Previous Exposure to Amphetamine Enhances the Subsequent Locomotor Response to a D₁ Dopamine Receptor Agonist When Glutamate Reuptake Is Inhibited

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The role of nucleus accumbens (NAcc) glutamate (GLU) and D₁ dopamine (DA) receptor activation in the expression of locomotor sensitization to amphetamine (AMPH) was investigated in rats. Rats were preexposed to either AMPH or saline, and 2 weeks later their locomotion was assessed after a microinjection into the NAcc of the selective glutamate reuptake blocker *L-trans*-pyrrolidine-2,4-dicarboxylic acid (PDC) (10 nmol per side), the D₁-like DA receptor agonists SKF82958 (2.4 nmol per side) and SKF38393 (3.1 nmol per side), the D₂-like DA receptor agonist quinolorane (3.1 nmol per side), or AMPH (6.8 nmol per side). All compounds other than quinolorane increased locomotion when infused into the NAcc. Only AMPH, however, produced enhanced locomotion in AMPH relative to saline-preexposed rats. When additional rats were tested after NAcc

infusions of PDC together with either SKF82958 or quinolorane, enhanced locomotion was observed in AMPH relative to saline-preexposed rats after NAcc PDC + SKF82958. These results suggest that in the NAcc, increased GLU neurotransmission and activation of D₁ DA receptors, neither of which is by itself sufficient, together contribute to the expression of locomotor sensitization by AMPH. They stress, with other findings, the importance of GLU–DA interactions in the NAcc not only in the generation of acute stimulant drug effects but in sensitized responding to these drugs as well.

Key words: dopamine; D₁- and D₂-like dopamine receptors; glutamate; nucleus accumbens; amphetamine; sensitization; locomotor activity; *L*-PDC; SKF82958; SKF38393; quinolorane

Repeated exposure to psychomotor stimulants such as amphetamine (AMPH) leads to sensitization of their locomotor response (Kalivas and Stewart, 1991). The nucleus accumbens (NAcc) receives dopaminergic axonal projections from the ventral tegmental area and has been implicated in the expression of this effect (Perugini and Vezina, 1994a; Cador et al., 1995). Ultrastructural anatomical studies of this site indicate that some of the terminals of the descending glutamate (GLU) projections from cortex and those of ascending dopamine (DA) mesencephalic projections come in close apposition to each other and form synaptic contacts with the same intrinsic NAcc neurons (Sesack and Pickel, 1990, 1992). Such a configuration provides the structural basis for a possible interaction between GLU and DA at the synaptic level in the NAcc.

A number of studies have shown that both DA and GLU neurotransmission in the NAcc are altered by repeated exposure to psychomotor stimulants. For example, previous exposure to psychomotor stimulant drugs leads to enhanced stimulant-induced DA overflow in the NAcc (Kalivas and Stewart, 1991; Vezina, 1996), altered locomotor responding to NAcc infusions of GLU receptor-specific ligands (Pierce et al., 1996; Kim and Vezina, 1998), and enhanced inhibition of intrinsic NAcc neurons by cocaine and D₁ DA receptor but not D₂ DA receptor agonists (Henry and White, 1991, 1995; Wolf et al., 1994). Enhanced cocaine-induced NAcc GLU overflow in stimulant-preexposed

animals has also been reported (Pierce et al., 1996; Reid and Berger, 1996), although some have observed only increased aspartate overflow (Robinson et al., 1997) and others have observed no effect after amphetamine challenge (Xue et al., 1996; Wolf, 1998). GLU and DA also appear to interact to influence each other's synaptic release in the striatum and NAcc (Youngren et al., 1993; Smith et al., 1995; Taber et al., 1996; Kalivas and Duffy, 1997; Reid et al., 1997; Segovia et al., 1997; West and Galloway, 1997; Dalia et al., 1998). Thus, although reflecting complex effects, these data collectively suggest that GLU and DA may interact in a number of ways in the NAcc to influence the expression of sensitization by psychomotor stimulants (Freed, 1994; Wolf, 1998; Vezina and Kim, 1999).

To further assess this possibility, the locomotor response of rats previously exposed to amphetamine was assessed after infusion into the NAcc of compounds known to increase extracellular levels of GLU [*L-trans*-pyrrolidine-2,4-dicarboxylic acid (PDC)] or DA (AMPH) or to directly activate D₁ (SKF38393, SKF82958) or D₂₋₃ DA (quinolorane) receptors. To specifically

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examine the contribution of GLU–DA interactions, the effects of PDC and D_1 or D_{2-3} DA receptor activation were examined separately as well as in combination. Results indicate that in the NAcc, increased levels of extracellular GLU and activation of D_1 DA receptors, neither of which is by itself sufficient, together contribute to the expression of locomotor sensitization by AMPH.

MATERIALS AND METHODS

Subjects. Male Sprague Dawley rats weighing 250–275 gm on arrival from Harlan Sprague Dawley (Madison, WI) were housed individually in a 12 hr light/dark reverse cycle room with food and water available *ad libitum*. They were anesthetized with ketamine (100 mg/kg, i.p.) followed by xylazine (6 mg/kg, i.p.) 4–7 d after arrival, placed in a stereotaxic instrument with the incisor bar positioned 5.0 mm above the interaural line, and implanted with chronic bilateral guide cannulas (22 gauge; Plastics One, Roanoke, VA) aimed at the NAcc (anteroposterior, +3.4; lateral, ± 1.5 ; dorsoventral, -7.5 from bregma and skull) (Pellegrino et al., 1979). Cannulas were angled at 10° to the vertical, positioned 1 mm above the final injection site, and secured with dental acrylic cement anchored to stainless steel screws fixed to the skull. After surgery, 28 gauge obturators were placed in the guide cannulas, and rats were returned to their home cages for a 10 d recovery period. At the completion of the experiments, rats were anesthetized and perfused via intracardiac infusion of saline and 10% formalin, brains were removed and post-fixed in 10% formalin for 1 week, and coronal sections (40 μ m) were subsequently stained with cresyl violet for verification of injection cannula tip placements. All testing was conducted during the animals' dark cycle.

Drugs and intracranial microinjections. The competitive inhibitor of GLU reuptake, PDC (10.0 nmol per side), the D_1 DA receptor agonists ($\pm$)-SKF82958 HBr [2.4 nmol (1 μ g) per side] and R(+)-SKF38393 diHCl [3.1 nmol (1 μ g) per side], the D_{2-3} DA receptor agonist quinlorane diHCl (Sautel et al., 1995) [3.1 nmol (1 μ g) per side], the D_1 DA receptor antagonist R(+)-SCH23390 HCl [0.8 nmol (1 μ g) per side], and the D_2 DA receptor antagonist S(-)-eticlopride HCl [2.7 nmol (1 μ g) per side] were obtained from Research Biochemicals International (Natick, MA). All were dissolved in water, and small aliquots stored at -80°C . Immediately before use, frozen aliquots of the drugs were diluted in sterile 0.9% saline and prepared either separately or as a mixture. S(+)-AMPH sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile 0.9% saline and injected intraperitoneally (pre-exposure; 1.0 mg/kg) and into the NAcc [test for sensitization; 6.8 nmol (2.5 μ g) per side]. All doses refer to the weight of the salt and are based on previous reports of the locomotor effects of PDC (Kim and Vezina, 1999) and DA receptor agonists and antagonists (Vezina et al., 1991; Meyer et al., 1993; Vezina, 1996; Swanson et al., 1997). Solution pHs ranged from 5.5 to 7.0, values well within the limits of rat brain buffering power (Chesler, 1990). Bilateral intracranial microinjections into the NAcc were made in the freely moving rat. Injection cannulas (28 gauge) connected to 1 μ l syringes (Hamilton, Reno, NV) via PE-20 tubing were inserted to a depth of 1 mm below the guide cannula tips. Injections were made in a volume of 0.5 μ l per side over 30 sec. Sixty seconds later, the injection cannulas were withdrawn, the obturators were replaced, and rats were placed immediately in the activity boxes.

Locomotor activity. A bank of 12 activity boxes was used to measure locomotor activity. Each box (22 $\times$ 43 $\times$ 33 cm) was constructed of opaque plastic (rear and two side walls), a Plexiglas front-hinged door, and a tubular stainless steel ceiling and floor. Two photocells, positioned 3.5 cm above the floor and spaced evenly along the longitudinal axis of each box, estimated horizontal locomotion. Two additional photocells, positioned on the side walls 16.5 cm above the floor and 5 cm from the front and back walls, estimated rearing. Separate interruptions of photocell beams were detected and recorded via an electrical interface by a computer situated in an adjacent room. The activity boxes were kept in a room lighted dimly with red light.

Design and procedure. The sensitization experiments consisted of two phases: a drug preexposure phase and a test for sensitization. During the drug preexposure phase, different groups of rats were administered either saline (1 ml/kg, i.p.) or AMPH (1 mg/kg, i.p.) on four occasions, one injection every 3–4 d. Immediately after the first and fourth injections, rats were placed in the activity boxes for 2 hr. They were returned to their home cages after the second and third injections. On the test for sensitization, 2 weeks after the last preexposure injection, animals were

Figure 1. Locomotion (*A*) and rearing (*B*) observed after microinjection of PDC, SKF82958, SKF38393, quinlorane, or AMPH into the NAcc 2 weeks after preexposure to amphetamine or saline IP. Only NAcc AMPH produced enhanced locomotor-activating effects in AMPH relative to saline-preexposed rats. Data are shown as group mean ($\pm$ SEM) locomotion and rearing counts observed during the first and second hour of a 2 hr test. Numbers at the base of the different columns indicate *n* per group. * $p < 0.05$, *** $p < 0.001$; significantly more counts in AMPH relative to saline-preexposed animals at the indicated time as determined by *post hoc* Scheffé comparisons after ANOVA.

administered their designated infusion bilaterally into the NAcc and placed immediately in the activity boxes for 2 hr. In all cases, rats were habituated to the activity boxes for 1 hr before the NAcc infusion.

In a separate control experiment designed to assess the D_1 DA receptor specificity of SKF82958, rats in different groups were first habituated to the activity boxes for 1 hr after which they were administered their respective NAcc infusion and returned to the activity boxes for an additional 2 hr.

The data were analyzed with two-way and three-way between-within ANOVA. In the former case, NAcc infusion was the between factor and time the within factor (see Table 1). In the latter case, preexposure condition and NAcc infusion were the between factors and time the within factor (see Figs. 1, 2). *Post hoc* Scheffé comparisons were made according to Kirk (1968).

RESULTS

Histology

Only rats with injection cannula tips located bilaterally in the NAcc were included in the data analyses. Of the total of 145 rats tested, 6 were excluded for failing to meet this criterion. No neuronal damage was observed other than that produced by the insertion of the cannulas.

Previous exposure to AMPH leads to enhanced locomotor responding to NAcc AMPH but not to NAcc PDC, SKF82958, SKF38393, or quinlorane

Figure 1 shows the locomotor activity counts obtained in rats preexposed 2 weeks earlier to AMPH or saline and tested after NAcc infusion of either PDC, SKF82958, SKF38393, quinlorane, or AMPH. As expected, all test compounds other than

Figure 2. D_1 , but not D_{2-3} , DA receptor activation in the NAcc produces enhanced locomotor responding when GLU reuptake is locally inhibited in AMPH preexposed rats. Data are shown as group mean ($\pm$ SEM) locomotion (*A*) and rearing (*B*) activity counts obtained after the sensitization test injection. *Insets* show total counts obtained in the first hour of testing. *Numbers* of rats in each group are indicated at the base of the different columns. + denotes mixture injections. The remaining *symbols* indicate significant differences as revealed by *post hoc* Scheffé comparisons after ANOVA. * $p < 0.05$, *** $p < 0.001$; AMPH compared with saline-preexposed rats tested with PDC + SKF82958. *C*, Location of the microinjection cannula tips in the NAcc of rats included in the data analyses. The line drawings are from Paxinos and Watson (1986). *Numbers* to the right indicate millimeters from bregma. Symbols represent the different groups: ○, saline (preexposure, i.p.)—PDC + SKF82958 (test, intra-NAcc); ●, AMPH—PDC + SKF82958; □, saline—PDC + quinelorane; ■, AMPH—PDC + quinelorane.

quinelorane increased locomotion and rearing when compared with NAcc saline ($p < 0.05$ – 0.001). These locomotor effects were mostly restricted to the first hour of testing, although in the case of SKF82958, increased locomotor activity continued into the second hour. Quinelorane decreased locomotor activity somewhat throughout testing, although this effect did not achieve statistical significance (cf. Swanson et al., 1997). Of the compounds tested, however, only NAcc AMPH [in agreement with Paulson and Robinson (1991)] produced enhanced locomotion and rearing in AMPH compared with saline-preexposed rats ($p < 0.05$ – 0.001). The remaining compounds increased locomotion and rearing but to a similar extent in the two preexposure conditions. The above p values were determined by *post hoc* Scheffé comparisons after an ANOVA that found multiple significant effects, including effects of NAcc infusion [$F_{(5,62)} = 29.9$ and 27.1 ; $p < 0.001$] as well as significant NAcc infusion $\times$ preexposure condition [$F_{(5,62)} = 6.6$ and 6.4 ; $p < 0.001$], and NAcc infusion $\times$ preexposure condition $\times$ time interactions [$F_{(5,62)} = 3.4$ and 6.7 ; $p < 0.01$ – 0.001] for locomotion and rearing, respectively.

Previous exposure to AMPH leads to enhanced locomotor responding to NAcc SKF82958 in the presence of PDC

When challenged with NAcc PDC + SKF82958, rats preexposed 2 weeks earlier to AMPH showed levels of locomotion and rearing that were significantly higher than those displayed by saline-preexposed rats (Fig. 2*A,B*). The ANOVA conducted on these data again showed multiple significant effects, including effects of NAcc infusion [$F_{(1,21)} = 7.1$ and 9.5 ; $p < 0.05$ – 0.01] as well as significant NAcc infusion $\times$ preexposure condition $\times$ time interactions [$F_{(7,147)} = 2.0$ and 7.2 ; $p < 0.5$ – 0.001], for locomotion and rearing, respectively. *Post hoc* comparisons revealed that the enhanced locomotor effects of NAcc PDC + SKF82958 were restricted to the first hour of testing ($p < 0.5$ – 0.001) (Fig. 2*A,B*, *insets*). No significant differences were detected between AMPH and saline-preexposed rats at any time points when these were challenged with PDC + quinelorane. In saline-preexposed rats, NAcc PDC + SKF82958 elicited significantly more locomotion and rearing in the first 15 min of testing than NAcc PDC + quinelorane ($p < 0.05$ – 0.001).

Table 1. The increased locomotion and rearing produced acutely by SKF 82958 in the NAcc is D₁ DA receptor dependent

Acute NAcc microinjection	Locomotion		Rearing	
	1st hr	2nd hr	1st hr	2nd hr
SKF82958 (12)	404.3 ± 41.4***	182.8 ± 29.5	177.5 ± 24.8***	65.3 ± 13.7
SAL (9)	303.0 ± 37.8	74.0 ± 24.6	84.0 ± 13.9	26.0 ± 5.3
SKF82958 + SCH23390 (6)	287.3 ± 33.9	109.3 ± 14.6	108.2 ± 28.0	34.5 ± 9.7
SKF82958 + eticlopride (5)	381.0 ± 33.1***	138.0 ± 17.3	188.6 ± 50.1***	71.0 ± 22.4
SCH23390 (5)	255.8 ± 10.8	129.4 ± 23.1	130.6 ± 16.8	40.8 ± 12.4
Eticlopride (7)	199.0 ± 28.7	99.7 ± 15.1	89.6 ± 10.2	32.3 ± 8.0

Data are shown as group mean (±SEM) locomotion and rearing counts during the first and second hour of a 2 hr test. Numbers in parentheses indicate *n*/group. ****p* < 0.001, significantly more counts by SKF82958 and SKF82958 + eticlopride rats relative to all remaining animals at the indicated times as determined by *post hoc* Scheffé comparisons after two-way between-within ANOVA. + denotes mixture injections.

The location of injection cannula tips in the NAcc of the rats that were included in this experiment are illustrated in Figure 2C.

Locomotor activating effects of SKF82958 are D₁ DA receptor specific

The D₁ DA receptor specificity of SKF82958 was assessed directly in a separate control experiment. Table 1 shows that the locomotor-activating effects of SKF82958 were blocked when coinjected into the NAcc with the D₁ DA receptor-specific antagonist SCH23390 (0.8 nmol per side) but spared when coinjected with the D₂ DA receptor-specific antagonist eticlopride (2.7 nmol per side). Thus, under the present conditions, SKF82958 appeared to produce its effects on locomotion in a D₁ DA receptor-dependent manner.

DISCUSSION

The present results demonstrate that in a manner similar to AMPH, simultaneous activation of D₁ DA receptors and blockade of GLU reuptake in the NAcc produces enhanced locomotor responding in AMPH compared with saline-preexposed rats. These results, together with the additional finding that these manipulations failed to produce sensitized responding when administered by themselves, clearly illustrate the importance of GLU–DA interactions in the NAcc in the expression of AMPH-induced locomotor sensitization.

It has been shown that NAcc infusion of the AMPA receptor agonist AMPA enhances locomotor responding in cocaine-preexposed rats, relative to saline-preexposed rats, and that the AMPA/kainate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione in the NAcc abolishes sensitized responding to systemic cocaine challenge (Pierce et al., 1996). This finding of increased AMPA receptor responsiveness in cocaine-sensitized rats is consistent with others showing a significant increase in NAcc GluR1 levels in cocaine-preexposed rats (Churchill et al., 1999), although evidence for decreased responsiveness has been suggested by electrophysiological studies (White et al., 1995; Wolf, 1998). In contrast, the metabotropic GLU receptor (mGluR) antagonist (RS)-α-methyl-4-carboxyphenylglycine, but not the mGluR agonist 1-aminocyclopentane-*trans*-1,3-dicarboxylic acid, was found to produce enhanced locomotor activity when microinjected into the NAcc in AMPH compared with saline-preexposed rats (Kim and Vezina, 1998). These findings indicate that NAcc GLU may differentially impact locomotor activity in stimulant-preexposed animals depending on the GLU receptor subtype activated. Thus, the present results showing that increasing extracellular levels of

GLU with NAcc PDC (Griffiths et al., 1994) increased locomotion equally in AMPH- and saline-preexposed rats may reflect the net outcome of simultaneously activating multiple subtypes of GLU receptors in this site.

The lack of sensitized locomotor responding to NAcc infusions of D₁ DA receptor agonists in AMPH-preexposed rats is consistent with previous reports (Perugini and Vezina, 1994b; Pierce and Kalivas, 1995). In apparent contrast to these results, it has been shown in electrophysiological experiments that previous exposure to psychomotor stimulant drugs leads to enhanced D₁ (but not D₂) DA receptor sensitivity in the NAcc (Henry and White, 1991; Wolf et al., 1994) that may persistently accompany the expression of behavioral sensitization (Henry and White, 1995). It must be noted, however, that in these experiments, D₁ DA receptor supersensitivity was always observed in the presence of iontophoretically applied GLU. Importantly, when experiments were conducted in the absence of GLU and the ability of SKF38393 to inhibit Na⁺ current was assessed using whole-cell patch-clamp recordings in NAcc neurons dissociated from cocaine- and saline-preexposed rats, enhanced D₁ DA receptor sensitivity was not observed (Zhang et al., 1998). Interestingly, the direction of the modulation by DA of NAcc medium spiny neuron firing has also been shown to be dependent on the glutamatergic tone imposed on these cells by descending GLU projections from cortex (Gonon and Sundstrom, 1996). Whatever the manner in which these effects impact the firing of intrinsic NAcc output neurons and, as a consequence, the generation of locomotor activity, it is intriguing that they very much parallel the present findings showing that enhanced locomotor responding to D₁ DA receptor activation was observed only in the presence of GLU reuptake block in rats previously exposed to AMPH.

Elevating extracellular levels of GLU either directly or indirectly with PDC has been reported to increase extracellular levels of DA in both the striatum and the NAcc (Youngren et al., 1993; Taber et al., 1996; Segovia et al., 1997; West and Galloway, 1997), whereas NAcc DA agonists and psychomotor stimulants increase GLU levels in this site (Smith et al., 1995; Kalivas and Duffy, 1997; Reid et al., 1997; Dalia et al., 1998; Wolf, 1998). However, it remains to be determined whether GLU or a D₁ DA receptor agonist is also capable of evoking enhanced increase of DA or GLU overflow, respectively, in sensitized animals. Previous exposure to psychomotor stimulant drugs has been shown to lead to enhanced cocaine-induced overflow of GLU and DA as well as aspartate in the NAcc (Pierce et al., 1996; Reid and Berger, 1996;

Xue et al., 1996; Robinson et al., 1997). These findings reflect the ability of such drugs to simultaneously recruit both of these hyper-responsive neurotransmitter pathways, and as a consequence, this may lead to the generation of sensitized locomotor activity. How these events are integrated postsynaptically in the NAcc to produce sensitized locomotor responding remains unknown, however. It is possible that such events may initially take the form of extrasynaptic or volumetric type interactions similar to what has been suggested in the striatum (Lannes and Micheletti, 1994), considering the fact that no direct synapses have been found between GLU and DA terminals, despite their close apposition to each other as they form synapses with intrinsic NAcc cells (Sesack and Pickel, 1990, 1992). Then, enhanced glutamatergic input to the NAcc, by acting at GLU receptors in this site, may regulate incoming dopaminergic signals (or vice versa), possibly by acting on second messenger pathways with which they are coupled and thereby influence the generation of locomotor activity (Vezina and Kim, 1999).

Interactions between PDC and D₂ DA receptor activation were not observed in the present study, suggesting in a manner consistent with previous studies (Henry and White, 1991; Wolf et al., 1994) a more important role for enhanced NAcc D₁ DA receptor sensitivity in the expression of sensitization by psychomotor stimulants. Quinelorane has been shown to inhibit AMPH-induced locomotion by activating postsynaptic D₂₋₃ DA receptors (Thorn et al., 1997). Similar, although relatively shorter, effects may have been produced in the present study with PDC in that in the initial 15 min of testing, animals administered PDC + quinelorane (regardless of preexposure condition) exhibited less locomotor activity than saline-preexposed rats administered PDC + SKF82958. It was recently reported that SKF82958 (and possibly other benzazepines including SKF38393) can block potassium channels (Nisenbaum et al., 1998) and that SKF82958, in particular, may possess D₂ DA autoreceptor agonist properties (Ruskin et al., 1998). Although these studies used relatively high agonist concentrations, it was also difficult to compare them with those used in the present experiments because different routes of administration were used. It is clear from the control data shown in Table 1, however, that under the present conditions, the locomotor-activating effects of SKF82958 were D₁ DA receptor specific.

In summary, the present results demonstrate that sensitized locomotor activity in AMPH-preexposed rats can be elicited by coinjection into the NAcc of PDC together with a D₁ DA receptor agonist. The additional finding that neither of these substances administered alone is capable of producing this effect clearly illustrates the importance of interactions between GLU and D₁ DA receptors in the NAcc in the expression of locomotor sensitization by AMPH.

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