

## Central Itching Modulation : A Human PET Study

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## VIII. 1. Central Itching Modulation : A Human PET Study

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### **Introduction**

Itching can be defined as “an unpleasant sensation associated with the desire to scratch”<sup>1)</sup>. Scratching behavior in atopic dermatitis can become just as unbearable and debilitating as chronic pain, leading to depression and suicidal thoughts. Generally, antihistamines are prescribed for patients with allergic diseases to suppress itching symptoms through the blockade of histamine H1 receptors (H1R)<sup>2)</sup>. However, administration of antihistamines, especially of the first generation, interfere with the activities of daily living and with work that requires full alertness, since they elicit sedation and impair various cognitive functions such as psychomotor speed and learning<sup>3)</sup>. The unpleasant sensation caused by itching can also be reduced by cooling. Skin cooling can reduce itch sensation without aggravation while scratching tends to aggravate the symptom and while antihistamines often cause sedation. Interestingly, Murray reported that the itching sensation, when itch and pain stimuli were applied to different parts of the body, was lower than the itching alone. They predicted the presence of the central itch modulation system, though details of the system were not understood<sup>4)</sup>. However, as far as the authors know, little has been reported focusing on the itch inhibitory mechanism by cooling in the brain. Even it is still unclear whether such mechanism exists in human brains or not.

Therefore, in the present study, we investigated the mechanism of itch modulation by cooling in human brains using PET and H<sub>2</sub><sup>15</sup>O.

## Methods

Fifteen healthy male volunteers (mean  $\pm$  SD of age,  $22 \pm 2.3$  years old) were included in the present study. Subjects with a history of allergy, atopic eczema or other dermatological diseases were excluded from the study. Written informed consent was obtained from each subject and the study was performed in compliance with the relevant laws and institutional guidelines.

In the present study, PET measurement was conducted under 6 different conditions as follows: Condition 1) saline stimulus, Condition 2) mild itching stimulus with 0.001 % histamine solution, Condition 3) intense itching stimulus with 0.01% histamine solution, Condition 4) dual stimulations of intense itching (0.01 % histamine) and cold pain (5°C) (dual stimuli), Condition 5) cold pain stimulus (5°C), and the resting condition (condition 6).

Two different concentrations of histamine solution were used in the present study to verify the dose-dependency. The histamine solutions (0.01% and 0.001%) were prepared by dissolving histamine to saline. Two ml of the histamine solution was infiltrated into a square electrode pad (2 cm x 2 cm), which was attached to the back of the right foot. Itch sensation was elicited by the electrical subcutaneous penetration of the histamine solution with iontophoresis system (UI-2060, Uniflows, Japan). In the present study, the electrical current given by the iontophoresis was 1 mA. The duration of the iontophoretic stimuli was 2 min (total charge: 120 mC, 1 mA x 120 sec). A saline condition served as a control for the itching stimuli where the saline solution (2 ml) was applied to the subjects in the same way as itching stimulus conditions using iontophoresis. No stimulus was given to the left foot in the following three conditions: 1) saline, 2) mild and 3) intense itching stimulus conditions. In the dual stimuli condition, the intense itching and cold pain stimuli were simultaneously applied to the right and left feet, respectively. For cold pain stimulus, thermocooler (Thermal cycler, Japan) was used to keep the skin temperature of the back of the left foot at 5°C, where the areas to be stimulated by iontophoresis and cold pain were controlled to be equal (2 cm x 2 cm). The cold pain stimulus was given to the left foot for 2 min simultaneously with the intense itching stimulus. The sequence of conditions 3 (intense itching stimulus) and 4 (dual stimuli) were randomized among the subjects. We employed the cold pain stimulus condition in order to examine whether the regional cerebral blood flow (rCBF) changes observed in the dual stimuli was attributable to the cold

pain stimulus to the left foot or not. A control for the cold pain stimulus condition was the resting condition.

All subjects closed their eyes during PET scanning. Time intervals between scans were more than 10 min in order to eliminate the effect of previous itch and/or cold pain sensations. After each scanning, intensity and unpleasantness of subject's itch sensation was scaled with visual analog scales ranging from 0 to 10. When subjects feel no itch sensation on their right foot, the scale will be "0". When the itch intensity and unpleasantness is the worst in their past experience, the score will be "10".

The cerebral blood flow (CBF) images were obtained at whole brain level using a PET scanner (Shimadzu SET-2400W, Japan). PET measurement was performed for 70 sec. Subjects were injected with approximately 5.4 mCi (200 MBq) of [ $^{15}\text{O}$ ]-H<sub>2</sub>O through antecubital vein for each scan.

The CBF images obtained were processed and analyzed by Statistical Parametric Mapping (SPM) software (SPM99; Wellcome Department of Cognitive Neurology, London, U.K.). After realignment for intra-subject motion correction, all images were stereotaxially normalized, using linear and non-linear transformations into a standard space of Talairach and Tournoux. The normalized images were then smoothed using a 16 x 16 x 16 mm Gaussian filter. The values of rCBF were expressed as ml 100 g<sup>-1</sup> min<sup>-1</sup>, adjusted using ANCOVA and scaled to a mean of 50 ml / 100 g / min. The significant increase or decrease in rCBF was evaluated according to the general linear model at each voxel.

To test the hypotheses on specific rCBF changes, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the *t*-statistics. To discover brain regions related to the histamine stimulus, CBF images during the intense itching stimulus were compared to those during the saline stimulus. CBF images during the intense itching stimulus were compared to those during the dual stimuli to detect any rCBF difference between the conditions. The effect of cold pain stimulus on the brain activity was investigated by comparing CBF images in the cold pain stimulus condition to those in the rest. The *t*-value of each voxel was transformed into normally distributed *Z*-statistics. For each comparison, voxels with a *Z*-value higher than 2.99, corresponding to  $p < 0.001$  (uncorrected), were considered to represent regions with significant change in rCBF.

The changes of subjective feelings of itch intensity and unpleasantness were compared among the mild itching, the intense itching and the dual stimuli conditions with ANOVA and multiple comparison (Tukey). A probability of less than 0.05 was

considered to be statistically significant.

We performed volume of interests (VOI) analysis with SPM to compare the brain activity related to itching among the conditions such as the mild itching, the intense itching and the dual stimuli conditions. We determined the localization of the peak activation related to the intense itching stimulus as compared to the saline stimulus condition. Mean voxel values were calculated among the voxels including the peak and also exceeding a threshold of  $Z > 2.99$ . Mean of these voxel values reflected rCBF since all voxel values in the CBF images were scaled to a mean of 50 ml / 100 g / min. The rCBF changes in the mild itching, the intense itching and the dual stimuli conditions in comparison to the saline stimulus condition were examined by ANOVA and multiple comparison (Tukey). A probability of less than 0.05 was considered to be statistically significant.

## **Results**

Itch sensation induced by histamine increased in a dose-dependent fashion and decreased when the cold pain stimulus was given on the right foot (Fig.1). The significant increases of regional cerebral blood flow (rCBF) caused by histamine stimuli using iontophoresis were observed in the left anterior cingulate cortex (BA24), the left thalamus, the right anterior parietal cortex (BA40), the right posterior parietal cortex (BA7), the bilateral dorsolateral prefrontal cortex (BA46) and the right premotor cortex (BA6) (Fig.2). Activations in the itching-related brain regions were decreased by cold pain stimulus simultaneously given to the opposite side of the itching stimulus, as compared to itching alone (Fig.2). In addition, the midbrain including periaqueductal gray matter (PAG) was activated only during the simultaneous stimulation of itching and cold pain (Fig.3).

## **Discussion**

Several investigators have proposed hypotheses to account for the inhibitory mechanism of itch sensation by cooling in the central nervous system (CNS). However, it has been still unclear whether such a system exists in the human brain or not.

Subjective feelings of itch intensity and unpleasantness increased with the increment of histamine concentration, and the itch intensity during the dual stimuli was significantly lower than that during the intense itching stimulus (Fig.1). These results suggested that itch sensation was suppressed by the cold pain stimulus simultaneously given to the contralateral side of the itching stimulus. These results supported the presence of the itch modulation mechanism in the human brain<sup>4</sup>.

The rCBF in the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), the posterior parietal cortex and the premotor cortex increased with the increment of histamine concentration and decreased in the dual stimuli of itching and pain (Fig.2). Interestingly, midbrain including the periaqueductal gray matter (PAG) was activated during the dual stimuli as compared to the intense itching stimulus alone as shown in Fig.3. The midbrain did not show even any tendency toward increased rCBF in the cold pain stimulus condition or in the intense itching stimulus condition. PAG is known as the central pain modulation system. PAG neurons project axons down to the dorsal horns of the spinal cord via medulla and raphe nuclei, where they suppress the activity of nociceptive neurons<sup>5</sup>. Furthermore, in the animal study, it was demonstrated that spinal neuronal responses to histamine were markedly suppressed by electrical stimulation to the midbrain PAG<sup>6</sup>. In views of the previous reports, it was suggested that the activation of PAG was associated with the attenuation of the itch intensity and of the itch related-brain activity during the dual stimulations of itching and cold pain. Our results supported the hypothesis that the descending inhibitory mechanism of PAG for pain would also work for itch modulation.

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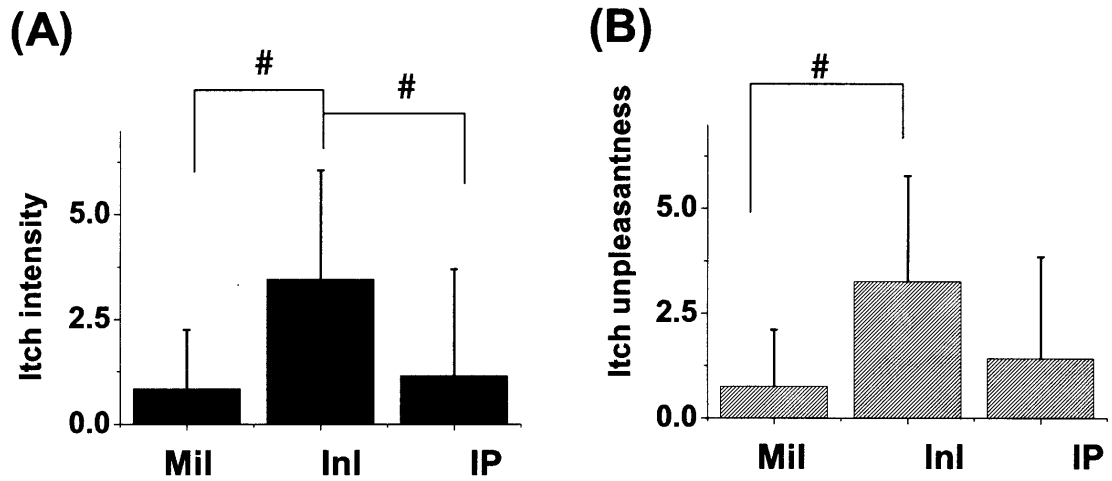


Fig. 1. The increases in subjective feelings of itch intensity (A) and unpleasantness (B) (mean and SD) in the mild itching stimulus (MiI), the intense itching stimulus (InI) and the dual stimulations of intense itching and cold pain (IP) conditions in comparison to the saline stimulus condition are shown. #:  $p < 0.05$  by ANOVA and post-hoc multiple comparison (Tukey).

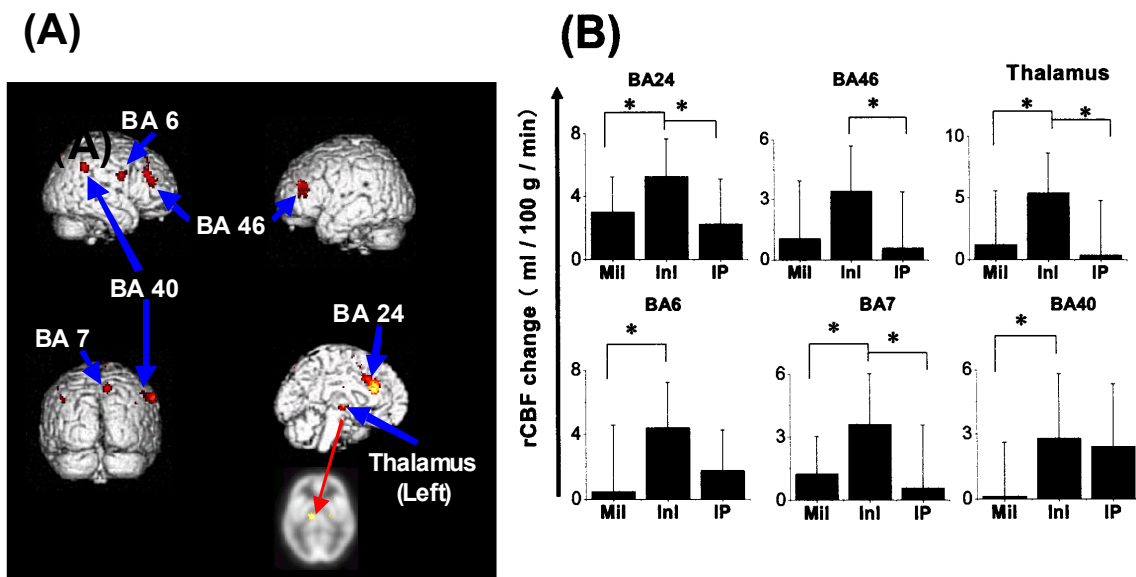


Fig. 2. (A) Areas of significant rCBF increase during the intense itching stimulus as compared to the saline stimulus (uncorrected  $p$  value  $< 0.001$ ). Red arrow shows the left thalamus on a transaxial slice of the PET template. (B) The change in rCBF (mean and SD) from the baseline (saline stimulus) in each brain region related to itching. Abbreviations: MiI = mild itching stimulus, InI = intense itching stimulus, IP = dual stimulations of intense itching and cold pain, L = left hemisphere and R = right hemisphere. \*:  $p < 0.05$  by ANOVA and post-hoc multiple comparison (Tukey).

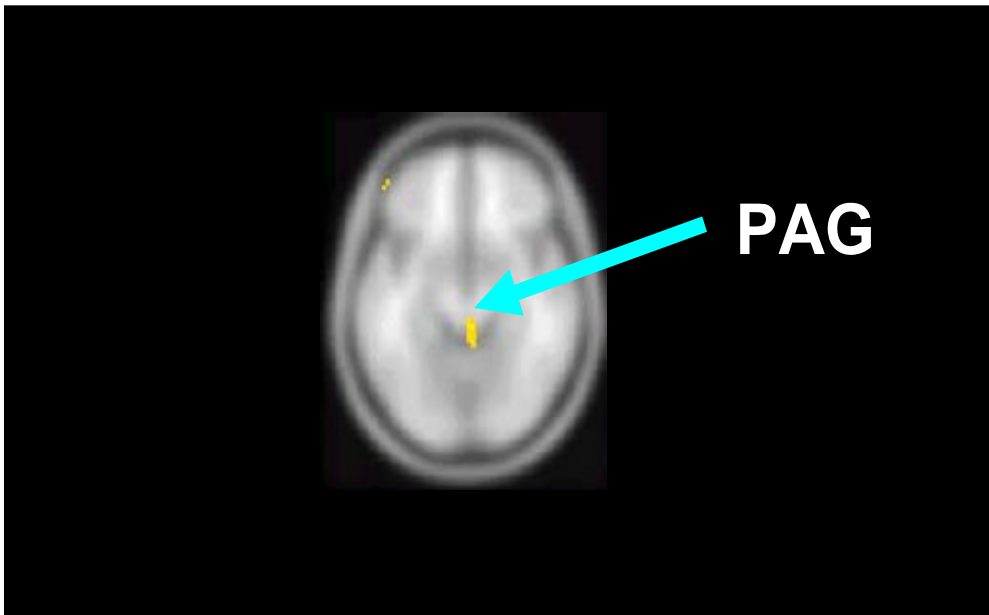


Fig. 3. Areas of rCBF increase during the dual stimuli as compared to the intense itching stimulus (uncorrected p value < 0.005). Blue arrow shows PAG on a transaxial slice of the MRI template.