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The Type IV Phosphodiesterase Inhibitors, Ro 20-1724 and Rolipram, Block the Initiation of Cocaine Self-Administration

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KNAPP, C. M., M. M. FOYE, D. A. CIRAULO AND C. KORNETSKY. *The type IV phosphodiesterase inhibitors, Ro 20-1724 and rolipram, block the initiation of cocaine self-administration.* PHARMACOL BIOCHEM BEHAV **62**(1) 151–158, 1999.—The hypothesis that the selective activation of cyclic AMP (cAMP) signal transduction pathways will suppress the initiation of cocaine self-administration was examined in this investigation. To test this hypothesis, the effects of the administration of the cAMP-specific (type IV) phosphodiesterase inhibitors, rolipram and Ro 20-1724, on cocaine self-administration were determined. The effects of Ro 20-1724 treatment on operant responding for food also were examined. Both cocaine and food were delivered following a fixed-ratio 5 schedule. A significant increase in the latency for the delivery of the first cocaine infusion and a reduction in the number of infusions obtained per session were produced by treatment with either rolipram or Ro 20-1724. Similar effects on responding for food were seen with Ro 20-1724 administration. Responding after drug-induced delays tended to be at control levels. These results suggest that cAMP-specific phosphodiesterase inhibitors may inhibit the initiation of operant responding for either cocaine or food. However, the extent to which these actions involve specific effects on central motivational systems as opposed to other mechanisms remains to be determined. © 1998 Elsevier Science Inc.

Cocaine Self-administration Phosphodiesterase inhibitor Food reinforcement Rolipram Ro 20-1724 cAMP

THE initiation of cocaine self-administration is suppressed by the administration of either of the dopamine D_1-like receptor agonists, SKF 82958 (22) or SKF 77434 (11). SKF 82958 and the highly selective D_1-like agonist, SKF 81297, will block the reinstatement of self-administration responding produced by cocaine priming (22). These results suggest that D_1-like agonists may have an inhibitory effect on cocaine seeking behavior.

A primary mode of action of dopamine D_1 receptor agonists involves the elevation of intracellular cyclic AMP (cAMP) levels through stimulation of adenylate cyclase and the resultant enhancement of cAMP-dependent protein kinase (PKA) activity (1,4,8,9,24). The inhibitory effects of D_1-like agonists on the initiation of cocaine self-administration, then, may be mediated by cAMP signal transduction pathways. This suggests that compounds that elevate cAMP levels in the brain might also suppress responding for cocaine.

The administration of cAMP-specific phosphodiesterase (type IV) inhibitors, including rolipram and Ro 20-1724, will increase cAMP levels in several brain regions including the striatum, cortical areas, and the cerebellum (18). To test the hypothesis that activation of cAMP pathways suppresses the initiation of cocaine acquisition, rolipram and Ro 20-1724 were administered to animals prior to the start of cocaine self-administration sessions. To assess how type IV phosphodiesterase inhibitors can influence nondrug-motivated responding, the effects of Ro 20-1724 administration on a food reinforced operant task was examined.

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METHODS

Apparatus

Test sessions in both the cocaine self-administration and food reinforcement experiments were conducted in two-lever operant chambers (MED Associates, St. Albans, VT). The operant chamber (23 × 23 × 40 cm) is housed inside a sound-attenuating chamber with a Plexiglas window located on a center door. The operant chamber contains two levers placed 7.54 cm above a grid floor, and has two lights located 5.5 cm above the levers. The experimental programs controlled and the data collected by an IBM compatible computer using MED-PC software.

Animals

Male Wistar rats (Taconic, Germantown, NY) were used in each of these experiments. These animals ranged in weight between 350 and 425 g. They were housed individually in hanging wire cages under a 12-L:12-D cycle. Six animals were used in the Ro 20-1724 and four rats in the rolipram cocaine self-administration experiments. In the Ro 20-1724 food-reinforced operant task experiment, six animals were tested—four rats that had been used in the cocaine self-administration experiments, and two with no prior history of drug exposure.

Cocaine Self-Administration

During the catheter implantation procedure animals were first anesthetized with a 50 mg/kg (IP) dose of pentobarbital. Supplementary doses of chloral hydrate, 160 mg/kg (IP), were administered as needed. A silastic catheter (Plastics One, Roanoke, VA) was implanted surgically into the right external jugular vein, which was extended into the right atrium. The free end of the catheter was threaded subcutaneously and exited via an incision made on the scalp (2). The cannula assembly was then affixed to the skull with stainless steel screws and cranioplastic cement. Animals received postsurgical care for 5 days.

After recovery from surgery catheters were checked for patency each morning by infusing 0.1 ml of 10 U/ml heparinized saline. After infusion, the syringe was drawn back and checked for blood. If blood could not be drawn, 0.1–0.3 ml of 10 U/ml heparin solution was infused and drawn back until blood appeared. Streptokinase (0.5 ml), dissolved in 30 U/ml heparin solution, was infused after the completion of every daily self-administration session. Animals' food intake was restricted to allow them to maintain but not gain body weight.

Prior to surgery, rats were handled daily for 2 weeks and then trained to lever press for food reward (45 mg Noyes pellets). Approximately 6 days after surgery, rats were shaped to self-administer the training dose (0.3 mg/kg/infusion) of cocaine on a continuous reinforcement (CRF) schedule for a minimum of 5 days. Prior to each session, a three second primer injection was infused to displace the heparinized saline and fill the catheter with drug. When animals were reinforced, a stimulus light flashed for six seconds followed by a 20-s time out. Lever presses during this period were not reinforced. A second lever in the chamber was inactive; lever presses were counted but were not reinforced. Rats were advanced to a fixed ratio 5 (FR5) reinforcement schedule when 28 reinforcements in a 3-h session had been reached on the CRF schedule for 3 consecutive days. At this point the dose of cocaine deliv-

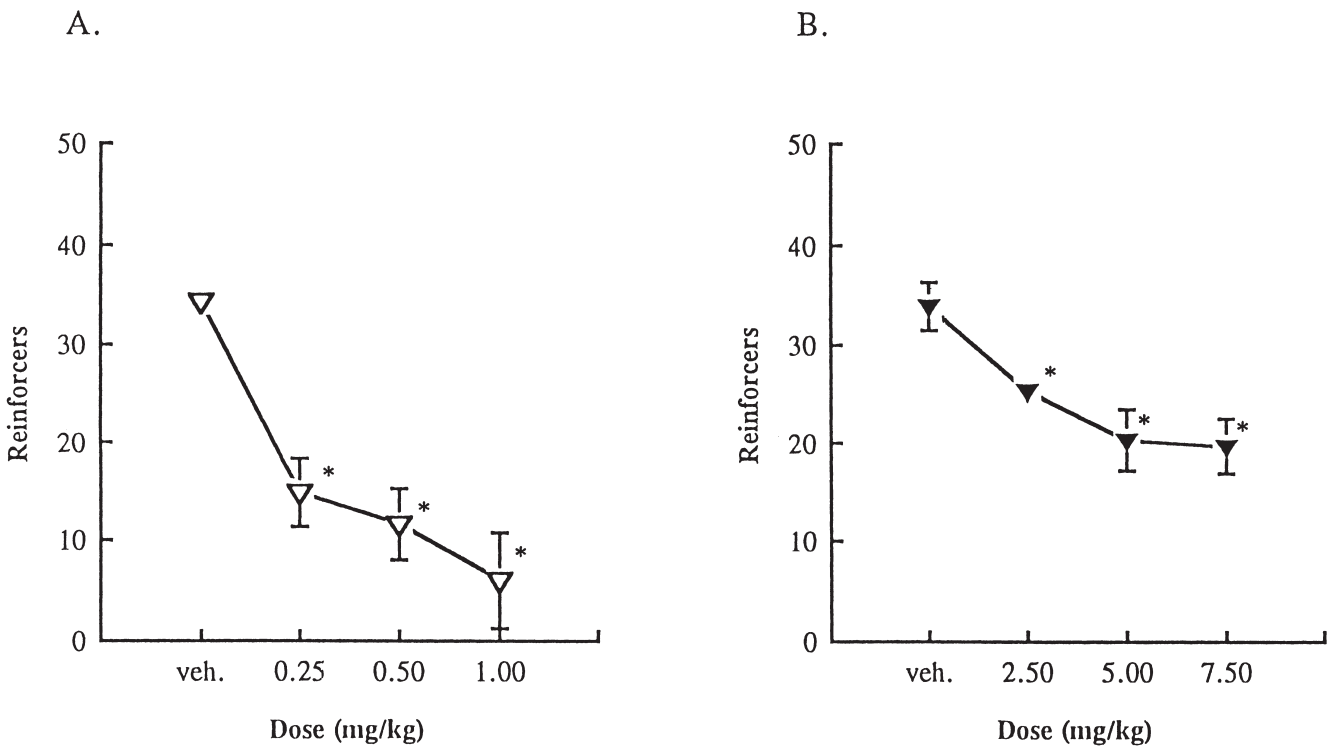

FIG. 1. Mean number (±SEM) of cocaine infusions self-administered during a 3-h session following the administration of either (a) rolipram or (b) Ro 20-1724. *Denotes a significant difference ($p < 0.05$) from vehicle values.

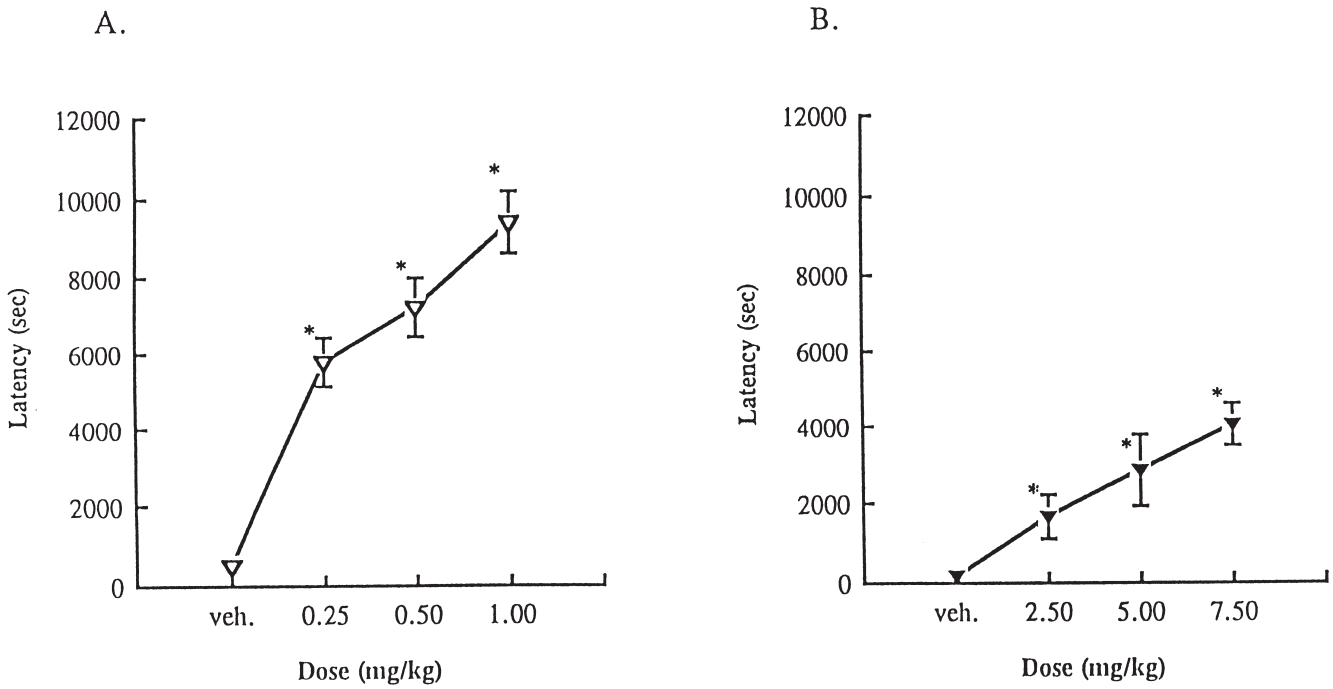

FIG. 2. Mean latencies for the delivery of the first cocaine infusion during a 3-h test session after the administration of either (a) rolipram or (b) Ro 20-1724. *Denotes significant difference ($p < 0.05$) from vehicle values.

ered was increased to 0.6 mg/kg infusion. On the FR5 schedule, rats were limited to a maximum of 160 reinforcements in a 3-h session. The criterion for stable baseline was met when the number of reinforcements obtained per sessions varied by less than 25% for 3 consecutive days. Sessions were conducted daily excluding weekends.

Food Reinforced Operant Responding

Only the effects of Ro 20-1724 treatment were examined in this experiment. Animals were tested for operant responding reinforced by food pellets delivered under a FR5 schedule. Time-out periods were not included in the program that regulated the delivery of food pellets. Experimental sessions were 1-h in duration.

Drugs

Cocaine was dissolved in 0.9% saline. Ro 20-1724 (Research Biochemicals International, Natick, MA) was suspended in 1% Tween normal saline solution. Rolipram (Research Biochemicals International) was dissolved in a small volume of ethanol, which was then dissolved in a 1% Tween-80 saline solution. This solution contained 10% ethanol by volume.

Rolipram and Ro 20-1724 were both injected intraperitoneally. Drug doses and vehicle were administered in random order. Rolipram was administered in doses of 0.25, 0.5, and 1 mg/kg. Each dose was tested twice. Three doses of Ro 20-1724, 2.5, 5, and 7.5 mg/kg, were administered and, in most cases, animals were tested twice with the same dose.

Data Analysis

Repeated-measures ANOVA's were used to compare baseline vs. vehicle (control) data and drug treatments and vehicle data (23). For the rolipram cocaine self-administration and the Ro 20-1724 food-reinforced operant tasks Dunnett's test was used for pair-wise comparisons of vehicle and drug treatment data. Data were not obtained for one animal for one dose of Ro 20-1724 in the Ro 20-1724/cocaine self-administration experiment. Consequently, for this experiment data were analyzed using a general linear model for repeated-measures ANOVAs. Pair-wise comparisons were performed using repeated-measure ANOVAs contrasts for vehicle and drug treatment data.

RESULTS

Following the administration of rolipram animals tended to become less mobile than usual and on some occasions would exhibit mild pstosis and rapid respiration. Similar effects were seen in rats treated with Ro 20-1724. Although animals treated with either rolipram or Ro 20-1724 were less active than when untreated, they retained muscle tone and were readily responsive to external stimuli. One animal did not receive a 7.5 mg/kg dose of Ro 20-1724 in the cocaine self-administration experiment because it appeared to be particularly sensitive to the effects of this agent on activity and became hypothermic at the 5 mg/kg dose.

In the rolipram/cocaine self-administration experiment, animals at baseline (the untreated condition) self-administered a mean of 31.5 (SEM ± 4.1) infusions of cocaine per 3-h session. The mean latency for the delivery of the first cocaine infusion was 486 (±243) s. The number of cocaine reinforcers delivered and the latency for the delivery of the first cocaine infusion did not differ significantly between the vehicle and baseline conditions.

The administration of rolipram significantly decreased the mean number of cocaine infusions received per session to be-

low control values in a dose dependent manner, $F(3, 9) = 20.7$, $p = 0.001$ (Fig. 1). Mean latency for delivery of the first cocaine infusion was significantly increased above vehicle values by rolipram administration in a dose-dependent manner, $F(3, 9) = 29.7$, $p < 0.001$ (Fig. 2). Animals, after the rolipram induced delay, most often lever pressed for cocaine at vehicle treatment rates (see Fig. 3 for a representative cumulative record sample). A short rapid burst of responding was sometimes evident when animals initiated lever pressing after a delay. On a few occasions at the higher doses regular rates of responding were not apparent until some time had passed after the delivery of the first cocaine infusion.

For the Ro 20-1724/cocaine self-administration experiment, the mean number of cocaine infusions obtained under baseline conditions was 28.6 (±1.9) This value was significantly less than the 34 (±2.5) mean number of infusions that were delivered after vehicle administration, $F(1, 5) = 26.0$, $p = 0.004$}. This was a consistent effect with the number of cocaine reinforcers obtained after vehicle administration being higher than the mean number of infusions delivered at baseline for each animal every time that vehicle was injected. Mean latency for the delivery of the first cocaine infusion under baseline conditions was 298.7 (±82.2) s, and was significantly greater than the mean latency [179.8 (±69.2)] for the vehicle treatment condition, $F(1, 5) = F = 19.2$, $p = 0.007$.

The mean number of cocaine infusions received per session differed significantly among the Ro 20-1724 and vehicle treatment groups, $F(3, 14) = 22.0$, $p < 0.001$. In comparison to the effects of vehicle treatment, the mean number of cocaine infusions received were significantly less after the administra-

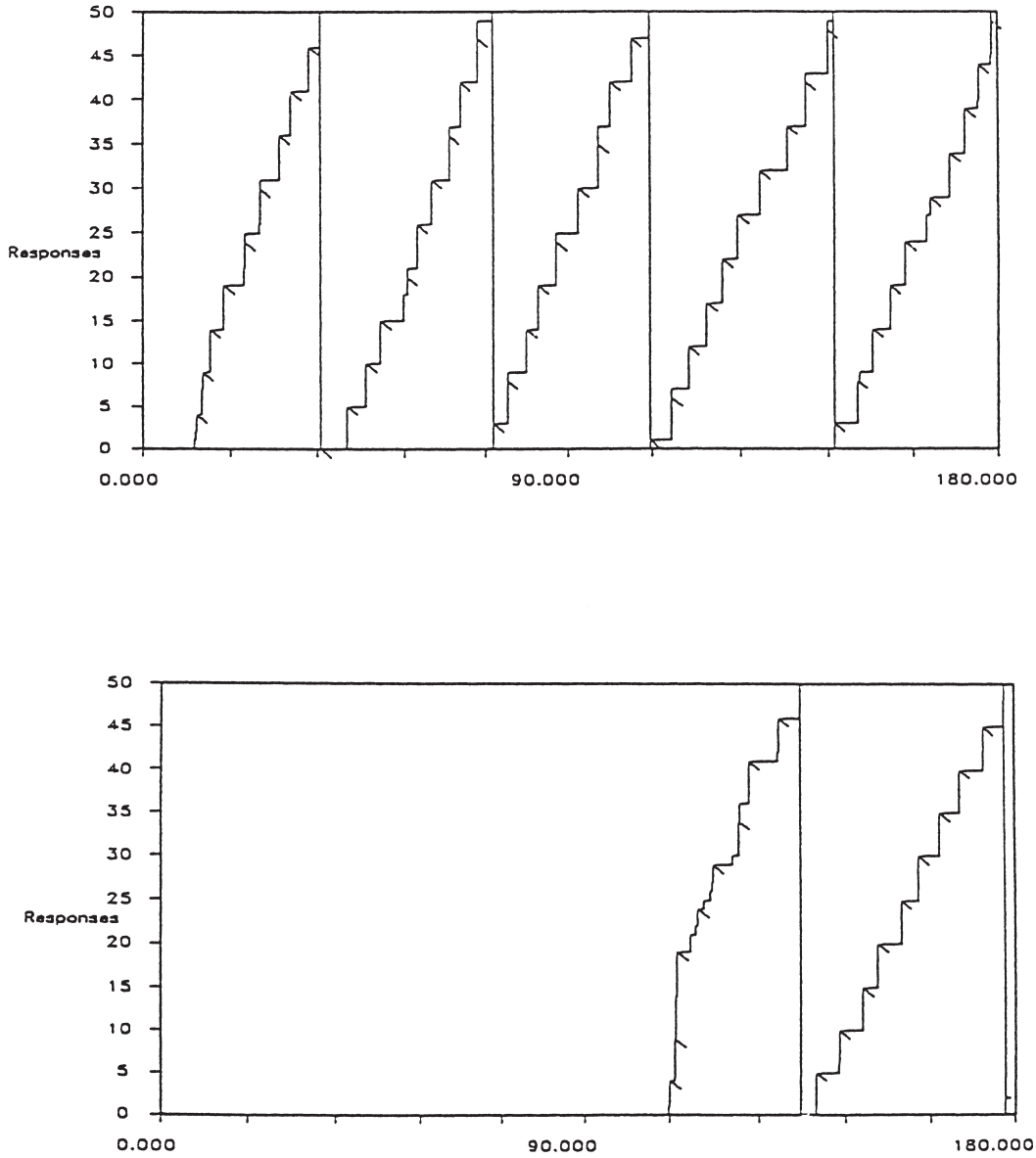

FIG. 3. Representative cumulative record samples for responses during a cocaine self-administration session vs. time in minutes obtained after the administration of (top) vehicle and (bottom) rolipram 0.5 mg/kg. Hatch marks indicate the delivery of a cocaine infusion.

tion of Ro 20-1724 at 2.5 mg/kg, $F(1, 5) = 16.5$, $p = 0.01$, 5 mg/kg, $F(1, 5) = 43.7$, $p = 0.001$, and 7.5 mg/kg, $F(1, 4) = 38.5$, $p = 0.003$, doses (Fig. 1). Mean latency values for the delivery of the first cocaine infusion among Ro 20-1724 and vehicle treatments were significantly different, $F(3, 14) = 13.1$, $p < 0.001$. Compared to the mean latency obtained for vehicle administration, latencies were significantly increased by the administration of 2.5 mg/kg, $F(1,5) = 8.92$, $p = 0.03$, 5 mg/kg, $F(1, 5) = 8.8$, $p = 0.03$, and 7.5 mg/kg, $F(1, 4) = 45.2$, $p = 0.003$, doses of Ro 20-1724 (Fig. 2). Animals lever pressed at control rates following Ro 20-1724-induced delays in responding. A representative sample of responding in an animal treated with vehicle and 5 mg/kg Ro 20-1724 is shown in Fig. 4.

For the food-reinforced task both the mean latency for the delivery of the first food pellet and the mean number of pellets received per session did not differ significantly between the vehicle and baseline conditions. Latency for delivery of the first reinforcer in this task was increased above vehicle values by administration of Ro 20-1724 in a dose-dependent manner, $F(3, 15) = 10.0$, $p < 0.001$ (Fig. 5). The mean number of food pellets obtained per session were significantly less than for the vehicle treatment condition at each of the doses of Ro 20-1724 administered, $F(3, 15) = 36.3$, $p < 0.001$.

DISCUSSION

The administration of either of the phosphodiesterase inhibitors, rolipram or Ro 20-1724, suppressed the initiation of cocaine self-administration. These agents have been shown to selectively inhibit cAMP-specific (type IV) phosphodiesterase

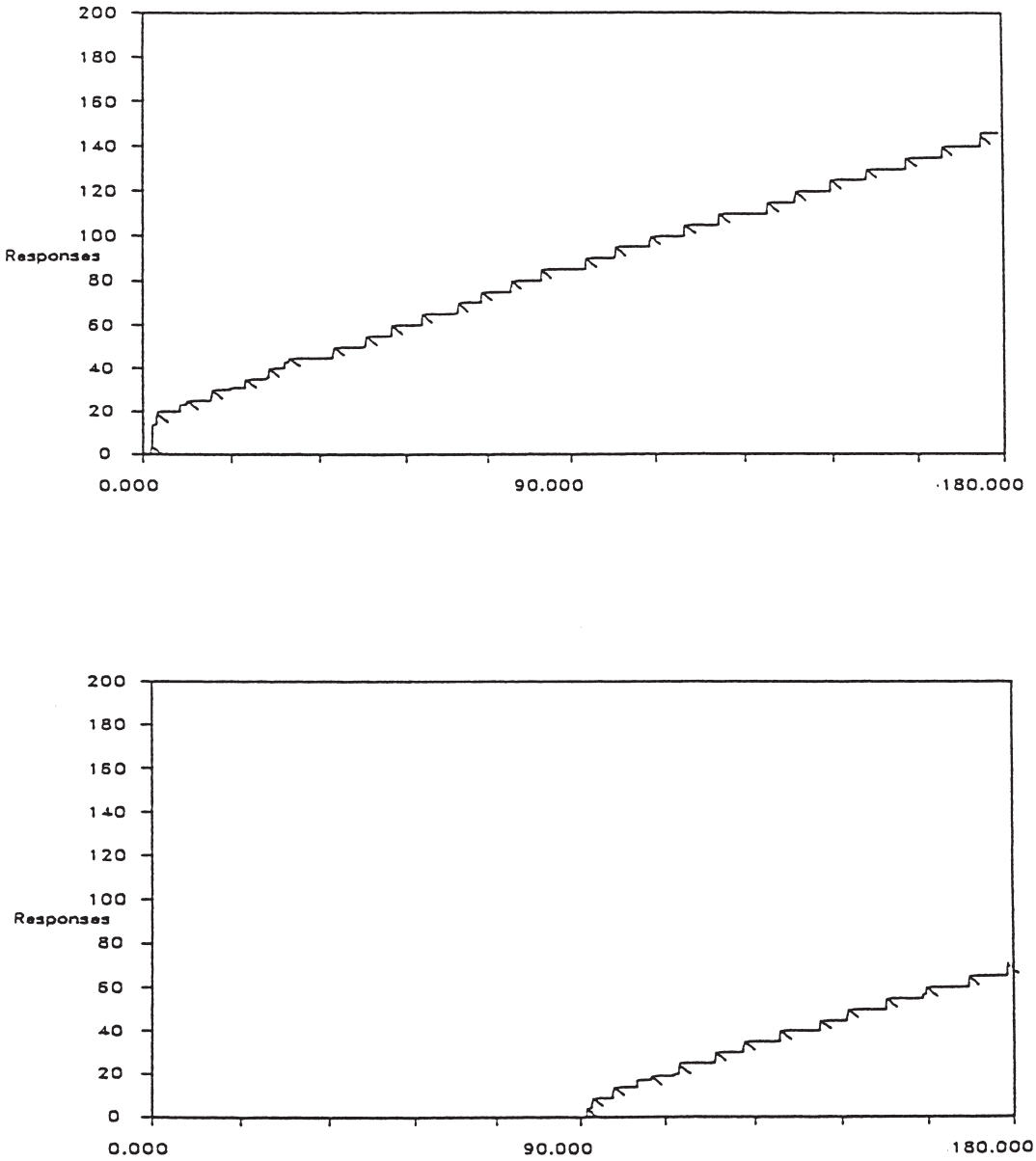

FIG. 4. Representative cumulative record samples for responses during a cocaine self-administration session vs. time in minutes obtained after the administration of (top) vehicle and (bottom) Ro 20-1474 5 mg/kg. Hatch marks indicate the delivery of a cocaine infusion.

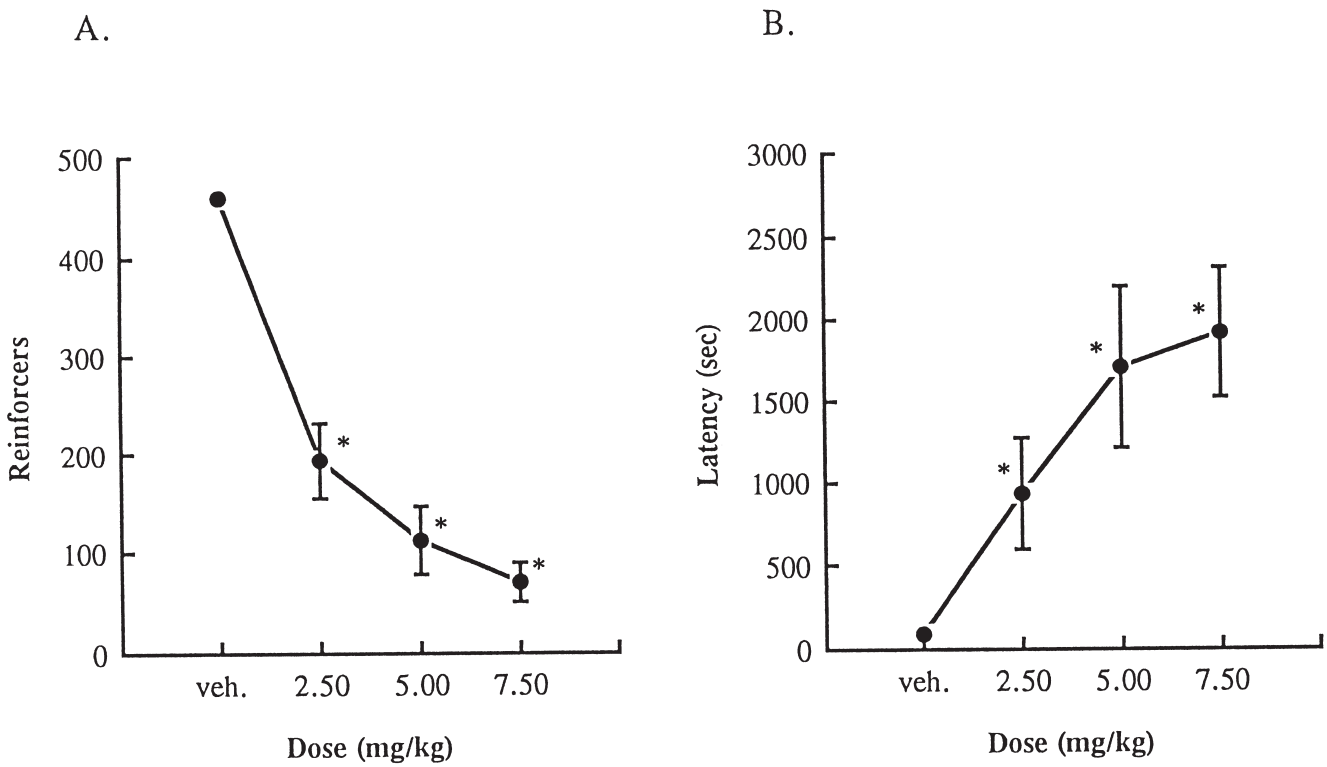

FIG. 5. (a) Mean number of food pellets delivered as a function of Ro 20-1724 dose. (b) Mean latencies for the delivery of the first food pellet during a one hour session as a function Ro 20-1724 dose. *Indicates a significant ($p < 0.05$) difference for vehicle values.

(16,26), and they produce increases in brain cAMP levels at doses within the range of those used in this experiment (18). The inhibition of cocaine self-administration produced by these agents, then, may be attributable to the activation of cAMP signal transduction pathways. However, this action does not appear to be specific for cocaine-driven behavior because similar effects were observed on responding for food.

The suppressant actions of rolipram and Ro 20-1724 on cocaine self-administration are shared by other compounds. Both the partial dopamine D_1 receptor agonist, SKF 77434 (11) and the nonselective adenosine agonist, 5′-N-ethylcarboxamidoadenosine (NECA) (12) will both inhibit the initiation of cocaine self-administration. If animals treated with these compounds begin to respond for cocaine they do so at control rates. SKF 77434 appears to be nonselective in its actions, also suppressing the initiation of responding for food. Administration of high doses of the dopamine D_2 family receptor agonist bromocriptine will inhibit the initiation of cocaine self-administration (6). Response rates following bromocriptine induced suppression of responding for cocaine are markedly less than control values. This suggests that bromocriptine may be acting as a cocaine substitute.

In the Ro 20-1724/cocaine self-administration experiment the number of cocaine infusions delivered per session were slightly greater after the administration of the 1% Tween-80 vehicle than for the baseline condition. This was a consistent effect, but the reason for it remains unclear. No difference in response rates between the 1% Tween-80 vehicle and baseline conditions were detected for the food reinforced operant task, although it should be kept in mind that rates of responding were higher on the food than on the cocaine reinforced task. Also, no difference in response rates was found between the baseline and 1%-Tween-ethanol treatment conditions in the rolipram/cocaine self-administration experiment. It should be noted that baseline response rates were slightly higher in the rolipram, as opposed to the Ro 20-1724 experiment.

Inspection of cumulative records indicated that for treatment with either rolipram or Ro 20-1724, rates of responding for cocaine, once animals began lever pressing for cocaine did not markedly differ from those observed on vehicle treatment days. Rolipram readily enters the brain and concentrations of this agent in the brain parallel those in plasma (13). Rolipram concentrations in the brain decline in two phases—the first with a half-life of 14 min, and the second with a half-life of 1 h. This compound, then, is substantially cleared from the brain when animals were observed to start responding for cocaine at 1.5 to 2.5-h after drug injection.

One explanation for the inhibition of cocaine self-administration produced by either rolipram or Ro 20-1724 administration is that these agents act as substitutes for cocaine by acting on the reward-related processes that are activated by psychomotor stimulants. There is little evidence, however, that supports this idea. The psychomotor stimulant, amphetamine, does not share the discriminative stimulus properties of the cAMP-specific phosphodiesterase inhibitor, rolipram (19). Ro 20-1724 at low doses produces only extremely modest reductions in brain-stimulation reward thresholds (14). A 0.5 mg/kg dose of rolipram either elevates reward thresholds or blocks responding for rewarding brain stimulation (unpublished observations). Thus, systemic administration of rolip-

ram, at doses that block responding for cocaine, may not activate pathways that are involved in mediating the rewarding effects of cocaine.

The locomotor hyperactivity and stereotyped behavior produced by the stimulant methamphetamine can be attenuated by administration of rolipram (7). This suggests that rolipram and related compounds may antagonize some of the actions of psychomotor stimulants. Rolipram can decrease the firing of dopaminergic neurons within the ventral tegmental area (21) and dopamine utilization within the striatum (10). The reduction in dopaminergic activity produced by cAMP-specific phosphodiesterase inhibitors, then, may account for some of the behavioral effects of these agents. Because the mesolimbic dopaminergic system has been implicated in regulating the processes involved in the seeking and intake of drugs and other reinforcers, it is possible that cAMP-specific phosphodiesterase inhibitors may suppress the initiation of cocaine self-administration and also possibly operant responding for food through their actions on this system. However, rolipram also has been shown to enhance noradrenergic system activity (10,20,21). This effect might also play a role in mediating the effects of cAMP phosphodiesterase inhibitors on cocaine and food acquisition behaviors.

The administration of either rolipram or Ro 20-1724 often produced effects that are characteristically associated with the administration of agents that elevate cAMP levels in the brain (25). These effects include decreased mobility, visible salivation, rapid respiration, and mild ptosis. It is possible that the inhibition of the initiation of cocaine self-administration resulting from either rolipram or Ro 20-1724 administration is attributable to the debilitating effects of these drugs, perhaps involving peripheral effects, and not to a specific action on central motivational systems. Responding that followed rolipram- or Ro 20-1724–induced delays in the initiation of cocaine responding tended to be at control rates. If animals had been debilitated by these agents the expectation would be that animals would start responding in an irregular manner and at lower than usual rates and, as they began to recover, that response rates would increase as their condition began to improve. Following Ro 20-1724–induced delays in responding on the food-reinforced task, animals made hundreds of lever presses to obtain food. This sort of vigorous responding also is not consistent with the aftermath of drug induced malaise. A 0.32 mg/kg dose of rolipram will decrease the amenesic effects of electric convulsive shock in a three-panel runway test (3), suggesting that animals are not severely cognitively impaired by this agent at this dose. The alpha-2 adrenergic agonist, dexmedetomidine can have hypnotic effects in the rat. The extent of loss of righting reflex produced by this drug is reversed by rolipram (0.275 mg/kg, IP) treatment (17). This suggests that the rolipram-induced hypomobility is not attributable to a general central nervous system depressant effect.

The finding that the administration of Ro 20-1724 increased the latency for delivery of the first food pellet and decreased the total number of pellets obtained per session at doses that were the same as those that had similar effects on responding for cocaine self-administration indicates that cAMP-specific phosphodiesterase inhibitors may not act selectively on the systems involved in drug-seeking behavior. In the rhesus monkey, treatment with either rolipram or Ro 20-1724 produced decreased responding on a fixed interval-300 second shock avoidance task (5). In rats performing under a differential reinforcement of low rate response schedule, rates of delivery of water reinforcements were increased and response rates were decreased dose dependently by administration of either rolipram or Ro 20-1724 (15). These results suggest that cAMP phosphodiesterase inhibitors can have a depressant effect on operant responding for a variety of reinforcers. However, the extent to which the suppression of cocaine self-administration produced by the administration of either rolipram or Ro 20-1724 in our investigation may be attributable to an impaired ability to make appropriate responses and not due to changes in central motivational systems is unclear.

There is some evidence that rats could have responded in the experiments described here for cocaine earlier than they did after the administration of either rolipram or Ro 20-1724. During an hour-long test session for water delivered under a DRL schedule, rats lever pressed approximately 50 times after the administration of rolipram (0.3–1 mg/kg) and about 20 times following injection of a large dose of Ro 20-1724 (10 mg/kg) (15). These drugs when administered in this study at similar doses suppressed the initiation of cocaine self-administration for longer than an hour. Other evidence that animals are able to respond soon after the administration of a type IV phosphodiesterase inhibitor includes the finding that rats will start responding for brain stimulation reward immediately after administration of a 0.25 mg/kg dose of rolipram, and the majority of animals tested will similarly respond for BSR after injection of a 0.5 mg/kg dose of this agent (unpublished observations).

The results of this study indicate that the administration of the cAMP-specific phosphodiesterase inhibitors, rolipram and Ro 20-1724, may produce inhibition of the initiation of cocaine self-administration. The response suppressant effects of Ro 20-1724 were shown to occur for food as well as for cocaine-reinforced operant tasks. The suppression of cocaine-seeking behavior produced by the systemic administration of type IV phosphodiesterase inhibitors may result from the elevation of brain cAMP levels and a resultant negative modulatory influence on motivational systems. The inhibitory effects of these agents on mesolimbic dopaminergic neutransmission is consistent with this notion. The possibility, however, that these cAMP-specific phosphodiesterase inhibitors suppress cocaine by other mechanisms such as the adverse peripheral effects of these drugs cannot be entirely ruled out at this time.

ACKNOWLEDGEMENTS

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