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Effects of Histidine on Working Memory Deficits Induced by the 5-HT_{1A}-Receptor Agonist 8-OH-DPAT

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ABSTRACT—We investigated the effects of histidine on spatial memory deficits induced by the 5-HT_{1A}-receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Working memory deficits were elicited by 8-OH-DPAT without affecting reference memory. Histidine improved the working memory deficit induced by 8-OH-DPAT at doses causing a significant increase in brain histamine content. This finding suggests that the histaminergic system regulates 8-OH-DPAT-induced working memory deficit.

Keywords: Histidine, 8-Hydroxy-2-(di-*n*-propylamino)tetralin, Radial maze performance

It is known that the brain histaminergic system modulates learning and memory process in experimental animals (1 – 4). In step-through active avoidance task in rats, histamine facilitated the impaired memory retrieval induced by aging or hippocampal lesions in rats (5, 6). α-Fluoromethylhistidine, the specific inhibitor of histidine decarboxylase caused a memory deficit both in the active avoidance response and radial maze task (1, 4). On the other hand, Oishi et al. (7) reported that histaminergic activity in the brain is regulated by 5-HT_{1A} receptors from the finding that the histamine turnover in whole mouse brain was significantly inhibited by the 5-HT_{1A} agonists, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). In addition, in regard to serotonin, there is strong evidence for the role of this amine in the mechanisms underlying learning and memory (8 – 10). For instance, Carli and Samanin (8) found that 8-OH-DPAT impairs spatial navigation by stimulating postsynaptic 5-HT_{1A} receptors at doses causing no apparent changes in motor behavior or motivations in a water maze. However, the interaction between 5-HT_{1A} receptors and histaminergic receptors in cognition processes has not been elucidated. The present study was undertaken to clarify whether or not histamine is involved in the spatial memory deficit induced by 8-OH-DPAT using the eight-arm radial maze task in rats.

Male Wistar rats, 7-week-old and weighing 190 – 220 g, were used (Nippon SLC, Shizuoka). All animals were maintained in an air-conditioned room controlled for temperature (24 ± 2°C) and humidity (55 ± 15%). They were housed in individual cages with a 12-h light-dark cycle (lights on 0800 – 2000 h). Prior to behavioral tests, the body weight of rats was gradually reduced over a period of 1 week to 80 – 85% of their free-feeding weight, and then the animals were kept on a restricted diet for the rest of the experiment. Water was given ad libitum.

The experimental apparatus and procedures were described in our previous report (1). Briefly, to familiarize the rats with the radial maze prior to training they received one daily habituation trial for two days. After adaptation, all rats were trained with one trial per day. In each trial, a single food pellet (45 mg each; Bio-Serv, Frenchtown, NJ, USA) was placed in the food cup in 4 out of 8 arms. The rat was placed on a platform in the middle of the 8-arm radial maze and allowed to make an arm choice to obtain food pellets until all 4 pellets were eaten or 10 min elapsed. In the drug test, we used only rats that had made 3 or more correct choices and either one or no errors during the first 4 choices in each of 5 consecutive days. The following indices of maze performance were used to represent accuracy: 1) reference memory errors (entry into arms that were never baited); 2) working memory errors (re-entry into the baited or unbaited arms that had been previously chosen). Histidine monohydrochloride (Wako Pure Chemical Industries, Ltd., Osaka) and 8-OH-DPAT hydrobromide (Research Biochemicals International, Natick, MA, USA) were dissolved in saline. Ten rats were used for the behavioral test in each group. The test trial was given 15 min after intraperitoneal (i.p.) injection of 8-OH-DPAT. An i.p. injection of histidine was given 3 h before the test trial. The histamine content of the brain was determined by means of the method described previ-

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ously (4). Seven rats were used in each group. The animals were sacrificed 3 h after injection of histidine and the brain was quickly removed and placed on ice. Brain regions were dissected according to the procedure described by Glowinski and Iversen (11). Histamine content was determined using a high performance liquid chromatograph equipped with a fluorometric detector (CCP and 8010 Series; Tosoh, Tokyo).

One-way analysis of variance with Kruskal-Wallis test and Dunnett's test were used to test for significance for the 8-arm radial maze and biological data, respectively. A difference of $P<0.05$ was regarded as significant.

8-OH-DPAT caused a significant impairment of working memory at doses of 0.2 and 0.5 mg/kg, while it had no effect on reference memory (Fig. 1).

Figure 2 shows the effect of histidine on working memory deficit after 8-OH-DPAT was administered.

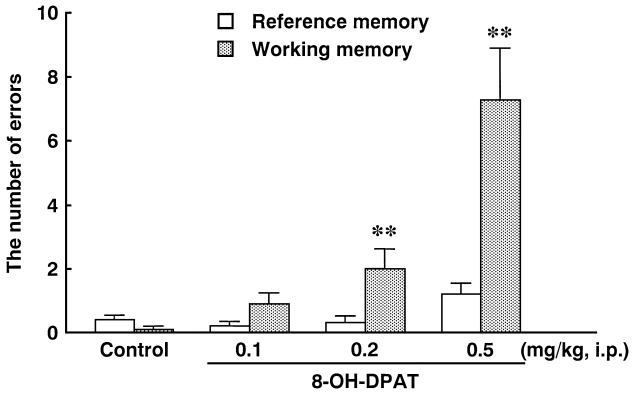

Fig. 1. Effects of 8-OH-DPAT on reference and working memory of radial maze performance in rats. Each value shows the mean ± S.E.M. of 10 rats. **$P<0.01$, as compared with the saline-treated control group.

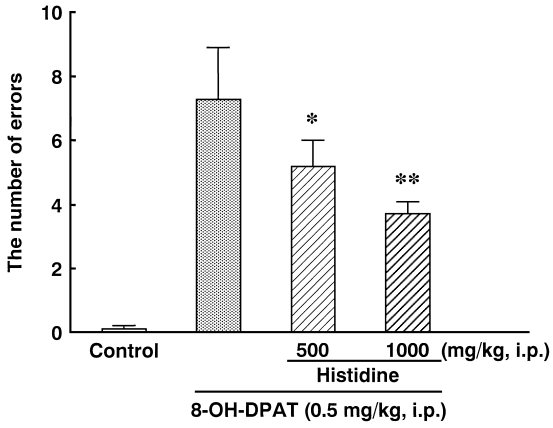

Fig. 2. Effects of histidine on 8-OH-DPAT-induced working memory deficits of radial maze performance in rats. Each value shows the mean ± S.E.M. of 10 rats. *$P<0.05$, **$P<0.01$, as compared with the 8-OH-DPAT-treated group.

Table 1. Changes in brain histamine contents after intraperitoneal injection of histidine

	Histamine contents (ng/g tissue)		
	Control	Histidine (500 mg/kg)	Histidine (1000 mg/kg)
Cerebral cortex	24.4 ± 2.4	62.9 ± 1.4**	101.3 ± 3.5**
Hippocampus	13.7 ± 2.6	31.8 ± 2.8**	41.6 ± 3.3**
Striatum	59.0 ± 3.3	110.3 ± 5.0**	118.3 ± 3.9**
Thalamus	104.9 ± 6.1	149.4 ± 3.6**	188.0 ± 5.0**
Hypothalamus	321.8 ± 31.4	665.6 ± 28.3**	797.4 ± 58.9**

Each value shows the mean ± S.E.M. of 7 rats. **$P<0.01$, as compared with the saline-treated control group.

Histidine significantly antagonized 8-OH-DPAT-induced working memory impairment at doses of 500 and 1000 mg /kg, i.p. Histidine at doses of 500 and 1000 mg/kg significantly increased histamine contents in the cerebral cortex, hippocampus, striatum, thalamus and hypothalamus (Table 1).

In the present study, we found that 8-OH-DPAT elicited working memory deficit without affecting reference memory. Winter and Petti (10) reported that in the spatial learning paradigm with the eight-arm radial maze, 8-OH-DPAT produced a significant dose-related decrease in efficiency, suggesting that 5-HT_{1A} receptor may play a role as a serotonergic receptor subtype in memory. However, it remains to be clarified which memory, working memory or reference memory, is closely related with 5-HT_{1A} receptor. Ohno et al. (12) reported that in a three-panel runway task, 8-OH-DPAT at a dose of 1.0 mg/kg significantly increased the number of errors in a test of working memory, but it had no effect on errors in a test of reference memory. Our findings are essentially in agreement with Ohno et al. (12). Working memory impairment induced by 8-OH-DPAT was reversed by histidine at doses of 500 and 1000 mg/kg, i.p. As shown in Table 1, histamine contents were significantly elevated by i.p. injection of histidine. In particular, there were marked increases in histamine contents in the cerebral cortex, hippocampus and hypothalamus. Thus, we speculated that the effect of histidine was exhibited by histamine generated in the brain. Ohno et al. (12) found that intrahippocampal injection of 8-OH-DPAT significantly increased the number of working memory errors, suggesting that activation of postsynaptic 5-HT_{1A} receptors in the hippocampus leads to the impairment of working memory. In addition, it was also reported that rat hippocampus has a high density of 5-HT_{1A} receptors (13). We previously reported that i.c.v. injection of histamine and i.p. injection of histidine resulted in an improvement of memory deficit induced by hippocampal lesions in rats (5). These results suggest that interaction between the histaminergic and serotonergic mechanism may arise

at the hippocampus and have a significant role in learning and memory. As shown in the text, however, histidine showed no complete antagonistic effect on 8-OH-DPAT-induced working memory error even at a dose of 1000 mg /kg, which caused sufficiently an elevation of histamine contents in the brain. It was thought at the time that the serotonergic system is responsible for the effects of 8-OH-DPAT that were unaffected by histidine.

In conclusion, the findings in this study suggest that the histaminergic system is closely related with 5-HT_{1A}-mediated working memory.

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