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ORIGINAL INVESTIGATION

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Effects of rolipram on scopolamine-induced impairment of working and reference memory in the radial-arm maze tests in rats

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Abstract *Rationale:* Rolipram, a selective inhibitor of cyclic AMP-specific phosphodiesterase (PDE4), has been shown to enhance scopolamine-induced impairment of working memory. However, its effect on reference memory, which appears to be related to the level of cyclic AMP (cAMP), has not been investigated yet; in addition, the mechanism involved in its effects on memory remains to be elucidated. *Objectives:* To investigate the effects of rolipram on working and reference memories impaired by scopolamine and the involvement of cAMP. *Methods:* By administration (IP) of rolipram and forskolin, an activator of adenylyl cyclase (AC), the effects of both drugs on the number of correct choices and errors in experiment 1 and, the frequency of both working memory errors and reference memory errors in experiment 2 were observed in two eight-arm radial maze tasks in rats. *Results:* In experiment 1, rolipram (0.01–1.0 mg/kg) attenuated the scopolamine-induced (0.5 mg/kg) increase in the total number of errors in dose- and time-dependent manners. The minimum effective dose of rolipram was 0.05 mg/kg and the effects lasted nearly 60 min. By contrast, forskolin (1.0–10.0 mg/kg) failed significantly to affect any of the above indices altered by scopolamine. In experiment 2, rolipram (0.05 and 0.1 mg/kg) decreased the frequencies of both working and reference memory errors that were elevated by scopolamine. Forskolin did not alter either type of error at a dose that increased the exploration time. *Conclusion:* Rolipram may exert its effects of reversing both working and reference memory impairments via increased cyclic AMP concentrations in certain signal transduction pathways, rather than by a generalized increase in cAMP.

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Introduction

Rolipram, a specific inhibitor of type 4 cyclic AMP-specific phosphodiesterase (PDE4), increases intracellular cAMP by inhibiting its hydrolysis. A number of studies have shown that rolipram produces antidepressant-like effects in animals and improves symptoms in patients with depression (Zeller et al. 1984; Hebenstreit et al. 1989; O'Donnell 1993; O'Donnell and Frith 1999). It also suppresses orofacial diskinetic movements induced by chronic treatment with the antipsychotic drug haloperidol (Sasaki et al. 1995a, 1995b), blocks behavioral sensitization induced by repeated administration of methamphetamine (Iyo et al. 1996), and increases the acoustic startle responses elicited by brief electrical stimulation of brainstem nuclei (Kehne et al. 1991). These results suggest that PDE4 inhibitors such as rolipram might play an important role in the regulation of CNS functions in vivo. Studies have shown that cAMP, protein kinase A (PKA) and its target transcription factor cAMP response element binding protein (CREB), play important roles in memory, especially long-term memory (Randt et al. 1982; Romano et al. 1996; Guzowski and McGaugh 1997; Kogan et al. 1997; Barros et al. 1999). Antisense oligodeoxynucleotides (ODN) against CREB mRNA disrupt hippocampal CREB protein levels and impair long-term memory in adult rats (Guzowski and McGaugh 1997). Intra-hippocampal injection of norepinephrine or 8-Br-cAMP, a PKA stimulator, reverses the amnesic effect of the calcium-calmodulin-dependent protein kinase II (CaMKII) inhibitor KN-62, which indicates that the cAMP/PKA cascade is involved in memory processes in the hippocampus (Barros et al. 1999).

Early studies have shown that rolipram, as well as some other PDE4 inhibitors, given peripherally at doses (>10 mg/kg, IP) that elevate cAMP levels in the brain,

enhances retention in passive avoidance tasks in mice (Villiger and Dunn 1981; Randt et al. 1982). Recently, rolipram has been shown to ameliorate scopolamine-induced impairment of learning and memory in rats and mice (Egawa et al. 1997; Imanishi et al. 1997). Although both isomers of rolipram are effective in the enhancement of scopolamine-impaired memory, (–)-rolipram is more potent than the (+)-isomers; (±)-rolipram exhibits a broader dose-response function than the (–)- and (+)-isomers (Egawa et al. 1997). Studies completed so far have focused on working memory rather than reference memory; reference memory appears to be more related to long-term memory and to the level and function of cAMP. Rolipram has been shown to potentiate and extend long-term potentiation (LTP) generated by a single tetanic train in the CA1 region of the hippocampus in mice, while LTP is highly related to long-term memory (Barad et al. 1998). Such an effect suggests that rolipram improves not only working memory but reference memory as well. Further, at doses below 0.1 mg/kg, rolipram seems not to increase the overall level of cAMP in the rat brain (Wachtel et al. 1987). However, at doses as low as 0.01 mg/kg, it improves working memory impaired by scopolamine (Egawa et al. 1997). Thus, it is likely that a generalized increase in cAMP levels does not underlie the effects of rolipram on memory. Rather, increases in cyclic AMP concentrations in certain signal transduction pathways may be of primary importance.

In the present study, the first experiment assessed the dose- and time-dependent effects of rolipram on working memory in the radial-arm maze task in rats. The second experiment investigated the effects of rolipram on both working and reference memory. To examine the efforts of generalized increases in cAMP in the tests, the effects of forskolin were tested.

Materials and methods

Subjects

Fifty-nine male Sprague-Dawley rats, weighing 250–300 g at the beginning of the experiment, were housed in groups of two or three in clear plastic cages with wood shavings in a room that was kept at a constant temperature (22°C) and on a 12-h on/12-h off light cycle (light on at 0600 hours). Water was freely available but food was restricted to 16 g per day, in order to keep body weights at 80–85% of free-feeding levels. All experiments were carried out according to the "NIH guide for the care and use of laboratory animals" (revised 1996).

Apparatus

The radial-arm maze consisted of eight arms with walls and a central octagonal platform (26 cm in diameter). The arms (60 cm long, 10 cm wide and 12 cm high) were made of transparent Plexiglas mounted on an opaque platform and were elevated 70 cm from the floor. A small food well with opaque walls was positioned at the end of each arm. A transparent plastic hub (26 cm in diameter and 30 cm in height) was placed in the center of the maze. Experiments were performed in a lighted room, which contained several extra-maze visual cues.

Procedure

Experiment 1

About 1 week after initial housing, rats were weighed and handled for 2 days before they were placed into the maze for 5 min in groups of four or five with food pellets [fruit cereal (Great Value, WAL-MART Inc., Bentonville, Ariz., USA); each split into three parts, 4–5 pellets per rat] scattered randomly throughout the maze (2 days). On day 5, rats were allowed to habituate to the maze individually for 10 min, 2–3 times a day at an interval of more than 1 h, for 3 consecutive days. During each habituation session, the rat was allowed to move freely in the maze to obtain food pellets. For each training session, the rat was placed on the center platform of the maze and was restricted from entering the arms by a transparent octagonal hub for 30 s before the hub was lifted. The rat was then allowed to move freely throughout the maze.

For testing, all eight arms were baited. The session continued until all the food pellets were collected or 10 min passed, whichever occurred first. Four parameters were recorded to assess the performance of the rat: 1) the number of correct choices; 2) the number of errors, which was defined as entering an arm that had already been entered in the first eight entries; 3) test duration (s), i.e. the time required to complete the task; and 4) the total number of errors before all the food pellets in the eight arms were collected. After about ten sessions of the early training, rats tended to obtain a stable performance. If a test animal reached the criterion of more than seven correct choices (of the first eight entries) in three successive sessions, drug tests began. Rats were tested with different treatments every 3–4 days but not more than 4 times.

Experiment 2

The pre-training was the same as that in experiment 1. On day 5, rats were placed individually in the center of the maze for 5 min with food pellets placed close to the food well at the end of each arm, while on day 6, pellets were placed in the food wells. Rats were trained two sessions a day. On day 7, four randomly selected arms were baited with 1 pellet of food each; the baited arms were kept unchanged throughout the experiment. During testing, the rat was restricted to the center platform of the maze for 15 s before it was allowed to move freely in the maze until it collected the 4 pellets of food or until 10 min passed, whichever occurred first. Four parameters were recorded: 1) working memory errors; i.e., entries into baited arms that had already been visited during the same session; 2) reference memory errors; i.e., entries into unbaited arms; 3) total arm entries; and 4) the time (s) spent in the collection of all the pellets in the maze. If the working memory error was zero and the average reference memory error was less than one in five successive sessions, the rats began the drug tests. Rats were tested every 4–5 days with different treatments but not more than 3 times.

Drug treatments

Rolipram (Schering AG, Berlin, Germany) and forskolin (Hoeschst Celanese Pharmaceuticals, Somerville, N.J., USA) were generously provided by their manufacturers. Scopolamine was purchased from Sigma Chemical Co. (St Louis, Mo., USA). Rolipram was dissolved while forskolin was suspended in saline containing 10% dimethyl sulfoxide (DMSO); scopolamine was dissolved in saline alone. Rolipram was injected IP 15 min prior to scopolamine, which was administered IP 30 min before the test. Forskolin was administered IP 30 min prior to the test. For the time-course experiment, each time point was determined individually; each rat was tested at different pretreatment times on separate test days.

Statistical analysis

In experiment 1, the average exploration time, which was used as a measure of general locomotor activity, was calculated as the test

duration divided by the total number of entries into the arms. The data were analyzed by analyses of variance followed by Dunnett's multiple comparison tests.

In experiment 2, two types of frequencies were used to estimate working or reference memory: frequency of working memory errors and frequency of reference memory errors. The frequency was calculated as the number of working memory errors or reference memory errors divided by the total number of entries into the arms. The average exploration time was calculated as the time spent in the completion of the maze divided by the total number of entries into arms. The data were analyzed by analyses of variance followed by Dunnett's multiple comparison tests.

All values are presented as means± SEM.

Results

Experiment 1

Figure 1A and B shows the mean of the total number of errors and the exploration time, respectively, in the radial-arm maze test. Compared to the vehicle control (saline+saline), scopolamine significantly increased the total number of errors (P<0.01); this effect was reversed by rolipram in a dose-dependent manner [F(6,64)=5.38, P<0.001]. The minimum effective dose of rolipram was 0.05 mg/kg. Scopolamine did not alter the exploration time in this experiment (P>0.05 versus vehicle). However, a higher dose of rolipram (1 mg/kg) increased the exploration time (P<0.01 versus scopolamine).

In scopolamine-treated rats, rolipram (0.05 mg/kg) increased the number of correct choices 15 and 30 min after its administration (P<0.05); at the post-treatment time of 60 and 120 min, rolipram tended to increase the number of correct choices, but this effect was not statistically significant. While rolipram did not affect the exploration time, it decreased the total number of errors in a time-dependent manner. This effect was significant 15 min after the injection (P<0.05) (Table 1).

Forskolin (1–10 mg/kg) tended to decrease the total number of scopolamine-induced errors, but this effect was not statistically significant [F(3,33)=1.74, P>0.1] (Table 2). It did not significantly alter the exploration time either [F(3,33)=0.1, P>0.9] (Table 2).

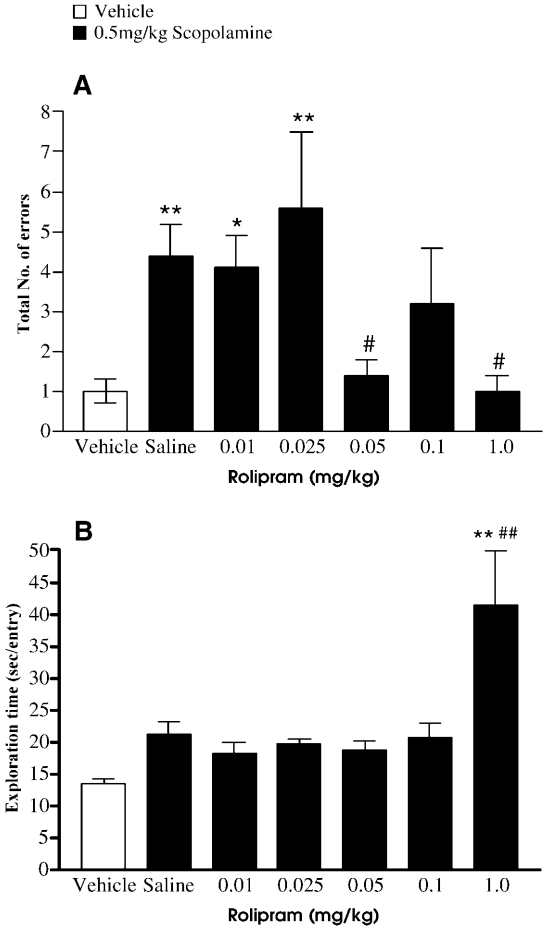

Fig. 1 Effects of rolipram on scopolamine-induced changes in the total number of errors (**A**) and the exploration time (**B**) in the radial-arm maze test in rats. Data are expressed as mean±SEM (*P<0.05, **P<0.01 versus vehicle; #P<0.05, ## P<0.01 versus saline. n=6–17 rats per group)

Table 1 Time-course of the effects of rolipram on the number of correct choices, the total number of errors and the average exploration time in the radial-arm maze test in scopolamine (0.5 mg/kg)-treated rats. Data are expressed as mean±SEM. n=number of animals in group

Time (min after injection)	n	Number of correct choices	Total number of errors	Average exploration time (s/entry)
Saline+scopolamine				
15	18	6.3±0.2	4.1±0.7	21.7±1.9
30	10	6.4±0.2	3.8±1.1	20.1±1.2
60	8	6.5±0.5	4.5±1.9	17.2±1.5
120	8	6.0±0.3	5.9±2.8	18.1±1.7
0.05 mg/kg rolipram+scopolamine				
15	11	7.2±0.2*	1.4±0.4*	18.8±1.4
30	10	7.1±0.3*	2.0±0.9	20.0±1.7
60	8	7.3±0.3	2.4±1.3	20.0±3.9
120	10	6.5±0.4	5.9±1.9	18.7±2.4

*P<0.05 compared to corresponding saline value

Table 2 Effects of forskolin on scopolamine-induced changes in the total number of errors and average exploration time in the radial-arm maze test in rats. Data are expressed as mean±SEM. n=number of animals in group

Forskolin (mg/kg)	Scopolamine (mg/kg)	n	Total number of errors	Average exploration time (s/entry)
Vehicle	0	10	1.5±0.5	11.8±0.7
0	0.5	9	4.7±1.1	28.1±8.4
1.0	0.5	9	5.6±1.1**	25.3±6.3
3.0	0.5	9	4.2±0.8	26.8±4.5
10.0	0.5	9	2.3±0.8	30.4±5.5

**P<0.01 compared to vehicle

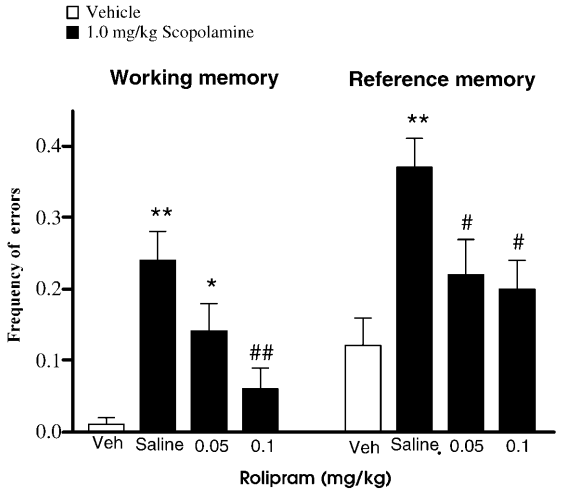

Fig. 2 Effects of rolipram on scopolamine (1.0 mg/kg)-induced impairment of working memory and reference memory in the radial-arm maze test in rats. Data are expressed as mean±SEM [*P<0.05, **P<0.01 versus vehicle (Veh); #P<0.05, ##P<0.01 versus saline+scopolamine. n=7–10 rats per group]

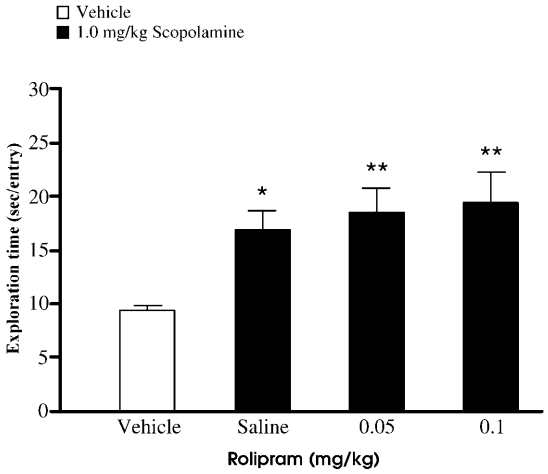

Fig. 3 Effects of rolipram on scopolamine-induced changes in the exploration time in the radial-arm maze test in rats. Data are expressed as mean±SEM (*P<0.05, **P<0.01 versus vehicle. n=7–10 rats per group)

Table 3 Effects of forskolin (10 mg/kg) on scopolamine (1 mg/kg)-induced changes in working and reference memories in the radial-arm maze test in rats. Data are expressed as mean±SEM. n=number of animals in group

Treatment (mg/kg)	n	Frequency of working memory errors	Frequency of reference memory errors	Average exploration time (s/entry)
Vehicle	10	0.01±0.01	0.12±0.04	9.4±0.4
Saline+scopolamine	10	0.24±0.04**	0.37±0.04**	17.0±1.8**
Forskolin+scopolamine	7	0.17±0.08	0.25±0.11	24.1±2.7**##

**P<0.01 compared to corresponding vehicle, ##P<0.01 versus saline+scopolamine

Experiment 2

At the dose of 0.5 mg/kg, scopolamine did not significantly affect either working or reference memory errors, or the exploration time (data not shown). However, at 1 mg/kg, scopolamine increased these three indices (P<0.01) (Fig. 2, Fig. 3). Rolipram (0.05 and 0.1 mg/kg) dose-dependently decreased the frequencies of both working memory errors [F(2,25)=5.32; P<0.05] and reference memory errors [F(2,25)=5.43, P<0.05] that had been elevated by scopolamine (Fig. 2). At either dose, rolipram did not alter the exploration time [F(2,25)=0.70, P>0.1] (Fig. 3).

As shown in Table 3, forskolin, at a dose of 10 mg/kg, which significantly potentiated the scopolamine-induced increase in the exploration time (P<0.01), did not decrease the frequency of either working memory errors or reference memory errors.

Discussion

The radial-arm maze test is one of the most useful models to evaluate learning and memory in rodents. Although many studies have shown that such a test could be widely used to measure working memory, it also has been applied to the study of reference memory in recent years (Prior et al. 1997; Cassel et al. 1998; White and Best 1998). Working memory refers to mnesic processes encoding items related to the temporal/personal context of a single event or a test situation, while reference memory encodes context-independent rules and procedures that are specific to a given situation and which remain valid each time this given situation is encountered (Olton 1983; Cassel et al. 1998).

Scopolamine, a muscarinic receptor antagonist, has been used to establish the animal model for the impairment of learning and memory. This is because central cholinergic systems play an important role in the process of learning and memory; its hypofunction may induce aspects of dementia such as memory loss and disorientation in Alzheimer' disease (Marighetto et al. 1993). Although some studies have shown that scopolamine disrupts only working memory, rather than reference memory (Beatty and Bierly 1985), the present study indicated that scopolamine impaired both working and reference memory significantly, which is consistent with the effects of intra-hippocampal injection of scopolamine (Buhot et al. 1995). These data indicate that cholinergic neurons in the hippocampus are involved in the regulation of both working and reference memories.

The first experiment focused on working memory, which was sensitive to scopolamine. This effect is in agreement with previous studies (Beatty and Bierly 1985; Egawa et al. 1997). Rolipram decreased the total number of errors induced by scopolamine. It did not change the exploration time, which was inferred to be a measure of general locomotor activity. At a dose of 1 mg/kg, however, rolipram potentiated the scopolamine-induced increase in the exploration time. These results are consistent with a previous study (Egawa et al. 1997). The effect of rolipram lasted 30 min; its effects were not statistically significant 60 min after administration. Rolipram has been shown to increase cAMP levels in the frontal cortex, striatum and cerebellum in the rat brain (Schneider 1984). The concentration of cAMP in brain regions returns to control levels 60–120 min after rolipram injection (Randt et al. 1982). Considering the dose of rolipram they used (10 mg/kg) was much higher than that used in the present experiment (0.05 mg/kg), the time-course of rolipram in the behavioral test is consistent with that reported for changes in brain cAMP. These results suggest that the enhancement of rolipram in memory be related to the elevation of central cAMP levels elicited by rolipram. However, the negative data with forskolin suggest that a generalized increase in cyclic AMP is insufficient to affect memory positively. Rather, cyclic AMP responses in certain signal transduction pathways may be critical.

In experiment 2, at the dose used in the first experiment (0.5 mg/kg), scopolamine did not affect working memory or reference memory (data not shown). Thus, the dose was increased to 1.0 mg/kg, which impaired both types of memory. Rolipram reversed scopolamine-induced impairment of both working and reference memories in this experiment. While previous studies have shown that rolipram can enhance working memory (Egawa et al. 1997; Imanishi et al. 1997), the present finding is the first indication that it also can affect reference memory. This suggests that PDE4 may be involved in processes associated with retrieval of long-term memory. Such an interpretation is consistent with previous work that shows an involvement of cAMP and cAMP-mediated processes in long-term memory (Guzowski and McGaugh 1997; Kogan et al. 1997). The results described above suggest an interaction between PDE4 and muscarinic receptors in the regulation of learning and memory, which is also supported by the results of related studies (Egawa et al. 1997; Imanishi et al. 1997; Barad et al. 1998). Further, chronic treatment with rolipram upregulates NMDA receptors in the hippocampus in rats, but it does not affect muscarinic cholinergic receptors (Kato et al 1997). Therefore, instead of altering muscarinic receptors, changes in cAMP levels appear to be involved in the effects of rolipram on scopolamine-induced impairment of memory. This interpretation is supported by the consistency of the time courses in the behavioral effects of rolipram in experiment 1 and the elevation of brain cAMP levels by rolipram (Marighetto et al. 1993).

Forskolin, an adenylyl cyclase activator, has been shown to cause various changes in behavior, such as reductions in locomotor activity and increases in the incidence of grooming and head twitches, after peripheral administration, which are related to increases in brain cAMP levels (Wachtel et al. 1987). In experiment 2, treatment with forskolin also significantly potentiated the scopolamine-induced increase in exploration time, which provides an index of locomotor activity (Wachtel et al. 1987). However, at the dose tested, forskolin failed to significantly affect either working memory or reference memory impaired by scopolamine. In other behavioral tests, forskolin also has been found not to mimic the effects of rolipram (Kehne et al. 1986; O'Donnell 1993). Since the ability of rolipram to elevate cAMP depends on the rate of its formation by adenylyl cyclase, it may produce a pattern of changes distinct from those produced by forskolin. This may account, in part, for the differential effects of rolipram and forskolin observed in the present study. Alternatively, it is possible that effects of rolipram independent of its ability to increase cAMP may contribute to its effects on memory.

Scopolamine increased the exploration time significantly in experiment 2, but not in experiment 1. This might be because that a higher dose of scopolamine (1 mg/kg) was used in the former than that in the latter (0.5 mg/kg).

In conclusion, it has been found that rolipram reverses scopolamine-induced impairment of both working and reference memory, presumably by increasing central cAMP levels via its inhibition of cAMP degradation in certain signal transduction pathways. This provides additional support for a role of cyclic AMP-mediated signal transduction in memory. The specific mechanisms involved in mediating the cAMP/PKA system that are involved in the effects of rolipram on memory remain to be elucidated.

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