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The Effects of a Selective cAMP Phosphodiesterase Inhibitor, Rolipram, on Methamphetamine-Induced Behavior

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The effects of rolipram, a selective cAMP phosphodiesterase inhibitor, on locomotor activity, rearing, and stereotyped behavior (sniffing, repetitive head movements) induced by methamphetamine (MAP) over 1 hour were investigated in rats. Coadministration of rolipram (4 mg/kg IP) significantly attenuated the responses of locomotor activity, rearing and repetitive head movements to MAP (2,4 or 8 mg/kg IP). Rolipram (0.5, 1, 2, or 4 mg/kg IP) dose-dependently inhibited locomotor hyperactivity and rearing induced by 4 mg/kg of MAP. The rearing was completely inhibited by 4 mg/kg of rolipram, whereas the maximal inhibition of the locomotor hyperactivity was about 50%. However, rolipram did not alter MAP-induced sniffing and repetitive head movements. These results indicate that there is heterogeneity in the response of MAP-induced behavior to rolipram, suggesting that MAP-induced behavioral alteration may be partly regulated by cAMP levels in the brain. ***[Neuropsychopharmacology 13:33–39, 1995]***

KEY WORDS: *Methamphetamine; Dopamine; Cyclic adenosine 3',5'-monophosphate (cAMP); Rolipram; Rat*

Methamphetamine (MAP) or amphetamine (Amp) causes psychosis (Angrist and Gershon 1970; Bell 1973; Connel 1958) in which specific symptoms are similar to those in paranoid schizophrenia (Ellinwood 1969; Griffith et al. 1972). Therefore, MAP or Amp psychosis has been considered as a model of schizophrenia (Sato et al. 1983; Snyder 1979). It has been reported that neuroleptics ameliorate MAP or Amp psychosis (Angrist et al. 1974; Sato et al. 1983). In animals MAP or Amp produces locomotor hyperactivity and stereotyped behavior and the blockade of either dopamine D_1 or D_2 receptors is also reported to attenuate these responses (Christensen et al. 1984; Iorio et al. 1983; Mailman et al. 1984; Molly and Waddington 1986; Ujike et al. 1989). Furthermore, MAP has been reported to increase extracellular dopamine levels in rats (Kazahaya et al. 1989). Consequently, it is suggested that MAP- or Amp-induced behaviors in animals and psychosis in human may be mainly mediated by increased dopamine levels in the synaptic cleft via dopamine D_1 and D_2 receptors.

Arguments that dopamine D_1 and D_2 receptors may affect behavior either by synergistic or opposing interactions or by independent effects (Arnt 1987; Clark and White 1987; Pugh et al. 1985; Seeman and Grigoriadis 1987; Waddington and O'Boyle 1989; Walters et al. 1987) complicate an understanding of the possible roles of dopamine D_1 and D_2 receptors in MAP-induced behavioral changes. On the other hand, it is known that dopamine D_1 receptors increase cyclic

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adenosine 3',5'-monophosphate (cAMP) levels by stimulating adenylate cyclase activity, whereas dopamine D_2 receptors are either unlinked to, or inhibit, this enzyme (Kebabian and Caine 1979; Seeman 1980). Furthermore, recent studies have indicated that cAMP may play an important role for the induction of immediate-early genes, such as c-fos, following MAP or Amp administration (Graybiel et al. 1990; Kashiwa et al. 1993; Konradi et al. 1994; Nguyen et al. 1992; Norman et al. 1993), which may be related to not only the acute effects but also the long-term residual effects of the drugs, such as behavioral sensitization. However, it has been reported that MAP and Amp treatments reduce dopamine-sensitive adenylate cyclase activity (Barnes et al. 1987) and cAMP levels in the striatum (Yaginuma et al. 1992). Therefore, it is important to investigate the roles of cAMP in MAP- or Amp-induced behavior for understanding the molecular events related to cAMP in MAP or Amp.

Rolipram is a selective cAMP phosphodiesterase inhibitor that enhances the availability of cAMP levels in brain by the inhibition of cAMP metabolism (Wachtel 1982) in the absence of direct stimulation of neurotransmitter receptors (Schneider et al. 1986) or alteration of dopamine release and metabolism (Kehr et al. 1985). It has been reported that rolipram induces hypothermia and hypokinesia in rodents (Smith 1990; Wachtel 1983), but the drug reversed the hypothermia and hypokinesia of monoamine-depleted mice with reserpine treatment (Wachtel 1983). These results suggest that increased cAMP levels under a monoamine-depleted state improve hypokinesia and that increased cAMP levels may inhibit hyperactivity under a hypermonoaminergic state due to antagonism to desensitized adenylate cyclase activity.

In the present study we examined the behavioral effects of rolipram on the behaviors induced by a single MAP administration in order to investigate further links between cAMP levels and MAP-induced behaviors.

MATERIALS AND METHODS

Animals

Sixty-six male Wistar rats (weighing 240–320 g) were used. The animals were housed in groups of 3 animals to a cage. They were maintained under standard conditions (12 hour–12 hour light–dark cycle: light on from 600 to 1800 hours, room temperature 23 ± 0.5°C, humidity 55 ± 5%) with free access to food and to water for at least 1 week before being subjected to experimental manipulation. All experiments presented followed the National Center of Neurology and Psychiatry Animal Care Guideline.

Drugs

Rolipram (a gift from Meiji Seika Co.) was suspended in physiological sodium chloride solution containing 10% w/v Cremophor EL^R (CEL; polyethoxylated castor oil, BASF, Ludwigshafen, Germany). Methamphetamine was dissolved in physiological saline. Rats in groups that were treated with MAP received an IP injection of MAP (2, 4, or 8 mg/kg) followed by an IP injection of either vehicle or 4 mg/kg of rolipram, or an IP injection of 4 mg/kg of MAP followed by an IP injection of rolipram (0.5, 1, 2, or 4 mg/kg). The rats in the control group received an IP injection of saline followed by an IP injection of vehicle. Other rats received an IP injection of saline followed by an IP injection of rolipram (4 mg/kg). Each injection was in a volume of 0.1 ml per 100 g of body weight.

Behavioral Experiments

The rats were placed in a square, transparent plastic cage with dimensions of 287 × 287 mm for the inner bottom area and of 350 mm in height, that was set on SCANET SV10 (see later), 15 minutes before drug injection. Following injection, the rats were replaced in the cage and behavioral measurements and scoring were started.

Measurements of Locomotor Activity and Rearing. Locomotor activity and rearing were measured using an animal movement analyzing system (SCANET SV-10, MATYS, Toyama, Japan; Asakura et al. 1992). The system consisted of two rectangular enclosures (440 × 300 mm). The side walls (60 mm high) of the enclosure were equipped with 144 pairs of photosensors. They were located at intervals of 5 mm and 30 mm high from the bottom edge of the enclosure. The upper enclosure and lower enclosure were set with their photosensors 30 mm high and 150 mm high from the cage floor, respectively. Each pair of photosensors was scanned every 0.1 s to detect animal movement. An intersection of two paired photosensors (10-mm interval) of the lower enclosure was counted as one locomotor activity. An intersection of photosensors of the higher enclosure was counted as a rearing movement. The data collected for the 60 minutes following the drugs injection were used for analysis.

Behavior Rating. The intensity of stereotype (comprehensive stereotype assessment) was assessed using the method of Akiyama et al. (1982): 0, asleep or still; 1, locomotion with normal exploration and normal pattern of sniffing; 2, hyperlocomotion with repetitive exploratory behavior, rearing, or increased rate of sniffing; 3, discontinuous sniffing with periodic locomotion activity; 4, continuous compulsive sniffing without locomotion. We also rated sniffing, repetitive head move-

ments, and grooming separately as follows; 0, not observed, 1; questionable, 2; slightly observed, 3; moderately observed, 4; intensely observed, 5; almost continuously observed. Scores were taken for 1 minute every 10 minutes following the drug injection. Scores for the 6 time points were cumulated for each behavior.

Statistics

The responses of locomotor activity and rearing frequency to MAP (2, 4, or 8 mg/kg IP) were evaluated by one-way analyses of variance (ANOVA) followed by the Fisher PLSD test, and those of comprehensive stereotype, sniffing, head movement, and grooming were evaluated by the Kruskal-Wallis test followed by the Mann-Whitney *U*-test. The locomotor activity and rearing frequency between MAP groups and the control group (saline with vehicle), and the scores of behavior rating between the two groups were analyzed by the Mann-Whitney *U*-test. The influence of rolipram on the responses of locomotor activity and rearing to MAP was evaluated by two-way ANOVA, and as post hoc analysis, the effect of rolipram at each MAP dose was evaluated by the Mann-Whitney *U*-test and the effects of rolipram on the scores of behavior rating were evaluated by the Mann-Whitney *U*-test at each MAP dose. The dose effects of rolipram on MAP-induced augmentation of locomotor activity and rearing frequency were analyzed by one-way ANOVA followed by the Fisher PLSD test, and those of the scores of behavior rating were analyzed by the Kruskal-Wallis test followed by the Mann-Whitney *U*-test. The criterion level of significance is $p < 0.05$.

RESULTS

Each dose of MAP administered (2, 4, or 8 mg/kg IP) significantly increased locomotor activity as compared with saline and vehicle-treated rats ($p < .001$). There was no significant dose effect of MAP on the activity. Coadministration of rolipram (4 mg/kg IP) significantly attenuated locomotor activity response to MAP at 2 mg/kg and 4 mg/kg of MAP ($p < .05$; Figure 1A). Rolipram (0.5, 1, 2, or 4 mg/kg IP) significantly and dose-dependently inhibited MAP (4 mg/kg IP)-induced locomotor hyperactivity ($p < .001$), and the maximum inhibition was about 50% (Figure 2A).

The rearing response to MAP was bell-shaped ($p < 0.01$), with the highest score at 4 mg/kg. Coadministration of rolipram almost completely blocked the response to MAP (A × B, $p = .0047$; Figure 1B). Rolipram significantly and dose-dependently suppressed rearing induced by MAP (4 mg/kg IP) ($p < .01$; Figure 2B).

MAP significantly and dose-dependently increased intensity of comprehensive stereotype ($p < .05$). Coadministration of rolipram (4 mg/kg IP) significantly decreased the intensity at 2 mg/kg of MAP but did not alter the response to the other dose of MAP (Table 1). The high intensity induced by MAP (4 mg/kg IP) was not affected by coadministration of rolipram (0.5–4.0 mg/kg IP) (Table 2).

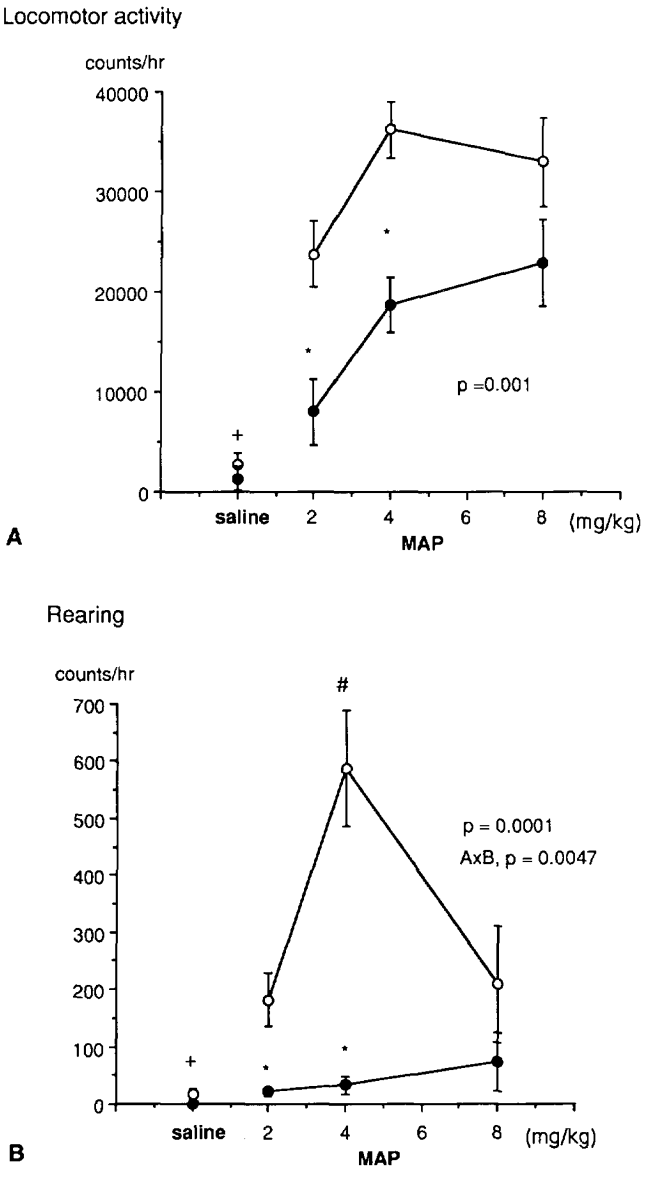

Figure 1. Influences of rolipram (4 mg/kg IP) on the behavioral response, i.e., locomotor activity (**A**) and rearing (**B**) to MAP in rats. Data collected for 60 minutes were used. (*Open circles*, vehicle; *closed circles*, rolipram.) Error bars indicate SEM ($n = 6$). $^{+}$ $p < .05$ as compared to MAP treatment assessed by Fisher PLSD. # $p < .01$ vs. 4 mg/kg and 8 mg/kg of MAP. * $p < .001$ vs. vehicle at the same dose of MAP. The p value given represents the value for a significant main effect of coadministration of rolipram or (A × B) a significant interaction between factors.

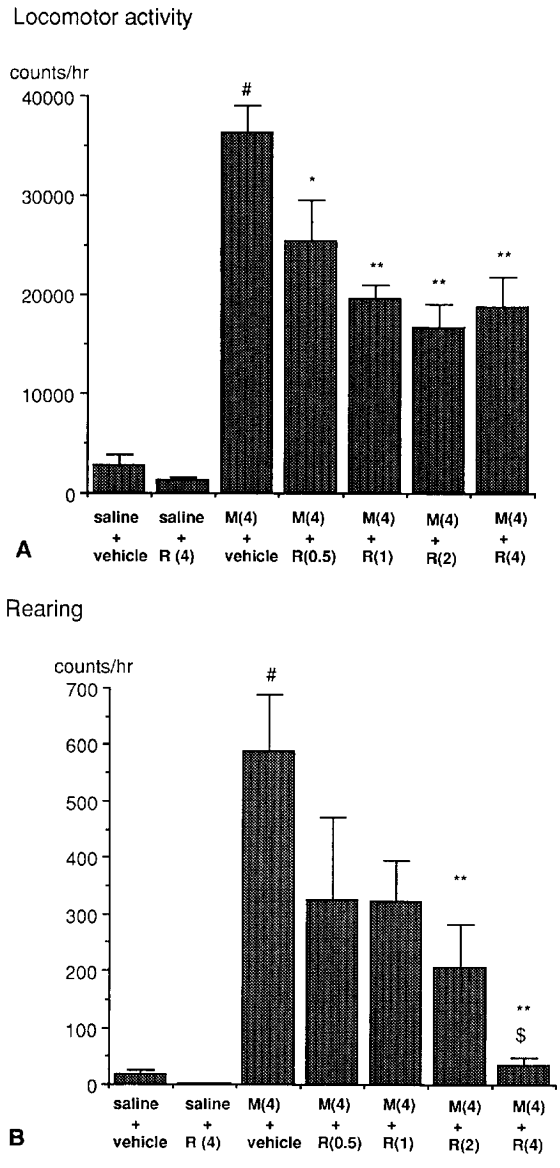

Figure 2. The dose-effects of rolipram on MAP (4 mg/kg IP)-induced behaviors, i.e., locomotor activity (**A**) and rearing (**B**) to MAP in rats. Data collected for 60 minutes were used. M(x) and R(y) indicate x mg/kg of methamphetamine and y mg/kg of rolipram, respectively. Columns and error bars indicate mean values and SEM ($n = 6$). # $p < .05$ vs. the control group. * $p < .05$ and ** $p < .001$ vs. 4 mg/kg of MAP with vehicle. $ $p < .05$ vs. 4 mg/kg of MAP with 2 mg/kg of rolipram.

MAP significantly induced sniffing ($p < .0001$), but there was no dose effect on the behavior. Coadministration of rolipram did not alter the response to MAP (Table 1) or the intensity induced by MAP (4 mg/kg IP) (Table 2).

MAP significantly induced repetitive head movements ($p < .0001$), but there was no dose effect on the behavior (Table 1). Coadministration of rolipram (4 mg/kg) significantly increased the response to MAP at 8 mg/kg ($p < .05$; Table 1). However, there was no significant dose effect of rolipram on the movements after testing with 4 mg/kg of MAP (Table 2).

The incidence of grooming was very low. No significant effect of MAP or of rolipram was observed (Tables 1 and 2).

There was no significant difference in MAP-induced behaviors or movement between rats treated with saline and vehicle and those treated with saline and rolipram (4 mg/kg IP).

DISCUSSION

It was reported that only a high dose of rolipram (20 mg/kg) increased dopamine levels in postmortem tissue samples of rat brain (Kehr et al. 1985). We observed no influence of 4 mg/kg of rolipram on MAP (4 mg/kg IP)-induced increase in extracellular dopamine levels in rat striatum using an in vivo microdialysis (data not shown). Therefore, we considered that the effects of rolipram on MAP-induced behaviors were mainly due to the modulation of dopamine transmission in postsynaptic levels.

In the present study rolipram dose-dependently suppressed MAP-induced rearing, partly suppressed MAP-induced locomotor hyperactivity, and hardly affected MAP-induced stereotyped behaviors, including sniffing and repetitive head movements. At the maximal dose, where rearing was completely suppressed, rolipram significantly attenuated the locomotor and rearing responses to MAP, whereas it did not alter the responses of intensity of comprehensive stereotype and sniffing to MAP. As MAP dose increased, the incidence of head movements decreased and coadministration of rolipram significantly altered the response to MAP, which may suggest that the response to MAP was attenuated by rolipram. However, as no dose-effect of rolipram on the movements was observed, it may be difficult to conclude the significance of the effect of rolipram on the MAP-induced movements. MAP-induced locomotor hyperactivity, rearing, sniffing, and head movements have been suggested to be mediated via mainly dopamine D_2 receptors (Christensen et al. 1984; Iorio et al. 1983; Mailman et al. 1984; Ujike et al. 1989). The differential effects of rolipram on these movements or behaviors may be partly due to a different manner of linkage of dopamine D_2 receptors to adenylate cyclase. As rearing may be induced by MAP via D_2 receptors that inhibit adenylate cyclase, the rolipram-induced increase in cAMP levels may reduce the rearing. It has been reported that local injections of the dopamine D_1 agonist SKF 38393 into nucleus accumbens generate locomotor hyperactivity (Dreher and Jackson 1989; Essman et al. 1993);

Table 1. The Influence of Rolipram (4 mg/kg IP) on the Behavioral Response to MAP[a]

	Comprehensive Stereotypy Assessment		Sniffing		Head Movement		Grooming	
MAP Dose	**Vehicle**	**Rolipram**	**Vehicle**	**Rolipram**	**Vehicle**	**Rolipram**	**Vehicle**	**Rolipram**
Saline	1.2[b] ± 0.5	1.3 ± 0.3	3.3[b] ± 0.80	0.7 ± 0.7	0.7[b] ± 0.2	0.0 ± 0.0	1.0 ± 0.5	3.0 ± 1.1
2 mg/kg	10.2 ± 0.8	5.5[c] ± 1.5	22.7 ± 1.2	18.3 ± 2.9	19.0 ± 1.5	14.0 ± 2.8	1.0 ± 0.7	3.7 ± 1.0
4 mg/kg	13.2 ± 0.8	12.0 ± 1.7	26.0 ± 0.6	25.5 ± 1.2	17.3 ± 1.5	17.7 ± 1.9	0.0 ± 0.0	0.7 ± 0.7
8 mg/kg	15.7[d] ± 2.0	17.3 ± 1.2	23.0 ± 1.5	25.3 ± 0.7	13.7 ± 0.8	19.2[c] ± 1.3	0.0 ± 0.0	0.0 ± 0.0

Each data point represents mean ± SEM.

[a] Influences of rolipram (4 mg/kg IP) on the behavioral response, i.e., intensity of comprehensive stereotypy, sniffings, repetitive head movements, and grooming to MAP in rats are shown in this table. The cumulative scores of each behavior rated for 1 minute every 10 minutes for 60 minutes were used.

[b] $p < .001$ as compared to MAP treatment assessed by Mann-Whitney *U*-test.

[c] $p < .05$ vs MAP with vehicle group at the same dose of MAP evaluated by Mann-Whitney *U*-test.

[d] $p < .05$ vs. 2 mg/kg of MAP evaluated by the Kruskal-Wallis test followed by Mann-Whitney *U*-test.

not only D_2 receptors that inhibit adenylate cyclase but also D_1 receptors may be involved, so that rolipram only partly suppressed MAP-induced hyperactivity. On the other hand, as MAP-induced stereotyped behavior, sniffing, and repetitive head movements were hardly affected by coadministration of rolipram, these behaviors may be mediated via dopamine D_2 receptors that are not linked to adenylate cyclase and may not be influenced by an increase in cAMP levels induced by rolipram.

It has been reported that rolipram induced grooming and the dose effects were bell-shaped (Wachtel 1982). In the present study coadministration of rolipram (4 mg/kg) with 2 mg/kg of MAP showed a trend to induce grooming, and an increase in the dose of rolipram with MAP tended to decrease grooming. However, the incidence of grooming was very low and no reliable effect of rolipram on grooming was observed in the present series of studies. Therefore, although the dopamine D_1 agonist SKF 38393 has been reported to induce grooming (Ujike et al. 1990), and the treatment with rolipram alone can be expected to enhance dopamine transmission via dopamine D_1 receptors, mechanisms other than D_1 receptor stimulation may also be involved in the occurrence of grooming.

The present results suggest that behavioral alteration induced by MAP may be partly regulated by cAMP levels in brain, that is, it may be partly suppressed by an increase in cAMP levels. It might also be suggested that rolipram may be able to attenuate some types of psychotic symptoms in MAP psychosis or schizophrenia in humans. However, to confirm the interaction of rolipram with dopamine D_1 and D_2 more precisely, it may be necessary to investigate the influence of the drug on the behaviors induced by selective compounds to D_1 and D_2 receptors in further studies. A certain limitation, furthermore, may be considered in discussing the motor-impairing effects of rolipram in the present study. Although our findings provide evidence that rolipram attenuates the behavioral augmentation induced by MAP, this may in part reflect nonspecific motor-impairing effects of rolipram. To investigate this possibility, it would be necessary to determine whether rolipram also suppresses the behavioral augmentation induced by nonmonoaminergic motor stimulants, such as strychnine and caffeine as well.

Table 2. The Effects of Rolipram on MAP (4 mg/kg IP)-Induced Behaviors[a]

Rolipram Dose	Comprehensive Stereotypy Assessment	Sniffing	Head Movement	Grooming
Vehicle	13.2 ± 0.8	26.0 ± 0.6	17.3 ± 1.5	0.0 ± 0.0
0.5 mg/kg	14.5 ± 1.5	22.7 ± 0.9	16.3 ± 1.7	0.0 ± 0.0
1 mg/kg	12.3 ± 0.8	24.8 ± 1.2	18.3 ± 1.7	1.2 ± 0.8
2 mg/kg	9.3 ± 1.5	24.0 ± 1.7	14.8 ± 1.7	0.5 ± 0.5
4 mg/kg	12.0 ± 1.7	25.5 ± 1.2	17.7 ± 1.9	0.7 ± 0.7

[a] The dose effects of rolipram on the scores of behavior rating in rats are shown in this table. The cumulative scores of each behavior rated for 1 minute every 10 minutes for 60 minutes were used. The data were analyzed by Kruskal-Wallis test. There was no significant dose effect of rolipram on MAP-induced behaviors. Each data point represents mean ± SEM.

CONCLUSION

We hypothesized that behaviors related to hyperdopaminergic activity were influenced by changes in cAMP levels by exogenous manipulations. The present study indicated that rolipram, a selective cAMP phosphodiesterase inhibitor, inhibited methamphetamine-induced locomotion and rearing, suggesting that an increased cAMP level in the brain may partly suppress behaviors related to hyperdopaminergic activity.

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