Published in final edited form as:

Behav Neurosci. 2006 June ; 120(3): 542–553.

Dissociating Ventral and Dorsal Subicular Dopamine D₁ Receptor Involvement in Instrumental Learning, Spontaneous Motor Behavior, and Motivation

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Abstract

A series of experiments investigating the role of dopamine D₁ receptors in the ventral subiculum (vSUB) and dorsal subiculum (dSUB), 2 subregions of the hippocampal formation, found that D₁ receptor antagonism (3.0 nmol/0.5 µl SCH-23390 bilaterally) in the vSUB impaired instrumental learning and performance, reduced break point in progressive ratio (PR) tests, and produced an intrasession decline in responding during test sessions, but had no effect on spontaneous motor or food-directed behavior. In contrast, D₁ receptor blockade in the dSUB had no effect on instrumental learning, performance, PR break point, or food-directed behavior, but reduced spontaneous motor behavior. These results suggest a dissociation between the vSUB and dSUB with respect to the role of dopamine in various aspects of motivated and motor behavior. Further, D₁ activation in the vSUB may be a critical component of motivational arousal associated with learned contextual cues.

Keywords

subiculum; instrumental learning; dopamine D₁ receptors; motivation; rats

An emerging neural model of learning and plasticity in relation to motivation involves the coactivation of *N*-methyl-D-aspartate (NMDA) and dopamine D₁ receptors in a highly distributed cortico-striatal-limbic network. In view of the convergence of D₁ and NMDA receptors on the dendrites of medium spiny or pyramidal neurons throughout this network and their direct physical interactions (Lee et al., 2002; Pei, Lee, Moszczynska, Vukusic, & Liu, 2004), co-occurrence of NMDA and D₁ receptor activation is now thought to initiate and modulate the induction of intracellular transcriptional and translational cascades, leading to changes in gene expression and synaptic plasticity, thereby reconfiguring neural networks and, ultimately, behavior (Abel & Lattal, 2001; Hyman & Malenka, 2001; Koob & Le Moal, 2001; O'Donnell, 2003; Wickens, Reynolds, & Hyland, 2003). For example, initial instrumental learning requires NMDA activation in the nucleus accumbens core (NAcc), basolateral amygdala (BLA), central nucleus of the amygdala (CeA), medial prefrontal cortex (mPFC), and posterior lateral striatum, but not the nucleus accumbens shell, anterior dorsal striatum, dorsal subiculum (dSUB), or ventral subiculum (vSUB). D₁ activation in the NAcc, BLA, CeA, and mPFC appears to be necessary for initial instrumental learning as well.

The mesocorticolimbic dopamine system, originating in the ventral tegmental area (VTA), innervates the amygdala, nucleus accumbens, striatum, and prefrontal cortex, as well as the hippocampus, in particular, the subiculum and CA1 fields (Gasbarri, Packard, Campana, &

Pacitti, 1994; Gasbarri et al., 1996; Gasbarri, Verney, Innocenzi, Campana, & Pacitti, 1994; Verney et al., 1985). Moreover, autoradiographic studies have demonstrated the existence of D₁ receptors in many of those areas, including the subiculum and hippocampus (Kohler, Ericson, & Radesater, 1991). This complex network mediates many reinforcer-related processes, including different forms of learning, goal-directed behavior, and addiction (Beninger & Miller, 1998; Cardinal, Parkinson, Hall, & Everitt, 2002; Kelley & Berridge, 2002). As one node in this complex network, the NAcc is uniquely positioned, as a component of the basal ganglia, to integrate information from cortical and limbic structures and modulate motor output associated with goal-directed behavior (Groenewegen et al., 1991). It is interesting to note that glutamatergic afferents from the hippocampus via the vSUB (Groenewegen, Vermeulen-Van der Zee, te Kortschot, & Witter, 1987; Yang & Mogenson, 1987) modulate dopamine efflux in the NAcc by way of a D₁/NMDA receptor mechanism in the NAcc (Floresco, Blaha, Yang, & Phillips, 2001) and a D₁ receptor mechanism in the vSUB (Zornoza et al., 2005). Thus, these data suggest that as a key structure within this network implicated in learning and motivated behavior, the hippocampus–subiculum and, in particular, D₁ receptors in the subiculum may play an important role.

Indeed, the hippocampus has been studied a great deal because of its crucial role in learning and memory (Eichenbaum, Stewart, & Morris, 1990; Mishkin, Vargha-Khadem, & Gadian, 1998), especially in relation to the phenomenon of long-term potentiation (LTP), which forms the basis of the synaptic plasticity model of the neural mechanisms that underlie learning (Morris et al., 2003). In accordance with the dopamine–glutamate theory of neural plasticity, experiments with hippocampal slices have demonstrated that heterosynaptic coactivation of dopamine and NMDA receptors is required for early phase LTP (E-LTP) and is a sufficient condition for late-phase LTP (L-LTP; O'Carroll & Morris, 2004). Moreover, dopamine produces enhancements of both E-LTP and L-LTP, effects that are blocked by the administration of the D₁ receptor antagonist SCH-23390 (Huang & Kandel, 1995; Otmakhova & Lisman, 1996), suggesting D₁ receptor-dependent mechanisms. Therefore, many studies have shown that dopamine in hippocampal models is a key component of the initiation of cellular plasticity.

Thus, given the strong implication of hippocampal involvement in learning and memory and the putative role of D₁ receptor activation in neural plasticity, it is likely that D₁ receptor activation in the subiculum contributes to the neural changes that accompany learning. Indeed, recent data from Sun and Rebec (2003) have suggested an important role for the ventral hippocampus in positively reinforced (with cocaine) lever pressing. The present experiments explored the role of D₁ receptor blockade within two sites in the hippocampal formation, the dSUB and vSUB, in instrumental learning and spontaneous motor and food-directed behavior. Because instrumental learning requires a coordinated pattern of activity integrating motivational, emotional, and motoric information and circuitry (Salamone & Correa, 2002), D₁ receptor antagonism was examined in three separate behavioral tests. The first experiment investigated the effects of D₁ receptor antagonism on initial instrumental learning. In a second experiment, the effects of D₁ antagonism on spontaneous locomotor and feeding behavior were tested to assess the possible motoric and motivational deficits produced by drug infusions. To more directly test the effects of D₁ receptor antagonism in the hippocampus on motivation, a third experiment used a progressive ratio (PR) schedule of reinforcement. PR schedules arrange reinforcers for progressively more responses and are considered the gold-standard tests of the potential motivational effects of behavioral and neural manipulations.

Method

Subjects

Male Sprague–Dawley rats (Harlan Teklad, Madison, WI) were housed in pairs in polyethylene cages in a colony room with a 12-hr light–dark cycle. They were approximately 90 days old at the start of experimentation and weighed approximately 300 g each. They were weighed and handled daily and provided with food and water ad libitum prior to surgery. Following recovery from surgery, each rat was reduced to 85% of its ad libitum weight. During food restriction and prior to the start of testing, rats were given approximately 3 g of sucrose pellets in their home cages per day; the 85% weight was maintained for the remainder of the experiment. Care of the rats was in accordance with University of Wisconsin—Madison Animal Care Committee guidelines.

Apparatus

Instrumental chambers—Instrumental learning sessions were conducted in eight identical, commercially constructed instrumental chambers (Coulbourn Instruments, Allentown, PA) enclosed in sound-attenuating, ventilated chests. Fans provided some masking noise continuously throughout the session. Two retractable levers, approximately 6 cm apart, could be projected into the chamber on the right-side wall. Spaced equally between the two levers was a feeder trough into which 45 mg of Bio-Serv (Frenchtown, NJ) sucrose pellets could be delivered. The feeder trough was equipped with a photo sensor such that the number and timing of nose pokes into the tray could be recorded. Above the feeder trough were a row of three stimulus lights (red, yellow, and green) and a 28-V houselight. Experimental events were arranged and recorded via a personal computer in the same room as the chambers, running Graphic State Notation (Version 1.013-00; Coulbourn Instruments, Allentown, PA), interfaced with L91-04S Habitest Universal Lincs (Coulbourn Instruments, Allentown, PA).

Locomotion and feeding cages—Clear polycarbonate cages (24 cm × 45 cm × 21 cm) with a wire mesh floor and wire lid with a water bottle served as test cages for the unconditional effects of drug infusions. Two small ceramic dishes filled with sucrose pellets were affixed to the mesh floor with pliable putty. Data were obtained via an event recorder connected to a PC. Measures included latency to eat, amount of sucrose eaten, amount of time spent feeding, number of feeding bouts, number of center crossings, and number of rears.

Surgery

Rats were anesthetized with a ketamine/xylazine mixture (100/10 mg/kg) and placed in a standard stereotaxic surgery device (incisor bar at −5.0 mm; flat skull). Indwelling stainless cannulas (23 gauge) were implanted bilaterally and secured to the skull with stainless steel screws and dental cement. Cannulas were aimed 2.5 mm above the vSUB or 1.5 mm above the dSUB. Stainless steel stylets prevented occlusion of the cannulas. Coordinates (flat skull, in mm) were vSUB: AP −6.0 from bregma, LM ±4.3 from midline, and DV −6.2 from the skull surface; and dSUB: AP −6.0, LM ±2.7, and DV −2.0.

Drugs and Microinfusions

The selective D₁ antagonist R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH-23390) was dissolved in isotonic sterile saline. A dose of 1 µg (3 nmol) SCH-23390 or vehicle (saline) were administered via bilateral intracerebral microinfusions in a volume of 0.5 µl each side. Previous studies indicated that this dose is effective in similar behavioral tests, while not producing major motor impairments (Andrzejewski, Spencer, & Kelley, 2005). After removing the stylets, injectors (30 gauge) were inserted 2.5 mm or 1.5 mm below the tips of the guide cannulas to the site of the infusion (DV

−8.7 mm for vSUB and DV −3.5 mm for dSUB). A Harvard Apparatus (South Natick, MA) pump, set at a rate of 0.32 μ l/min, infused drug or vehicle for 1 min 33 s, followed by 1 min of diffusion time. The injectors were removed and the stylets replaced. Rats were immediately placed in the instrumental chambers or locomotor and feeding cages after microinfusions.

Experimental Design and Behavioral Testing

The effects of SCH-23390 (vehicle vs. 3.0 nmol) infused into the vSUB or dSUB were investigated in three experiments: (a) initial instrumental learning and performance, (b) a PR schedule of reinforcement, and (c) spontaneous locomotor and feeding behavior. The initial instrumental learning experiment used a standard lever-pressing procedure in a mixed between-groups/within-subjects design. PR schedules, which require progressively more responses per reinforcer, are considered general tests of motivation because, for example, food deprivation has been shown to be directly related to the ratio in which rats stop responding, also known as the *break point*. That is, with increasing amounts of food deprivation (e.g., 95%, 85%, 75% of ad lib weight), break points increase, meaning that the more hungry the rats are, the more responses for each food pellet they emit (Hodos, 1961). The PR schedule used a between-groups design. Spontaneous locomotor and feeding experiments used a within-subjects design such that each rat received both vehicle and drug injections in a random order.

Initial instrumental learning—All sessions lasted 15 min. Rats were habituated to the chamber for three sessions on consecutive days before testing. Prior to the first two habituation sessions, rats were given a mock infusion, in which an injector was lowered to the end of the cannulas but not into brain tissue, the microdrive pump was turned on, but no drug was infused. Rats were then immediately placed into the chambers with both levers retracted. With the houselight on, sucrose pellets were delivered into the food trough on a random-time 15-s (delivered with an average interval of 15 s) schedule during the first session and on a random-time 30-s (RT-30s) schedule on subsequent sessions. The number and timing of nose pokes into the tray were recorded. Prior to the third session, rats were given a vehicle infusion as specified above. Again, they were placed in the chambers immediately after the infusion, with both levers retracted, the houselight on, and pellets delivered into the trough on an RT-30s schedule. Rats were matched on the basis of the frequency of nose poking and randomly assigned to one of the two groups (vehicle or 3.0 nmol SCH-23390).

Prior to the next five sessions (Sessions 1–5), rats were infused with drug or vehicle, depending on group assignment, and placed immediately into the instrumental chamber. The right lever was projected into the chamber, and lever presses were immediately reinforced with one pellet—a fixed ratio-1 (FR-1) schedule. After 50 reinforcers were earned in any one session, the contingencies changed to a random ratio-2 (RR-2) schedule; each lever press was reinforced with a probability of .5. The RT-30s schedule was maintained for the first two infusion sessions (Sessions 1 and 2) to ensure some degree of arousal and exploration: a conjoint FR-1(RR-2)/RT-30s schedule. The behavioral contingencies remained the same regardless of infusion type throughout the entirety of the experiment.

Prior to Sessions 6–10, no infusions were given, but prior to Session 11, an infusion was given to test for performance effects. A 12th session with no infusion was conducted to look at possible carryover effects of the drug infusion.

Following Session 12, each group of vSUB-cannulated rats was divided further into two groups and assigned to receive SCH-23390 or vehicle prior to the 13th session. Therefore, 3 previously drug-treated rats received drug, 3 previously drug-treated rats received vehicle, 3 previously vehicle-treated rats received drug, and 3 previously vehicle-treated rats received vehicle prior to Session 13. This yielded a 2×2 factorial design, with previous drug experience as one factor and current drug state as the second factor, with 3 subjects in each combination. Session 13

was conducted to test the possible discriminative and/or unconditional effects of the drug infusion. For example, previously drug-naïve rats that received a drug infusion prior to Session 13, tested the unconditional effects of the drug, whereas the previously drug-treated rats that received a vehicle infusion prior to Session 13 tested the potential discriminative function of the infusion procedure on performance. This 13th session was not conducted in Experiment 2 because there was no effect of drug infusions on performance during Session 11 (see Results for additional rationale).

Progressive ratio schedule of reinforcement—For this experiment, rats received 4, 15-min sessions of lever-press retraining on a random ratio-4 schedule of reinforcement (each response had a .25 probability of being reinforced). These four sessions were run to ensure a fairly high rate of lever pressing and to prevent floor effects during the PR test. In other words, if rats were lever pressing at a low rate, the PR schedule would probably induce ratio strain quickly and lead to low break points regardless of drug condition. The RR training therefore ensured a good range of break points suitable for between-groups comparisons. Prior to a fifth session, rats received an infusion of either SCH-23390 or vehicle randomly and were placed in the chambers. The reinforcement contingencies were changed to a PR 4 (starting at 1:1, 5, 9, 13, etc.). Each reinforcer that was earned incremented the work requirement (ratio) for the next reinforcer by four responses. The test session lasted 45 min. Dependent measures include the break point (the last ratio completed by the rat before failing to respond) and responses per minute. The rats used in the instrumental learning condition of experimentation were used as subjects in the PR condition for both placements.

Locomotion and feeding—Locomotion and feeding control experiments investigated the effects of drug infusions on spontaneous locomotion and feeding behavior. Surgery, handling, and deprivation conditions were identical to those of instrumental learning experiments. All rats were habituated to the apparatus prior to testing. Then, following a within-subjects design, each rat received SCH-23390 (3.0 nmol) or vehicle immediately prior to being placed in the locomotor and feeding cages. Experimentation was conducted on consecutive days, in a randomized order for each rat, to which the experimenter was masked. For the vSUB, the 12 rats from the instrumental learning experiment were used in the locomotor and feeding experiment, while 9 naïve rats were used in the dSUB. The total amount of sucrose eaten, eating duration, number of feeding bouts (meals), latency to begin eating, number of center crossings, and number of rears were recorded and serve as the dependent variables in this portion of experimentation.

Histological Analysis

After the completion of the experiment, all rats were deeply anesthetized with sodium pentobarbital and perfused transcardially with isotonic saline followed by 10% formalin. Brains were stored in 10% sucrose–10% formalin mixture before sectioning. Sixty- μ m sections were stained with cresyl violet and examined under light microscopy for location of infusion sites.

Statistical Analysis

For the initial instrumental learning experiment, lever presses and nose pokes were analyzed by multifactor analysis of variance, with drug treatment (vehicle vs. SCH-23390) as the between-groups factor, and sessions as the within-subjects factor. Lever presses and nose pokes were analyzed by dividing the experiment into four phases: Sessions 1–5 (infusion sessions), Sessions 6–10 (no-infusion sessions), performance test/recovery Sessions 11–12 (infusion–no infusion), and Session 13 (for vSUB). Typically, statistically significant effects of sessions are found in learning experiments like the present one. That is to say, lever presses generally increase as the number of sessions increase. Therefore, unless otherwise noted, the effects of

sessions are not reported and can be assumed to be statistically reliable. This reduces the number of statistics reported and highlights the most interesting features of the experiments. Data from the locomotion and feeding control experiment were analyzed with dependent-samples *t* tests. PR tests were analyzed using *t* tests. Post hoc between-treatment comparisons, when indicated, were conducted using Tukey's honestly significant difference.

Analysis of the Microstructure of Behavior

Statistical analyses were supplemented by detailed, microstructural behavioral analyses of instrumental learning experiments by exporting raw data files from the Colbourn system into Excel. Lever presses, nose pokes, earned sucrose pellets (eRs, or *earned reinforcers*), and sucrose pellets delivered by the random-time schedule (fRs, or *free reinforcers*) that occurred during each rat's session were time-stamped by Graphic State Notation. The order of events and their temporal relation were analyzed by counting all the dyads of events that occurred. For example, a nose poke could be followed by a lever press, an fR or another nose poke, yielding three types of dyads (nose poke–lever press, nose poke–fR, or nose poke–nose poke). A nose poke could not precede an eR; only lever presses could come before eRs. The dyads were used to compute conditional probabilities: For example, the probability of a lever press given that a nose poke had just occurred was the number of nose poke–lever press dyads divided by the total number of nose pokes, or nose poke–lever press + nose poke–fR + nose poke–nose poke. These conditional probabilities were averaged across rats per session and differentiated by group assignment. Additionally, within-session response patterns were analyzed, particularly in the within-subjects portions of the initial instrumental learning and PR experiments.

Results

Histology

Figure 1 shows the representative locations of the injector tips for subjects in the three experiments. For the initial operant learning experiment, there were 12 rats with appropriate cannulas placements in the vSUB (6 in each group). Eleven of these rats also served in the locomotor and feeding and the PR experiments (one rat died after the first injection of the locomotor and feeding experiment; its data are included in the instrumental learning experiment). In the dSUB, 15 rats were determined to have appropriate placements for the instrumental learning experiment. Eleven of these rats were subjects in the locomotor and feeding experiment. Lastly, 11 naïve rats were found to have appropriate placements in the dSUB in the PR experiment.

The injector locations schematized in Figure 1 show the range of placements in the subiculum. Although the injector tips were clearly located in the subiculum, diffusion to other nontarget structures may be of some concern. Unfortunately, no quantitative data on the degree of diffusion of the infusions were collected. However, the small injection volume, our extensive experience with microinfusions, and the rather large target area qualitatively support the contention that the infusions were in the subiculum.

D₁ receptor antagonism in the vSUB, but not in the dSUB, impairs instrumental learning and performance—The results of the initial instrumental learning experiment are presented in Figure 2. Figures 2A and 2C show the average number of lever presses per session per group (vehicle and SCH-23390) across sessions, and Figures 2B and 2D show the mean number of nose pokes into the food trough per session, for the vSUB and dSUB, respectively.

As can be seen in Figure 2A, SCH-23390 infusions into the vSUB impaired initial instrumental learning. Although the main effect of treatment was not statistically reliable, $F(1, 10) = 2.601$,

$p = .138$, the more relevant Treatment $\times$ Sessions interaction was statistically significant, $F(4, 40) = 4.301$, $p = .005$, suggesting a differential effect of treatment across sessions. Post hoc comparisons within each session revealed a significant difference between treatment groups during Sessions 4 and 5 (noted by the asterisks on Figure 2A).

During Sessions 6–10, there was no effect of treatment in the vSUB, $F(1, 10) = .040$, $p = .845$, but the interaction was again reliable, $F(4, 40) = 9.143$, $p < .001$, and $F(4, 40) = 2.622$, $p = .05$. Post hoc comparisons did not show any differences between treated groups within each of the five sessions, although there were differences within treatment groups across sessions.

Finally, analyses of lever pressing during Sessions 11–12 revealed a nonsignificant treatment effect, $F(1, 10) = 1.860$, $p = .20$, but a statistically significant interaction, $F(1, 10) = 31.154$, $p < .001$. Of greatest interest was the interaction, upon which post hoc comparisons were conducted. As can be seen in Figure 2A, a drug treatment effect was statistically significant ($p = .016$) during Session 11 but not within Session 12 ($p = .853$).

As can be seen in Figure 2B, there were no treatment effects on nose pokes during Sessions 1–5, $F(1, 10) = 0.071$, $p = .796$; Sessions 6–10, $F(1, 10) = 1.285$, $p = .283$; or Sessions 11–12, $F(1, 10) = 0.007$, $p = .936$. The interaction during Sessions 11–12, $F(1, 10) = 8.756$, $p = .014$, was statistically reliable; however, the only difference was within the drug-treated group between Session 11 and 12.

Although the effect on SCH-23390 infusions in the vSUB on lever presses and nose pokes during Session 11 was statistically reliable, there are at least two explanations of the effect. The first is that the drug unconditionally reduced performance regardless of previous learning history. The second is that the presence of the drug signaled the absence of pellets, due to the experience of Sessions 1–5, thereby producing a discriminative effect. To test these possibilities, the two vSUB treatment groups were divided in half and randomly assigned to receive either drug or vehicle prior to Session 13. This yielded a 2×2 design with previous drug history as one factor and current drug state as the other factor. The data from Session 13 are contained within Figure 2A. Because there was no effect of the previous history, $F(1, 8) = 0.065$, $p = .806$, the figure shows the combined data (regardless of history). The only statistically reliable effect was for the current condition, $F(1, 8) = 7.232$, $p = .028$; the interaction was not statistically reliable, $F(1, 8) = 1.453$, $p = .262$. These results strongly suggest that the drug unconditionally decreased lever pressing.

In contrast to the results of D_1 antagonism in the vSUB, there were no statistically reliable main effects or interactions of D_1 antagonism in the dSUB on initial instrumental learning (Figure 2C) during Sessions 1–5, $F(1, 13) = 1.652$, $p = .22$; Sessions 6–10, $F(1, 13) = 0.604$, $p = .45$; or Sessions 11–12, $F(1, 13) = 0.019$, $p = .89$. More important to note is that the interactions were not statistically reliable (F s = 1.385, 1.465, and 0.882), which suggests that lever pressing was changing (increasing) at about the same rate for both groups across sessions.

In comparing the different effects of SCH-23390 infusions in the vSUB and dSUB, a close look at Figures 2A and 2C suggests that the vehicle-treated groups were lever pressing at different rates. This difference in baselines between vehicle-treated groups is not uncommon and provides part of the rationale for running a vehicle-infusion control group. Previous experience with this preparation has produced a fair amount of interexperiment variability between vehicle-infused control groups. However, the principal comparison in the present experiments was between drug-infused and vehicle-infused groups in the same site, rather than differences in drug effects between sites.

In terms of nose poking, as shown in Figure 2D, there were no treatment effects during Sessions 1–5, Sessions 6–10, or Sessions 11–12 (F s = 1.105, 0.005, and 0.286, respectively). No

interactions during Sessions 1–5 or Sessions 11–12 were noted ($F_s = 0.956$ and 0.021 , respectively). The interaction during Sessions 6–10 was statistically significant, $F(4, 52) = 2.769$, $p = .037$. Post hoc tests revealed that the only difference was within the vehicle-treated group (nose poking during Session 6 was generally lower than during the other sessions).

D₁ antagonism in the vSUB, but not the dSUB, produces an intrasession decline in responding—During Sessions 11 and 13, following an SCH-23390 infusion in the vSUB, an intrasession decrement in responding was noted. That is, when placed in the box after infusions, the drug-treated rats appeared to respond at baseline (e.g., high) rates but then decreased responding throughout the session. The results of the within-session response analysis are presented in Figure 3; for comparison purposes, the same analysis conducted on the responding of dSUB treated groups is also presented even though no performance deficit was noted. For this reason, a 13th session was not run with dSUB infusions, thereby obviating the intrasession analysis.

As can be seen in the leftmost panels of Figure 3, the effects of SCH-23390 on responding emerged in a time-dependent manner in both Sessions 11 and 13. Initial rates of responding (e.g., during Minutes 1–6) were similar between the two groups but diverged quickly thereafter. Recall that the vSUB drug-treated group in Session 13 included 3 drug-naïve rats and that all 3 individual drug-naïve rats showed a similar within-session decrease in responding. The vehicle-treated group in Session 13 also included 3 formerly drug-treated rats. In contrast, the within-session pattern of responding was similar for the two groups that received infusions in the dSUB. Taken together, these analyses suggest an unconditional effect of drug infusions in the vSUB on within-session responding that emerged within a session.

Microstructure of Initial Instrumental Learning

Exploratory analyses on the effects of SCH-23390 infusions into the vSUB and dSUB on the microstructure of initial instrumental learning are presented in Figure 4. Four measures are shown for vehicle-treated and drug-treated groups across Sessions 1–12 (Session 13 for the vSUB is not shown) for each of the two infusion target sites. The two vSUB treatment groups did differ with respect to several measures, especially during the first phase (infusion sessions, Sessions 1–5). For example, in Figure 4A, the probability of a lever press given a nose poke— $p(LP|NP)$ —in the drug-treated group did not reach levels that are comparable with the vehicle-treated group until Session 7 or 8. In Figure 4B, it appears that the probability of a nose poke given a reinforcer decreased only slightly for the drug-treated group, whereas the vehicle-treated group decreased more rapidly. It is interesting to note that neither the reinforcer–nose poke latency—the same dyad as $p(NP|Reinf)$ —nor the nose poke–lever press latency appeared affected by the drug infusions in the vSUB (see Figures 4C and 4D). The rightmost panels show that in the dSUB, with the exception of the latency between a nose poke and a lever press (see Figure 4G, NP-LP latency; cf. Figure 4C), the vehicle-treated and drug-treated groups did not differ to any great extent. This lack of difference appeared to be consistent across the three phases of the experiment (i.e., Sessions 1–5, 6–10, and 11–12).

Progressive Ratio Schedule of Reinforcement

The main results of the PR tests conducted with infusions of SCH-23390 into the vSUB and dSUB are presented in Figure 5. As shown in Figure 5, infusions of SCH-23390 into the vSUB prior to the PR test session reduced break point, $t(10) = -4.948$, $p < .001$. Infusions of SCH-23390 in the dSUB, however, had no statistically significant effect, $t(10) = 1.424$, $p = .185$. As was noted in the earlier section on initial instrumental learning, above, SCH-23390 infusions into the vSUB unconditionally reduced instrumental lever pressing in a time-dependent fashion within session. Thus, it was of interest to analyze the within-session changes

in response rate during the PR tests because a similar decrement in responding within session would be expected.

As can be seen in Figure 6A, the effects of SCH-23390 infusions into the vSUB on instrumental responding emerged in a time-dependent fashion once again. That is to say, initial rates of responding during the PR test sessions following SCH-23390 infusion (e.g., through the first 5 min or so) were similar to rates of responding in which a vehicle infusion preceded the session. However, responding precipitously declined to near zero rates. In contrast, rates of responding following a vehicle infusion did decrease throughout the session but in a much more gradual fashion. Moreover, response rates following dSUB infusions were not differentiated by drug condition (see Figure 6B).

Spontaneous Locomotion of Feeding Behavior

Figure 7 displays the results of the spontaneous locomotor and feeding behavior experiment. There were 9 rats with cannula placements within the dSUB and 12 rats with placements in the vSUB.

As shown in Figures 7A–7F, vSUB infusions produced no discernible effects on sucrose eaten, $t(11) = 0.98$, $p = .34$; total eating duration, $t(11) = -0.07$, $p = .94$; number of meals, $t(11) = 1.18$, $p = .26$; center crossings, $t(11) = 0.78$, $p = .45$; or rearing, $t(11) = 1.09$, $p = .30$; although latency to begin eating, $t(11) = -2.06$, $p = .06$, was nearly significant. As shown in Figures 7G, 7H, 7J, and 7K, SCH-23390 infusions into the dSUB had no effect on total sucrose eaten, $t(8) = 0.26$, $p = .80$; total eating duration, $t(8) = 0.02$, $p = .98$; number of meals, $t(8) = 2.18$, $p = .07$; or latency to begin eating, $t(8) = -0.76$, $p = .48$. Infusions did, however, reduce center crossings, $t(8) = 2.47$, $p = .05$, and rears, $t(8) = 2.77$, $p = .03$, as shown in Figures 7I and 7L.

Discussion

As the major output structure of the hippocampus, the subiculum projects to the entorhinal cortex, perirhinal cortex, prefrontal cortex, anterior cingulate cortex, thalamus, hypothalamus, nucleus accumbens, and amygdala (S. M. O'Mara, Commins, Anderson, & Gigg, 2001; Witter & Groenewegen, 1990). Given the widespread interest in the function of the hippocampus proper (e.g., CA1 and CA3) and the interconnectivity of many cortical and subcortical structures with the subiculum, surprisingly little research has been conducted on the physiology, pharmacology, or function of the subiculum (S. O'Mara, 2005; S. M. O'Mara et al., 2001). Moreover, the possible differentiation of ventral and dorsal subicular function has received even less attention, and relatively little work has been completed on the role of dopamine D₁ receptors in these structures.

The present experiments suggest dissociable roles for the vSUB and dSUB in instrumental learning, performance, and spontaneous motor behavior, thereby elucidating some of the behavioral functions of the subiculum. The present results also point to a distinct role for D₁ receptor activation in the vSUB in instrumental learning (in contrast to NMDA receptor activation), thereby contributing to the understanding of the pharmacology of the subiculum. In sum, D₁ receptor activation in the vSUB, but not in the dSUB, appears necessary for initial instrumental learning, whereas spontaneous motor behavior is affected by D₁ receptor blockade in the dSUB but not in the vSUB. The results also suggest that dopamine is clearly involved in motivational processes within the vSUB but not in the dSUB. These are the first experiments to suggest separate and distinct roles for D₁ receptors in two regions of the subiculum, complementing previous work showing a functional distinction between the ventral and dorsal regions of the hippocampal formation (Bannerman et al., 1999, 2002; Caine, Humby, Robbins, & Everitt, 2001; Pothuizen, Zhang, Jongen-Relo, Feldon, & Yee, 2004).

In related work, Baldwin, Holahan, Sadeghian, and Kelley. (2000) showed no effects of NMDA receptor blockade on initial instrumental learning or performance in either the vSUB or the dSUB, which appears to contradict the present results. Given that both D₁ receptor blockade and NMDA receptor blockade in the subiculum alter neural activity but do not abolish it, the present results point to important differences in the functions of the two receptors even though there is strong evidence of an important interaction. For example, electrophysiological evidence suggests that dopamine in the subiculum suppresses glutamatergic neuro-transmission onto subicular neurons by a D₁ receptor-mediated mechanism (Behr, Gloveli, Schmitz, & Heinemann, 2000). Thus, D₁ receptor blockade in the subiculum increases activity of subicular neurons, which in turn could explain the present impairments. Presumably, NMDA receptor blockade would produce the opposite effect but would not result in impairments in instrumental learning. Inactivation of the subiculum with infusions of GABA agonists, in future experiments, would serve to further elucidate the role of the subiculum in appetitive learning.

D₁ Antagonism in the Ventral Subiculum Impairs Instrumental Learning and Performance but Does Not Affect Spontaneous Motor or Food-Directed Behavior

Blockade of D₁ receptors in the vSUB impairs initial instrumental learning and performance (see Figure 2A) but leaves spontaneous motor and food-directed behavior intact (see Figures 7C and 7F). The effects of D₁ antagonism in the vSUB on performance of instrumental behavior appear unconditional in that infusions in drug-naïve rats prior to Session 13 reduced lever pressing in a similar fashion to drug-experienced rats. Moreover, previously drug-treated rats, which received a vehicle infusion prior to Session 13, were not impaired, attenuating a discrimination learning explanation. Another possible explanation of the present results, that general motivation for food was reduced, is not consistent with the lack of an effect of vSUB SCH-23390 infusions on the likelihood that the rat would retrieve a sucrose pellet when delivered, the latency between the pellet delivery and its retrieval (see Figures 4B and 4D), the amount of sucrose eaten, total eating duration, number of meals, or latency to start eating (see Figures 7A, 7B, 7D, and 7E). Presumably, if food motivation was reduced, the probability of retrieving a pellet after delivery, or the latency to retrieve the pellet, or the number of pellets eaten, and so forth would have been influenced by D₁ receptor blockade in the vSUB.

However, in a more direct test of motivation, vSUB infusions of SCH-23390 reduced break point in the PR tests (see Figure 5), which indeed suggests a motivational effect (Hodos, 1961). Most interesting, though, is the consistent intrasession reductive effect of vSUB SCH-23390 on instrumental responding, whether in the performance test phase of the initial instrumental learning experiment or in the PR experiment. If motivational processes were reduced, the intrasession decline in responding might be expected. In other words, responding decreased within sessions as if the rats became increasingly disinterested in working for sucrose pellets even though, when given free access in other tests, they ate them readily.

Conceptually speaking, the term *motivation* refers to a myriad of processes interacting in several ways. One important motivational process, hunger versus satiety (or *appetite*), did not appear affected by SCH-23390 infusions into the vSUB because, when rats were given free access to sucrose pellets, measures of the quantity, duration, and initiation of eating were the same following drug infusions as they were following vehicle infusions (see Figures 7A, 7B, 7D, and 7E). In addition, the hedonic value, or *liking*, of the sucrose pellets did not appear to be influenced by D₁ receptor antagonism in the vSUB for the same reasons. This appears consistent with a prominent theory of dopamine function in reinforcement, Berridge and Robinson's (1998) incentive-salience theory. In particular, these results are consistent with the view that dopamine does not mediate the hedonic value of food but still has an important role in motivation, namely, *wanting* (Berridge & Robinson, 1998) or willingness to work for food rewards. In accordance with this view, Salamone and colleagues (Salamone & Correa, 2002;

Salamone, Correa, Mingote, & Weber, 2003) have proposed that dopamine controls a feature of wanting or an activational component that invigorates behavior to obtain food. Indeed, a large body of literature exists showing dopaminergic control over response cost or effort (Cousins, Sokolowski, & Salamone, 1993; Cousins, Wei, & Salamone, 1994; Salamone, Cousins, McCullough, Carriero, & Berkowitz, 1994; Salamone, Wisniecki, Carlson, & Correa, 2001). For example, Salamone et al. (2001) shaped lever pressing on fixed ratio schedules of reinforcement prior to nucleus accumbens dopamine deletion and found, in contrast to vehicle-treated rats, that subsequent responding was a function of the response requirement, with the highest ratios suppressing response rates the most even when the response:reinforcer ratio was constant (e.g., 100 responses:2 pellets, 300 responses:6 pellets). However, Salamone's and Berridge and Robinson's theories focus primarily on the role of dopamine in the nucleus accumbens and do not directly address D₁ receptor function in the vSUB. Thus, the present data suggest that, perhaps somewhat surprisingly, dopamine in the vSUB is a critical component of the activation arousal aspects of incentive motivation.

D₁ Antagonism in the Dorsal Subiculum Reduces Spontaneous Motor Behavior but Not Initial Instrumental Learning, Performance, Progressive Ratio Break Point, or Food-Directed Behavior

Initial instrumental learning does not require D₁ receptor activation in the dSUB, nor does D₁ antagonism in the dSUB produce any discernible performance effects on instrumental lever pressing or nose poking (see Figures 2B and 2D) once conditioned. In addition, D₁ antagonism in the dSUB does not reduce motivation because break point was not lowered in the PR tests. In contrast, there was a consistent and reliable reduction of spontaneous motor behavior with SCH-23390 infusions in the dSUB, namely, a reduction of center crossing and rears (see Figure 7). In addition to this effect on spontaneous motor behavior, the increase in nose poke–lever press latency (see Figure 4F) could be interpreted as another motor deficit produced by D₁ antagonism in the dSUB. Although lever pressing requires forceful depression of the lever and, therefore, some motor coordination, it does not require locomotion to another spatial location. The nose poke–lever press latency, however, does require the rat to move from the food trough to the lever. In a recent demonstration, the activity of dSUB neurons best correlated with the location and speed of a rat in a testing environment and not with the familiarity of objects, as once proposed (Anderson & O'Mara, 2004). Furthermore, lesions of the dSUB impair spatial navigation (Pothuizen et al., 2004), produce hyperactivity, disrupt T-maze performance (Bannerman et al., 1999, 2002), and leave rats hyperreactive to startle, but do not affect cocaine-reinforced lever pressing (Caine et al., 2001). S. O'Mara (2005) argued that one of the principal functions of the dSUB is the processing of information related to space and movement. In conjunction with these reports, the present data are consistent with the idea that the dSUB plays an important role in spatial navigation and movement but not in instrumental learning or performance. The data also extend the findings of others to suggest that D₁ receptor activation in the dSUB is involved in this function.

Ventral Subicular Control of Nucleus Accumbens Dopamine and Arousal

If the present results are consistent with the incentive-salience theory of dopamine function and dopamine release in the vSUB is required for motivational arousal, one possible mechanism of action could be the well-described ventral subicular influence on dopamine release in the NAcc. Data from microdialysis studies have shown that electrical stimulation of the vSUB increases locomotor activity and dopamine levels in the accumbens (Taepavarapruk, Floresco, & Phillips, 2000). The increase in motor activation is blocked by systemic SCH-23390 injections, which suggests a D₁ receptor-mediated mechanism. NMDA receptor stimulation in the vSUB also increases dopamine efflux in the accumbens, an effect that relies on a potent excitation of VTA dopamine neurons (Floresco, Todd, & Grace, 2001). Moreover, the excitatory glutamatergic afferents to the NAcc from the vSUB responsible for the increased

dopamine release in the accumbens are indeed modulated by D₁ receptors in the vSUB (Zornoza et al., 2005). Briefly, retrodialysis of SCH-23390 in the vSUB blocks the locomotor-activating effects of, and the increased dopamine release in the NAcc by, NMDA stimulation of the vSUB. Moreover, intra-accumbens infusions of amphetamine, a potent dopamine agonist, also produce an increase in locomotor activity, which is abolished by vSUB lesions (Burns, Robbins, & Everitt, 1993). Therefore, it is likely that in the present experiments, dopamine release in the NAcc was reduced by infusions of SCH-23390 in the vSUB. In addition, it is our contention that this reduced the activational effects of dopamine release in the NAcc, an effect that produced the performance deficit in the initial instrumental learning experiment and, most interestingly, caused the intrasession decline in instrumental responding.

Another, more speculative mechanism for the motivational attenuating effects seen here could be the vSUB's influence on hypothalamic–pituitary–adrenal (HPA) axis function. S. O'Mara (2005) argued that the primary function of the vSUB is to inhibit the HPA axis, especially in the axis's response to stress. Although sucrose-reinforced lever pressing is not typically thought of as a stressful condition, corticosterone levels in the rat increase shortly before food consumption (Honma, Honma, & Hiroshige, 1984; Micco, McEwen, & Shein, 1979). Adrenalectomy reduces overall food consumption (Kumar & Leibowitz, 1988) and facilitates extinction of appetitive-reinforced runway behavior, a classic hippocampus-dependent appetitive learning task (Micco et al., 1979), effects that are reversed by administration of corticosterone. It is interesting to note that peripheral corticosterone administration also increases accumbens dopamine, especially during eating, and stimulates locomotor activity, effects that are abolished by neurochemical depletion of accumbens dopamine (Piazza et al., 1996). These data point to an important link between appetitive events/rewards and HPA axis function because glucocorticoids appear to mediate some of the rewarding effects of food, most likely via stimulation of mesencephalic dopaminergic transmission (Piazza & Le Moal, 1997). Therefore, given the extensive link between dopamine and glucocorticoids and a link between vSUB and HPA axis function, it is quite possible that D₁ antagonism in vSUB influenced HPA axis function in a way that reduced motivational-arousing signals involved in food presentation.

Contextual Arousal Via Ventral Subiculum D₁ Receptors Decreases Intrasession Instrumental Responding

Figures 3 and 6 clearly show that D₁ receptor antagonism in the vSUB, but not in the dSUB, produced an intrasession decline in instrumental responding independent of previous drug history or conditioning. In addition, supplemental analyses on previously published data (not shown) have confirmed that the pattern of decline is specific to D₁ antagonism in the vSUB and not to D₁ antagonism in the NAcc (Hernandez, Andrzejewski, Sadeghian, Panksepp, & Kelley, 2005) or amygdala (Andrzejewski et al., 2005), even when D₁ antagonism produces a performance deficit, as it did in the NAcc. Sun and Rebec (2003) demonstrated a similar intrasession decline in lever pressing with lidocaine inactivation of the vSUB. Using two separate tests of drug reinstatement, drug-paired conditional-stimuli-induced and cocaine-induced, they showed that initial rates of lever pressing (in the first 10-min block) in lidocaine-treated rats were nearly identical to rates of responding in vehicle treated rats. However, in both reinstatement tests, rates of responding decreased within the session, akin to the decrease observed in the present experiments. Sun and Rebec interpreted their results by noting the role of the vSUB in contextual learning. For example, Floresco, Seamans, and Phillips (1996) found that lidocaine inactivation of the vSUB impaired acquisition of an escape response in the Morris water maze. Radial-arm maze performance is also disrupted by lidocaine inactivation of the vSUB (Floresco, Seamans, & Phillips, 1997), but not learning which arms have been baited previously, which suggests that the vSUB is involved in the short-term processing of contextual cues. The contextual cues, as well as drug-paired conditional stimuli, strongly influence the

reinstatement of drug seeking; these cues are often interpreted as activating an internal state of craving that drives drug seeking and taking. Recently, it has been shown that cues that predict the availability of primary reinforcer can evoke instrumental responding in the absence of those reinforcing events, an effect that is impaired by D₁ antagonism in the NAcc (Yun, Nicola, & Fields, 2004). In the context of the present results, then, D₁ receptor blockade in the vSUB may influence the processing of contextual cues in the experimental chamber that ordinarily maintain a level of activity necessary for ongoing instrumental performance. In this light, then, D₁ receptors in the subiculum are probably not involved in the neural plasticity underlying instrumental, action–outcome learning but are involved in the association of incentive cues with appropriate behavior.

Summary

Dopamine D₁ receptor antagonism of two separate regions of the subiculum, one of the major output structures of the hippocampus, produces dissociable effects on instrumental learning, behavior, spontaneous motor behavior, and motivation. D₁ receptor antagonism in the vSUB impairs instrumental learning and performance and reduces break point in a PR test, but appears to leave spontaneous motor behavior and food-directed responding intact. In contrast, the effects of D₁ receptor antagonism in the dSUB appear to be primarily on spontaneous motor behavior; D₁ receptor activation in the dSUB is not required for initial instrumental shaping of a lever press or performance of lever pressing once conditioned. These data contribute to the growing body of literature suggesting important and dissociable roles for D₁ receptor activation in the subiculum on learning and memory. Given that the vSUB appears to be involved in the short-term processing of contextual cues and that D₁ receptors in the vSUB modulate NAcc dopamine efflux, we propose that D₁ receptor activation in the vSUB is necessary for the processing of important contextual-invigorating cues. Those contextual cues in the experimental chamber appear to promote and maintain a level of activity and arousal, which is necessary to maintain lever pressing. Thus, D₁ receptors in the vSUB are part of an extended network of structures that are involved in initial instrumental learning by providing the motivational processing necessary to promote and maintain lever pressing.

Acknowledgements

This research was supported by National Institute on Drug Abuse Grants DA016465 to Matthew E. Andrzejewski and DA04788 to Ann E. Kelley.

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Figure 1.

Histological reconstructions of cannula placements in the dorsal subiculum (dSUB) and ventral subiculum (vSUB) are represented in schematic form. Histological sections were examined under light microscope and the site of the infusion estimated. Numbers beside each slide represent millimeters from bregma. Schematic diagrams are reprinted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), by G. Paxinos and C. Watson, pp. 206–208 (Figures 42–44), copyright 1998, with permission from Elsevier.

Figure 2.

Effects of infusions of the D₁ antagonist SCH-23390 in the ventral subiculum (vSUB) and dorsal subiculum (dSUB) on instrumental learning, performance, and nose poking. Rats received infusions of SCH-23390 or vehicle prior to Sessions 1–5, prior to Session 11, and prior to Session 13 (vSUB only), but not prior to Sessions 6–10 or Session 12. Panels A and C show the mean number of lever presses per session per group ($\pm$ SEM) with infusions in the vSUB or dSUB, respectively. Panels B and D show the mean number of nose pokes per session per group ($\pm$ SEM) for vSUB and dSUB. No statistical reliable main effect of treatment or interaction on nose poking was found. ** $p < .01$, compared with vehicle, revealed by Tukey post hoc comparisons.

Figure 3.

The effects of SCH-23390 infusions on intrasession response rates during Sessions 11 (A) and 13 (B) for ventral subiculum (vSUB) infused rats and Session 11 (C) for dorsal subiculum (dSUB) infused rats. A and B show the mean number of lever presses per minute ($\pm$ SEM) for vSUB treated rats across the 15-min sessions. No statistically significant differences were found in dSUB treated groups. * $p < .05$, ** $p < .01$, compared with vehicle using Tukey post hoc comparison method.

Figure 4.

Microstructural behavioral analysis of D1 antagonism in the ventral subiculum (vSUB) and dorsal subiculum (dSUB). A and E show the mean conditional probability ($\pm SEM$) of a lever press (LP) given that a nose poke (NP) was the last recorded event— $p(LP|NP)$ —in the vSUB and dSUB, respectively. B and F show the probability of an NP given that a reinforcer (Reinf) was the last recorded event— $p(NP|Reinf)$. C and G show the average latency between an NP and an LP, the same dyad used to compute the $p(LP|NP)$. D and H show the latency between a Reinf delivery and an NP, once again, the same dyad used to compute the $p(NP|Reinf)$.

Figure 5.

Effects of SCH-23390 infusions in the ventral subiculum (vSUB) and dorsal subiculum (dSUB) on Progressive Ratio 4 performance. The mean break point ($\pm$ SEM) of the last ratio completed before the rat ceased responding per group is plotted for vSUB treated rats in A and for dSUB treated rats in B.

Figure 6.

The effects of SCH-23390 infusions on intrasession response rates during the progressive ratio (PR) test session for ventral subiculum (vSUB) treated rats in A and for dorsal subiculum (dSUB) treated rats in B. The mean rate of responding per minute ($\pm SEM$) per group is plotted over the course of the 45-min test session.

Figure 7.

Effects of SCH-23390 infusions in the ventral subiculum (vSUB) and dorsal subiculum (dSUB) on measure of food-directed and spontaneous locomotor behavior. A–F show the effects of SCH-23390 in the vSUB compared with vehicle controls ($M \pm SEM$). No statistically reliable effects were found in vSUB treated rats. G–L show the effects of SCH-23390 infusions in the dSUB compared with vehicle. * $p < .05$, dependent t tests.