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European Journal of Pharmacology 321 (1997) 273–278

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Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents

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Received 1 July 1996; revised 9 December 1996; accepted 10 December 1996

Abstract

The effects of rolipram, a cAMP-specific phosphodiesterase (phosphodiesterase 4) inhibitor, on experimentally-induced amnesia were examined using a 3-panel runway paradigm in rats and a passive avoidance task in mice. Scopolamine, cerebral ischemia induced by four-vessel occlusion and electric convulsive shock impaired working memory in the 3-panel runway task. Rolipram at 0.1 mg/kg reduced the increase in errors induced by scopolamine or cerebral ischemia. Rolipram at 0.32 mg/kg also reduced the increase in errors induced by electric convulsive shock. Dibutyryl cAMP also had similar effects in 3-panel runway experiments. In the passive avoidance task, rolipram reversed the impairments of the avoidance response induced by scopolamine, cycloheximide and electric convulsive shock at 10, 10 and 3 mg/kg, respectively. These results indicate that rolipram ameliorates impairments of learning and memory in rats and mice, and suggest that rolipram might ameliorate the impairments of learning and memory by elevating cAMP levels.

Keywords: Rolipram; cAMP; Learning; Memory; 3-Panel runway; Passive avoidance

1. Introduction

Rolipram, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone, is a phosphodiesterase inhibitor which is selective for the Ca^{2+}/calmodulin-independent and cAMP-specific isozyme of phosphodiesterase (phosphodiesterase 4) (Beavo, 1988). It has been found that rolipram increases brain cAMP levels in vitro (Donaldson et al., 1988) and in vivo (Schneider, 1984) studies. Rolipram exhibited antidepressant activity in various animal experiments (Przegalinski and Bigajska, 1983; Wachtel and Schneider, 1986), and in a clinical study (Eckmann et al., 1988). This effectiveness is thought to be due to a stimulatory effect on noradrenergic transmission by both enhancement of noradrenergic turnover presynaptically (Schoffelmeer et al., 1985) and inhibition of cAMP degradation postsynaptically (Wachtel, 1983).

Some phosphodiesterase inhibitors are thought to possess a cerebral vasodilating effect (Hudlicka et al., 1981) and/or cerebral activating effect (Nicholson and Angersbach, 1986), and have been used for the treatment of cognitive dysfunction (O'Connolly et al., 1986).

In the present study, in order to evaluate the feasibility of rolipram as a drug for cognitive dysfunction, we examined the effect of rolipram on impairments of learning and memory, using a 3-panel runway paradigm in rats and a passive avoidance task in mice. The effect of dibutyryl cAMP, a membrane-penetrating analogue of cAMP, on 3-panel runway performance was also examined to consider the possible involvement of cAMP in the anti-amnesia action of rolipram.

In the 3-panel runway paradigm, working memory has been shown to be impaired by intraperitoneal administration of scopolamine, intra-hippocampal injection of ethylcholine aziridinium ion, a neurotoxic analogue of choline, and cerebral ischemia induced by four-vessel occlusion (Furuya et al., 1988; Yatsugi et al., 1989). The ameliorating effects of compounds on experimentally induced impairments of working memory have been demonstrated by using a repeated acquisition procedure in this paradigm (Yamamoto et al., 1990, 1993).

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PII S0014-2999(96)00969-7

2. Materials and methods

2.1. Subjects

Male Wistar rats (from SLC or JCL, 7–11 weeks, 150–250 g) were used for the 3-panel runway paradigm, and male ddY mice (SLC, 5 weeks, 25–30 g) were used for the passive avoidance task.

2.2. 3-Panel runway paradigm in rats

The details of the apparatus can be found in our previous reports (Furuya et al., 1988; Yamamoto et al., 1990). The apparatus for this experiment is composed of a start box, a goal box and four consecutive choice points. Each choice point consists of three panel gates. A food deprived rat is prevented from passing through two out of three gates in each choice point by a front stopper (incorrect gates) and can pass only one gate (correct gate). When rat reaches the goal box, it can obtain a food pellet. Rats were trained in two separate schedules described below.

In scopolamine and cerebral ischemia experiments, each rat was trained with six consecutive trials every 2 min (1 session) per day. The sequence of correct panel gate locations for each rat was held constant within a session, but was changed for the next session. The number of errors (the number of pushes against incorrect gates) and the latency to obtain a food pellet were recorded for each trial of a session. The learning criterion was fewer than eight errors summed from the second to the sixth trials of a session. A rat was used in the experiment if it achieved this criterion in three consecutive sessions. The impairment of working memory was produced by 0.56 mg/kg of scopolamine or 5 min of cerebral ischemia. It has been demonstrated previously that these treatments elicit constant and moderate impairments of runway performance (Furuya et al., 1988; Yatsugi et al., 1989). Scopolamine was administered 15 min before the first trial of the session, and rolipram or dibutyryl cAMP was injected i.p. 15 min prior to the scopolamine treatment. Cerebral ischemia was produced by four-vessel occlusion (Pulsinelli and Brierley, 1979). The rats meeting the criterion described above were anesthetized with 35 mg/kg, i.p. of pentobarbital Na, if necessary followed by inhalation of diethyl ether, and the bilateral vertebral arteries were electrically cauterized with a bipolar coagulator. Then threads were placed around the bilateral common carotid arteries. After the session on the next day, the common carotid arteries of a rat were exposed by pulling the treads and occluded with clips for 5 min. The rats that did not lose the righting reflex during ischemia were not used for further experiments. Rolipram or dibutyryl cAMP was injected i.p. immediately after reperfusion of the common carotid arteries, and 30 min before the first trial of the test session performed 24 h after ischemia.

For the electric convulsive shock studies, each rat was trained in another protocol, in which a pair of sessions was carried out over 2 days with a 2- or 3-day rest between. One pair consisted of three trials as a training session on the first day and six trials as a test session on the next day with the same sequence of correct panel gate locations. The sequence of correct panel gate locations was changed for the next pair of sessions. The number of errors was counted for each trial of both sessions. A rat meeting the criterion that the number of errors in the first trial of a test session was less than three was used for the experiment. Electric convulsive shock (50 mA, 1 s) was applied immediately after the training session to produce the impairment of learning and memory. Rolipram was administered i.p. just before the application of electric convulsive shock.

2.3. Passive avoidance task in mice

A two-compartment apparatus ($30 \times 9 \times 9$ cm) was used. In the acquisition trial, each mouse was placed individually in the light compartment. When the animal entered the dark compartment, a foot shock of 0.4 mA was delivered through the grid floor until the mouse returned to the light compartment. The impairment of the passive avoidance response was induced by the i.p. administration of 1 mg/kg of scopolamine or the s.c. injection of 200 mg/kg of cycloheximide 30 min before the acquisition trial, or by the application of electric convulsive shock (40 mA, 0.5 s) immediately after the acquisition trial. Rolipram was i.p. injected simultaneously with scopolamine or cycloheximide, or injected just after the application of electric convulsive shock. In the retrieval trial performed 24 h later, the latency to enter the dark compartment was measured until a cut-off time of 300 s in scopolamine and cycloheximide experiments or 600 s in the electric convulsive shock experiment.

2.4. Drugs

Rolipram (racemate, Schering) was suspended in 1% methylcellulose solution. Scopolamine hydrochloride, cycloheximide and dibutyryl cAMP (all from Sigma) were dissolved in saline. These drugs were administered in a volume of 1 ml/kg and 10 mg/kg to rats and mice, respectively.

2.5. Data analysis

In the scopolamine and cerebral ischemia experiments with the 3-panel runway paradigm, the number of errors in the first trial and those summed from the second to the sixth trials were separately analyzed using a one-way analysis of variance (ANOVA) followed by the Bonferroni test. In the electric convulsive shock experiments with the 3-panel runway paradigm, the number of errors in the first

trial of the test session among the groups was also assessed by one-way ANOVA followed by the Bonferroni test. The significant difference between the number of errors in the first trial of the training session and that in the first trial of the test session in each group was also assessed by paired *t*-test. In the passive avoidance studies, the latency of each group was analyzed by using the Mann-Whitney U-test.

3. Results

3.1. 3-Panel runway paradigm in rats

Scopolamine at a dose of 0.56 mg/kg significantly increased the number of errors summed from the second to the sixth trials (Fig. 1AFig. 2A) and also prolonged the total latency to obtain a food pellet in all six trials from the control of 43 ± 2 s to 100 ± 8 s in the experiment with rolipram, or from 29 ± 3 s to 154 ± 32 s in the experiment with dibutyryl cAMP. Similarly, 5 min of cerebral ischemia increased the number of errors (Fig. 1BFig. 2B) and prolonged the latency from 29 ± 2 s to 86 ± 23 s in the experiment for rolipram or from 33 ± 2 s to 53 ± 4 s in the experiment with dibutyryl cAMP, although bilateral cauterization of vertebral arteries had no marked effect (data not shown). Although rolipram did not affect the runway performance of normal rats, it reduced the increase in the number of errors induced by scopolamine ($F(2,28) = 6.52$, $P < 0.01$), an effect that reached significance for 0.1 mg/kg ($P < 0.01$) (Fig. 1A). Rolipram also reversed the increase in errors induced by cerebral ischemia ($F(2,13) = 4.58$, $P < 0.05$), an effect that reached significance for 0.1 mg/kg ($P < 0.01$) (Fig. 1B). Rolipram failed to antagonize the prolonged latency induced by scopolamine and cerebral ischemia. Also, dibutyryl cAMP reduced the increase in errors induced by scopolamine at 100 mg/kg ($F(1,8) = 6.01$, $P < 0.05$) (Fig. 2A) and tended to reverse the increase in errors induced by cerebral ischemia at 32 mg/kg ($F(1,12) = 4.25$, $P = 0.062$) (Fig. 2B). Dibutyryl cAMP at 32 mg/kg and 10 mg/kg did not have a marked effect on the impairment induced by scopolamine and cerebral ischemia, respectively (data not shown).

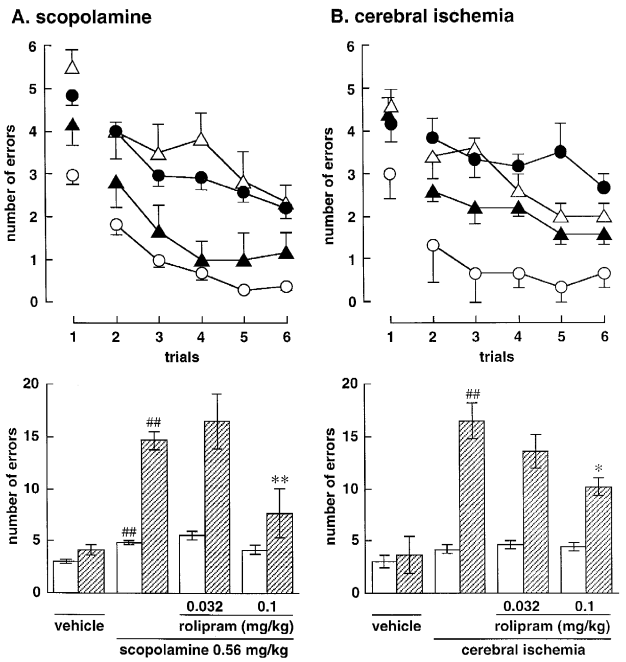

Fig. 1. Ameliorating effect of rolipram on scopolamine (A)- and cerebral ischemia (B)-induced impairments of 3-panel runway performance in rats. In upper panels, each point represents the mean ± S.E. recorded in each trial of a session (○, control; ●, scopolamine (A) or cerebral ischemia (B); △, rolipram 0.032 mg/kg; ▲, rolipram 0.1 mg/kg). In lower panels, each column represents the mean ± S.E. in the first trial (open columns) and those summed from the second to sixth trials (hatched columns) within a session. The significant differences from the control group ($^{\#\#} P < 0.01$) and from the scopolamine or cerebral ischemia group ($^{*} P < 0.05$, $^{**} P < 0.01$) were determined by one way ANOVA followed by the Bonferroni test.

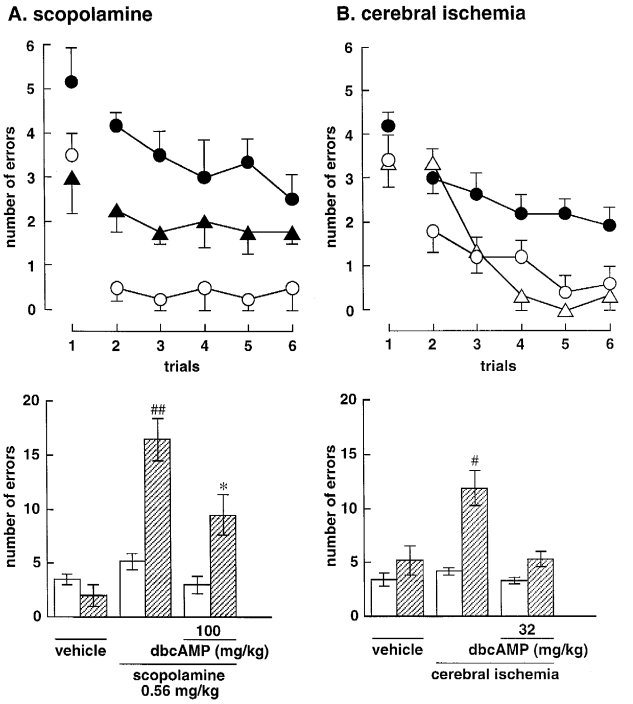

Fig. 2. Ameliorating effect of dibutyryl cAMP (dbcAMP) on scopolamine (A)- and cerebral ischemia (B)-induced impairments of 3-panel runway performance in rats. In upper panels, each point represents the mean ± S.E. recorded in each trial of a session (○, control; ●, scopolamine (A) or cerebral ischemia (B); ▲, scopolamine + dibutyryl cAMP 100 mg/kg (A); △, cerebral ischemia + dibutyryl cAMP 32 mg/kg (B)). In lower panels, each column represents the mean ± S.E. in the first trial (open columns) and those summed from the second to sixth trials (hatched columns) within a session. The significant differences from the control group ($^{\#} P < 0.05$, $^{\#\#} P < 0.01$) and from the scopolamine group ($^{*} P < 0.05$) were determined by one way ANOVA followed by the Bonferroni test.

Fig. 3 shows the results of the electric convulsive shock experiment. In the control group, which did not receive electric convulsive shock, the number of errors in the first trial of the test session was significantly fewer than that of the training session ($P < 0.05$). The result indicates that rats could remember the location of the correct panel gate even after 24 h. The number of errors in the first trial in the test session was increased by electric convulsive shock application to a level similar to that of the first trial of the training session ($F(1,40) = 15.46$, $P < 0.01$), which indicates an impairment of working memory. Rolipram inhibited the increase in errors in the first trial in the test session ($F(2,32) = 4.56$, $P < 0.05$) and reversed the increase in errors significantly and almost completely at 0.32 mg/kg ($P < 0.01$).

3.2. Passive avoidance task in mice

Scopolamine-, cycloheximide- and electric convulsive shock-treated groups showed shortened latencies, which indicates an impairment of passive avoidance performance (Fig. 4). Rolipram at 10 mg/kg significantly improved the scopolamine-induced impairment, but exhibited no effect at a higher dose. Rolipram also ameliorated dose dependently the cycloheximide- and electric convulsive shock-induced impairments. The minimum effective dose was 10 mg/kg and 3 mg/kg against the impairments induced by cycloheximide and electric convulsive shock, respectively. It was confirmed that rolipram at the doses used for the experiments affected neither the sensitivity to foot shock nor the retrieval latency in normal mice.

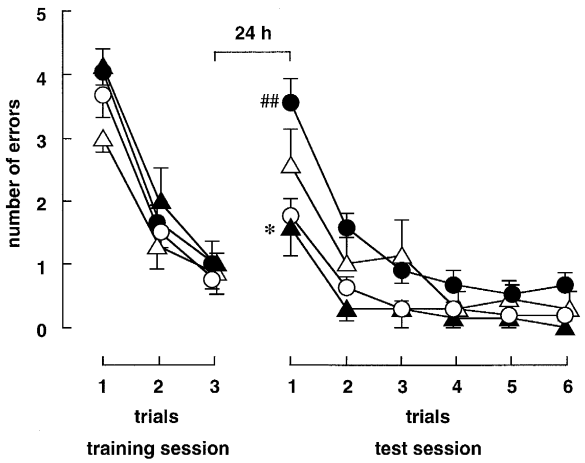

Fig. 3. Ameliorating effect of rolipram on retrograde amnesia induced by the application of electric convulsive shock. Rats were trained in three trials as a training session on the first day and in six trials as a test session on the next day with the same sequence of correct panel gate locations. Electric convulsive shock (50 mA, 1 s) was applied immediately after the training session. Each point represents the mean ± S.E. (○, control; ●, electric convulsive shock; △, +rolipram 0.1 mg/kg; ▲, +rolipram 0.32 mg/kg). The significant differences from the control group ($^{\#\#}P < 0.01$) and from the electric convulsive shock group ($^{*}P < 0.05$) were determined by one-way ANOVA followed by the Bonferroni test.

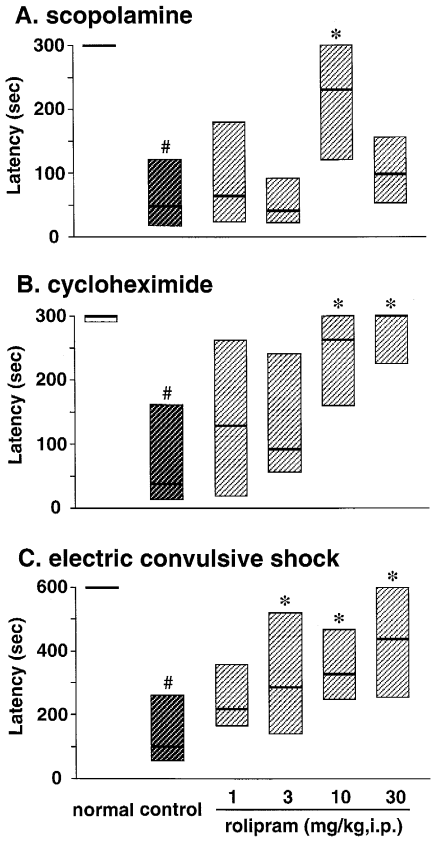

Fig. 4. Ameliorating effect of rolipram on the deficits of passive avoidance response induced by scopolamine (A), cycloheximide (B) and electric convulsive shock (C). A bold horizontal line in a column indicates median latency, and the upper and lower lines of each column indicate interquartile ranges. The significant differences from the normal (vehicle-treated or no electric convulsive shock) group ($^{\#}P < 0.05$) and from the control (scopolamine, cycloheximide or electric convulsive shock) group ($^{*}P < 0.05$) were determined by the Mann-Whitney's U-test.

4. Discussion

Some phosphodiesterase inhibitors have been shown to enhance learning and memory function and to ameliorate experimentally induced amnesia or cognitive dysfunction in both animals and humans. For example, vinpocetine, a vinka alkaloid, which selectively inhibits Ca^{2+}/calmodulin-dependent cAMP phosphodiesterase, suppresses scopolamine- and hypoxia-induced retrieval deficits of the passive avoidance response in rats (De Noble et al., 1986), and enhances memory in normal healthy volunteers (Subhan and Hindmarch, 1985). Also propentofylline, an alkylxanthine derivative, improves the decreased ability to learn shuttle avoidance behavior of spontaneously hypertensive rats and cycloheximide-induced amnesia in a mouse

passive avoidance task (Goto et al., 1987) and is clinically effective against cerebrovascular dementia (Ohtomo et al., 1986). Another alkylxanthine derivative, denbufylline, which selectively inhibits phosphodiesterase 4, as does rolipram, is also effective against the passive avoidance deficit induced by transient forebrain ischemia in Mongolian gerbils (Nicholson et al., 1989).

Cyclic AMP has been considered to play a crucial role in learning and memory function. Like phosphodiesterase inhibitors, forskolin, an activator of adenylate cyclase, prevents memory dysfunction in rats (Ando et al., 1987). In fact, cAMP injection into the lateral ventricle is effective against the experimental amnesia in mice (Chutae et al., 1981). Moreover, intraventricular treatment with 8-bromo cAMP, an analogue of cAMP, accelerates conditioned learning behavior in rats (Danilova et al., 1985). In addition, long-term potentiation, which is thought to serve as a mechanism for learning and memory, is induced by analogues of cAMP without any tetanic stimuli (Frey et al., 1993; Nguyen et al., 1994).

In the present experiments, rolipram improved the working memory deficits of rats induced by scopolamine, cerebral ischemia, and also improved the retrograde amnesia of long-term (24 h) memory induced by electric convulsive shock application. In addition, rolipram improved the deficits of the passive avoidance response in mice induced by scopolamine, cycloheximide and electric convulsive shock. It has already been demonstrated that rolipram elevates brain cAMP levels in vitro (Donaldson et al., 1988) and in vivo (Randt et al., 1982; Schneider, 1984). Indeed, the doses reported to increase brain cAMP in mice or rats are consistent with the doses effective in our experiments. These results strongly suggest that the anti-amnesia effect of rolipram can be attributed to its action to increase levels of cAMP. In order to examine the involvement of cAMP in the ameliorating effect of rolipram on the impairments of learning and memory, we used dibutyryl cAMP, a membrane-penetrating analogue of cAMP, to assess whether or not it improved the impairments. A number of studies have examined the central action of analogues of cAMP such as dibutyryl cAMP instead of cAMP (Wachtel and Loschmann, 1986; Weiner and Olson, 1973). In fact, dibutyryl cAMP is detected in rat brain after its peripheral administration (Tachizawa et al., 1974). The fact that dibutyryl cAMP also ameliorated the scopolamine- and cerebral ischemia-induced deficits of 3-panel runway performance strongly supports the hypothesis that rolipram ameliorates the impairments of learning and memory by elevating cAMP levels.

It is not clear how cAMP improves the impairments of learning and memory. A significant decrease in cAMP production by electric convulsive shock was reported in rat brain (Newman et al., 1986). Therefore, rolipram might reverse the electric convulsive shock-induced deficits of 3-panel runway and passive avoidance performance by alleviating the reduction of cAMP. However, no consistent decrease in cAMP contents was reported in scopolamine-, cerebral ischemia- and cycloheximide-treated animals. This might indicate that rolipram affects other systems that are disrupted by the above treatments via an elevation of cAMP. Indeed, analogues of cAMP have been reported to promote the activity of cholinergic neurons and to potentiate acetylcholine responses (Nakamura et al., 1994; Fu, 1993). Rolipram has been reported to accelerate noradrenergic transmission both pre- and post-synaptically (Wachtel, 1983; Schoffelmeer et al., 1985) and it might reverse the dysfunction of noradrenergic transmission induced by cerebral ischemia (Kogure et al., 1974). In addition, the elevation of brain cAMP by rolipram might result in activation of protein kinases for phosphorylation of proteins or in modulation of a variety of monoaminergic neurotransmitters which may be involved in the memory process (Randt et al., 1982). Furthermore, cAMP modifies Ca^{2+} homeostasis, which is very important in neuronal excitability.

It is very interesting that adenylate cyclase activity is reduced in Alzheimer patients (Lemmer et al., 1989). This fact may indicate that elevating the cAMP level in the brain, for instance by use of phosphodiesterase inhibitors, is a potential method for the treatment of Alzheimer disease.

In summary, we demonstrated the anti-amnesia effects of rolipram in the 3-panel runway paradigm with rats and in the passive avoidance task with mice. Rolipram might ameliorate the impairment of learning and memory by elevating cAMP levels. The results obtained here suggest its usefulness in the clinical treatment of cognitive dysfunction.

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