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Effects of vasopressin on histamine H_1 receptor antagonist-induced spatial memory deficits in rats

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Abstract

The effects of [Arg^8] vasopressin on histamine H_1 receptor antagonist-induced memory deficits were investigated using the eight-arm radial maze performance test in rats. Pyrilamine and diphenhydramine as well as scopolamine induced memory deficits characterized by increases in the number of total errors, reference memory errors and working memory errors. [Arg^8] vasopressin improved not only scopolamine–but also pyrilamine–and diphenhydramine-induced memory deficits, although a high dose of [Arg^8] vasopressin was needed to antagonize pyrilamine-induced memory deficits. The effects of pyrilamine on the brain [Arg^8] vasopressin content were studied, and the hippocampus [Arg^8] vasopressin content was shown to be decreased after pyrilamine injection. From these observations, it seems likely that [Arg^8] vasopressin participates in not only the cholinergic system but also the histaminergic system in spatial memory.

Keywords: [Arg^8] vasopressin; Histamine H_1 receptor antagonist; Reference memory; Working memory

1. Introduction

Histamine plays an important role in learning and memory via histamine H_1 receptors (De Almeida and Izquierdo, 1986; Kamei and Tasaka, 1993). There have been reports that impaired learning and memory were observed with decreases in brain histamine content due to α-fluoromethylhistidine treatment (Kamei et al., 1993; Chen et al., 1999). In addition, histamine H_1 receptor antagonists such as pyrilamine, diphenhydramine and chlorpheniramine were shown to impair various kinds of learning behavior such as shuttle box avoidance and step-through active avoidance in rats (Tasaka et al., 1986; Kamei et al., 1990).

On the other hand, it has been reported that [Arg^8] vasopressin exerts a long-term facilitatory effect on learning and memory processes in aversion-conditioning studies (Kovács and de Wied, 1994). In addition, Kovács et al. (1977) reported that [Arg^8] vasopressin influences memory processes through interaction with cerebral catecholaminergic metabolisms. Recently, the relationship between histaminergic neurons and vasopressin neurons has attached a great deal of attention. For instance, it has been shown that histamine stimulates the secretion of [Arg^8] vasopressin from the magnocellular neurons to the peripheral blood when administered centrally (Kjær et al., 1994a). In addition, the level of [Arg^8] vasopressin mRNA in the paraventricular nucleus was increased after intracerebroventricular injection of histamine (Kjær et al., 1994b). However, the interactions of the vasopressin and histaminergic systems in cognition have not been elucidated. The present study was performed to clarify the effects of [Arg^8] vasopressin on histamine H_1 receptor antagonist-induced memory deficits using the eight-arm radial maze performance test in rats, in comparison with scopolamine-induced memory deficits.

2. Materials and methods

2.1. Animals

Male Wistar rats, 7 weeks old at the beginning of the experiment (weighing 180–200 g, Nippon SLC, Shizuoka, Japan), were used. All animals were maintained in an air-conditioned room with controlled temperature (24 ± 2 °C) and humidity ($55 \pm 15\%$). The amount of food was adjusted daily so that body weight was maintained at

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80–85% of the free feeding level before the experiment. Water was given ad libitum.

2.2. Experimental apparatus and procedure

The apparatus used was described in our previous report (Chen et al., 1999). The procedure was as follows. To familiarize the rat with the radial maze, they received 1 daily habituation for 2 days prior to training. The first day, food pellets (45 mg, each, Bio-Serv, A Holton Industries, Frenchtown, NJ, USA) were scattered over the entire maze surface, and three or four rats were simultaneously placed on the radial maze and allowed to take pellets freely. The next day, a pellet was placed in the food cup in each of the eight arms, and a rat was allowed to explore freely until it had taken all the pellets. After adaptation, all rats were trained with 1 trial per day. In each trial, only four arms were baited, and the sequence was never changed throughout the experiment. A rat was placed on the center platform that was closed off by a door. After 20 s, the door was opened and the rat was allowed to make arm choice to obtain food pellets until all four pellets had been eaten or 10 min had elapsed. Rats were trained continually until reaching a criterion of at most 1 error per trial for five successive trials. The number of entries into the unbaited arms was scored as the total error. The first entry into never-baited arms was scored as a reference memory error, while a re-entry into arms where the pellet had already been taken was scored as a working memory error.

2.3. Measurement of [Arg^8] vasopressin contents

The brain was quickly removed and placed on ice, and dissected according to the procedure of Glowinski and Iversen (1966). The tissues were weighed and boiled in HCl for 10 min. The homogenized sample was then centrifuged twice at $10{,}000 \times g$ for 45 min. The supernatant was dried in a vacuum rotator (Speedvac SC100, Savant Instruments, Farmingdale, NY, USA) with a refrigerated condensation trap (RT400, Savant) and stored at -80 °C (Miura et al., 1995). Determination of [Arg^8] vasopressin contents was performed using an enzyme immunoassay kit (EIAH-8103, Peninsula Laboratories, San Carlos, CA, USA).

2.4. Drugs

Pyriramine maleate (Sigma, St. Louis, MO, USA), diphenhydramine hydrochloride (Sigma) and scopolamine hydrobromide (Sigma) were dissolved in saline and injected intraperitoneally, and [Arg^8] vasopressin (Sigma) was dissolved in saline and injected subcutaneously.

All procedures involving animals were conducted in accordance with the guidelines of the Animal Care and Use Committee, Faculty of Pharmaceutical Sciences, Okayama University.

2.5. Data analysis

One-way analysis of variance (ANOVA) with Kruskal–Wallis test was used for statistical analysis of the results in the radial maze, and Student's *t*- was used for analysis of the brain [Arg^8] vasopressin content. A difference of $P < 0.05$ was regarded as statistically significant.

3. Results

3.1. Effects of histamine H_1 receptor antagonists on radial maze performance

Pyrilamine at doses of 10 and 20 mg/kg showed no significant effects on the numbers of total errors, reference memory errors or working memory errors. However, at a dose of 35 mg/kg this drug caused significant increases in the numbers of total errors, reference memory errors and working memory errors (Fig. 1). Similar findings were obtained with diphenhydramine; at doses of 5 and 10 mg/kg, it showed no significant effect, but at a dose of 20 mg/kg, it caused significant increases in all 3 parameters (Fig. 1). Pyrilamine at 35 mg/kg, diphenhydramine at 20

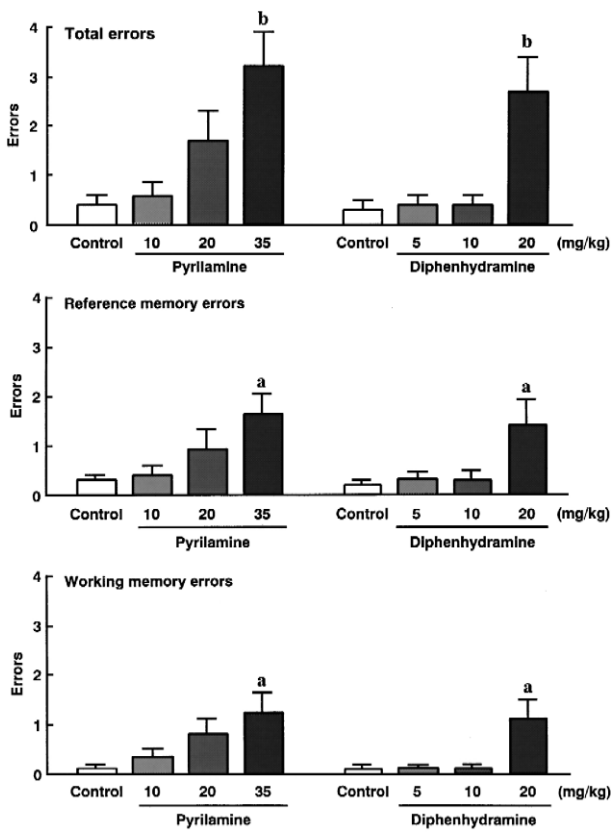

Fig. 1. Effects of histamine H_1 receptor antagonists on radial maze performance in rats. Trials were performed 30 min after intraperitoneal injection of histamine H_1 receptor antagonists. Each value represents the mean ± S.E.M. of 9–11 rats. [a,b]: Significantly different from control ($P < 0.05$ and $P < 0.01$, respectively).

Table 1
Effects of [Arg^8] vasopressin on histamine H_1 receptor antagonist- and scopolamine-induced memory deficits
Trials were performed 30 min after histamine H_1 receptor antagonists and scopolamine (intraperitoneal) and [Arg^8] vasopressin (subcutaneous) injection. Each value represents the mean ± S.E.M. of 7–9 rats.

Drugs		Total errors	Reference memory errors	Working memory errors
Pyrilamine (35 mg / kg)				
+ Saline (control)		3.43 ± 0.37	2.00 ± 0.31	1.38 ± 0.32
+ [Arg^8] vasopressin	0.1 μg/kg	1.50 ± 0.60[a]	0.75 ± 0.31[a]	0.67 ± 0.37
	1 μg/kg	0.75 ± 0.37[b]	0.50 ± 0.27[b]	0.25 ± 0.16[a]
Diphenhydramine (20 mg / kg)				
+ Saline (control)		2.75 ± 0.31	1.50 ± 0.27	1.25 ± 0.37
+ [Arg^8] vasopressin	0.01 μg/kg	1.38 ± 0.56[a]	0.63 ± 0.26[a]	0.63 ± 0.26
	0.1 μg/kg	0.50 ± 0.27[b]	0.38 ± 0.18[a]	0.13 ± 0.13[a]
Scopolamine (0.5 mg / kg)				
+ Saline (control)		3.13 ± 0.43	1.80 ± 0.26	1.27 ± 0.37
+ [Arg^8] vasopressin	0.01 μg/kg	1.69 ± 0.67[a]	1.00 ± 0.30[a]	0.62 ± 0.37
	0.1 μg/kg	0.69 ± 0.36[b]	0.38 ± 0.18[b]	0.23 ± 0.17[a]

[a] Significantly different from control ($P < 0.05$).
[b] Significantly different from control ($P < 0.01$).

mg/kg and scopolamine at 0.5 mg/kg showed the same potency. Therefore, these doses were used to estimate the antagonistic effects of [Arg^8] vasopressin.

3.2. Effects of [Arg^8] vasopressin on histamine H_1 receptor antagonist- and scopolamine-induced memory deficits

The results are shown in Table 1. [Arg^8] vasopressin at a dose of 0.1 μg/kg showed a significant effect on pyrilamine-induced memory deficit without working memory errors. At a dose of 1 μg/kg, it significantly inhibited the pyrilamine-induced increases in the numbers of total errors, reference memory errors and working memory errors. On the other hand, [Arg^8] vasopressin showed more potent inhibitory effects on diphenhydramine- and scopolamine-induced memory deficits than on pyrilamine-induced memory deficit; at a dose of 0.01 μg/kg, [Arg^8] vasopressin showed a significant effects on diphenhydramine- and scopolamine-induced increases in the numbers of total errors and reference memory errors. At a dose of 0.1 μg/kg, [Arg^8] vasopressin significantly improved both diphenhydramine- and scopolamine-induced increases in the numbers of total errors, reference memory errors and working memory errors.

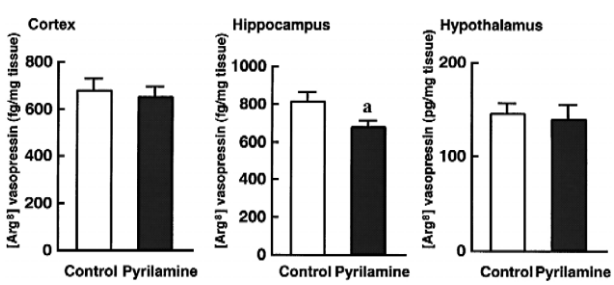

Fig. 2. Effects of pyrilamine on brain [Arg^8] vasopressin content. [Arg^8] vasopressin was measured 30 min after intraperitoneal injection of pyrilamine. Each value represents the mean ± S.E.M. of 6–7 rats. [a]: Significantly different from control ($P < 0.05$).

3.3. Effects of pyrilamine on brain [Arg^8] vasopressin contents

Pyrilamine at a dose of 35 mg/kg showed no effect on the [Arg^8] vasopressin contents of the cortex or hypothalamus. However, the hippocampus [Arg^8] vasopressin content was significantly decreased by pyrilamine at this dose (Fig. 2).

4. Discussion

Reference memory and working memory can be measured in the radial maze test. In the present study, the procedure involved placing food pellets in four of eight arms to differentiate between reference and working memory (Okaichi et al., 1989; Dietrich and Allen, 1997).

Both reference memory errors and working memory errors were inhibited by pyrilamine and diphenhydramine. We have reported that pyrilamine and diphenhydramine caused inhibition of shuttle box avoidance and step-through active avoidance responses in rats when administered by intravenous injection or oral administration (Tasaka et al., 1986; Kamei et al., 1990). These experiments were generally regarded as testing reference memory errors. The present results are the first evidence that pyrilamine and diphenhydramine inhibit working memory errors in the radial maze test. On the other hand, scopolamine inhibited both reference and working memory errors. Okaichi et al. (1989) and Lydon and Nakajima (1992) also reported that

scopolamine impaired both reference and working memory errors in the eight-arm radial maze test. This finding is essentially the same as those of the present study. Diphenhydramine was more effective than pyrilamine in causing memory deficits in the radial maze test. It is well known that anti-cholinergic properties are responsible for memory deficits in cognition (Watts et al., 1981). Diphenhydramine has been shown to have potent anti-cholinergic properties (Kubo et al., 1987). On the other hand, it was reported that pyrilamine had relatively weak anti-cholinergic activity (Kubo et al., 1987). This is why diphenhydramine was more effective than pyrilamine in inhibiting the radial maze performance.

As shown in the present study, [Arg^8] vasopressin had antagonizing effects not only on scopolamine-induced memory deficits but also on those induced by histamine H_1 receptor antagonists. Diphenhydramine-induced deficits were antagonized by [Arg^8] vasopressin to a greater extent than pyrilamine-induced deficits. This finding can also be explained by the more potent anti-cholinergic activity of diphenhydramine as compared to pyrilamine. Fujiwara et al. (1997) suggested that [Arg^8] vasopressin and its metabolites improved scopolamine-induced memory deficits by promoting acetylcholine release from the hippocampus.

A higher dose of [Arg^8] vasopressin caused decreases in the numbers of both reference and working memory errors induced by histamine H_1 receptor antagonists and scopolamine. Dietrich and Allen (1997) reported that [Arg^8] vasopressin metabolites produced a faster rate of acquisition of reference and working memories in the radial arm maze task. These observations suggest that [Arg^8] vasopressin enhances both reference and working memories in the radial arm maze task.

As described in the text, pyrilamine-induced memory deficits were also antagonized by [Arg^8] vasopressin, although a high dose was necessary. As described previously, pyrilamine has only weak anti-cholinergic activity. Therefore, to investigate why [Arg^8] vasopressin showed antagonistic effects on pyrilamine-induced memory deficits, the brain [Arg^8] vasopressin contents were measured after injection of pyrilamine; our results indicated that hippocampal [Arg^8] vasopressin content was significantly decreased. Hippocampal [Arg^8] vasopressin plays an important role in learning and memory in rats (Alescio-Lautier and Soumireu-Mourat, 1998). From these findings, it seems likely that the pyrilamine-induced memory deficit was due to a decrease in the hippocampal [Arg^8] vasopressin content. These observations suggested that [Arg^8] vasopressin and histamine have functional interactions in learning and memory.

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