IV. 3. Imaging of Histamine H1 Receptors in Human Brain and Impaired Cognitive Performance Induced by Second Generation Antihistamines


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Introduction

Histamine plays important roles in various physiological functions of immune, gastrointestinal and nervous systems. In the immune system, histamine is released by mast cells and trigger type-I allergic reactions causing urticaria and seasonal rhinitis, etc. In the gastrointestinal system, histamine is associated with secretion of gastric acid. In the peripheral nervous system, it is involved in perception of pain and itchiness. In the central nervous system, it is associated with a wide range of functions such as arousal, cognition, learning and memory, regulation of sleep-wake cycle, appetite control, seizures, aggressive behaviors, and so on mainly through histamine H1 receptors (H1R).

Histaminergic neurons are exclusively located in the tuberomamillary nucleus of the posterior hypothalamus. They are projecting to almost all regions of the brain\textsuperscript{1).} Arousal and cognition are among the main roles of brain histamine and H1R. These functions could be well demonstrated by a fact that histamine H1R antagonists, or antihistamines (AH), prescribed for treatment of allergic disorders, often induce sleepiness and psychomotor deficits\textsuperscript{2-4).} The mechanism causing such CNS side effects has been understood that AHs, penetrating brain blood barrier (BBB), occupies H1Rs in the brain. Classical first generation AHs often have significant sedative effects, while AHs of newer generations tend to be less sedative. Evaluating side effects of different AHs is of clinical and social importance because they sometimes induce car accidents etc. Since measurement of subjective sleepiness was not always reliable, various objective testing methods have been introduced. We have been utilizing positron emission tomography (PET) with \textsuperscript{11}C-doxepin as a radioactive ligand to understand the roles of H1Rs in the living
human brain\textsuperscript{2-5}). In this report, we demonstrate results of comparative study on different second generation AHs using PET.

**Methods**

In the present study, subjective sleepiness was measured using Stanford Sleepiness Scale (SSS)\textsuperscript{6}, and psychomotor performance was examined using a tachistoscope testing system (Iwatsu Inc., Japan)\textsuperscript{2,3} in healthy young Japanese volunteers (n = 16, ranging 20-28 years old). Measurement was done twice; before and 90 min after oral administration of each AHs such as fexofenadine 120mg (FEX: a non-sedative AH introduced recently) and cetirizine 20mg (CET: a slightly sedative second generation AH) at both maximum doses per day in Japan, and hydroxyzine 30mg (HYD: a sedative AH which served as a positive control in this study), in a double-blind placebo controlled crossover design. In this testing procedure, each subject was requested to sit on a chair, facing to a computer display in which target stimuli were presented. The subjects were requested to hold a button in their each hand and to press a right/left button immediately after the target stimulus appeared in the corresponding side of the display, respectively (choice reaction task, in short, CRT), as well as they were requested to press a right button each time the target stimulus was presented in the display regardless of its laterality (simple reaction task, in short, SRT). Additionally, the subjects were requested to press the right button only when Arabic numerals were presented in the display and to ignore when hiragana (Japanese phonetic alphabets) were presented (visual discrimination task, in short, VDT). This VDT consisted of 4 sessions with different exposure durations of target stimuli (3,5,7 and 20 millisecond). The appearing order of exposure durations was randomized.

Additionally, 10 out of the 16 volunteers were also examined by PET with \textsuperscript{11}C-doxepin for measurement of histamine H1 receptor occupancy (H1RO). H1RO values were calculated by Logan’s graphical analysis from binding potential (BP) images obtained from 90 min-dynamic scan images\textsuperscript{3,4}. Finally, Scores of SSS, reaction time in psychomotor tests measured by the tachistoscope system, and H1RO measured by PET were statistically examined between FEX and CET using ANOVA followed by multiple comparisons by Glanz test.
Results

The results of SSS and psychomotor tests demonstrated that FEX seemed to be less sedative than CET though the difference was at threshold level (Fig. 1). PET investigation revealed that almost no H1R in the cerebral cortex were occupied by FEX while CET occupied approximately 20 to 50% of H1Rs (p<0.01)(Fig. 2). Measurement of histamine H1RO by PET seemed to be one of the most reliable techniques to evaluate CNS side effects of different AHs.

Discussion

Roles of brain H1R have been thought to exist in arousal and cognition\textsuperscript{3,7}, learning and memory, seizures\textsuperscript{8}, pain perception\textsuperscript{9}, and so on. To understand functions of specific proteins such as H1R, knockout mice experiment is useful and can provide an ideal opportunity to analyze the specific functions of individual mammalian genes. Homozygous H1R knockout mice manifested significantly diminished diurnal variation in locomotor activity in contrast to significant variation in wild-type mice\textsuperscript{10}. Scientific investigations on H1 knockout mice have significant merits although brain histamine’s roles equivalent to humans are not always deduced. It would be important to take both animal and human findings into consideration before drawing conclusions on each specific receptors.

As for the human study, positron emission tomography (PET) is one of ideal tools that enables us to obtain biochemical and physiological information non-invasively. Neuroreceptor imaging with PET is important because currently no other device would be able to substitute. \textsuperscript{11}C-doxepin has been a potent molecular tool to visualize distribution of H1R in human brain\textsuperscript{2,7}. Our present and previous studies with AHs have demonstrated that histamine is playing very important roles in maintaining arousal and good psychomotor performance in human.

In general, newly introduced second generation AHs occupy 10 to 50% while classical first generation AHs occupy 50 to 80% of H1Rs in the brain\textsuperscript{2-4}. Fexofenadine (FEX) manifested much lower H1RO (0%) and milder sedation than cetirizine (CET), one of typical second-generation AHs (Fig. 1 and 2). It is easy to understand that sedative side effects of AHs are induced by blockade of H1R by AHs since severity of the side effects correlated to H1RO. Difference in H1RO among different AHs would be because of different permeability of AHs to penetrate BBB, regulated by influx and efflux proteins such as p-glycoprotein.
In summary, roles of histamine and H1R in arousal and cognition were confirmed both in knockout mice and in human subjects. PET with $^{11}$C-doxepin seems to be a more sensitive tool than psychomotor testing for differential comparisons of AHs.

References


![Graph](image)

Fig. 1. Results of visual discrimination task (VDT). Results of response time (RT) measurement are demonstrated ($n = 16$). The change rates in RT in each subject were obtained by dividing RT$_{post}$ by RT$_{pre}$ (* $p<0.05$, ** $p<0.01$). Statistical examination was done by ANOVA followed by multiple comparisons.)
Fig. 2. Brain images demonstrating differences in binding potentials after administration of different antihistamines, fexofenadine and cetirizine and placebo (sagittal slice). Binding potential of fexofenadine is equal to that of placebo, while that of cetirizine is lower than those of both placebo and fexofenadine.