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Intra-BLA or Intra-NAc Infusions of the Dopamine D_3 Receptor Partial Agonist, BP 897, Block Intra-NAc Amphetamine Conditioned Activity

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Recent studies have shown that both systemic and intra-nucleus accumbens (NAc) or intra-amygdala administration of dopamine D_3 receptor ligands modulate reward-related learning. A previous study (H. Aujla, H. Sokoloff, & R. J. Beninger, 2002) showed that systemic administration of the partial dopamine D_3 receptor agonist BP 897 selectively blocked the expression, but not the acquisition, of amphetamine-conditioned activity. This suggested the hypothesis that intra-NAc or intra-basolateral amygdala (BLA) BP 897 would attenuate the expression, but not the acquisition, of amphetamine-conditioned activity. Rats were habituated to activity-monitoring chambers for 5 days, for 1 hr each day. Conditioning occurred on the next 3 days, followed by a single 1-hr test session. Intra-NAc or intra-BLA infusions of BP 897 during test, but not during conditioning, attenuated intra-NAc amphetamine conditioned activity. Results indicate that the ability of BP 897 to attenuate the expression of conditioned activity is mediated in part by the NAc and BLA.

Reward-related learning involves the ability of a previously neutral stimulus to elicit approach and/or consummatory behaviors following conditioning to a primary reinforcer such as food or abused drugs (e.g., amphetamine). Animal models of reward-related learning have strongly implicated dopamine in intracranial self-stimulation (ICSS) (Breese & Cooper, 1974; Robertson & Mogenson, 1978; Rolls et al., 1974), conditioned place preference, conditioned activity, and responding for conditioned reward (see Beninger & Miller, 1998, for a review). Central administration studies have revealed that manipulation of dopamine in structures such as the nucleus accumbens (NAc; see Di Chiara, 2002, for a review) or the basolateral amygdala (BLA; Hitchcott, Harmer, & Phillips, 1997; Rezayof, Zarrindast, Sahraei, & Haeri-Rohani, 2002; See, Kruzich, & Grimm, 2001) can modulate reward-related learning. Thus, both NAc and BLA dopamine have been strongly implicated in reward-related learning.

Traditionally, studies have focused on dopamine D_1 and D_2 receptor families. However, the dopamine D_3 receptor has also gained attention as a possible target for the treatment of schizophrenia (Sokoloff et al., 1992) and drug addiction (Le Foll, Schwartz, & Sokoloff, 2000). D_3 receptors are not as widely distributed in the brain as D_1-like and D_2 receptors; the dopamine D_3 receptor is localized predominately in the Isles of Calleja, the NAc, and the amygdala (Levant, 1998). This distribution makes the D_3 receptor a conspicuous candidate for influencing reward-related learning. Until recently, there has been a dearth of information regarding the role of the D_3 receptor in reward-related learning due to the lack of highly specific agents for this receptor.

One such agent is the partial dopamine D_3 receptor agonist, 1-(4-(2-naphthoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine hydrochloride (BP 897). In a previous study (Aujla, Sokoloff, & Beninger, 2002), we found that intraperitoneal administration of BP 897 blocked the expression, but not the acquisition, of amphetamine-conditioned activity in rats. This finding was consistent with the findings of Pilla et al. (1999) that BP 897 selectively blocked cocaine seeking but not cocaine taking. Thus, BP 897 selectively blocked the ability of a conditioned stimulus to elicit response without modifying the incentive salience of a primary reinforcer.

The effectiveness of BP 897 in attenuating the expression of behavioral responses to conditioned reinforcers and the localization of dopamine D_3 receptors in brain regions that have been implicated in reward suggest the hypothesis that intra-NAc or intra-BLA BP 897 will attenuate the expression of conditioned activity in rats. Thus, following a habituation period to activity monitors, we administered intra-NAc amphetamine to rats over a series of conditioning trials and then evaluated conditioned activity on an amphetamine-free test trial. The effect of BP 897 on the acquisition and expression of amphetamine-conditioned activity was investigated by observing activity levels on the test trial in rats receiving intra-NAc or intra-BLA BP 897 during the conditioning sessions or test session.

Method

Subjects

Treatment of rats was in accordance with guidelines of the Animals for Research Act (1990) and the Canadian Council on Animal Care (Olfert, Cross, & McWilliams, 1993) and was approved by the Queen's University Animal Care Committee. Experimentally naive male albino Wistar rats (N = 96; Charles River, Canada) weighing between 200 and 275 g on arrival were housed in pairs in clear Plexiglas shoebox-style cages. The

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colony room was temperature controlled (21 ± 1°C) with lights off from 0700 to 1900. Rats were handled for 1 week prior to the start of the experiment and were maintained on a free feeding (Purina rodent laboratory chow #5001; Nestlé Purina, St. Louis, MO) and drinking schedule.

Drugs

A dose of BP-897 (1.0 μg/0.5 μl; Bioprojet, Paris, France) was prepared afresh each day in dimethyl sulfoxide. A dose of amphetamine (20 μg/0.5 μl; USP, Rockville, MD) was also prepared afresh each day in sterile water.

Surgery

Rats were anesthetized with an oxygen flow containing 4% isoflurane. During surgery, we adjusted the concentration of isoflurane to maintain a deep level of anesthesia. Rats were then placed into a stereotaxic device. An incision was made along the midline, the scalp was retracted, and the area surrounding bregma was cleaned and dried. The incisor bar was adjusted so that the skull was level between lambda and bregma. Two stainless steel guide cannulas (0.64 mm in diameter, 13 mm long) were lowered through two small holes drilled through the skull according to the following coordinates for the shell region of NAc: 1.2 mm anterior to bregma, 1.5 mm lateral to the midline, and 6.7 mm ventral to the surface of the skull; and for the BLA: 2.8 mm posterior to bregma, 5.0 mm lateral to the midline, and 7.7 mm ventral to the surface of the skull (Paxinos & Watson, 1998). The cannulas were anchored to the skull with four stainless steel screws and dental cement. Stainless steel pins (0.31 mm in diameter) were inserted into the guide cannulas to ensure that they remained unoccluded. Each rat received a 0.2-ml subcutaneous injection of the analgesic buprenorphine (10% in saline solution) at the onset of surgery and 8–12 hr after surgery for pain relief. In addition, lidocaine with epinephrine was injected (0.3 ml) in several locations around the incision site for local analgesia. Animals were allowed to recover for 1 week prior to testing, and during this time pins were replaced daily.

Intracranial Drug Administration

A 10.0-μl microsyringe (Hamilton, Reno, NV) mounted on an infusion pump (Model 355, Sage Instrument; Freedom, CA) was used to infuse the drug at a constant rate of 1.0 μl/min. The injection cannulas, cut 1.0 mm longer than the implanted guide cannulas, were made from stainless steel tubing (0.31 mm in diameter). Polyethylene tubing was used to attach injection cannulas to the microsyringe. Drug injections (0.5 μl) were delivered over a 30-s interval, and the injection cannulas remained in place for an additional 30 s to promote diffusion.

Conditioned Activity Apparatus

Activity was measured as a function of "beam breaks" across 14 pairs of photocells positioned at 5 cm and 15 cm above the floor. Chambers were six Plexiglas boxes (50 cm × 40 cm × 40 cm) housed in Styrofoam-insulated wooden boxes with Plexiglas fronts. Boxes were painted black on the interior and illuminated with incandescent bulbs. Flooring consisted of metal bars spaced approximately 1 cm apart. See Beninger, Cooper, and Mazurski (1985) for a complete description of the conditioned activity apparatus.

Procedure

Rats received five 1-hr habituation trials, one each day, over 5 days during which no drug was administered. Five trials were the minimum deemed necessary to ensure that novelty-induced locomotion was not reflected in activity counts by the fifth habituation session. Habituation sessions also ensured that activity changes between the conditioning and test session were not confounded by a decrease in novelty-induced activity. The conditioning phase began on the next day and consisted of three 1-hr sessions, one each day. Injections were made immediately before each conditioning session. The single 1-hr test session followed the last conditioning session and was also preceded by injections given immediately prior to the session. Sessions were conducted from 1900 to 0700. Groups received intra-NAc and/or intra-BLA infusions of BP 897 (1.0 μg/0.5 μl/side) and/or amphetamine (20.0 μl/0.5 μl/side) during conditioning and/or testing according to the regimen in Table 1.

Histological Analysis

Following behavioral testing, all animals were sacrificed by carbon dioxide gas exposure and decapitated. Brains were extracted immediately and placed in a 10% formalin/sucrose solution. At least 2 days following extraction, brains were frozen and sliced in 70-μm coronal sections using a microtome. Brain slices were mounted on glass slides and stained with Nissl cell-body stain. Verification of injection sites was performed by an observer who was blind to the behavioral results. Animals were considered to be cannulated properly if the entire tips of both cannulas were located in the region of core or shell of the NAc or the BLA.

Results

Histology

Histological examination revealed that of the 96 rats that underwent surgery, 82 placements were considered to be in the target

Table 1
Experimental Groups

		Conditioning		Test		
Group	Treatment	NAc	BLA	NAc	BLA	*n*
1	sal (NAc)–sal (NAc)	sal		sal		10
2	amph (NAc)–sal (NAc)	amph		sal		11
3	amph + BP (NAc)–sal (NAc)	amph + BP		sal		10
4	sal (NAc)–BP (NAc)	sal		BP		10
5	amph (NAc)–BP (NAc)	amph		BP		11
6	amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA)	amph	BP	sal	sal	11
7	amph (NAc) + sal (BLA)–sal (NAc) + BP (BLA)	amph	sal	sal	BP	10
8	sal (NAc) + sal (BLA)–sal (NAc) + BP (BLA)	sal	sal	sal	BP	9

Note. NAc = nucleus accumbens; BLA = basolateral amygdala; sal = saline; amph = amphetamine; BP = BP 897.

region of the NAc and/or BLA (see Figures 1 and 2). Final numbers were sal (NAc)–sal (NAc), $n = 10$; amph (NAc)–sal (NAc), $n = 11$; amph (NAc) + BP–sal (NAc), $n = 10$; sal (NAc)–BP (NAc), $n = 10$; amph (NAc)–BP (NAc), $n = 11$; amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA), $n = 11$; amph (NAc) + sal (BLA)–sal (NAc) + BP (BLA), $n = 10$; and sal (NAc) + sal (NAc)–sal (NAc) + BP (BLA), $n = 9$.

Conditioned Activity

The dependent measure in the conditioned-activity paradigm was the number of photocell beam breaks made during a 60-min session in the activity monitor. Activity in the first four sessions may have been confounded by novelty-induced activity and was excluded. Thus, only the last habituation day was included for the purposes of statistical analysis. For the purposes of analysis activity, counts during the conditioning phase were presented as an average. The data were analyzed with a two-way mixed design analysis of variance (ANOVA) and Tukey's honestly significant difference post hoc analysis. The between-subjects factor was the treatment condition, and the within-subjects factor was paradigm phase.

The mean (± *SEM*) habituation scores for the groups were quite consistent, as seen in Figure 3. As expected, the test day score for the group conditioned with intra-NAc amphetamine and tested following intra-NAc saline (Group 2 in Figure 3) was higher than that of the sal (NAc)–sal (NAc) control group (Group 1). When intra-NAc or intra-BLA BP 897 was administered with intra-NAc amphetamine during conditioning (Groups 3 and 6), it had no apparent effect on establishment of the conditioned activity effect. Animals receiving intra-NAc or intra-BLA BP 897 during the test following conditioning with intra-NAc and intra-BLA saline (Groups 4 and 2) showed little change in activity compared with control rats. Conditioned activity was not seen in the groups conditioned with intra-NAc amphetamine and given intra-NAc or intra-BLA BP 897 in the test (Groups 5 and 7).

Habituation and test results were subjected to a two-variable mixed ANOVA with repeated measures on phase and independent groups. Results yielded a significant Group × Phase interaction, $F(7, 74) = 13.274$, $p < .001$, showing that the phase effect differed among the groups. Subsequent tests of simple effects of phase for each group confirmed that a significant conditioned activity effect was seen in the amph (NAc)–sal (NAc), $F(1, 74) = 50.36$, $p < .001$; amph (NAc) + BP (NAc)–sal (NAc), $F(1, 74) = 38.35$, $p < .001$; and amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA) groups, $F(1, 74) = 70.57$, $p < .001$. The phase effect was not significant for the remaining groups (i.e., ps $> .05$). As expected, groups treated with intra-NAc amphetamine showed increased motor activity (see Table 2). A two-variable mixed design ANOVA with repeated measures on days and independent groups revealed only a main effect of group, $F(7, 74) = 31.62$, $p < .001$. Post hoc (Tukey) comparisons of the 3-day averages revealed that the amph (NAc)–sal (NAc), amph (NAc) + BP (NAc)–sal (NAc), amph (NAc)–BP (NAc), amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA), and amph (NAc) + sal (BLA)–sal (NAc) + BP (BLA) groups differed from the sal (NAc)–sal (NAc), sal (NAc)–BP (NAc), and sal (NAc) + sal (BLA)–sal (NAc) + BP (BLA) groups and not from each other. It is notable that although the increase in

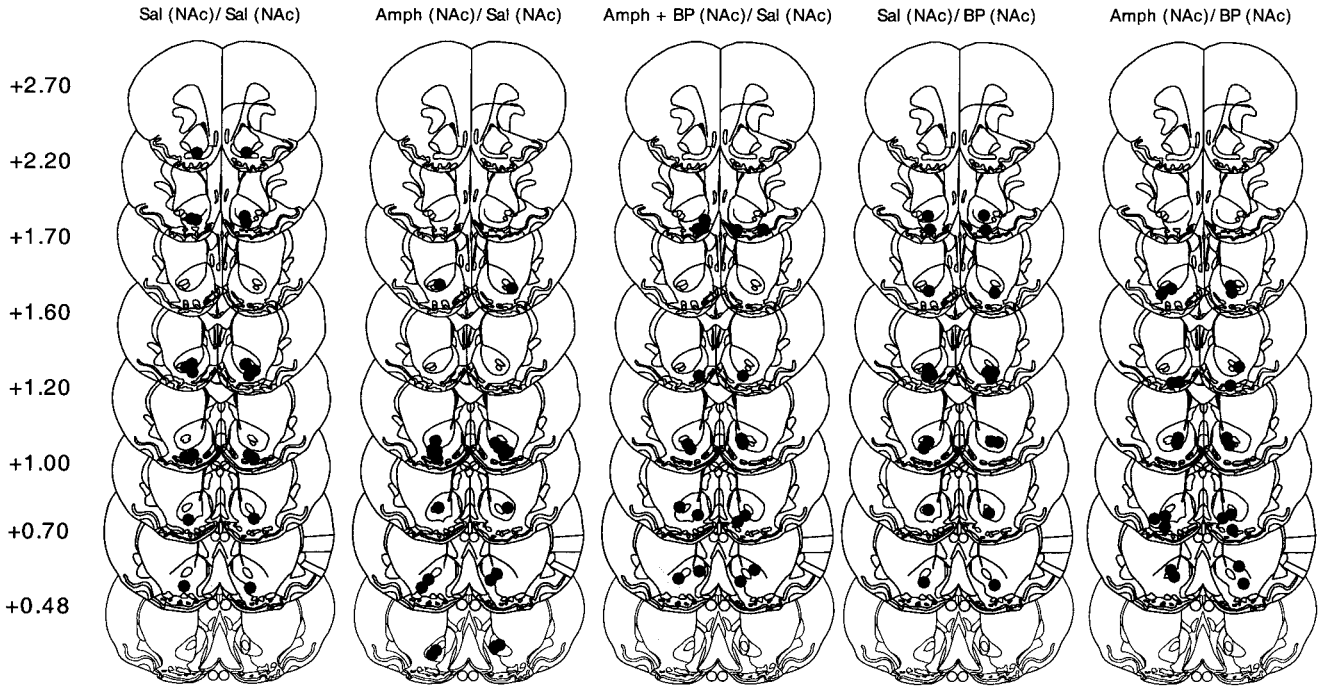

Figure 1. Location of injector tips for Groups 1–5. Numbers to the left of the sections indicate the distances (mm) rostral to bregma. Sal = saline; NAc = nucleus accumbens; amph = amphetamine; BP = BP 897. Reprinted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, Plates 0.48 to 2.70, Copyright 1998, with permission from Elsevier.

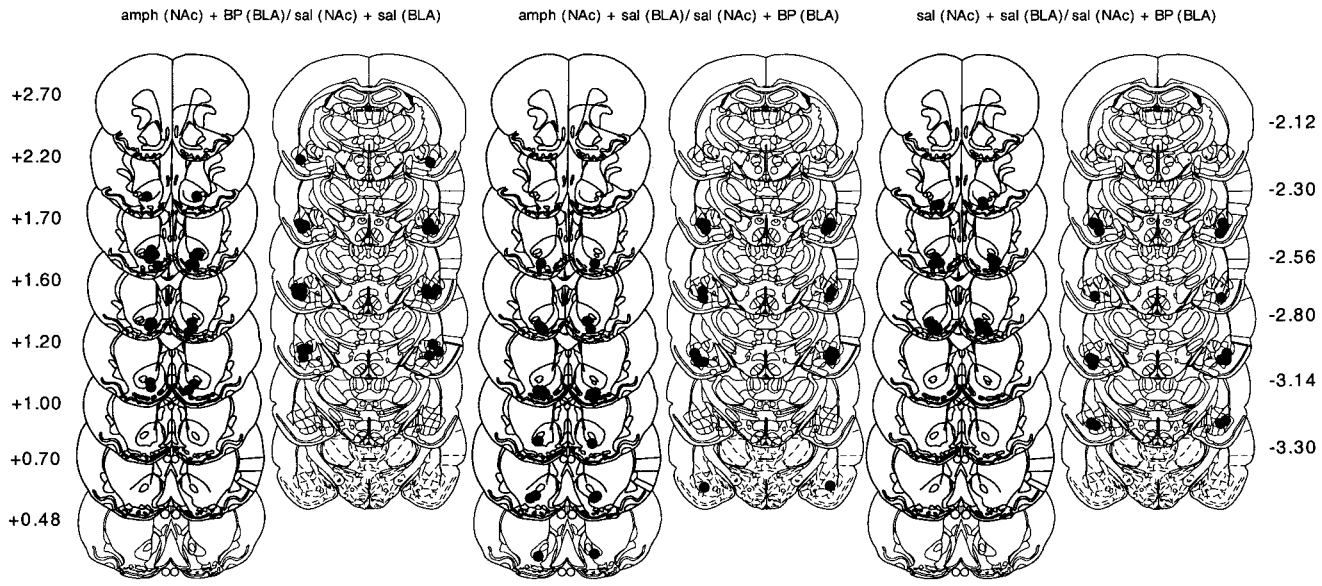

Figure 2. Location of injector tips for Groups 6–8. Numbers to the left indicate the distances (mm) rostral to bregma for nucleus accumbens placements, and those to the right indicate the distances caudal to bregma for basolateral amygdala placements. amph = amphetamine; NAc = nucleus accumbens; BP = BP 897; BLA = basolateral amygdala; sal = saline. Reprinted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, Plates −3.30 to −2.12, 0.48 to 2.70, Copyright 1998, with permission from Elsevier.

activity during conditioning in the amph (NAc)–BP (NAc) and amph (NAc) + sal (NAc)–sal (NAc) + BP (BLA) groups was similar to that seen in the other groups conditioned with amphetamine, conditioned activity was not seen in these groups.

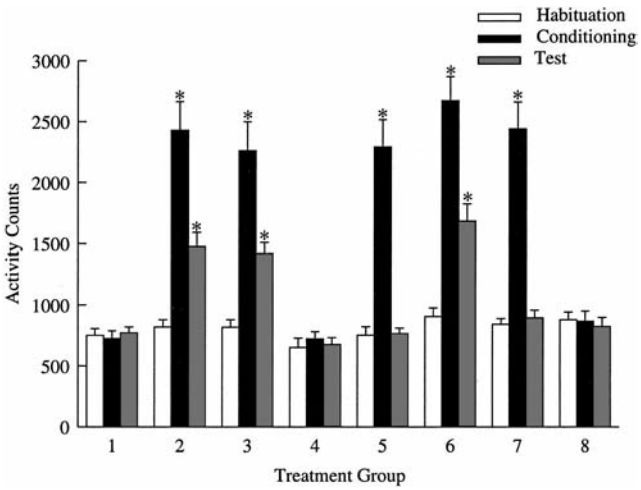

Figure 3. Habituation, conditioning, and test session activity counts for subject groups. 1 = sal (NAc)–sal (NAc), 2 = amph (NAc)–sal(NAc), 3 = amph (NAc) + BP (NAc)–sal (NAc), 4 = sal (NAc)–BP (NAc), 5 = amph (NAc)–BP (NAc), 6 = amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA), 7 = amph (NAc) + sal (BLA)–sal (NAc) + BP (BLA), and 8 = sal (NAc) + sal (NAc)–sal (NAc) + BP (BLA). sal = saline; NAc = nucleus accumbens; amph = amphetamine; BP = BP 897; BLA = basolateral amygdala. The asterisks indicate significant difference from habituation in tests of simple effects of phase following a significant interaction of phase in an analysis of variance.

Discussion

The current results may be summarized as follows: (a) Infusions of intra-NAc amphetamine either alone, coinjected with BP 897 into the NAc, or coinjected with BP 897 into the BLA, prior to conditioning sessions produced conditioned activity on an amphetamine-free test session; (b) infusions of intra-NAc or intra-BLA BP 897 prior to the test session blocked conditioned activity; and (c) coadministration of intra-NAc or intra-BLA BP 897 with intra-NAc amphetamine prior to conditioning sessions did not attenuate unconditioned or conditioned activity.

Le Foll, Frances, Diaz, Schwartz, and Sokoloff (2002) have shown that BP 897 blocks the expression of cocaine-conditioned activity in mice, and Aujla et al. (2002) have found that systemically administered BP 897 blocked the expression, but not the acquisition, of amphetamine-conditioned activity. The current behavioral findings agree with these studies and, furthermore, suggest that the block of the expression of conditioned activity observed with systemic BP 897 may be mediated by the BLA and the NAc. The finding that systemic BP 897 did not attenuate the acquisition of conditioned activity was also observed with intra-NAc or intra-BLA BP 897. In the present study, we did not observe any change in unconditioned locomotor activity in either the NAc or BLA groups receiving BP 897 concurrently with amphetamine compared with those receiving amphetamine alone. Thus, intra-NAc or intra-BLA BP 897 blocked conditioned activity but not unconditioned activity.

It should be noted that the present study did not set out to target either the shell or core subregions of the NAc. There is literature evaluating these two subregions with respect to reward-related learning, reviewed by Di Chiara (2002), but there is no consensus on the contribution of each. As we did not differentiate these two structures in our surgical procedure and the drugs may have

Table 2
Activity Counts (± SEM) During Conditioning

Group	Treatment	Day 1	Day 2	Day 3	Average
1	sal (NAc)–sal (NAc)	767.10 ± 58.68	736.30 ± 71.38	668.8 ± 60.34	724.07 ± 63.47
2	amph (NAc)–sal (NAc)	2,405.55 ± 216.42	2,351.91 ± 237.31	2,526.73 ± 255.39	2,428.06 ± 236.37*
3	amph + BP (NAc)–sal (NAc)	2,191.00 ± 235.74	2,266.8 ± 226.48	2,326.00 ± 247.04	2,261.27 ± 236.42*
4	sal (NAc)–BP (NAc)	704.60 ± 44.82	736.00 ± 67.95	726.70 ± 60.56	722.43 ± 57.78
5	amph (NAc)–BP (NAc)	2,251.73 ± 274.48	2,282.46 ± 141.35	2,341.00 ± 252.46	2,291.73 ± 222.77*
6	amph (NAc) + BP (BLA)–sal (NAc) + sal (BLA)	2,473.27 ± 121.17	2,636.46 ± 195.50	2,899.18 ± 274.38	2,669.64 ± 197.01*
7	amph (NAc) + sal (BLA)–sal (NAc) + BP (BLA)	2,179.70 ± 109.59	2,523.10 ± 262.19	2,612.5 ± 287.17	2,438.4 ± 219.65*
8	sal (NAc) + sal (BLA)–sal (NAc) + BP (BLA)	811.22 ± 64.36	866.78 ± 81.68	921.78 ± 104.28	866.59 ± 83.44

Note. sal = saline; amph = amphetamine; NAc = nucleus accumbens; BP = BP 897; BLA = basolateral amygdala.
* Significantly different from sal (NAc)–sal (NAc), sal (NAc)–BP (NAc), and sal (NAc) + sal (BLA)–sal (NAc) + BP (BLA).

diffused into both subregions, the present results do not contribute to the core versus shell debate with respect to the involvement of these structures in Pavlovian conditioning.

The results from the current study on the ability of BP 897 to modulate locomotor activity elicited by unconditioned versus conditioned stimuli are consistent with previous studies examining the effects D_3 agents have on primary and secondary reinforcement. Pilla et al. (1999) found that systemic BP 897 was able to attenuate cocaine-seeking behavior normally elicited by a conditioned reinforcer but did not affect cocaine-taking behavior that was driven by primary reinforcement. Alternatively, Duarte, Lefebvre, Chaperon, Hamon, and Thièbot (2003) have shown that systemic BP 897 was effective in attenuating both the acquisition and the expression of a cocaine-induced place preference. Furthermore, Duarte et al. (2003) also found that no effect was found when examining either morphine- or food-induced place preference. Parsons et al. (1996) have shown that intra-NAc infusion of the D_3 agonists quinelorane or 7-OH-DPAT decreased cocaine self-administration, and Carr, Yamamoto, Omura, Cabeza de Vaca, and Krahne (2002) have reported that systemic administration of U99194A, a selective dopamine D_3 receptor antagonist, failed to affect lateral hypothalamic ICSS but did augment amphetamine-potentiated lateral hypothalamic ICSS, suggesting that D_3 receptor activation can modulate response for primary reinforcers. These differential effects of D_3 agents on response for primary reinforcers may be related to their different pharmacological actions. Thus 7-OH-DPAT is a full agonist at the D_3 receptor but is less selective at D_3 receptors versus D_2 receptors than the partial agonist BP 897 (Gyertyan & Gal, 2003). Results provide good evidence that the D_3 receptor is important in mediating the ability of conditioned reinforcers to elicit response but mixed evidence regarding the role of the D_3 receptor in primary reinforcement.

Hitchcott, Bonardi, and Phillips (1997) have shown that postsession intra-amygdala infusion of the dopamine D_3 receptor agonist 7-OH-DPAT, but not the D_1-like receptor agonist SKF-38393 or the mixed D_2/D_3 receptor agonist quinpirole, enhanced approach to a conditioned reward, supporting the involvement of amygdala D_3 receptors in reward-related learning. Furthermore, this enhancement was reversed with postsession administration of the D_3 antagonist nafadotride (Phillips, Harmer, & Hitchcott, 2002). Unlike the present results with BP 897, these results may implicate D_3 receptors in primary reinforcement. Besides the use of different pharmacological agents, another difference between the study of Hitchcott, Bonardi, and Phillips (1997) and the present study is the use of posttraining versus pretraining injections. Further studies are needed to resolve the effects of these differences.

The involvement of both the NAc and BLA in reward-related learning coupled with the BLA projections to the NAc (Alheid, 2003) presents the possibility that these two structures may coordinate control over the acquisition and/or expression of reward-related learning. Hitchcott and Phillips (1998) found that postsession intra-amygdala infusions of the dopamine D_3 receptor agonist 7-OH-DPAT enhanced the ability of an amphetamine-conditioned stimulus to elicit conditioned locomotor responses. This effect was not observed with respect to an unpaired stimulus, thus ruling out a general effect of 7-OH-DPAT on locomotor activity. These results further implicate D_3 receptors in primary reinforcement but underscore the need to further evaluate the effects of time of injection.

The present finding that intra-NAc or intra-BLA BP 897 blocks intra-NAc amphetamine-conditioned activity is consistent with previous findings that implicate dopamine D_3 receptors in conditioned cue-elicited responding for reward. In addition, the present findings seek to integrate the growing D_3 literature with findings implicating both the NAc and BLA in conditioned cue-elicited, but not stress- or drug-elicited, reinstatement (see Kalivas & McFarland, 2003, for a review). In the current study, only one dose of amphetamine (20 μg/0.5 μl) and one dose of BP 897 (1.0 μg/0.5 μl) were used. The dose of amphetamine used in the current study was similar to one that has been found to be effective in producing conditioned activity in a previous experiment (Sutton, McGibney, & Beninger, 2000). The dose of BP 897 was the first dose chosen and was found to be effective. Examination of further doses would be useful in examining the dose-response profile of BP 897 but was beyond the scope of this preliminary study.

The mechanism underlying the effects of BP 897 remains unknown. BP 897 is a selective and partial dopamine D_3 receptor agonist both in vitro and in vivo (Pilla et al., 1999) but has also been reported to be a D_3 receptor antagonist in vitro (Wicke & Garcia-Ladona, 2001; Wood et al., 2000) and therefore may produce its effects by acting on D_3 receptors. The present observation of decreased conditioned activity with BP 897, but no effect on amphetamine-stimulated activity or normal levels of activity in undrugged animals, makes it unlikely that BP 897 simply reduces locomotor activity. Furthermore, previous studies have shown that conditioned activity based on amphetamine or cocaine is resistant to the effects of dopamine receptor antagonists (Beninger & Hahn, 1983; Beninger & Herz, 1986; Poncelet, Dangoumau, Soubrie, &

Simon, 1987), suggesting that during conditioning, dopamine produces learning by changing the strength of nondopaminergic synapses (Beninger, 1983; Kelley, 1999; Miller, Wickens, & Beninger, 1990; Wickens, 1990).

Further work is needed to examine how BP 897 acting on D_3 receptors may account for these effects. One possibility is that BP 897 acts on D_3 receptors located on non-dopaminergic cells in the NAc to modulate their activity either there or at terminals in the ventral tegmental area (Diaz et al., 2000); these may be the cells that undergo modified inputs through the action of dopamine (Reynolds & Wickens, 2000). Another possibility is that BP 897, acting as a receptor agonist, reduces the activity of dopaminergic cells in the ventral tegmental area (20, 18) that project to forebrain targets. As a mixed agonist and antagonist, BP 897 may exert its action at multiple sites.

Shaham, Shalev, Lu, and De Wit (2003) provided an excellent review on the neuroanatomical substrates that underlie cue-, drug-, and stress-induced reinstatement of drug seeking. Although the current study did not examine drug seeking per se, there are interesting parallels to be made with the conditioned environmental cues that induce activity in the current design and those that involve cue-induced reinstatement of responding. Shaham et al. (2003) proposed that the BLA is involved in cue-induced reinstatement whereas the NAc may be more important for drug-induced reinstatement. Furthermore, experimental studies implicate dopamine D_1-like receptor antagonists and agonists as well as D_2-like receptor antagonists in cue-induced reinstatement based on cocaine. Further studies are needed to integrate the growing dopamine D_3 literature with these findings.

Future studies examining the dose response profile of BP 897 would increase confidence in the current findings and may provide useful information on what role the partial agonist properties of BP 897 may play in attenuating responding for conditioned cues. The ability of BP 897 to selectively disrupt responding for secondary reinforcers, without affecting the incentive salience of primary reinforcers, suggests an application on treating drug relapse in abstinent drug users.

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