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37 Pharmacological NIRS Study on the Effects of Antihistamine Drugs

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I. Introduction

Histamine is an endogenous substance that is present in both peripheral and brain tissues. The major ascending pathway of histamine in the brain starts from the tuberomammillary nucleus of the hypothalamus (Watanabe et al., 1983) and widely projects to the telencephalon including the basolateral amygdala, nucleus basalis magnocellularis, septum, hippocampus, and neocortex. Positron emission tomography (PET) studies in humans and baboons have shown high concentrations of H1 receptors in the frontal and temporal cortex but low concentrations in the cerebellum and brain stem (Villemagne et al., 1991). The descending pathway starts from the hypothalamus and projects to various nuclei in the brain stem. Histamine neurons fire at a low rate during sleep and a high rate during waking (Sakai et al., 1990), suggesting that histamine is involved in the control of sleeping and waking states. In support of this notion, knockout mice lacking H1 receptors exhibit impaired arousal and sleep-wake cycles (Yanai et al., 1999).

To control allergic reactions mediated by histamine in hypersensitive individuals, several different histamine antagonists have been produced. Antihistamine drugs are classified into two categories: sedative or first-generation drugs (e.g., ketotifen, oxatomide, and chlorpheniramine) and non-sedative or second-generation drugs (e.g., epinastine, fexofenadine, and

ebastine). Although sedation was generally regarded to be an unavoidable side effect of the first-generation H1-receptor antagonists, the second-generation H1 antagonists were specifically developed to minimize sedation. There is considerable evidence showing differential sedation effects of antihistamines on behavioural performances (Shamsi and Hindmarch, 2000; Tashiro et al., 2004, 2005; Theunissen et al., 2006a, 2006b; Turner et al., 2006), H1 receptor occupancy rates (Mochizuki et al., 2004; Tashiro et al., 2004, 2006; Yanai and Tashiro, 2007) and neural correlates of cognitive performance (Mochizuki et al, 2002; Tsujii et al., 2007). However, it remains relatively unknown whether these findings can be extended to behavioural performance and neural responses in young children.

Recently, we examined the effects of antihistamines on prefrontal cortex activities not only in adults but also in young children, using near-infrared spectroscopy (NIRS) (Tsujii et al., 2007, 2009, 2010). NIRS is a relatively new imaging technique for investigating cortical haemodynamic responses by measuring changes in the attenuation of near-infrared light passing through tissues. Since oxygenated haemoglobin (oxy-Hb) and deoxygenated haemoglobin (deoxy-Hb) have different absorption spectra in the infrared range, changes in the concentrations of oxy-Hb and deoxy-Hb can be calculated by detecting infrared light on the skull at two different wavelengths (approximately 787 and 827 nm). In general, enhanced oxy-Hb and reduced deoxy-Hb concentrations are associated with regional cortical activation. NIRS is noninvasive, robust against body movement, and has been validated as a suitable technique for investigating neural mechanisms in psychological experiments (Tsujii et al., 2010; Tsujii and Watanabe, 2009, 2010). In the present article, we review our recent studies that investigated the effects of antihistamine drugs on prefrontal cortex activities using NIRS. We initially describe an adult study (Tsujii et al., 2007), and then review our attempts to use the NIRS technique for psychopharmacological experiments in young children (Tsujii et al., 2009, 2010).

II. Effects of antihistamines on prefrontal cortex activities in adults

In the first study, we examined the prefrontal cortex activities using NIRS

while adult subjects performed a working memory task and selective attention task (Tsujii et al., 2007). The subjects were 12 right-handed Japanese volunteers aged 25.5±5.79 years (range, 20–39 years). A double-blind, placebo-controlled, crossover design was used. The subjects were required to attend the study centre on three separate days at 1-week intervals. Each study session started at 10:00. On arrival, the subjects received a single oral dose of epinastine 20 mg, ketotifen 1 mg, or placebo (Boehringer Ingelheim, Ingelheim/Rhein). After 3 hours, corresponding to the time required for the test agents to reach Cmax, the subjects completed three kinds of cognitive tasks (working memory, dichotic listening, and visual perception tasks) during which their cortical activities were measured using NIRS. The order of the cognitive tasks was balanced across the subjects. In addition, a self-rated psychological measurement was taken twice using a 100-mm visual analogue scale (VAS) (Tsujii et al., 2010), once before drug administration and then before undertaking the first cognitive task in each experiment.

The prefrontal cortex activities were measured during the performance of a working memory task. In this task, two test blocks were sandwiched between three baseline blocks. The subjects were required to remember six digits on the test blocks and one digit on the baseline blocks. Each block was presented for about 50 s. There were four trials of the test blocks and eight trials of the baseline blocks. Each trial began with the presentation of a central fixation cross for 800 ms, followed by the presentation of a set of one or six digits to be learned. Each digit was presented for 1 s. A blank display was then inserted for 2 s, followed by the probe digit until responses were noted. The subjects were required to indicate whether they thought the probe digit was contained within the learned stimulus set by pressing one of two mouse buttons as quickly and as accurately as possible.

The relative changes in the oxy-Hb and deoxy-Hb concentrations were measured using an ETG-7000 Optical Topography System (Hitachi Medical Co.). This device uses near-infrared light at two wavelengths with ranges around 787 and 827 nm. Two NIRS shells with 3×5 arrays of light emitters and detectors were used (distance between probes: 3 cm). This apparatus can measure the relative concentrations of oxy-Hb and deoxy-Hb at 22 measurement points in two areas of 15×6 cm each. The NIRS shells were placed on the following brain regions according to the task. In the working memory task, both shells were positioned over the prefrontal regions (one for the

right hemisphere and one for the left hemisphere). The locations of the shells were determined using the international 10–20 system (Okamoto et al., 2004). The most inferior medial channels of the left and right frontal hemispheres were located at Fp1 and Fp2, respectively.

We examined the treatment effects of first- and second-generation antihistamines on the working memory task in healthy adult subjects. Ketotifen detrimentally affected the subjective sleepiness, behavioural performance, and cerebral neural responses compared with epinastine and the placebo. Although many studies have revealed differential effects of first- and second-generation antihistamines on subjective sleepiness and behavioural performance (Shamsi and Hindmarch, 2000; Tashiro et al., 2004, 2005; Theunissen et al., 2006a, 2006b; Turner et al., 2006), the neural correlates of these phenomena have been relatively unknown. This study revealed for the first time that these drugs stimulate differential neural correlates of cognitive performance.

Working memory performance was severely disrupted by administration of ketotifen but not by administration of epinastine. Previously, Hindmarch and Shami (1999) found that triprolidine, a first-generation antihistamine, disrupted performance in a working memory task compared with ebastine, a second-generation antihistamine. However, these researchers did not examine the neural correlates of the drug effects during working memory performance. Recent NIRS studies have shown that the lateral prefrontal cortex is active during working memory processes (Tsujii et al., 2009; Tsujimoto et al., 2004). Therefore, we examined the treatment effects during working memory performance in these brain regions.

Our NIRS analyses showed that the lateral prefrontal cortex was significantly less activated after administration of ketotifen, but not after administration of epinastine. These observations are consistent with previous findings about the relationship between sedation and prefrontal cortex activation during working memory performance. It is well known that first-generation antihistamines have potent sedative effects (Shamsi and Hindmarch, 2000; Tashiro et al., 2004, 2005; Theunissen et al., 2006a, 2006b; Turner et al., 2006). Some recent functional MRI studies found that sleepiness and fatigue reduce prefrontal cortex activity during working memory processes (Choo et al., 2005; Mu et al., 2005; Thomas, 2005). Therefore, our findings provide a link between behavioural studies examin-

ing antihistamine effects and functional brain imaging studies investigating the effects of fatigue and sleepiness on prefrontal cortex activity during working memory performance.

III. Preschool children

In contrast to the adult population, it was not known whether these findings could be extrapolated to behavioural performance and neural responses in preschool children. Therefore, we examined the frontal cortex activities of preschool children during the performance of a spatial working memory task (Tsujii et al., 2010). The subjects were right-handed Japanese preschool children with a history of Japanese cedar pollinosis. Fifteen subjects (7 males and 8 females) aged 5.5±0.5 years (range, 4.5–6.7 years) were recruited. One subject who did not understand the task procedure was excluded from the analyses of the behavioural performance and neural responses, and three subjects who did not understand the concept of a VAS were excluded from the statistical analyses.

The basic protocol was similar to the experiments for adults (Tsujii et al., 2007). The subjects were required to attend the study centre on three separate days, and took a different test agent on each occasion. Each study session started at 10:00. Upon arrival, the subjects received a single oral dose of epinastine 10 mg, ketotifen 0.6 mg, or placebo (Nippon Boehringer Ingelheim Co. Ltd.). After 3 hours, the subjects completed a spatial working memory task during which their prefrontal cortex activities were measured by NIRS.

In the spatial working memory task, the trial began when a warning signal (white cross) appeared on the screen for 3 s. Sample cues (white squares) were then presented at two of eight peripheral locations for 2 s, followed by a delay period of 8 s. A white square was then presented as the test cue at one of the eight peripheral locations and, based on the working memory of the locations of the sample cues, the subjects were required to report whether the location of the test cue was identical to the locations at which any of the sample cues had appeared. The response was reported by pressing a button: “yes” was indicated by the right index finger and “no” was indicated by the right middle finger. When the subject responded, the

test cue was turned off and the trial ended. Each trial was followed by an inter-trial interval of 25 s.

The task involved 12 trials, in which the subjects should respond "yes" in six trials and "no" in six trials. The order of the conditions was randomly determined. The correct response ratios and reaction times were recorded for each subject. Trials in which the subject could not respond within 5 s were categorized as incorrect responses. The experiment required approximately 9 min in total. A break time was inserted between the first six trials and the second six trials. Before the NIRS recording, a practice session was conducted until the experimenter decided that the subjects understood the procedure. This procedure is well known to activate the lateral prefrontal cortex in preschool children (Tsujii et al., 2009; Tsujimoto et al., 2004).

We examined the treatment effects of the first- and second-generation antihistamines on the working memory task in the preschool children. Ketotifen detrimentally affected the behavioural performance and neural responses compared with epinastine and the placebo. Epinastine had no sedative effects on the behavioural performance and neural responses. These findings are consistent with previous findings in adult subjects, comprising behavioural studies (Shamsi and Hindmarch, 2000; Tashiro et al., 2004, 2005; Theunissen et al., 2006a, 2006b; Turner et al., 2006), PET studies (Mochizuki et al., 2004; Tashiro et al., 2004, 2006; Yanai and Tashiro, 2007), an EEG study (Theunissen et al., 2008) and an NIRS study (Tsujii et al., 2007). NIRS is considered to be suitable for developmental studies because of its excellent safety and robustness against body movements. Therefore, we were able to successfully introduce this new brain imaging technique into psychopharmacology studies and to confirm the differential sedative effects of first- and second-generation antihistamines on neural responses in preschool children.

Compared with the large number of studies that have been conducted in adults, there are few studies on the sedative effects of antihistamines in young children. Most of these studies used the P300 latency in auditory oddball tasks as an index of central nervous system function, and reported that first-generation antihistamines such as chlorpheniramine (Ng et al., 2004; Simons et al., 1994) and hydroxyzine (Simons et al., 1996) delayed the latency of P300 in children aged 6–12 years (Simons et al., 1994, 1996) and 7–14 years (Ng et al., 2004). P300 is an event-related potential that is

known to be associated with processes that update working memory information (Donchin, 1981) and with lateral prefrontal cortex activation in oddball tasks (Yoshimura et al., 1999; Clark et al., 2000). These previous results are consistent with our findings that ketotifen impaired the lateral prefrontal cortex activation during working memory processes. Our findings using NIRS in preschool children aged 4.5–6.7 years support the previous electrophysiologic findings from brain haemodynamic aspects.

Several authors have reported that the use of second-generation antihistamines can prevent or decrease the likelihood of sedative effects in young children. For example, Simons and colleagues reported that sedative effects do not occur in school-aged children after administration of terfenadine (Simons et al., 1994), fexofenadine (Simons et al., 2003), and levocetirizine (Simons et al., 2005). In addition, Stevenson et al. (2002) found that there are no adverse effects on behavioural or learning processes associated with even prolonged use of cetirizine in young children, although there is a report that cetirizine has mild sedative effects in children (Ng et al., 2004). These observations are consistent with our findings that epinastine did not reduce the behavioural performance or neural responses in the working memory task.

IV. School-aged children

In another study, we examined the frontal cortex activities of school-aged children during a verbal fluency task (Tsujii et al., 2009). The subjects were right-handed Japanese children aged 7–8 years with normal or corrected-to-normal vision. The basic protocol was similar to the experiments for adults (Tsujii et al., 2007) and preschool children (Tsujii et al., 2010). The subjects were required to attend the study centre on three separate days. Each study session started at 10:00. On arrival, the subjects received a single oral dose of epinastine 10 mg (Alesion dry syrup 1%; 1 g), ketotifen 0.6 mg (Zaditen dry syrup 0.1%; 0.6 g), or placebo. The doses were decided according to the manufacturer's recommendations for the age range. After 3 hours, corresponding to the time required for the test agents reach Cmax, the subjects completed a verbal fluency task during which their prefrontal cortex activities were measured by NIRS. In addition, a self-rated psychological meas-

urement was taken twice using a VAS, once before drug administration and then before undertaking the verbal fluency task with NIRS measurements.

Changes in the haemoglobin concentrations were measured during a letter version verbal fluency task. The subjects were instructed to write as many nouns as possible beginning with Japanese syllables (“a”, “ha”, and “ra”) without the use of repetitions and proper nouns. Stimulus syllables were counterbalanced for each treatment condition. The subjects sat in front of a desk with their eyes open throughout the experiment. They performed a verbal fluency task consisting of a base block (30 s), test block (60 s), and base block (30 s). The subjects were asked to rest during the base blocks and to perform the verbal fluency task during the test block. Prior to the main sessions when the neural responses were recorded by NIRS, practice sessions were conducted until the experimenter judged that the subjects understood the procedure.

We found that ketotifen, but not epinastine, significantly affected the behavioural performance and cerebral neural responses compared with the placebo. Ketotifen significantly enhanced the oxy-Hb concentration and reduced the deoxy-Hb concentration during the verbal fluency task. These findings are consistent with the NIRS findings obtained in adult subjects (Tsujii et al., 2007) and preschool children (Tsujii et al., 2010). Therefore, we can safely and successfully introduce this new brain imaging technique into psychopharmacological studies and demonstrate differential sedative effects of antihistamines on neural responses in young children.

The school-aged children also performed the spatial working memory task that was used in the experiments for preschool children. Unlike the preschool children, there was no significant difference between the two drugs in the school-aged children. This finding does not mean that drug differences were not present in the school-aged children. In fact, the verbal fluency task revealed a significant difference in these children. Consequently, we think that the spatial working memory task, which was adequate for the preschool children, was too easy for the school-aged children. A task that is too easy cannot activate the prefrontal cortex, thereby leading to a low detection power. We think that this is the reason why the spatial working memory task did not detect a significant difference between the first- and second-generation antihistamines in the school-aged children.

In contrast to the behavioural performance and haemodynamic respons-

es, no sedative effects were observed in subjective sleepiness analyses in the study. There was no significant difference among the two drugs, and only marginally different VAS scores were observed after versus before drug administration. It is often commented that subjective reports of sedation are not as reliable as objective tests, and that discrepancies between subjective and objective assessments of sedation are common (Ng et al., 2004). These observations suggest that subjective reports such as the VAS are not sensitive or reliable tools for examining sedation, particularly in young children.

V. Conclusions

In this paper, we have reviewed our recent studies examining the effects of antihistamines on prefrontal cortex activation in adults and young children during working memory and verbal fluency tasks, in which we measured the neural responses using NIRS. Ketotifen, as a first-generation antihistamine, impaired the behavioural performance and frontal cortex activation compared with epinastine, as a second-generation antihistamine, and the placebo. Sedative effects were not observed after epinastine administration. NIRS is a relatively new method that is suitable for examining neural responses, especially in young children. Our recent studies using NIRS have suggested that this technique has potential for facilitating our understanding of drug effects on neural activity, especially in young children.

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