

A role for D2 but not D1 dopamine receptors in the cross-sensitization between amphetamine and salt appetite

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Abstract

A history of sodium depletions has been found to potentiate the psychomotor as well as the rewarding effects of amphetamine, an indirect dopamine agonist. The present experiments were conducted to further define the role of dopamine receptor subtypes in this cross-sensitization effect. Rats with a history of sodium depletions were found to display psychomotor sensitization to a D2 but not a D1 direct agonist. Cross-sensitization between salt appetite and amphetamine was found to be blocked by a D2 but not a D1 antagonist. Together, these results implicate D2 but not D1 receptor function in the cross-sensitization seen after sodium depletions.

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1. Introduction

Behavioral sensitization is defined as a persistent increase in the response to a drug with repeated exposure (Stewart and Badiani, 1993). The administration of psychostimulants such as cocaine and amphetamine has been shown to promote an enduring potentiation in the locomotor and rewarding effects of these drugs as well as drug-induced plasticity in the mesolimbic dopamine system (Robinson and Kolb, 2004). In addition to the activational and motivational effects of drugs of abuse this system is thought to be critical to behaviors related to natural rewards such as food, sex and salt in the sodium-depleted rat (Kelley and Berridge, 2002). The discovery that drugs of abuse may target and induce plasticity in the same system responsive to natural rewarding stimuli has led to questions concerning shared mechanisms and the potential influence of previous experience on responses to drugs.

To address the potential relationship between these types of reward, induction of salt appetite was used as a model of a natural reward system. Sodium depletion is a strong homeostatic

challenge that produces a salt appetite. Rats depleted of sodium will seek out, work for and consume concentrated NaCl solutions they would otherwise avoid (McCutcheon and Levy, 1971). Interestingly, there are some properties of this model that resemble the features of psychostimulant administration. First, like drugs of abuse and other natural rewards, NaCl intake in the sodium-depleted rat is associated with dopamine release in nucleus accumbens (Frankmann et al., 1994). Second, multiple sodium depletions give rise to salt appetite sensitization, characterized by an increase in NaCl intake in animals with a previous depletion (Sakai et al., 1987). Third, this sensitization is associated with alterations in dendritic morphology in nucleus accumbens, similar to that shown after repeated drug administration (Roitman et al., 2002; Robinson and Kolb, 1997). Finally, a history of sodium depletion leads to a potentiation in the behavioral response to amphetamine, or cross-sensitization.

Cross-sensitization, a process whereby one treatment may facilitate the response to another, has been demonstrated to occur between drug classes (Vanderschuren et al., 1999; Robinson and Berridge, 1993) and between drugs of abuse and natural rewards (Fiorino and Phillips, 1999; Nocjar and Panksepp, 2002; Vitale et al., 2003). We have previously demonstrated the presence of reciprocal cross-sensitization between salt appetite and amphetamine (Clark and Bernstein, 2004a). A history of sodium depletion promotes a potentiation

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of the rewarding and locomotor effects of the drug and, conversely, repeated amphetamine administration produces a sensitized salt appetite similar to that produced by prior sodium depletions. The underlying mechanism of this cross-sensitization effect remains unknown and is the focus of the present studies.

Altered dopamine function has been implicated in drug sensitization as well as cross-sensitization between drugs of abuse and natural rewards (Fiorino and Phillips, 1999; Pierce and Kalivas, 1997; Vanderschuren et al., 1999). The aim of the present experiments was to define the role of dopamine in the cross-sensitization between salt appetite and amphetamine by administering dopamine agonists and antagonists to animals with and without a history of sodium depletion. In addition, because the striatum is made up of separate populations of medium spiny neurons expressing either D1-like or D2-like dopamine receptors, selective agonists and antagonists were used to define the selective involvement of these receptor subtypes.

2. General method

2.1. Subjects

Male Long–Evans rats weighing between 300 and 350 g, housed individually in hanging metal cages, were used for all experiments. Animals were maintained on a 12 h light/dark cycle; lights off at 7:00 PM, with free access to Teklad Rodent chow (Madison, WI) and water unless otherwise noted. All procedures were done in accordance with the Institutional Animal Care and Use Committee at the University of Washington.

2.2. Sodium depletion

To induce salt appetite, rats were depleted of sodium with procedures modified from Wolf (1982). Food and water were removed from all cages prior to the beginning of the experiment. Rats in the sodium-depleted group (history) were then given the diuretic furosemide (10 mg/kg, s.c.) while control animals (no history) received saline. To confirm diuresis, rats were weighed before and 3 h after injection. Sodium deficient chow and distilled water were provided to animals in the deplete group to maintain sodium depletion while standard chow and water were returned to animals in the control group. Twenty-four hours later food and water were removed from all cages and rats were given access to 3% NaCl solution for a 1 h salt appetite test. Standard chow and water were returned to all animals after the appetite test. The depletion procedure and testing was repeated 1 week later.

2.3. Locomotor activity tests

Horizontal locomotor activity was measured in an open field chamber equipped with photobeam rings (Truscan chamber 40.6 × 40.6 × 40.6 cm, Coulbourn Instruments, Allentown, PA). *X–Y* coordinates, obtained at a sample rate of 1/s, were used to determine the animal's position in the chamber.

Distance traveled was calculated by summing the sequential changes in position obtained from the coordinates throughout a trial.

3. Experiment 1

Rats with a history of sodium depletion show behavioral cross-sensitization to amphetamine, an indirect dopamine agonist, as evidenced by an increase in locomotor activity relative to animals with no such history. The underlying mechanism responsible for this potentiation in the behavioral response remains unknown. One possibility is that this treatment leads to enduring increases in dopamine receptor activity in the striatum. The purpose of this experiment was to examine the contribution of D1-like and D2-like dopamine receptors to cross-sensitization by comparing the locomotor activity produced by direct selective dopamine agonists in rats with and without a history of sodium depletion.

3.1. Method

3.1.1. Procedure

Twenty-eight male Long–Evans rats, history ($n=15$) and no history ($n=13$), were given two sodium depletions or sham treatments according to procedures described. One week later, all rats were tested for locomotor activation to either the D2 agonist quinpirole (Sigma, St. Louis, MO) or the D1 agonist A77636 (Sigma, St. Louis, MO) using methods adapted from Carr et al. (2001). Testing began with 30-min habituation sessions in the open field activity chamber once per day for three consecutive days. The baseline bars provided in Fig. 1A–C represent the first 15 min in the activity chambers during the last habituation session which occurred 1 day before testing with the dopamine agonists. Consistent with previous findings (Roitman et al., 2002; Clark and Bernstein, 2004a,b), there was no difference in general activity levels between animals with a history of sodium depletions and animals with no such history. On test day animals were injected in the home cage with either quinpirole (0.5 mg/kg i.p.) or A77636 (1 mg/kg i.p. or 3 mg/kg i.p.). Forty-five minutes later rats were placed in the open field chamber and activity was monitored for 1 h. This 60-min test session was divided into four 15-min bins for analysis. The doses of quinpirole and A77636 used in this experiment were chosen based on previous work showing the effects of food deprivation on locomotor activity induced by these doses (Carr et al., 2001). An additional assessment of the effect of these drugs relative to vehicle on activity was done in a separate group of non-depleted animals ($n=18$) using the same habituation and testing protocol.

3.1.2. Statistics

Mixed-factor ANOVA was used to compare within-group differences in distance traveled from baseline and to analyze overall group differences between animals with and without a history of sodium depletions. *t*-tests and the Bonferroni correction for multiple comparisons were used to compare group differences at relevant time points.

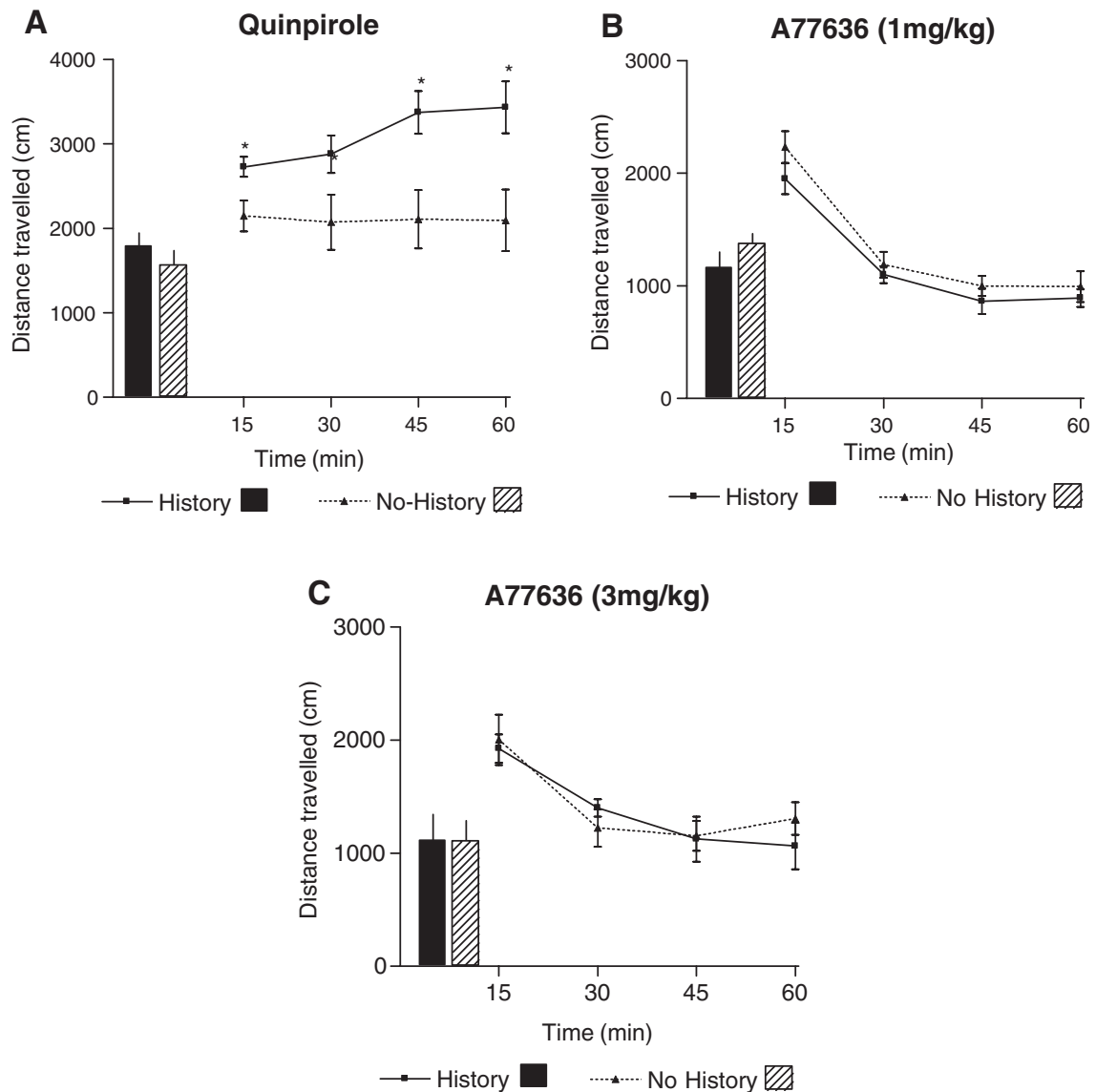


Fig. 1. Distance travelled during a 15 min baseline activity period (bars) and after administration of quinpirole (0.5 mg/kg) (A), A77636 (1 mg/kg) (B), and A77636 (3 mg/kg) (C). The History group received two episodes of sodium depletion, the No History group received control treatment. * $p < 0.05$ between the History and No History group.

3.2. Results

Rats with a history of sodium depletions showed significantly greater locomotor activation by quinpirole than rats without such a history. Distance traveled after quinpirole in both groups is depicted in Fig. 1A. Mixed-factor ANOVA revealed a significant elevation in locomotor activity relative to baseline [$F(4,56)=12.38$, $p < 0.001$], and a significant main effect of group [$F(1,14)=9.11$, $p < 0.01$]. Direct comparisons revealed significant elevations in distance traveled for animals with a history of sodium depletions at the 15 min [$t(14)=2.77$, $p < 0.05$], 45 min [$t(14)=3.03$, $p < 0.05$], and 60 min time points [$t(14)=2.83$, $p < 0.05$]. NaCl intake increased from 4.67 ml after the first depletion to 9.00 ml after the second depletion in sodium-depleted animals and from 1.42 ml to 1.57 ml in control animals. Paired sample t -tests confirmed this difference to be

significant in depleted [$t(8)=4.33$, $p < 0.01$] but not in control animals.

Animals in both groups displayed a significant elevation relative to baseline (black and stippled bars) in distance traveled after A77636. However, there were no differences between the two groups. Distance traveled after A77636 for animals with and without a history of sodium depletions is depicted in Fig. 1B. Mixed-factor ANOVA revealed a significant elevation in locomotor activity relative to baseline [$F(4,40)=35.49$, $p < 0.05$]. To verify that the absence of cross-sensitization was not merely due to the dose of D1 agonist chosen, the experiment was repeated using a higher dose (3 mg/kg). The experiment was identical to the first in all other respects. Both animals with a history of sodium depletion ($n=5$) and without ($n=5$) showed a significant elevation in distance traveled relative to baseline. There was no difference between groups at any time point.

Table 1
Total distance traveled during the 60-min activity test

Drug	Total distance (cm)	S.E.M. ^a
Saline	5993.25	277.29
Quinpirole (0.5 mg/kg)	4606.25	787.97
A77636 (1 mg/kg)	5424.40	457.29
A77636 (3 mg/kg)	7927.20	341.00

^a S.E.M.=standard error of the mean.

Distance traveled after A77636 for both groups is depicted in Fig. 1C. Mixed-factor ANOVA revealed a significant increase in locomotor activation relative to baseline [$F(4,32)=8.63$, $p<0.05$]. NaCl intake increased from 5.63 ml after the first depletion to 7.63 ml after the second depletion in depleted animals and from 0.45 ml to 0.94 ml in control animals. Paired sample t -tests confirmed this to be significant in depleted animals [$t(10)=2.24$, $p<0.05$] but not in controls.

Consistent with Carr et al., a separate experiment comparing the activity induced by quinpirole and A77636 to vehicle administration showed that only the 3 mg/kg dose of A77636 significantly elevated activity relative to vehicle. Mean total activity levels during the 60-min test session for all groups are depicted in Table 1. One-way ANOVA revealed a main effect of group [$F(3,14)=8.76$, $p<0.01$]. Post hoc comparisons showed that only the 3 mg/kg A77636 group significantly differed from the vehicle group [$t(7)=4.23$, $p<0.01$].

4. Experiment 2

The results of Experiment 1 indicate that, in addition to amphetamine, a history of sodium depletions produces behavioral cross-sensitization to a D2, but not a D1, direct dopamine agonist. This suggests that an alteration in dopamine function may play a role in cross-sensitization and that D2 receptors may

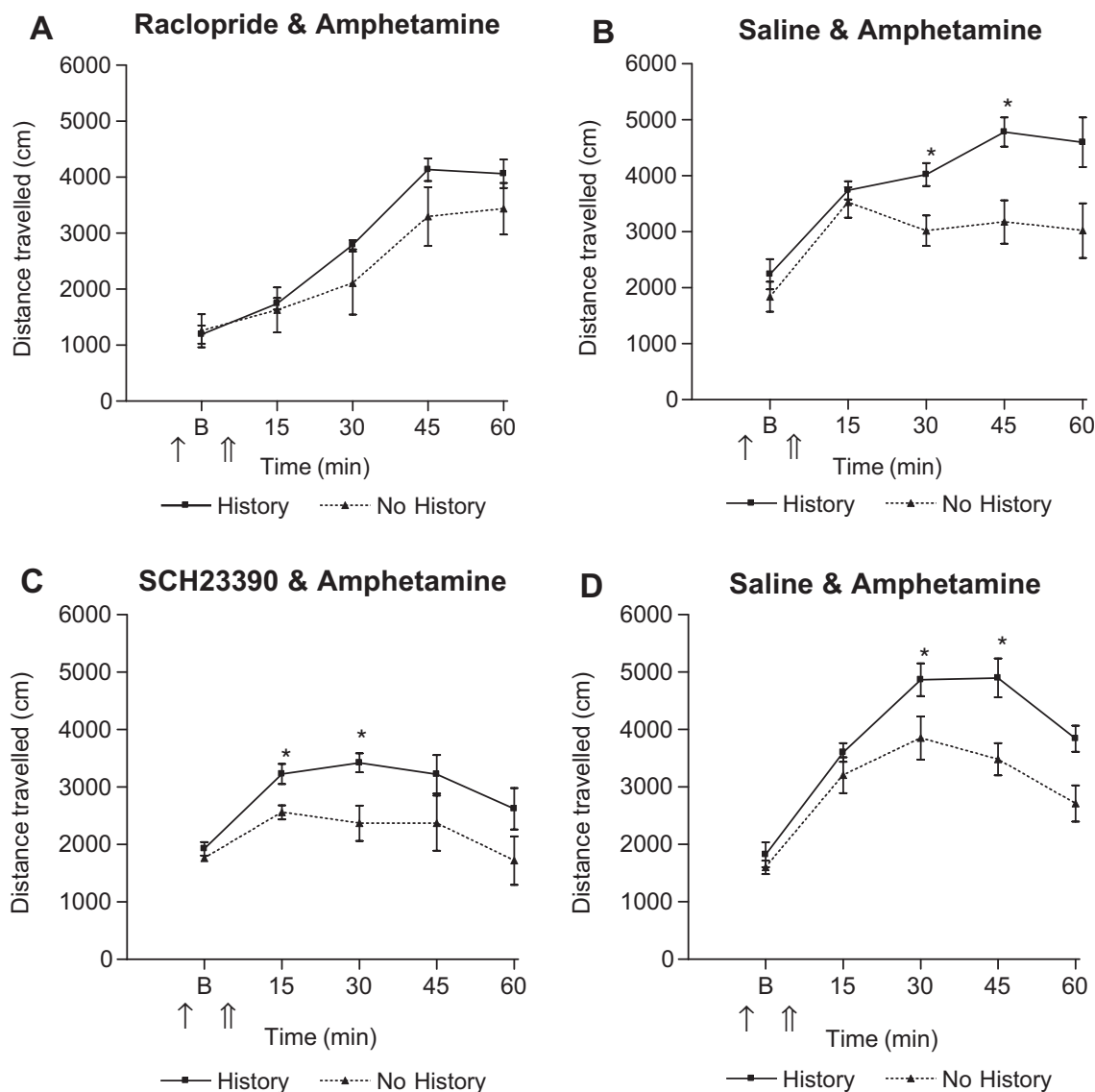


Fig. 2. Distance traveled during the 75-min activity test for animals injected with raclopride (0.2 mg/kg) prior to amphetamine (2 mg/kg) (A), saline prior to amphetamine (B, D) or SCH23390 (0.025 mg/kg) prior to amphetamine (C). ↑=time point for raclopride, SCH23390 or saline administration. ⇧=time point for amphetamine administration. * $p<0.05$ between the History and No History group.

be selectively involved. Another way to address this possibility is to administer dopamine antagonists in conjunction with amphetamine. The purpose of Experiment 2 was to evaluate the capacity of selective dopamine antagonists to block cross-sensitization of the locomotor response to amphetamine.

4.1. Method

4.1.1. Procedure

Forty-two male Long–Evans rats, history ($n=19$) and no history ($n=23$), were depleted of sodium twice or given sham treatments according to methods previously described. One week later all rats were tested for locomotor responses to amphetamine after administration of the D1 antagonist SCH23390 (Sigma, St. Louis, MO), the D2 antagonist raclopride (Sigma, St. Louis, MO) or saline. Each antagonist was tested separately, at different times, with different animals and saline control groups were included each time. Prior to testing animals were given two 30-min habituation sessions in the open field activity chamber. On test day rats were placed in the activity chamber for 15 min to establish a baseline, removed, injected with SCH23390 (0.025 mg/kg i.p.), raclopride (0.2 mg/kg i.p.) or saline and placed back in the chamber for an additional 15 min. Rats were then removed again, injected with amphetamine (2 mg/kg i.p.) and placed in the chamber for 60 min. The dose of amphetamine was based on previous demonstrations of cross-sensitization with this dose (Roitman et al., 2002; Clark and Bernstein, 2004a,b). The dose of SCH23390 was based on the evidence that this dose blocks the potentiation of amphetamine-induced psychomotor activation by food deprivation (Carr, 2002). Finally, the dose of raclopride was based on previous work showing that higher doses disrupt general activity levels (Roitman et al., 1997; Jackson et al., 1994).

4.1.2. Statistics

Mixed-factor ANOVA was used to compare within-group differences from baseline in distance traveled and to analyze group differences between animals with and without a history of sodium depletions. Separate analyses were conducted for each dopamine antagonist and saline group for a total of four. *t*-tests and the Bonferroni correction for multiple tests were used to test relevant time points. Finally, one-way ANOVA and planned contrasts were used to compare total distance traveled among the groups.

4.2. Results

Rats with and without a history of sodium depletion receiving raclopride prior to amphetamine showed a delayed but significant increase in locomotor activity. In addition, raclopride eliminated the differential response to amphetamine produced by a history of sodium depletions. Distance traveled for both groups of animals receiving raclopride is shown in Fig. 2A. Mixed-factor ANOVA revealed a significant elevation in distance traveled relative to baseline [$F(4,36)=54.08$, $p<0.001$] but no main effect of group. NaCl intake increased

from 5.20 ml after the first depletion to 7.30 ml after the second depletion in sodium-depleted animals and from 0.54 ml to 1.09 ml in control animals. Paired sample *t*-tests confirmed this difference to be significant in depleted [$t(9)=2.64$, $p<0.05$] but not in control animals.

Animals both with and without a history of sodium depletion given SCH23390 prior to amphetamine administration showed a blunted but significant increase in locomotor activity. Unlike those animals receiving raclopride and similar to animals receiving saline, rats with a history of sodium depletion showed significantly greater locomotor activation by amphetamine compared to rats with no such history. In other words, SCH23390 did not eliminate cross-sensitization. Distance traveled for animals given SCH23390 prior to amphetamine is shown in Fig. 2C. Mixed-factor ANOVA revealed a significant increase in distance traveled relative to baseline [$F(4,36)=8.91$, $p<0.001$], and a significant group effect [$F(1,9)=5.63$, $p<0.05$]. Direct comparisons between groups revealed significant elevations in distance traveled for animals with a history of sodium depletions at the 15 min [$t(9)=3.20$, $p<0.05$] and 30 min time points [$t(9)=2.83$, $p<0.05$]. NaCl intake increased from 4.66 ml to 6.33 ml in sodium-depleted animals and from

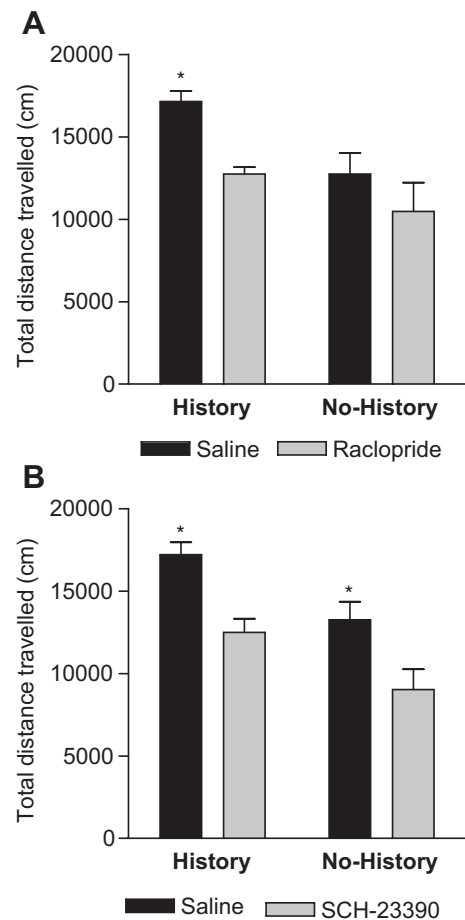


Fig. 3. Total distance traveled post-amphetamine injection in animals administered either raclopride (0.2 mg/kg) or saline (A), and animals administered SCH23390 (0.025 mg/kg) or saline (B). * $p<0.05$ between saline and raclopride or saline and SCH23390.

1.00 ml to 1.08 ml in controls. Paired sample *t*-tests confirmed this difference to be significant in depleted [$t(8)=2.42, p<0.05$] but not in control animals.

As previously reported, rats with a history of sodium depletions showed a significantly greater increase in locomotor activity induced by amphetamine compared to animals without such a history (cross-sensitization). Distance traveled for animals that received saline before amphetamine is illustrated in Fig. 2B and D. Mixed-factor ANOVA for the raclopride control group revealed a significant elevation in distance traveled relative to baseline [$F(4,32)=23.03, p<0.001$], and a significant main effect of group [$F(1,8)=8.28, p<0.05$]. Direct comparisons revealed significant elevations in distance traveled for animals with a history of sodium depletions at the 30 min [$t(8)=2.98, p<0.05$] and 45 min time points [$t(8)=3.44, p<0.01$]. Mixed-factor ANOVA for the SCH23390 control group revealed a significant increase in distance traveled relative to baseline [$F(4,32)=53.98, p<0.001$], and a significant main effect of group [$F(1,8)=6.38, p<0.05$]. Direct comparisons between groups revealed significant elevations in distance traveled for animals with a history of sodium depletions at the 45 min [$t(8)=3.23, p<0.05$] and 60 min time points [$t(8)=2.60, p<0.05$].

Finally, planned comparisons of total distance traveled revealed a significant reduction in amphetamine-induced activity by raclopride only in animals with a history of sodium depletions [$t(17)=2.46, p<0.05$]. SCH23390 was equally effective at reducing total activity in both groups: [$t(17)=2.85, p<0.05$] for animals with a history of sodium depletions and [$t(17)=2.97, p<0.05$] for animals with no such history. Total distance traveled for all experimental groups is depicted in Fig. 3A and B.

5. Discussion

Multiple sodium depletions produce salt appetite sensitization as well as behavioral cross-sensitization to amphetamine. The results of this study confirm behavioral cross-sensitization between salt appetite sensitization and amphetamine and support our previous demonstration that this protocol produces potentiation of general locomotor activity in addition to rearing (Clark and Bernstein, 2004b). The results of Experiment 1 indicate that a history of sodium depletion also leads to a potentiation of the behavioral response to a D2 but not a D1 direct dopamine agonist. The results of Experiment 2 show that cross-sensitization to amphetamine can be blocked by administration of a D2 but not a D1 antagonist. Combined, the results suggest that dopamine plays an important role in cross-sensitization and that D2 receptors may be selectively involved.

The first experiment assessed the contribution of dopamine receptors to cross-sensitization by measuring locomotor activation after the administration of direct dopamine agonists. Locomotor stimulation by quinpirole but not A77636 was significantly elevated in animals with a history of sodium depletion. The dose of quinpirole used in this study (0.5 mg/kg) suppresses DA neuron activity through occupation of D2

autoreceptors (Vanderschuren et al., 1999). Therefore, any locomotor stimulation should be due to the effect of quinpirole on post-synaptic D2 receptors. This suggests that the effect of inducing salt appetite sensitization on the response to amphetamine may be due, in part, to an alteration in post-synaptic D2 receptor function.

The finding of cross-sensitization to a D2 but not D1 agonist is consistent with an earlier report that examined the effect of food deprivation on responsiveness to these drugs (Carr et al., 2001). Food deprivation, another type of homeostatic challenge, potentiates the locomotor response to amphetamine and induces behavioral cross-sensitization to a D2 but not a D1 direct agonist. In addition, Foley et al. (2005) recently showed that a schedule of sucrose exposure also enhances the locomotor response to a D2 agonist. Finally, animals with a prior history of amphetamine treatment show behavioral cross-sensitization to a D2 but not a D1 agonist (Ujike et al., 1990; Vanderschuren et al., 1999; but see De Vries et al., 1998; Vezina, 1996; Kim et al., 2001 for the role of D1 receptors in the induction and expression of behavioral sensitization to psychostimulants). This finding adds to a growing list of similarities between salt appetite sensitization and drug sensitization.

The underlying mechanisms of salt appetite sensitization remain to be determined. However, much is known about the induction and expression of salt appetite. Sodium depletion reduces dopamine transporter activity in the nucleus accumbens (Roitman et al., 1999) and, as mentioned previously, NaCl intake increases dopamine release in the same structure (Frankmann et al., 1994). More recently, Lucas et al. (2003) demonstrated that NaCl intake in the sodium-depleted rat produces an elevation in enkephalin, which co-localizes with D2-like receptors, but not dynorphin, which co-localizes with D1-like receptors, in the nucleus accumbens. These results support the general proposition that enkephalin/D2 receptor expressing neurons are preferentially activated during salt appetite induction. In addition, previous data concerning the role of dopamine in salt appetite combined with the present findings implicating D2 receptor involvement in cross-sensitization suggest that this pathway may be an important link between salt appetite sensitization and responses to amphetamine.

The second experiment assessed the contribution of dopamine to cross-sensitization by measuring amphetamine-induced locomotor stimulation after selective blockade of D2 or D1 receptors with dopamine antagonists. Behavioral cross-sensitization between salt appetite sensitization and amphetamine was blocked by raclopride but not by SCH23390. This result differs from the study by Carr et al. (2001), which found that the D1 antagonist SCH23390 did block the effect of food deprivation on amphetamine-induced locomotor stimulation. Food deprivation is a model of an ongoing homeostatic challenge and its effect on behaviors related to drugs of abuse dissipate within a week of return to normal diet (Carr, 2002). In contrast, sodium depletion and subsequent salt appetite are discrete events and animals are in normal salt balance at the time of drug challenge. This disparity in the two models may reflect a fundamental difference between the effects of different types of homeostatic challenge

on reward processing. Coupled with the outcome of Experiment 1, the finding that only a D2 receptor antagonist will block cross-sensitization strongly implicates an alteration in D2 receptor function in this effect.

Finally, data from drug self-administration research have shown that D2 and D1 receptors play different roles in reward-seeking behaviors. Direct D2 agonists can reinstate cocaine seeking in animal models of drug relapse (De Vries et al., 1999), while co-administration of direct D1 agonists blocks reinstatement by cocaine priming injections (Self, 2004). Furthermore, De Vries et al. (1999) found that the extent to which a drug can produce behavioral cross-sensitization to another drug is predictive of its ability to induce drug-seeking as measured by the reinstatement paradigm. This is suggestive of a link between drug sensitization and the motivation to obtain drug. In support of this, Self et al. (1996) found that rats trained to self-administer cocaine, then given extinction trials until the behavior was extinguished, would resume drug-seeking (lever-pressing) after being given a D2 direct dopamine agonist. It was concluded from these data that the activation of D2 receptors could induce drug-seeking behaviors and that an alteration of D2 receptor function by previous drug experience could produce a sensitized pursuit of drug. Data from our laboratory indicate that salt appetite sensitization is accompanied by a potentiation in the pursuit of salt reward as measured by increases in breakpoint on a progressive ratio schedule of reinforcement (Clark and Bernstein, in press). Prior drug sensitization also produces this effect on breakpoint in animals self-administering cocaine (Lorrain et al., 2000). The findings from research on reinstatement combined with data from our laboratory concerning pursuit of salt reward in salt sensitized rats and the present results are suggestive of a link between altered D2 receptor function and sensitization of reward-seeking behavior.

References

- Carr KD. Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. *Physiol Behav* 2002;76(3):353–64.
- Carr KD, Kim GY, Cabeza de Vaca S. Rewarding and locomotor-activating effects of direct dopamine receptor agonists are augmented by chronic food restriction in rats. *Psychopharmacology* 2001;154(4):420–8.
- Clark JJ, Bernstein IL. Reciprocal cross-sensitization between amphetamine and salt appetite. *Pharmacol Biochem Behav* 2004a;78:691–8.
- Clark JJ, Bernstein IL. Sodium depletion is necessary but not sufficient for behavioral cross-sensitization to amphetamine. *Society for neuroscience abstracts*, vol. 30; 2004b.
- Clark JJ, Bernstein IL. Sensitization of salt appetite is associated with increased “wanting” but not “liking” of a salt reward in the sodium deplete rat. *Behav Neurosci* 2006;120(1):206–10 [Feb].
- De Vries TJ, Cools AR, Shippenberg TS. Infusion of a D-1 receptor agonist into the nucleus accumbens enhances cocaine-induced behavioural sensitization. *Neuroreport* 1998;9(8):1763–8 [Jun 1].
- De Vries TJ, Schoffelmeier AN, Binnekade R, Vanderschuren LJ. Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration. *Psychopharmacology* 1999;143(3):254–60.
- Fiorino DF, Phillips AG. Facilitation of sexual behavior and enhanced dopamine efflux in nucleus accumbens of male rats after D-amphetamine-induced behavioral sensitization. *J Neurosci* 1999;19(1):456–63.
- Foley KA, Fudge MA, Kavaliers M, Ossenkopp KP. Quinpirole-induced behavioral sensitization is enhanced by prior scheduled exposure to sucrose: a multi-variable examination of locomotor activity. *Behav Brain Res* 2006;167(1):49–56 [Feb 15].
- Frankmann SP, Broder L, Dokko JH, Smith GP. Differential changes in central monoaminergic metabolism during first and multiple sodium depletions in rats. *Pharmacol Biochem Behav* 1994;47(3):617–24.
- Jackson DM, Johansson C, Lindgren LM, Bengtsson A. Dopamine receptor antagonists block amphetamine and phencyclidine-induced motor stimulation in rats. *Pharmacol Biochem Behav* 1994;48(2):465–71.
- Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* 2002;22(9):3306–11.
- Kim JH, Perugini M, Austin JD, Vezina P. Previous exposure to amphetamine enhances the subsequent locomotor response to a D1 dopamine receptor agonist when glutamate reuptake is inhibited. *J Neurosci* 2001;21(5):RC133 [Mar 1].
- Lorrain DS, Arnold GM, Vezina P. Previous exposure to amphetamine increases incentive to obtain the drug: long-lasting effects revealed by the progressive ratio schedule. *Behav Brain Res* 2000;107:9–19.
- Lucas LR, Grillo CA, McEwen BS. Involvement of mesolimbic structures in short-term sodium depletion: in situ hybridization and ligand-binding analyses. *Neuroendocrinology* 2003;77(6):406–15.
- McCutcheon B, Levy C. Relationship between NaCl rewarded bar-pressing and duration of sodium deficiency. *Physiol Behav* 1971;8(4):761–3.
- Nocjar C, Panksepp J. Chronic intermittent amphetamine pretreatment enhances future appetitive behavior for drug- and natural-reward: interaction with environmental variables. *Behav Brain Res* 2002;128:189–203.
- Pierce CR, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Brain Res Rev* 1997;25:192–216.
- Robinson TE, Berridge KC. The neural basis of drug craving. *Brain Res Brain Res Rev* 1993;18:247–91.
- Robinson TE, Kolb B. Persistent structural modification in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. *J Neurosci* 1997;17(21):8491–7.
- Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* 2004;47(Suppl 1):33–46.
- Roitman MF, Schafe GE, Thiele TE, Bernstein IL. Dopamine and sodium appetite: antagonists suppress sham drinking of NaCl solutions in the rat. *Behav Neurosci* 1997;111(3):606–11.
- Roitman MF, Patterson TYA, Sakai RR, Bernstein IL, Figlewicz DP. Sodium depletion and aldosterone decrease dopamine transporter activity in nucleus accumbens but not in striatum. *Am J Physiol* 1999;267(5 pt 2):R1339–45.
- Roitman MF, Na E, Anderson G, Jones TA, Bernstein IL. Induction of salt appetite alters dendritic morphology in nucleus accumbens and sensitizes rats to amphetamine. *J Neurosci* 2002;22(11):RC225.
- Sakai RR, Fine WB, Epstein AN. Salt appetite is enhanced by one prior episode of sodium depletion in the rat. *Behav Neurosci* 1987;101:724–31.
- Self DW. Regulation of drug-taking and-seeking behaviors by neuroadaptations in the mesolimbic dopamine system. *Neuropharmacology* 2004;47(Suppl 1):242–55.
- Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. *Science* 1996;271(5255):1586–9.
- Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol* 1993;4:289–312.
- Vanderschuren LJ, Schoffelmeier AN, Mulder AH, De Vries TJ. Dopaminergic mechanisms mediating the long-term expression of locomotor sensitization following pre-exposure to morphine or amphetamine. *Psychopharmacology* 1999;143(3):244–53.
- Vezina P. D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. *J Neurosci* 1996;16(7):2411–20 [Apr 1].

- Ujike H, Akiyama K, Otsuki S. D-2 but not D-1 dopamine agonists produce augmented behavioral response in rats after subchronic treatment with methamphetamine or cocaine. *Psychopharmacology* 1990;102(4):459–64.
- Vitale MA, Chen D, Kanarek RB. Chronic access to sucrose solution enhances the development of conditioned place preferences for fentanyl and amphetamine in male Long–Evans rats. *Pharmacol Biochem Behav* 2003;74:529–39.
- Wolf G. Refined salt appetite methodology for rats demonstrated by assessing sex differences. *J Comp Physiol Psychol* 1982;96:1016–21.