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ORIGINAL INVESTIGATION

Nucleus accumbens PKA inhibition blocks acquisition but enhances expression of amphetamine-produced conditioned activity in rats

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Abstract
Rationale The nucleus accumbens (NAc) plays a central role in dopamine-produced reward-related learning. In previous studies, the cyclic adenosine monophosphate-dependent protein kinase (PKA) inhibitor Rp-Cyclic 3′,5′-hydrogen phosphorothioate adenosine triethylammonium salt (Rp-cAMPS) blocked the acquisition but not expression of NAc reward-related learning for natural rewards and the acquisition of psychostimulant drug conditioning.
Objectives The current study assessed the role of PKA in the expression of NAc amphetamine (amph)-produced conditioning using conditioned activity (CA).
Materials and methods After 5 days of habituation, a test environment was paired with bilateral NAc injections of amph (0.0 or 25.0 μg) and the PKA inhibitor Rp-cAMPS (0.0, 5.0, 10.0, or 20.0 μg) over three 60-min conditioning sessions separated by 48 h. To test for effects on expression, some groups received vehicle or amph alone before conditioning sessions and were injected with 0.0, 0.25, 5.0, or 20.0 μg of Rp-cAMPS before the single 60-min test session.
Results Amph produced acute increases in locomotion and robust CA. Rp-cAMPS impaired the acquisition of amph-produced CA but not its expression; in fact, it enhanced expression.
Conclusions Results show that PKA inhibition blocks the acquisition but not the expression of amph-produced conditioning.

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Introduction

The cyclic adenosine monophosphate-dependent protein kinase (PKA) pathway may play a central role in memory formation (Arnsten et al. 2005). Research implicates nucleus accumbens (NAc) dopamine (DA) in reward-related learning and memory (Baldwin et al. 2002; Beninger 1983; Carr and White 1986; Everitt et al. 1999; Setlow et al. 2002; Sutton and Beninger 1999). In NAc, DA agonists activate and inhibit PKA through D_1- and D_2-like receptors, respectively. Behavioral work has implicated PKA in the acquisition of learning for natural reward (Baldwin et al. 2002).

Psychostimulant drug addiction may be acquired through the sensitization of reward processes mediated by the mesolimbic DA system (Kelley 2004; Nestler 2005). Intracellular messengers known to mediate the effect of DA on reward-related learning were implicated in the acquisition of NAc amphetamine (amph)-related learning. PKA inhibition impairs the acquisition of conditioned place preference and conditioned activity (CA) produced by NAc injections of amph (Beninger et al. 2003; Sutton et al. 2000). Other intracellular messengers functionally related to PKA were also implicated, including extracellular signal-regulated kinase (ERK) (Gerdjikov et al. 2004; Valjent et al. 2000) and calcineurin (Gerdjikov and Beninger 2005). The acquisition of learning for natural rewards and amph conditioning may involve PKA and related intracellular messengers (Beninger and Gerdjikov 2004).

Intracellular cascades may be differentially involved in the acquisition and expression of learning produced by

either natural reinforcers or psychostimulant drugs. The expression of learning for natural reward does not appear to be under the control of PKA. Thus, PKA activation or inhibition did not affect the expression of lever-pressing for food (Baldwin et al. 2002). ERK inhibition was recently implicated in the expression of systemic cocaine- or methamphetamine-produced conditioned place preference (Miller and Marshall 2005; Mizoguchi et al. 2004); however, the role of PKA inhibition on the expression of NAc amph conditioning was not studied.

CA produced by NAc injections of amph has been used as a model of psychostimulant drug conditioning in an attempt to assess the contribution of PKA to acquisition (Sutton et al. 2000). In the current experiment, we used CA to assess the role of PKA in the expression of NAc amph-produced conditioning. Rats were conditioned with NAc amph and received a PKA inhibitor either before conditioning sessions or before testing. It was hypothesized that PKA inhibition in NAc will block acquisition but not expression of CA. Parts of this research were presented in abstract form (Swain and Beninger 2004).

Materials and methods

Animals and surgery

Male Wistar rats (Charles River, St. Constant, Quebec) weighing between 200 and 250 g on arrival were housed in pairs on a 12-h reversed light–dark cycle (lights on at 19:00 hours) at an average temperature of 21°C, humidity 40–70%. Water and food (LabDiet 5001, PMI Nutrition International, Brentwood, MO, USA) were freely available. Rats were handled for about 1 min every day for five consecutive days after arrival. The experimental protocol was approved by the Animal Care Committee at Queen's University and followed the "Principles of laboratory animal care" (http://www.nap.edu/readingroom/books/labrats/). All animals were treated in full compliance with the Animals for Research Act and relevant guidelines set by the Canadian Council on Animal Care.

Approximately 1 week after arrival at the colony, rats were anesthetized in an induction chamber using an inhalable anesthetic (5% isoflurane; Bimeda, Cambridge, Ontario, Canada) mixed with oxygen in a vaporizer system (Benson, Markham, Ontario, Canada) and administered at 1.0 l/min. Anesthetized animals were fitted to a stereotaxic apparatus and isoflurane was administered at a concentration of 2% or as needed to maintain anesthesia. For analgesia, buprenorphine hydrochloride in solution (0.15 mg/kg; Reckitt & Colman, Richmond, VA, USA) was injected subcutaneously preoperatively. Ketoprofen (1.5 mg/kg; Merial, Baie d'Urfé, Quebec) was injected immediately after surgery and on three subsequent days postoperatively. The experimenter shaved the rat's head and applied betadine solution with a cotton tip applicator before incising the skin. The head was adjusted so that lambda and bregma were on the same horizontal plane. Holes were drilled into the skull and 23 gauge (0.64 mm diameter) stainless steel guide cannulae were chronically implanted bilaterally into the NAc, with coordinates 1.6 mm anterior to bregma, 1.4 mm lateral to the midline, and 6.7 mm ventral from the skull surface (Paxinos and Watson 1998). The guide cannulae were held in place by four stainless steel screws and dental acrylic. Stainless steel wire stylets (0.31 mm in diameter) flush with the end of the guide cannulae were put in place to prevent occlusion. Rats were allowed approximately 1 week to recover before the start of behavioral testing.

Drug infusion

Rp-Cyclic 3′,5′-hydrogen phosphorothioate adenosine triethylammonium salt (Rp-cAMPS; Sigma-Aldrich, Oakville, Ontario, Canada) was dissolved in saline before the beginning of the experiment and stored at −20°C. Amph sulfate (USP; Rockvill, MD, USA) was dissolved in saline daily before each set of injections. For groups receiving Rp-cAMPS plus amph injections, the drugs were dissolved together in saline before the beginning of the experiment and stored at −20°C. Central injections into the NAc were made with a microinfusion pump (KD Scientific, Holliston, MA, USA). Injectors were glued to polyethylene tubing (0.75 mm, o.d.) filled with distilled water. The tubing was connected to two 10-μl microsyringes (Microliter #701; Hamilton, Reno, NV, USA) mounted on the microinfusion pump. Drugs were backloaded into the injectors by aspiration with the two syringes. Rats were hand-held as the experimenter removed the stylets from the guide cannulae and inserted the two injectors (0.31 mm, o.d.). The injectors projected 1.2 mm beyond the guide cannulae.

Saline (0.5 μl/side), amph (25.0 μg/0.5 μl/side), or Rp-cAMPS plus amph (5.0–20 μg of Rp-cAMPS + 25 μg amph 0.5 μl^{-1} $side^{-1}$) were injected bilaterally in saline over 30 s before conditioning sessions. We have previously reported reliable CA effects using 25 μg of amph in the NAc (Sutton et al. 2000). After the drug was delivered, the injectors were left in place for another 30 s to facilitate diffusion, after which they were slowly retracted from the guide cannulae. Rp-cAMPS (0.25, 5.00, or 20 μg $0.5 \mu l^{-1}$ $side^{-1}$) or saline was injected before test sessions. Behavioral testing started immediately after drug injection. Doses of Rp-cAMPS were similar to doses previously reported to impair NAc-mediated reward-related learning with natural reward (Baldwin et al. 2002) and amph conditioning (Beninger et al. 2003).

Apparatus

Clear rectangular Plexiglas testing chambers (50×40×40 cm) were equipped with 12 pairs of infrared sensors and emitters located on opposite sides of the walls (three on the short and four on the long side of the boxes). Photocells were 10 cm apart and 5 cm above the floor. Thus the infrared light beams formed a matrix of 20 squares of equivalent dimensions (approximately 10×10 cm) over the chamber surface. The rat had to travel the full distance between the beams for an activity count to be recorded. Two subsequent interruptions of a single beam or subsequent interruptions of perpendicular beams were not included in activity counts. Metal bars 1.0 cm apart formed the floor of the apparatus. Each of the testing chambers was housed in a dimly lit (2.5-W bulb mounted on the ceiling in the center of the apparatus) Styrofoam-insulated ventilated wooden box. Fans mounted on the back wall provided a constant background noise (70 dB). Photocell beam breaks were recorded on a 6809 microcontroller with custom-made software and transferred to a Macintosh computer for analyses. For further details of the apparatus, see Beninger et al. (1985).

Behavioral procedure

The experimental protocol consisted of three phases: five habituation, three conditioning, and one testing session. All sessions were 60 min long and occurred during the dark phase (0700–1900 hours).

During habituation sessions, carried out on five consecutive days, rats moved about the apparatus in a drug-free state. Conditioning sessions started on the day immediately after the last habituation session and were spaced by 48 h to allow more complete drug elimination. Rats were placed in the apparatus immediately after a single drug injection (saline, amph, or Rp-cAMPS + amph). A single testing session occurred 48 h after the last conditioning session immediately after a single Rp-cAMPS or saline injection.

There were 11 groups in all. Four groups were injected bilaterally in NAc with saline before each conditioning session; before the test session, these groups received either saline or Rp-cAMPS (0.25, 5.0, and 20.0 μg 0.5 μl^{-1} $side^{-1}$). These groups evaluated possible changes in activity from conditioning to test after saline and the possible effect on activity of Rp-cAMPS administered alone during the test

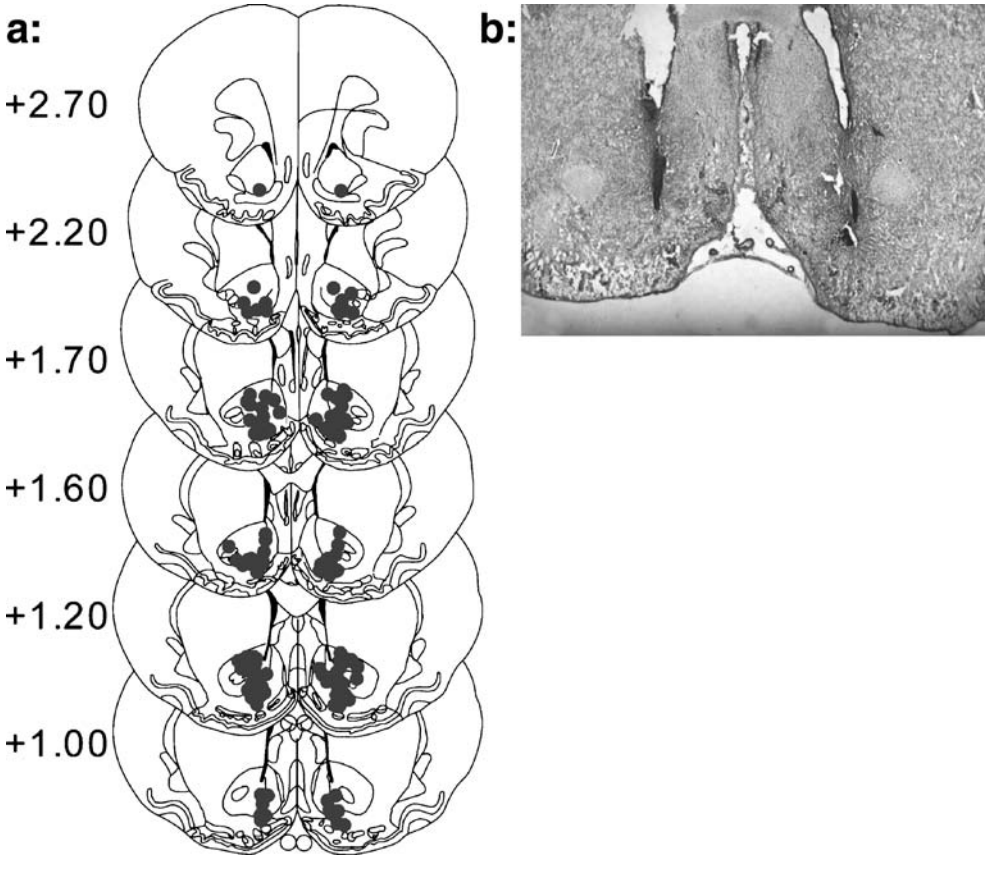

Fig. 1 **a** Drawings of coronal sections through the NAc indicating sites of infusion. Rats from all groups included in the analyses are shown. Injector sites may appear fewer than the reported number of rats because of overlap of placements. *Numbers to the left* indicate distance (mm) from bregma. **b** Photomicrograph depicting a representative NAc injector placement

session. Four groups were conditioned with amph (25 μg) either alone or plus Rp-cAMPS (5.0, 10, and 20 μg) and tested after saline, these groups evaluated the effects of Rp-cAMPS during conditioning on the establishment of CA. Three additional groups were conditioned with amph (25 μg) but tested after NAc Rp-cAMPS (0.25, 5.0, and 20.0 μg) to evaluate the effect of Rp-cAMPS on the expression of CA.

Data analysis

Locomotor activity was quantified as the total number of beam breaks per each 60-min session. Activity data from the last habituation day were compared among the groups using one-way between-subjects analysis of variance (ANOVA) to test for pretreatment differences. Activity counts averaged across the three conditioning sessions and from the single test day were similarly analyzed using separate one-way between-subjects ANOVA. Significant main effects were followed by pair-wise comparisons.

Histology

After completion of behavioral testing, rats were placed in an airtight chamber and killed with CO_2. Brains were removed and preserved in a 10% formalin solution for at least 72 h. Coronal sections 60 μm thick from throughout the cannulated region were obtained by slicing the brains on a cryostat at −20°C. The sections were mounted on gelatin-coated glass slides and stained with cresyl violet. Judgments about NAc cannula placements were made by an observer blind to the results for individual animals. Animals were classified as hits if the tips of both cannulae were located in the core or shell subregion of NAc.

Results

Histology

A total of 124 rats was tested. Twelve animals were excluded because one or both of their cannulae placements were outside of NAc leaving 112 rats for subsequent analyses. Figure 1 shows the location of cannulae tips for all animals included in the analyses.

Habituation

On the last habituation day, mean (±SEM) activity counts per group ranged from 563.9 (±69.3) to 935.4 (±83.6). A one-way between-subjects ANOVA revealed no significant effect of group on activity levels [$F(10, 101)=1.78$, n.s.; see Table 1].

Table 1 Mean (±SEM) locomotor activity counts/60-min session during the last of five drug-free habituation sessions

Conditioning[a]	Test: Rp-cAMPS dose[a]	Number of animals	Activity
Saline	0.0	16	563.9 (69.3)
	0.25	9	724.6 (92.4)
	5.0	5	716.8 (124.0)
	20.0	9	794.3 (92.6)
25.0 μg amph + 0.0 μg Rp-cAMPS	0.0	17	709.4 (67.3)
25.0 μg amph + 5.0 μg Rp-cAMPS	0.0	8	764.1 (98.8)
25.0 μg amph + 10.0 μg Rp-cAMPS	0.0	11	935.4 (83.6)
25.0 μg amph + 20.0 μg Rp-cAMPS	0.0	6	903.0 (113.2)
25.0 μg amph	0.25	11	591.1 (83.6)
	5.0	11	742.8 (83.6)
	20.0	9	773.6 (92.5)

Drug treatments refer to manipulations administered on subsequent conditioning or test sessions.
Amph Amphetamine
[a] All doses (μg 0.5 μl^{-1} $side^{-1}$) were administered bilaterally into NAc in saline.

Conditioning

Activity averaged across the three conditioning sessions among the four groups conditioned with saline was clearly lower than activity for the seven groups conditioned with amph (see Fig. 2). The one-way between-subjects ANOVA revealed a significant effect of group [$F(10, 101)=14.23$, $p<0.05$]. Planned single *df* comparisons (Keppel and Wickens 2004) revealed that during conditioning, the group conditioned with amph and tested with saline showed higher activity than the groups conditioned with saline and later tested with 0.0 [$F(1,101)=42.67$, $p<0.001$], 0.25 [$F(1,101)=27.00$], 5.0 [$F(1,101)=19.86$, $p<0.001$], or 20.0 μg [$F(1,101)=25.63$, $p<0.001$] of Rp-cAMPS. During conditioning, the group conditioned with amph and subsequently tested with saline did not differ significantly from any of the groups conditioned with amph alone or amph plus 5.0, 10.0, or 20.0 μg of Rp-cAMPS. These results indicate that amphetamine produced significant CA. Rp-cAMPS had no significant effect on baseline activity or acute amphetamine-produced activity.

Test

Groups conditioned with saline showed little change in activity levels whether tested with saline or Rp-cAMPS. The group conditioned with amph and tested with saline showed

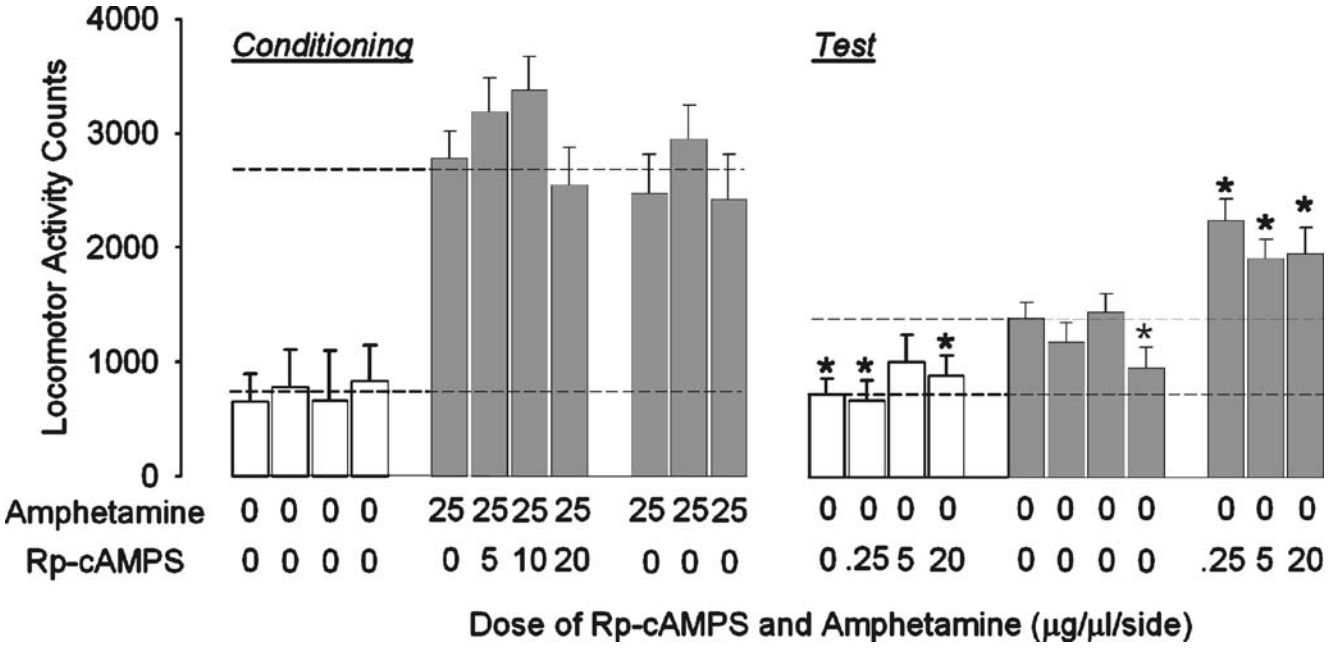

Fig. 2 Mean (±SEM) activity counts averaged over three 60-min conditioning sessions (*left panel*) and for a single 60-min test session (*right panel*). NAc amphetamine (0 or 25 µg 0.5 μl^{-1} $side^{-1}$) was administered immediately before conditioning sessions. Rp-cAMPS was administered before each of the three conditioning sessions (0, 5, 10, or 20 µg; delivered in the same injection as amphetamine) or test (0, 0.25, 5, or 20 µg 0.5 μl^{-1} $side^{-1}$). On the *left panel*, the *lower dashed line* shows average activity counts for the four groups receiving only saline during conditioning. The *higher dashed line* shows average activity counts for the four groups receiving 25 µg of amph and no Rp-cAMPS during conditioning. On the *right panel*, the *lower dashed line* shows average activity for the group receiving saline both during conditioning and on test. The *higher dashed line* shows the average activity for the group receiving amphetamine during conditioning and saline on test. *Asterisks* indicate significant difference from the group conditioned with 25 µg of amph alone and tested with saline ($p<0.05$, planned comparisons)

higher activity than groups conditioned with saline. The group conditioned with amph plus 20 µg of Rp-cAMPS showed a smaller activity level in the test than the group conditioned with amph and tested with saline. Groups conditioned with amph and tested with Rp-cAMPS showed even higher activity than the group conditioned with amph and tested with saline (see Fig. 2). A one-way between-subjects ANOVA was used to compare activity during the single test session among the 11 groups. The ANOVA revealed a significant effect of group [$F(10, 101)=9.75$, $p<0.01$]. Planned single *df* comparisons revealed that rats receiving amph during conditioning and saline on test showed higher activity than rats conditioned with saline and tested with 0.0 [$F(1, 101)=13.8$, $p<0.001$], 0.25 [$F(1, 101)=11.53$, $p<0.001$], or 20.0 µg of Rp-cAMPS [$F(1, 101)=5.64$, $p<0.05$)]. The difference from the 5.0 µg group did not reach significance possibly due to the lower number of rats remaining in that group ($n=5$) after histological determinations [$F(1,101)=2.17$, n.s.]. The group conditioned with amph and tested with saline also showed higher activity compared to the group conditioned with amph plus 20 µg of Rp-cAMPS [$F(1,101)=4.22$, $p<0.05$], but not compared to the two groups conditioned with amph plus Rp-cAMPS doses of 5.0 and 10 µg. These results indicate that the coinfusion of Rp-cAMPS attenuated the acquisition of amphetamine CA. Animals conditioned with amph and tested with all three doses of Rp-cAMPS showed higher activity than rats conditioned with amphetamine and tested with saline [for 0.25 µg of Rp-cAMPS $F(1,101)=14.52$, $p<0.001$; for 5.0 µg $F(1,101)=6.62$, $p<0.05$; and for 20.0 µg $F(1,101)=5.29$, $p<0.05$].

Discussion

The present study investigated the effect of PKA inhibition on the acquisition and expression of NAc amph-produced CA. Repeated NAc amph administration in a testing chamber acutely increased locomotion and also produced CA. That is, when rats were subsequently placed in the amph-paired chamber they showed higher activity than animals treated with saline during conditioning sessions. In previous experiments using the same apparatus and experimental parameters we showed that this effect is specific to the amph-paired environment (Sutton et al. 2000). In the current study, PKA inhibition during CA acquisition sessions did not significantly alter amph-produced unconditioned activity. However, it did significantly impair the acquisition of amph-produced CA. This result was obtained with a dose of 20 µg whereas Sutton et al. (2000) reported impairment with a 10-µg dose. The

difference is probably due to sampling error. Visual inspection of our Fig. 2 shows a trend for impairment absent only in the 10-μg group. PKA inhibition on test day had no effect on activity for rats conditioned with vehicle, suggesting the drug had no locomotor effects on its own. When administered to rats trained with amph, the PKA inhibitor enhanced the expression of CA. Thus PKA is necessary for the acquisition of amph-produced CA. The expression of CA, on the other hand, is not impaired but rather enhanced by PKA inhibition.

In the current experiment, PKA inhibition impaired the acquisition of NAc amph-produced CA. Drug-induced increases in locomotion are thought to reflect the motivational properties of the drugs suggesting conditioned locomotion based on amph as a model of drug-related reward learning (Wise and Bozarth 1987). Others have questioned the relationship between drug-induced CA and reward-related learning in anatomical studies (Brown and Fibiger 1993). Some authors have also questioned whether CA is a learning phenomenon because it is not sensitive to manipulations known to impair Pavlovian conditioning (Ahmed et al. 1998) and because the nature of the behavioral activation on test may be different from acute drug-produced locomotion (Martin-Iverson and Fawcett 1996). Other work points to a role of associative processes (Anagnostaras et al. 2002). This study does not contribute to the literature investigating the psychological basis of the CA effect. The study is in agreement with previous work showing CA with amph (Beninger and Hahn 1983) and blockade of its acquisition by NAc injection of the PKA inhibitor Rp-cAMP (Sutton et al. 2000). It also agrees with works implicating PKA in the acquisition and consolidation of NAc amph-produced conditioned place preference and in the acquisition of learning for natural reward, including lever pressing for food and food tray approach (Baldwin et al. 2002; Beninger et al. 2003; Gerdjikov and Beninger 2005; Jentsch et al. 2002). Intracerebral PKA inhibition also impaired the acquisition of cocaine-conditioned place preference and ventral tegmental area PKA inhibition impaired the acquisition of morphine-conditioned place preference (Cervo et al. 1997; Harris et al. 2004). PKA is implicated in the acquisition of drug reward (see review by Beninger and Gerdjikov 2005).

PKA inhibition did not impair the expression of CA based on NAc amph. This result is consistent with previous work suggesting that the expression of conditioned approach and lever pressing for food does not involve PKA (Baldwin et al. 2002). It is also consistent with previous work in which the nonspecific serine/threonine kinase inhibitor H7 had no effect on the expression of conditioned place preference produced by intracerebroventricular cocaine (Cervo et al. 1997). In the current study, the more specific agent Rp-cAMPS was injected directly into NAc to assess the role of PKA in the expression of amph CA. Taken together, these results strongly suggest that the expression of reward-related learning for natural rewards and psychostimulant drug-produced conditioning is independent of PKA activity.

The NAc can be subdivided into core and shell regions (Zahm 2000) and a number of studies suggest that these subregions may be differentially involved in reward-related learning and locomotion (Di Chiara 2002; Ikemoto et al. 2005; Parkinson et al. 1999; Phillips et al. 2003; Sellings and Clarke 2003). Our injection parameters did not permit a direct investigation of the relative contribution of the two subregions. In another work, lower injection volumes were used to study the differential role of each subregion (Fuchs et al. 2004).

In the current study, PKA inhibition on test day enhanced the expression of amph-produced conditioning while having no significant effect on locomotion in animals conditioned with saline. The enhancement did not show a dose dependency but was seen across all doses tested (0.25, 5, and 20 μg; Fig. 2). This lack of a dose dependency is not surprising. In previous conditioned place preference work, we have seen effects of Rp-cAMPS at the nanomolar range (Beninger et al. 2003). The observed enhancement of CA may reflect levels of second messenger activation similar to those driven by place preference conditioning cues. Consistent with the observed enhancement, the expression of lever pressing for cocaine is also enhanced by NAc PKA inhibition with Rp-cAMPS (Self et al. 1998); however, the effect of Rp-cAMPS in this paradigm may be parameter-specific (Lynch and Taylor 2005). It also involves animal-controlled psychostimulant administration, whereas in the current experiment the expression of psychostimulant conditioning effects was studied on extinction.

Conditioned reward-associated stimuli enhance DA activity (Schultz 2002). In the present study, exposure to the amph-associated box on the test day also likely enhanced DA release; the observed Rp-cAMPS enhancement of CA expression may therefore parallel reports of Rp-cAMPS enhancement of NAc DA agonist-produced locomotion. In one study looking at the effects of PKA inhibition on the acquisition of amph-conditioned place preference, Rp-cAMPS enhanced the acute locomotor effects of amph but did not produce increased locomotion when administered alone (Beninger et al. 2003). Perhaps paradoxically, while enhancing the acute effect of amph on locomotion, Rp-cAMPS impaired the acquisition of CA in the same experiment (Sutton et al. 2000). This finding is consistent with the marginal increases in amph-produced locomotion seen in groups cotreated with Rp-cAMPS during the acquisition phase of the current study (Fig. 2). The evidence suggests that Rp-cAMPS can enhance locomotion only in the presence of increased ongoing DA

activity. The neurochemical processes underlying these effects are not clear. PKA is inhibited by activation of D_2-like DA receptors and D_2-like receptor stimulation has stronger effects on locomotion than D_1-like receptor stimulation (Beninger et al. 1991). Inhibiting the PKA pathway with Rp-cAMPS seems to have similar effects on locomotion to those produced by D_2-like receptor activation. Therefore, some of the effects of D_2-like receptor activation on locomotion may be mediated by the inhibition of PKA. To our knowledge this hypothesis has not yet been tested.

In conclusion, the current study shows that PKA is necessary for the acquisition but not the expression of NAc amph-produced CA. These results are in agreement with previous experiments implicating PKA in the acquisition of drug-related learning and learning for natural rewards. This is the first report examining the role of PKA on the expression of NAc amph reward.

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