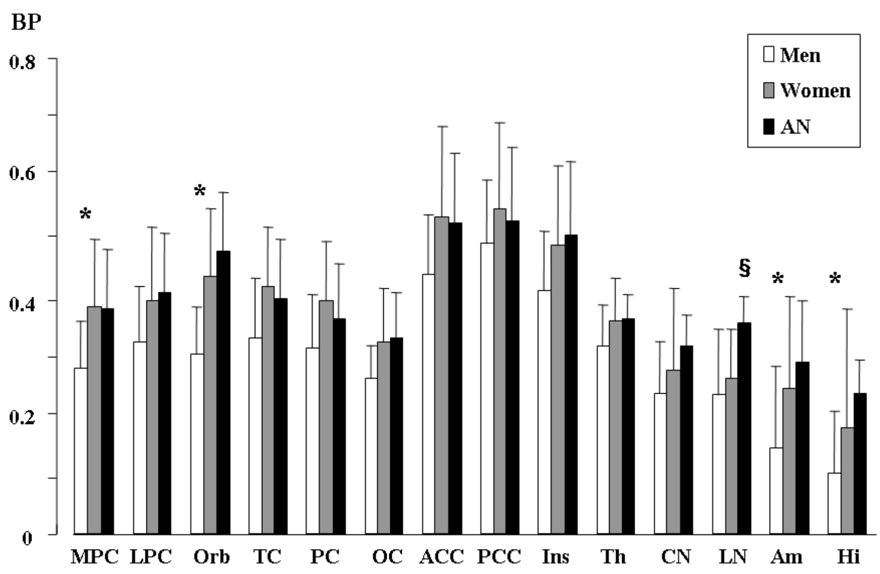

Figure 1. **(b)** ROI-based comparisons of BP of [^{11}C]doxepin in the left cerebral hemisphere.