

Coincident Activation of NMDA and Dopamine D₁ Receptors within the Nucleus Accumbens Core Is Required for Appetitive Instrumental Learning

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The nucleus accumbens, a brain structure ideally situated to act as an interface between corticolimbic information-processing regions and motor output systems, is well known to subserve behaviors governed by natural reinforcers. In the accumbens core, glutamatergic input from its corticolimbic afferents and dopaminergic input from the ventral tegmental area converge onto common dendrites of the medium spiny neurons that populate the accumbens. We have previously found that blockade of NMDA receptors in the core with the antagonist 2-amino-5-phosphonopentanoic acid (AP-5; 5 nmol) abolishes acquisition but not performance of an appetitive instrumental learning task (Kelley et al., 1997). Because it is currently hypothesized that concurrent dopamine D₁ and glutamate receptor activation is required for long-term changes associated with plasticity, we wished to examine whether the dopamine system in the accumbens core modulates learning via NMDA receptors.

Co-infusion of low doses of the D₁ receptor antagonist SCH-23390 (0.3 nmol) and AP-5 (0.5 nmol) into the accumbens core strongly impaired acquisition of instrumental learning (lever pressing for food), whereas when infused separately, these low doses had no effect. Infusion of the combined low doses had no effect on indices of feeding and motor activity, suggesting a specific effect on learning. We hypothesize that co-activation of NMDA and D₁ receptors in the nucleus accumbens core is a key process for acquisition of appetitive instrumental learning. Such an interaction is likely to promote intracellular events and gene regulation necessary for synaptic plasticity and is supported by a number of cellular models.

Key words: glutamate; plasticity; striatum; intracellular signals; rat; reinforcement; reward

The nucleus accumbens, a forebrain structure known to subserve behaviors governed by natural reinforcers, receives excitatory glutamatergic input from prefrontal cortex, hippocampus, thalamus, and amygdala (McGeer et al., 1977; Walaas and Fonnum, 1979; Young and Bradford, 1986; Fuller et al., 1987; Robinson and Beart, 1988), as well as a major dopaminergic innervation from the ventral tegmental area (Lindvall and Bjorklund, 1978). These innervations converge on the dendritic spines of the medium spiny neurons that populate the nucleus accumbens (Totterdell and Smith, 1989; Sesack and Pickel, 1990; Smith and Bolam, 1990). Therefore, these neurons are in a unique position to recognize context-driven patterns of activation and to transfer this information to planning and motor regions for appropriate behavioral responses (Houk et al., 1995). Recently, there has been much interest in the neuromodulatory effects of dopamine (DA) receptor activation on NMDA receptor state, as well as the intracellular mechanisms that may govern their interaction. For example, DA D₁ receptor activation in striatal slices potentiates responses mediated by NMDA receptor activation (an effect that is blocked by the D₁ receptor antagonist SCH-23390), whereas dopamine D₂ receptors have an attenuating effect (Cepeda et al., 1993; Cepeda and Levine, 1998). Moreover, DA receptor modulation of NMDA receptor-mediated responses is blunted in D_{1A}-deficient mutant mice (Levine et al., 1996). When corticostriatal excitation and dopaminergic activation are temporally coordinated, there is a long-lasting enhancement of synaptic strength in medium spiny neurons (Wickens et al., 1996). In a behavioral study, it was reported that impairment of learning of a one-trial inhibitory avoidance task attributable to post-trial systemic administration of NMDA antagonists is attenuated by systemic administration of low doses of dopamine agonists (Adri-

ani et al., 1998). Taken together, these emerging findings suggest that co-activation of dopamine D₁ and glutamate NMDA receptors is required for long-term changes associated with plasticity and perhaps certain forms of learning.

We have previously found that blockade of NMDA receptors in the accumbens core with the antagonist 2-amino-5-phosphonopentanoic acid (AP-5) completely abolishes acquisition but not performance of an appetitive instrumental learning task (acquisition of lever pressing for food; Kelley et al., 1997) and also disrupts spatial learning in the radial arm maze (Smith-Roe et al., 1999). Considering the substantial evidence for DA–NMDA receptor interactions at the physiological and molecular level, we hypothesized that such interactions may play a key role in learning subserved by the nucleus accumbens. Our first objective was to assess the effects of intra-accumbens core infusion of the D₁ dopamine receptor antagonist SCH-23390 in an appetitive instrumental learning task. However, a major obstacle to investigating the role of DA receptors in learning and to interpreting effects on behavior is the considerable motor impairment that often results with DA receptor antagonist treatment. Because we indeed found evidence of a motor impairment, we also examined the effects of very low doses of the D₁ antagonist as well as combinations of low doses of AP-5 and SCH-23390. We report here that co-activation of D₁ and NMDA receptors is necessary for appetitive instrumental learning.

MATERIALS AND METHODS

Animals and surgery. A total of 48 male Sprague Dawley rats (Harlan Sprague Dawley, Madison, WI) weighing 275–300 gm were used for these experiments. Care of animals was in accordance with institutional guidelines. Rats were housed two per cage in a temperature-controlled (21°C) and light-controlled (12 hr light/dark cycle) animal colony. For cannula implantation, rats were anesthetized with a ketamine-xylazine mixture (100 and 10 mg/kg, respectively; Research Biochemicals, Natick, MA). Standard stereotaxic procedures were used to implant bilateral 23 gauge stainless steel guide cannulas, with coordinates based on flat-skull stereotaxic orientation. Cannulas were secured with dental acrylic and stainless steel screws, and a wire stylet occluded the guide to maintain patency. For all experiments, rats were implanted with cannulas placed 2.5 mm above the nucleus accumbens core at the following coordinates: anteroposterior, +1.4 mm; lateromedial, ±1.7 mm from midline; and dorsoventral, –5.5

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mm from skull. After several days of recovery from surgery, all rats were put on a restricted diet that maintained body weight at 85% of free-feeding weight. Water was available *ad libitum* at all times in the home cage.

Drugs and microinfusions. The selective, competitive NMDA receptor antagonist AP-5 and the D₁ receptor antagonist SCH-23390 HCl were obtained from Research Biochemicals. All drugs were dissolved in isotonic sterile saline and kept at 4°C in 200 μ l aliquots. Intracerebral microinfusions were bilateral in a volume of 0.5 μ l/side. AP-5 was administered in a dose per side of 0.5 nmol (0.1 μ g), and SCH-23390 was administered in two doses: 3 nmol (1 μ g) and 0.3 nmol (0.1 μ g). Infusions of drug or vehicle were given by lowering 30 gauge injector cannulas to the site of infusion (−8.0 mm from skull). A Harvard Apparatus microdrive pump was used to administer drug infusions with an infusion time of 1 min 33 sec, followed by 1 min of diffusion time. The injectors were then removed, the stylets were replaced, and the rats were placed into the test apparatus immediately. For all experiments, rats were given two preliminary sham injections, in which a dummy injector was lowered through the guide to adapt them to the procedure.

Behavioral training. All rats (except those in the feeding and locomotion study described below) were trained in operant chambers (Coulbourn Instruments, Allentown, PA) equipped with two levers, a house light, and a red signal light. All stimulus events and data acquisition were controlled with a computer (Paul Fray, Cambridge, UK). Before training, rats were adapted to the food pellets (45 mg sucrose pellets). Additionally, the rats had preexposure for two 10 min sessions to the operant test cages with several pellets available *ad libitum* in the food tray (with no levers present). On the first test day and all days thereafter, rats were placed in the operant chamber for a 15 min session. Responding on one lever resulted in delivery of a food pellet on a variable ratio 2 schedule of reinforcement, rewarding an average of every two responses. The other lever was not distinguishable from the first lever but did not deliver a food pellet or alter house lighting. The correct lever was randomized among animals but was always the same for an individual animal. When a correct response was made, a food pellet was delivered into a food tray located in between the two levers. A photocell located in the food tray recorded nose pokes. Pellet delivery was accompanied by house light offset and illumination of a red stimulus light on the response panel (3 sec), as well as a light in the food tray. Dependent variables recorded included correct responses, incorrect responses, and nose pokes. Animals were tested between 9 A.M. and 2 P.M.

Experimental procedure. Rats were given the appropriate microinfusion immediately before the session for the first 4 test days. They were then tested without any infusion for days 5–9. On day 10, all animals received their initial treatment to test for performance effects once learning had occurred. Five groups of rats were given one of five different treatments: a high dose of SCH-23390 (3 nmol), $n = 7$; a low dose of SCH-23390 (0.3 nmol), $n = 8$; a low dose of AP-5 (0.5 nmol), $n = 8$; a combined infusion of the low doses of AP-5 and SCH-23390, $n = 7$, and saline vehicle, $n = 10$. Previous work in our laboratory has demonstrated that microinfusion of a 5 nmol dose of AP-5 completely blocks learning (Kelley et al., 1997), and the high dose of SCH-23390 effectively blocks DA receptors (Delfs and Kelley, 1990).

Feeding and locomotion in food-deprived rats. To examine the possibility of motor and motivational effects of these treatments on behavior, feeding and locomotion were observed in rats with the combined treatment of AP-5 and SCH-23390 and vehicle ($n = 8$) or with the 3 nmol dose of SCH-23390 and vehicle ($n = 8$) infused into the nucleus accumbens core. Rats were food-deprived in a manner similar to that described above. After infusion, the animals were placed immediately in a cage similar to their home cage and observed for 15 min using an event recorder. Behaviors recorded were locomotion (crossing center of cage) counts, rearing (counts and duration), feeding (bouts, total duration, and mean duration of a bout), food intake (grams), and latency to eat. A Latin square design was used to randomize drug and vehicle infusions. Rats were given two acclimation sessions of 15 min, during which they were given mock infusions. Test sessions were several days apart.

Histological analysis. At the completion of testing, all rats were deeply anesthetized with sodium pentobarbital and perfused transcardially with 0.9% saline followed by 10% formalin. The brains were stored in a 10% sucrose-formalin mixture for several days before sectioning. Brains were cut into 60 μ m sections and stained for Nissl substance with cresyl violet. The sections were examined with light microscopy, and estimated locations of infusion sites were recorded on atlas sections. All infusion sites fell within the boundaries of the accumbens core (histology results are shown in Fig. 4).

Statistical analysis. Learning data were analyzed using one-, two-, or three-factor ANOVA, with treatment as the between-subjects factor and days and lever as the within-subjects (repeated measures) factors in the multifactorial analyses. For each experiment, three separate analyses were performed: days 1–4 (acquisition during treatment), days 5–9 (acquisition/performance with no treatment), and days 9–10 (comparison of performance on treatment day 10 with performance on previous day of no treatment). The locomotor and feeding data were analyzed by a one-factor ANOVA.

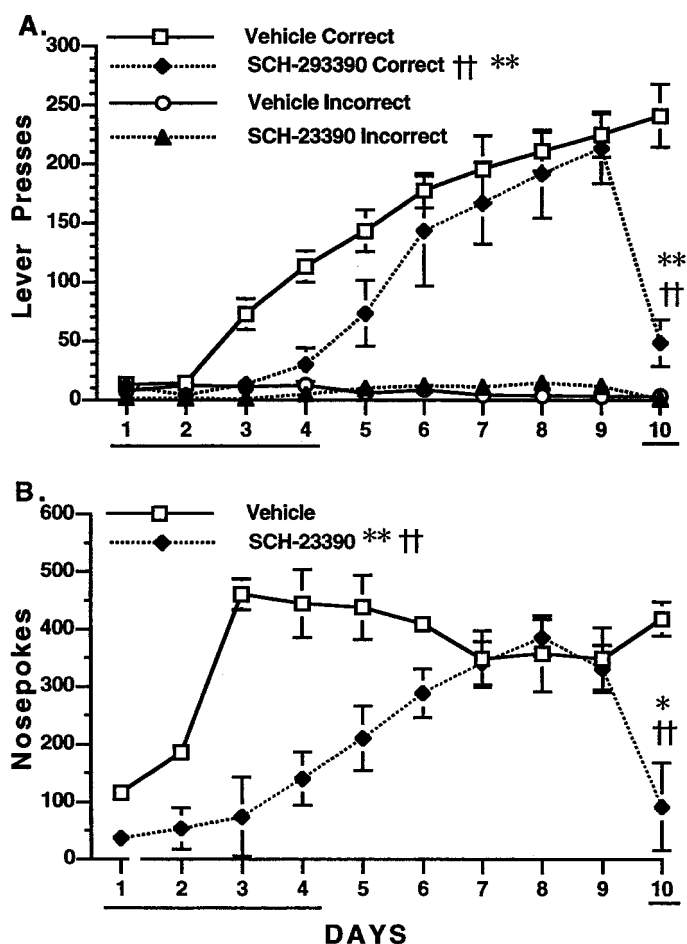


Figure 1. Influence of the high dose (3 nmol) of D₁ receptor antagonist infusion into the nucleus accumbens core on acquisition of lever pressing for sucrose pellets: correct and incorrect lever responses. Animals received intra-accumbens infusion of SCH-23390 (3 nmol) or vehicle (saline) on the first 4 test days; on the remaining training days, no infusion was given except on day 10, when animals received their initial treatments (*underscored* days indicate infusion days). *A*, Lever presses. $**p < 0.01$, treatment effect; $^{\dagger}p < 0.01$, interactions. *B*, Nose pokes into the food tray during learning. $**p < 0.01$, treatment effect; $^{\dagger}p < 0.01$, interactions. See Materials and Methods for statistical details.

RESULTS

Infusion of a high dose of SCH-23390 impairs instrumental learning and performance

As shown in Figure 1*A*, the 3 nmol dose of SCH-23390 infused into the nucleus accumbens impaired acquisition of lever pressing. Analysis of data from days 1–4 revealed a significant treatment effect [$F_{(1,15)} = 36.12$; $p < 0.0001$] as well as day \times treatment [$F_{(3,45)} = 11.25$; $p < 0.0001$], lever \times treatment [$F_{(1,15)} = 9.69$; $p < 0.007$], and day \times lever \times treatment [$F_{(1,3)} = 7.99$; $p < 0.0002$] interactions. There were no significant effects on days 5–9. Readministration of this dose strongly impaired performance on day 10, because comparison of days 9 and 10 revealed a treatment effect [$F_{(1,15)} = 12.09$; $p < 0.003$] as well as day \times treatment [$F_{(1,15)} = 25.16$; $p < 0.0002$], lever \times treatment [$F_{(1,15)} = 13.73$; $p < 0.002$], and day \times lever \times treatment [$F_{(1,15)} = 22.17$; $p < 0.0003$] interactions.

Rats treated with the high dose of SCH-23390 demonstrated a nose poking profile quite different from that of vehicle-treated rats (Fig. 1*B*). In vehicle-treated rats, this unconditioned behavior parallels the lever-pressing curve, increasing markedly as animals begin to learn and gradually leveling off. Analysis of days 1–4 showed a treatment effect [$F_{(1,15)} = 23.16$; $p < 0.0002$] and day \times treatment interaction [$F_{(1,3)} = 9.46$; $p < 0.0001$]. The day \times

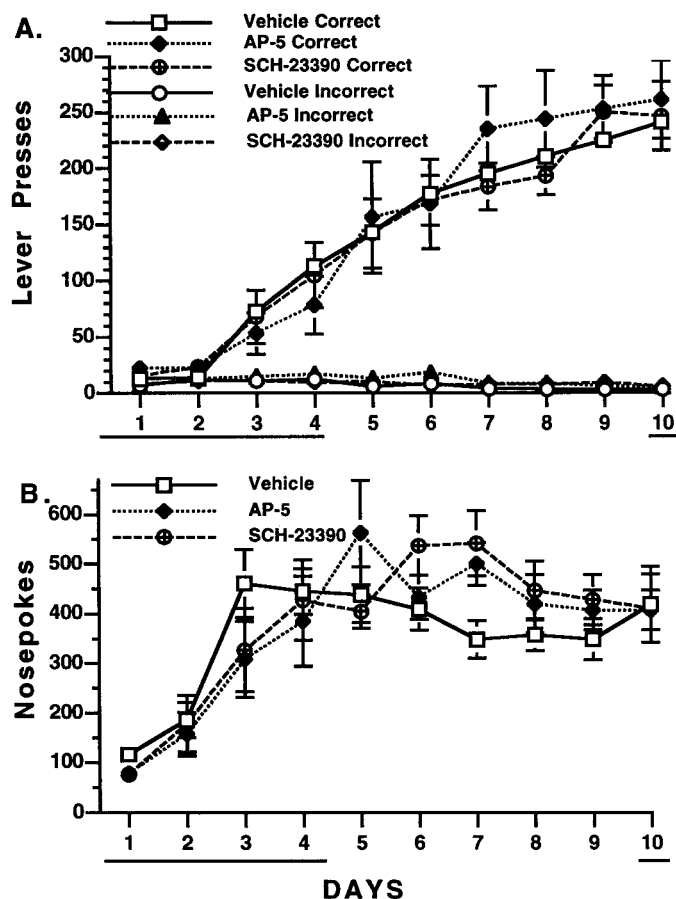


Figure 2. Influence of D₁ receptor antagonist SCH-23390 (0.3 nmol) or NMDA receptor antagonist AP-5 (0.5 nmol) infusion into the nucleus accumbens core on acquisition of lever pressing for sucrose pellets. See legend of Figure 1 for further details. *A*, Lever presses. *B*, Nose pokes. See Materials and Methods for statistical details.

treatment interaction [$F_{(1,3)} = 3.82$; $p < 0.008$] persisted for days 5–9. A dramatic decrease in nose poking was observed in SCH-23390-treated rats between days 9 and 10, revealing a treatment effect [$F_{(1,15)} = 6.14$; $p < 0.03$] and a day \times treatment interaction [$F_{(1,1)} = 12.16$; $p < 0.003$].

Low doses of SCH-23390 and AP-5 administered separately have no effect on learning

It can be observed from Figure 2*A* that intra-accumbens infusion of either the 0.3 nmol dose of the D₁ antagonist or the 0.5 nmol dose of the NMDA antagonist, administered separately, had no effect on response learning. The learning curve of drug-treated animals was similar to that of controls. There was also no effect of reinfusion on day 10. A similar profile was noted for nose pokes (Fig. 2*B*).

Co-infusion of low doses of SCH-23390 and AP-5 inhibits learning

In contrast to the lack of effect of low doses of SCH-23390 and AP-5 when infused separately into the nucleus accumbens core, co-infusion of these drugs clearly inhibited learning (Fig. 3*A*). Analysis of days 1–4 revealed a significant treatment effect [$F_{(1,15)} = 12.5$; $p < 0.003$] as well as day \times treatment [$F_{(3,45)} = 11.35$; $p < 0.0001$], lever \times treatment [$F_{(1,1)} = 9.438$; $p < 0.008$], and day \times lever \times treatment [$F_{(3,45)} = 9.21$; $p < 0.0001$] interactions. Drug-treated animals sampled the levers but did not begin to discriminate between them until day 4. The lever \times treatment effect [$F_{(1,15)} = 5.15$; $p < 0.04$] persisted on days 5–9, indicating a residual effect on learning. Comparison of days 9 and 10 revealed significant day \times treatment [$F_{(1,15)} = 6.90$; $p < 0.02$], lever \times treatment [$F_{(1,15)}$

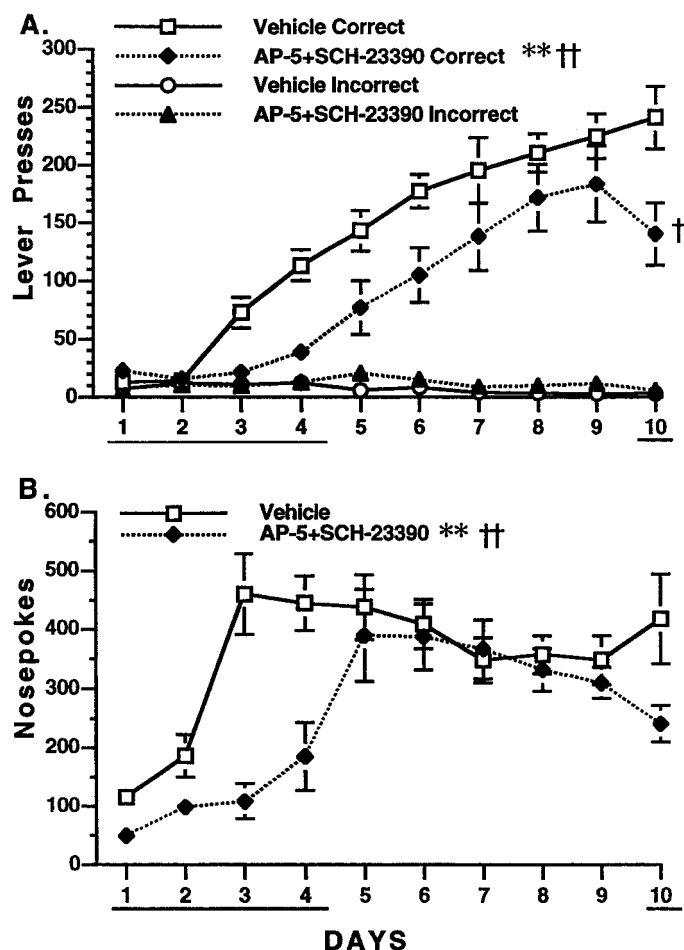


Figure 3. Influence of the co-infusion of D₁ receptor antagonist SCH-23390 (0.3 nmol) and NMDA receptor antagonist AP-5 (0.5 nmol) into the nucleus accumbens core on acquisition of lever pressing for sucrose pellets. See legend of Figure 1 for further details. *A*, Lever presses. *B*, Nose pokes. $^{**}p < 0.01$, treatment effect; $^{††}p < 0.01$, interactions. See Materials and Methods for statistical details.

$= 4.90$; $p < 0.04$], and day \times lever \times treatment [$F_{(1,15)} = 5.38$; $p < 0.03$] interactions. It can be observed in Figure 3*A* that performance declined somewhat after readministration of the combined drug treatment, whereas the performance of vehicle-treated rats continued to increase.

Analysis of days 1–4 revealed a significant treatment effect [$F_{(1,15)} = 15.74$; $p < 0.001$] and a day \times treatment interaction [$F_{(3,45)} = 9.37$; $p < 0.0001$] for nose poking behavior (Fig. 3*B*). Although a significant reduction in lever pressing occurred on day 10, nose poking in combined dose animals did not change significantly from day 9 to 10.

Combined infusion of AP-5 and SCH-23390 does not affect food intake or motor activity

Combined infusion of AP-5 (0.5 nmol) and SCH-23390 (0.3 nmol) into the nucleus accumbens core had no effect on locomotor or feeding behavior in hungry rats (Table 1). However, animals infused with the higher dose of SCH-23390 (3 nmol) had significantly fewer counts of locomotion [$F_{(1,7)} = 18.03$; $p < 0.004$] and engaged in longer bouts of feeding [$F_{(1,7)} = 7.56$; $p < 0.03$] yet did not differ in total food intake. Thus, the high dose of SCH-23390 infused into the accumbens core did not alter motivation to feed but did cause motor inhibition and prolonged bout length, eliciting a classic neuroleptic profile.

Figure 4 shows examples of representative histology from both an experimental (AP5- and SCH-23390-infused) rat and a control

Table 1. Feeding and motor behavior after intra-accumbens treatments in food-deprived rats (15 min test)

Behavioral indices	Treatment			
	Experiment 1		Experiment 2	
	VEH	AP-5/SCH	VEH	SCH
Locomotion	15 ± 2	15 ± 2	11 ± 2	4 ± 2*
Rears	22 ± 2	30 ± 4	14 ± 3	8 ± 3
Feeding duration (sec)	530 ± 32	485 ± 26	618 ± 42	660 ± 39
Average bout duration (sec)	25 ± 2	28 ± 3	41 ± 5	89 ± 18**
Total intake (gm)	3.6 ± 0.3	3.2 ± 0.2	4.3 ± 0.4	4.3 ± 0.3

Data represent means ± SEM. Locomotion is frequency of cage crossing. AP-5/SCH is the low-dose combination of the two drugs (AP-5, 0.5 nmol; SCH-23390, 0.3 nmol); SCH is the high dose of SCH-23390 (3 nmol). Average bout duration is the total duration per number of bouts.

* $P < 0.004$.

** $P < 0.05$.

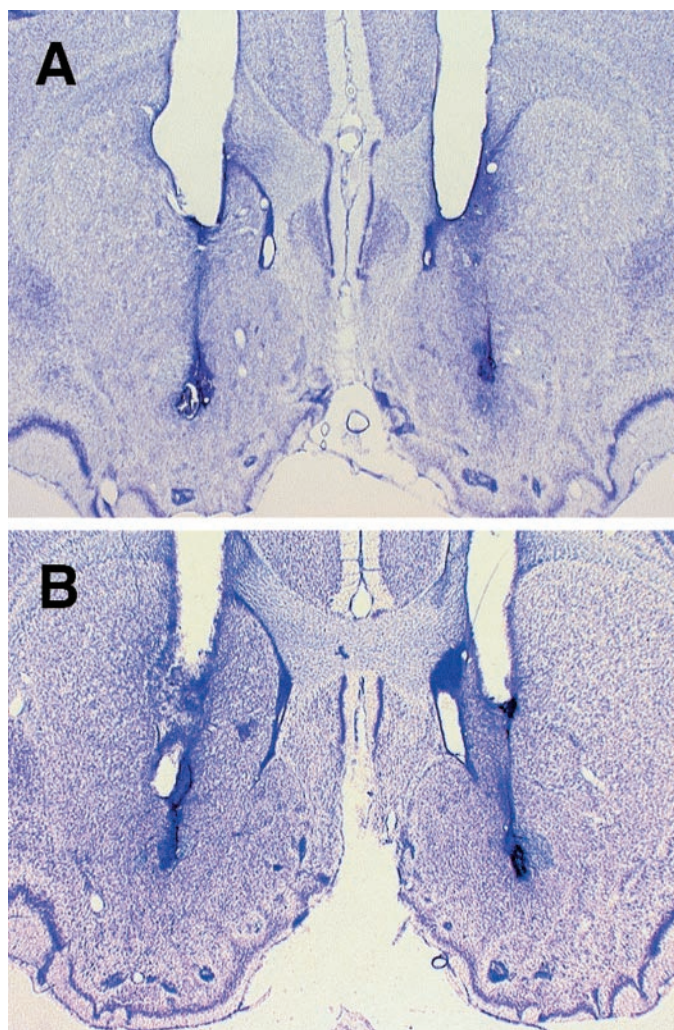


Figure 4. Representative histology from a rat infused with the co-treatment (SCH-23390, 0.3 nmol; AP-5, 0.5 nmol) as shown in *A* and from a rat infused with saline, as shown in *B*.

(saline-infused) rat. Cannula tracks from all rats were well localized in the nucleus accumbens core. Damage from microinjections was generally minimal, and there were no observable differences between drug- and saline-infused brains.

DISCUSSION

The results reported here suggest that coincident activation of dopamine D₁ receptors and glutamatergic NMDA receptors within

the nucleus accumbens core may be an important mechanism for appetitive response learning. Previous work has shown a nearly complete inhibition of such learning after infusion of an effective dose of the selective NMDA antagonist AP-5 into the accumbens core (Kelley et al., 1997; Baldwin et al., 2000). Given the convincing evidence for DA–NMDA interactions in cellular and molecular models of plasticity, it seemed logical to propose that such an interaction may participate in accumbens-mediated response learning. Although dopamine has been implicated in many theories of learning (Beninger, 1983; Ettenberg, 1989; Schultz et al., 1997; Berridge and Robinson, 1998), to our knowledge there has been no direct test of intra-accumbens selective DA antagonists on acquisition of instrumental learning. Data resulting from such an approach are quite difficult to interpret, because instrumental behavior is often very sensitive to the motor-inhibitory effects of DA antagonists (Fibiger et al., 1976; Salamone, 1987). Indeed, in the paradigm described here, learning appeared to be severely impaired with infusion of the higher dose of SCH-23390. However, once the task was learned, performance was also drastically reduced by the treatment, rendering interpretation of the initial “learning” effect more complex.

To circumvent this problem, we infused a dose of the D₁ antagonist one order of magnitude lower than the performance-impairing dose. A 10-fold lower dose of AP-5 than that necessary to inhibit learning was also tested. Neither of these treatments by itself was found to affect acquisition of the lever-pressing task. However, co-infusion of both the NMDA and D₁ antagonists together strongly impaired learning, suggesting that a critical level of co-activation of D₁ and NMDA receptors is necessary for learning. Because this treatment had no effect in control tests of motor behavior, it is unlikely that motor impairment could account for the learning deficit. Moreover, although the combined treatment lowered performance somewhat once the task was learned, this was a very small effect compared with that of the high dose of SCH-23390. This profile suggests a preferential role for DA–NMDA interaction in the early stages of motor learning, rather than in performance of learned motor behavior. It is important to note further that neither the combined dosage nor even the high dose of SCH-23390 had any effect on food intake, demonstrating that motivation for primary reward is not affected by blockade of DA D₁ receptors within the accumbens. This result supports previous work showing that treatment with low doses of SCH-23390 reduces lever pressing for food but actually increases food intake (Cousins et al., 1994).

It is also very interesting that nose poking behavior was impaired by the combined treatment of AP-5 and SCH-23390, an effect that appears to recover more quickly than the impairment of instrumental learning, from close inspection of Figure 3. Thus, although no overt inhibition of locomotor or feeding behavior was found, the combined treatment nevertheless appears to inhibit this form of

behavioral activation. Combined activation of NMDA receptors and DA D₁ receptors may also be necessary for enhancing arousal and promotion of behaviors that would serve to bring the animal in contact with potentially important environmental stimuli.

The present results provide additional evidence for emerging theories of DA D₁-NMDA receptor interactions in the control of activity of striatal medium spiny neurons (Cepeda and Levine, 1998). In anatomical terms, these two classes of receptors are localized on the same dendritic spines, providing a locus of close interaction. In rat striatal slices, a number of studies show that dopamine can enhance glutamate- and particularly NMDA receptor-mediated excitation (Cepeda et al., 1993, 1998; Galarraga et al., 1997; Harvey and Lacey, 1997; Hernandez-Lopez et al., 1997; Hu and White, 1997). For example, neuronal excitation evoked by NMDA was markedly potentiated by iontophoretic application of dopamine; the potentiation was mimicked by a D₁ agonist and blocked by co-application of SCH-23390 (Cepeda et al., 1993). Although DA has often been found to inhibit postsynaptic currents (Uchimura et al., 1986; Calabresi et al., 1987), *in vivo* models often report the opposite effect under particular conditions (Pierce and Rebec, 1995; Kiyatkin and Rebec, 1996). For example, Hernandez-Lopez et al. (1997) found that D₁ agonists or cAMP analogs enhanced evoked activation in medium spiny neurons when membranes were relatively depolarized, an effect that was dependent on L-type Ca²⁺ channels.

Molecular approaches also support a general convergence or interdependence between NMDA receptor- and D₁-mediated intracellular signal transduction. Studies using primary striatal cell cultures showed that dopamine D₁-induced immediate early gene (IEG) expression is dependent on NMDA receptor activation (Konradi et al., 1996). These studies also showed that blockade with NMDA antagonists reduced the ability of dopamine to induce phosphorylation of the cAMP response element-binding protein (CREB), a transcription factor activated in many forms of learning. Similar results were reported by Das et al. (1997), who found that NMDA-induced CREB phosphorylation was dependent on calcium/calmodulin-dependent protein kinase and that D₁-induced IEG expression and CREB phosphorylation was dependent on protein kinase A (PKA) activity. Another potential site of interaction is phosphorylation of NMDA receptors, which can occur via both PKA and calcium/calmodulin-dependent protein kinase (Leonard and Hell, 1997; Leonard et al., 1999). Thus, one can imagine a scenario in which temporal coordination of specific glutamate inputs with enhanced DA release would result in molecular integration of postsynaptic signals. Such resultant integration within the dendrites of medium spiny neurons could be a basis for the synaptic modification necessary for motor learning (Kotter, 1994; Kelley, 1999). In support of this hypothesis, we have recently found that PKA inhibitors also selectively impair response learning when infused into the accumbens core (Baldwin et al., 1999).

This hypothesis is further supported by evidence of neuronal plasticity within striatum in physiological models. Both long-term potentiation and long-term depression, phenomena hypothesized to underlie associative processes in learning, have been demonstrated in striatum and nucleus accumbens (Boeijinga et al., 1993; Lovinger et al., 1993; Pennartz et al., 1993; Kombian and Malenka, 1994; Calabresi et al., 1996; Charpier and Deniau, 1997). Most relevant to the present study is the demonstration of long-term enhancement of synaptic strength when corticostriatal excitation and dopaminergic activation are temporally coordinated (Wickens et al., 1996). For appetitive instrumental learning to occur, an animal must make an association between a motor response and the positive outcome of that response. It is possible that glutamate-coded afferent information arising from key corticolimbic structures, such as amygdala and prefrontal and cingulate cortex, may provide the sensorimotor and motivational information to medium spiny dendrites, whereas the primary reward of food (and/or motivational state of hunger) enhances DA release. The probability of temporal and spatial convergence of glutamate- and dopamine-coded signals may increase as the animal begins to gain experience

in the chamber. For example, Pavlovian cues (association of the environment with food) would activate the amygdalostratial pathway, preliminary and initially random contact with the food would activate dopamine, and experience with a positive outcome would promote bias toward correct response selection, which may be the domain of the prefrontostriatal pathway. Thus, a critical level of convergence may be reached to trigger intracellular gene expression that enables motor learning. In support of this hypothesis, parallel work has shown that NMDA receptor-dependent plasticity in amygdala and prefrontal cortex is also necessary for instrumental learning (Baldwin et al., 2000).

In summary, these findings suggest that coincident activation of dopamine D₁ and NMDA receptors in the nucleus accumbens core contributes to a process whereby animals acquire a new motor response that results in a positive outcome. Further work is required to know more precisely what intracellular signals and transcriptional alterations mediate the synaptic modifications necessary for such learning.

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