The dopamine D_3 receptor-preferring partial agonist BP 897 dose-dependently attenuates the expression of amphetamine-conditioned place preference in rats

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Previously we reported that systemic administration of the dopamine D_3 receptor-preferring partial agonist BP 897 blocked the expression, but not the acquisition, of amphetamine-conditioned activity. This suggested the hypothesis that BP 897 would block the expression, but not the acquisition, of amphetamine-conditioned place preference (CPP). Thus, during preconditioning rats had access to two chambers connected by a tunnel for three 15-min sessions. During eight conditioning days with the tunnel blocked, one chamber was paired with drug administration for four 30-min sessions, alternating with pairing of the other chamber with saline administration. In a drug-free test session, time on the drug-paired side was compared to time spent there in preconditioning; a significant increase was defined as a place preference. Systemic amphetamine (2.0 mg/kg) or amphetamine + BP 897 (1.0, 2.0 mg/kg) during conditioning produced a significant place preference, while administration of BP 897 (1.0 or 2.0 but not 0.5 mg/kg) during the test blocked the amphetamine-CPP. There was no evidence that BP 897 produced a conditioned aversion. Results supported the hypothesis that BP 897 would block expression, but not acquisition, of amphetamine-CPP. *Behavioural Pharmacology* 16:181–186 © 2005 Lippincott Williams & Wilkins.

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Introduction

The mesolimbic dopamine (DA) system has been implicated in reward in intra-cranial self-stimulation (Breese and Cooper, 1974; Rolls *et al.*, 1974; Robertson and Mogenson, 1978), conditioned activity and conditioned place preference (CPP) studies (for a review, see Beninger and Miller 1998). Injections of DA agonists, e.g. amphetamine or cocaine, into mesolimbic DA system structures, e.g. nucleus accumbens (NAc) (Phillips *et al.*, 1975) or amygdala (for a review, see Everitt *et al.*, 2003), are effective in modulating the acquisition or expression of behaviours conditioned to previously neutral stimuli. Furthermore, the application of DA receptor antagonists into these structures has been shown to disrupt the acquisition of this type of learning (Phillips *et al.*, 2002a).

Sokoloff *et al.* (1990) isolated and cloned the DA D_3 receptor, which was later found to be less widely distributed in the brain than the DA D_2 receptor. In addition to caudate regions and the islands of Calleja, mesolimbic structures contain large numbers of D_3 receptors (Levant, 1998). This suggested a potential role in reward for this receptor. Although the islands of Calleja contain the highest density of D_3 receptors in the brain, the functions of these structures remain poorly understood.

A DA agent with some specificity for the D_3 receptor is the partial agonist 1-(4-(2-naphthoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine HCl (BP 897), shown to be effective both *in vitro* and *in vivo* (Pilla *et al.*, 1999). Intraperitoneal administration selectively blocked cocaine-seeking but not cocaine-taking behaviour (Pilla *et al.*, 1999), and BP 897 blocked the expression, but not the acquisition, of amphetamine-conditioned activity (Aujla *et al.*, 2002). Intra-NAc or intra-amygdala BP 897 similarly blocked the expression but not the acquisition of conditioned activity based on NAc injections of amphetamine (Aujla and Beninger, 2004). Thus, BP 897 attenuates the ability of conditioned stimuli to elicit responses without affecting the ability of unconditioned rewards to control behaviour.

The CPP paradigm has been used extensively to assess reward-related learning in rats. Previous work has shown that systemic or intra-NAc DA agonists, such as amphetamine or cocaine, produce a place preference (Tzschentke, 1998). Gyertyan and Gal (2003) evaluated a number of D_3 receptor-preferring agents. They reported

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no difference between time spent in a cocaine (10 mg/kg)-paired versus a cocaine (10 mg/kg) + BP 897 (1.0 mg/kg)-paired chamber during a drug-free test session. These results were consistent with previous findings indicating a lack of effect of BP 897 on unconditioned reward (Pilla *et al.*, 1999; Aujla *et al.*, 2002; Aujla and Beninger, 2004); Gyertyan and Gal (2003) did not examine the effect of BP 897 prior to the test session on the expression of a cocaine-CPP.

In the current study, we evaluated the effect of BP 897 on the establishment and the expression of an amphetamine-CPP. Rats received drug or saline in one of two chambers in a three-chambered apparatus. Rats were then given free access to all chambers during a drug-free test day. The amount of time spent in each compartment was measured and a significant increase in time spent on the drug-paired side was interpreted as a CPP. As previous work has indicated that BP 897 selectively attenuates the expression, but not the acquisition, of conditioned responding for reward, we hypothesized that the administration of BP 897 would attenuate amphetamine-CPP when administered on an amphetamine-free test session, but not when administered prior to conditioning sessions.

Methods

Subjects

Treatment of rats was in accordance with the guidelines of the Animals for Research Act, the Canadian Council on Animal Care, and relevant university policies and was approved by the Queen's University Animal Care Committee. Experimentally naive male Wistar rats ($N = 72$) (Charles River, St-Constant, Quebec, Canada), weighing 225–250 g were housed in pairs in clear plastic shoebox-style cages with sterilized wood-chip bedding material. Animals were maintained in a temperature-controlled ($21 \pm 1^{\circ}C$) colony room on a reversed 12-hour light–dark cycle (lights off at 07.00 hours). Food (Purina rodent laboratory chow #5001) and water were freely available in the home cages throughout the experiment.

Apparatus

Four rectangular wooden boxes consisted of two compartments ($38 \times 27 \times 36$ cm) with removable Plexiglas covers connected by a tunnel ($8 \times 8 \times 8$ cm). The tunnel could be closed by inserting removable plastic guillotine-style doors. The two initially neutral compartments were visually distinct: each compartment wall consisted of either urethane-sealed wood or painted black-and-white vertical stripes (1 cm wide). The compartment floors were also distinct: one type was made of galvanized steel mesh, and the other was constructed of parallel stainless-steel bars (1 cm apart). Tunnel floors were constructed of galvanized sheet metal. The arrangement of walls and floor types was such that each box had a unique configuration. Six photocell emitters and detectors were located in each box: two in each compartment (height 5 cm) and one at each end of the tunnel (height 3 cm). A 6809 micro-controller using custom-made software, controlled by a Macintosh computer, was used to record beam breaks or the time spent in each compartment. For further details of the apparatus, see Brockwell *et al.* (1996).

Procedure

Using an unbiased CPP paradigm, the procedure consisted of three phases: preconditioning, conditioning and test. For all phases, animals were tested during the same time period (09.00–13.00 hours) each day and received one session per day.

Preconditioning

During three 15-min sessions, rats were exposed to the entire box. No drugs were administered during this phase. Rats were placed in a particular compartment designated as the start compartment. The start compartment was counterbalanced across rats: half of the rats started on the left side and the other half started on the right side of the conditioning chamber. The amount of time spent in each compartment was recorded.

Conditioning

During eight 30-min sessions, rats were confined to one compartment only, alternate compartments on alternate days. Intraperitoneal (i.p.) drug injections preceded placement into one compartment on days 1, 3, 5 and 7, while saline injections preceded placement into the other compartment on days 2, 4, 6 and 8. Rats received the following injections during conditioning and testing (i.e. conditioning/testing). A dose of 2.0 mg/kg of amphetamine (amph) was used in each group ($N = 12$; note: sal = saline):

- amph/sal
- amph/BP 897 (0.5 mg/kg)
- amph/BP 897 (1.0 mg/kg)
- amph/BP 897 (2.0 mg/kg)
- amph + BP 897 (1.0 mg/kg)/sal
- amph + BP 897 (2.0 mg/kg)/sal

The designation of the drug-paired compartment was counterbalanced, so that for half of the rats the start compartment (designated in preconditioning) was paired with drug, whereas for the other half it was paired with saline. The counterbalancing procedure was determined prior to the start of the current experiment; thus, the distribution of preconditioning durations did not influence assignment of conditioning chamber. On all conditioning days the number of beam breaks was recorded as a measure of activity.

Testing

During one 15-min test session, rats were exposed again to the entire apparatus with the guillotine doors removed. The amount of time spent in each compartment was recorded.

Drugs

D-Amphetamine sulphate (amph) (USP, Rockville, Maryland, USA) (2.0 mg/ml i.p.) was dissolved in sterile saline (sal), and this preparation was freshly made daily, a maximum of 30 min prior to the onset of the experiment. 1-(4-(2-Naphthoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine HCl (BP 897) (Bioprojet, Paris, France), dissolved in dimethylsulphoxide in doses of 0.5, 1.0 and 2.0 mg/kg, was freshly made daily.

Statistical analyses

A one-way ANOVA followed by simple effects analysis, comparing time spent in each compartment averaged over days of preconditioning, assessed possible compartment bias for each group. Planned *t*-tests, comparing time spent in the tunnel during the average of preconditioning days versus test for each group, assessed changes in tunnel time. Such changes could affect time spent on the drug-paired side independently of a change in side preference.

Planned *t*-tests, comparing time spent on the drug-paired side during preconditioning to time spent on the drug-paired side during test, were used to assess place preference. CPP occurs if animals spend significantly more time in the drug-paired compartment during the test session as compared to the average from the three preconditioning sessions. A one-way ANOVA followed by Tukey Honestly Significant Difference (HSD) *post-hoc* analysis, comparing time spent on the drug-paired side across treatment conditions, supplemented the initial analysis.

Two two-way ANOVAs followed by simple effects analysis were used to examine activity during conditioning sessions. An alpha level of 0.05 was used for all analyses.

Results

Place conditioning

There was no significant difference in time spent on the drug-paired side versus the vehicle-paired side during preconditioning in any of the groups (Table 1). There was no significant change in tunnel time from preconditioning to test in any of the treatment conditions (Table 2).

The change in time spent in the drug-paired side from preconditioning to test was used to evaluate place conditioning for each group (Fig. 1). The mean of the three preconditioning days for each group was used for the purpose of this analysis. There was a significant increase in time spent on the drug-paired chamber from preconditioning to test for the amph/sal [$t(11) = -3.44$, $P < 0.01$], amph/BP 0.5 [$t(11) = -2.66$, $P < 0.05$], amph + BP 1.0/sal [$t(11) = -2.84$, $P < 0.05$], and amph + BP 2.0/sal [$t(11) = -2.97$, $P < 0.05$] groups. There was no significant change in time spent on the drug-paired side for the amph/BP 1.0 [$t(11) = -0.23$, ns] and amph/BP 2.0 [$t(11) = 0.41$, ns] groups.

Mean preconditioning and test day results were subjected to a two-way mixed-design ANOVA followed by simple effects analysis. Results yielded a significant group by phase interaction [$F(5,66) = 2.59$, $P < 0.05$] as well as a significant main effect of group [$F(5,66) = 2.32$, $P < 0.05$] and phase [$F(1,66) = 10.87$, $P < 0.05$]. Simple effects analysis of group at each phase revealed a significant effect of group during the test day [$F(5,131) = 4.79$, $P < 0.01$] but not on the preconditioning days [$F(5,131) = 0.125$, ns]. Tukey HSD *post-hoc* tests revealed that the amph/BP 1.0 and the amph/BP 2.0 groups spent significantly less time on the drug-paired side than the amph/sal, amph/BP 0.5, amph + BP 1.0/sal, or amph + BP 2.0/sal group.

Locomotor activity

Amphetamine enhanced activity in all groups (Table 3). A three-way group × day × drug ANOVA revealed a main effect of drug [$F(5,66) = 1233.34$, $P < 0.01$] on activity during conditioning, revealing increased activity on the amphetamine-, amphetamine + BP 1.0-, or amphetamine + BP 2.0-paired side.

Discussion

The results can be summarized as follows: (1) amphetamine produced a place preference; (2) the DA D_3 receptor-preferring partial agonist BP 897, prior to the test session, dose-dependently blocked the place preference produced by amphetamine; (3) BP 897, prior to amphetamine conditioning sessions, did not

Table 1 Time (s) (±SEM) spent in the to-be-drug- and vehicle-paired sides during preconditioning, averaged over days

Treatment (dose)	Time (s)		*t*	*P*
	Vehicle	Drug		
amph/sal	419.75 (±19.06)	403.67 (±18.08)	0.24	ns
amph/BP 0.5	426.00 (±26.76)	406.08 (±26.29)	0.36	ns
amph/BP 1.0	435.42 (±25.69)	393.83 (±23.66)	0.84	ns
amph/BP 2.0	407.42 (±29.18)	413.75 (±23.92)	0.12	ns
amph + BP 1.0/sal	419.25 (±25.54)	403.67 (±21.87)	0.33	ns
amph + BP 2.0/sal	410.47 (±19.87)	431.14 (±20.27)	0.52	ns

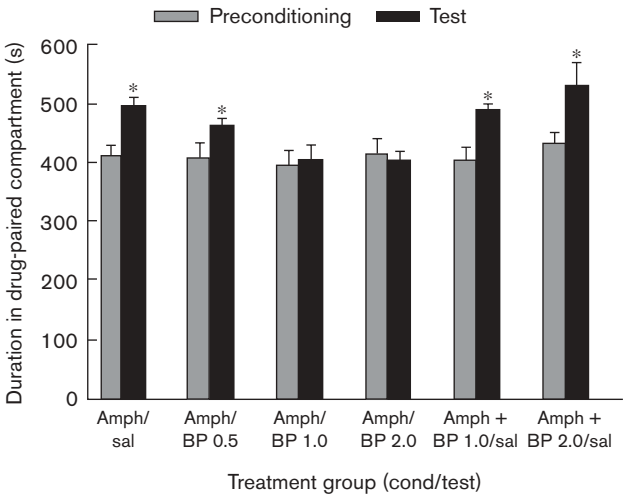
amph, amphetamine; BP, BP 897; ns, not significant; sal, saline; SEM, standard error of the mean.

Table 2 Tunnel time (s) (±SEM): preconditioning versus test

Treatment	Time (s)		*t*	*P*
	Pre-conditioning	Test		
amph/sal	69.42 (±2.99)	72.42 (±3.78)	0.69	ns
amph/BP 0.5	67.92 (±4.66)	71.42 (±2.79)	0.58	ns
amph/BP 1.0	70.75 (±3.89)	73.92 (±3.89)	0.69	ns
amph/BP 2.0	78.83 (±8.09)	71.50 (±4.66)	0.85	ns
amph + BP 1.0/sal	77.08 (±5.00)	67.25 (±4.47)	2.00	ns
amph + BP 2.0/sal	56.80 (±5.15)	52.00 (±5.87)	1.08	ns

amph, amphetamine; BP, BP 897; ns, not significant; sal, saline; SEM, standard error of the mean.

Fig. 1



Mean (+SEM) time (s) spent in the drug-paired chamber during preconditioning and test. *Significantly ($P<0.05$) different from preconditioning by *t*-test. Abbreviations: Amph, amphetamine; BP, BP 897; cond, conditioning; sal, saline.

attenuate place preference; (4) BP 897 had no significant effect on the activity-stimulating effects of amphetamine. Thus, there was dissociation between the effects of BP 897 on the acquisition and the expression of amphetamine-CPP.

An important consideration when evaluating place preference studies is state-dependent learning. It is possible that a drug, when administered in the conditioning or test sessions but not both, acts as a cue in such a way that learning does not generalize from one phase to the other. This alteration in a rat's 'state' may then confound any observed attenuation of place preference. However, there is good evidence that this was not the case. Thus, rats in the amph + BP 897 (1.0)/sal group and amph + BP 897 (2.0)/sal groups showed a place preference. This indicates that the presence of BP 897 during conditioning was not acting as a cue that was controlling behaviour.

The current findings are in agreement with previous studies showing that BP 897 selectively interferes with the ability of conditioned stimuli to control behaviour, while having no effect on the ability of primary rewards to condition behaviour. Thus, Pilla *et al.* (1999) found that systemic BP 897 blocked cocaine-seeking, but not cocaine-taking, behaviour in rats. Aujla *et al.* (2002) found that systemic BP 897 selectively blocked the expression, but not the acquisition, of amphetamine-conditioned activity in rats. Aujla and Beninger (2004) found that intra-NAc or intra-amygdala BP 897 similarly blocked the expression but not the acquisition of conditioned activity based on NAc injections of amphetamine.

Support for a possible role of the DA D_3 receptor in reward-related learning comes from a recent study showing that systemic administration of the D_3 receptor antagonist SB 277011-A, an agent more selective for D_3 versus D_2 receptors than BP 897, attenuated cocaine seeking under the control of a conditioned reward but did not affect cocaine reward (Di Ciano *et al.*, 2003). Also, Cervo *et al.* (2003) recently reported that BP 897 attenuated responding on a previously cocaine-reinforced lever in the presence of cocaine-associated cues. The current finding that BP 897 blocked expression but not acquisition does not preclude the possibility that higher doses of BP 897 given during acquisition might be effective. Within the dose range tested, the finding that BP 897 blocked expression but not acquisition of an amphetamine-CPP is in agreement with previous results.

Gyertyan and Gal (2003) evaluated the effects of a number of D_3 receptor-preferring agents, including BP 897, in CPP. Their finding that test session time in the BP 897 (1.0 mg/kg) + cocaine (10 mg/kg)-paired chamber was not significantly different from that in the cocaine (10 mg/kg)-paired chamber is consistent with the current finding that time spent in the drug-paired side in the BP 897 (1.0 mg/kg) + amphetamine (2.0 mg/kg) conditioned group was not significantly different from that of the amphetamine (2.0 mg/kg) alone group. Thus, BP 897 failed to disrupt the acquisition of a cocaine-CPP (Gyertyan and Gal, 2003). In addition to BP 897, Gyertyan and Gal (2003) found that other D_3 receptor-preferring agents, including the antagonists nafadotride, SB-277011 and U-99194A, as well as the agonists PD-128907 and 7-OH-DPAT, failed to influence

Table 3 Mean (±SEM) locomotor activity counts during conditioning session

	Treatment	Vehicle session				
		1	2	3	4	Average
1	amph/sal	259.67 ± 21.64	293.67 ± 24.47	316.25 ± 26.35	292.88 ± 29.00	304.40 ± 25.37
2	amph/BP 0.5	330.17 ± 27.51	294.42 ± 24.58	286.83 ± 23.90	317.33 ± 26.45	307.31 ± 25.61
3	amph/BP 1.0	302.25 ± 25.19	297.67 ± 24.81	281.42 ± 23.45	290.17 ± 24.18	292.88 ± 24.41
4	amph/BP 2.0	248.17 ± 20.68	258.17 ± 21.51	352.42 ± 29.37	246.92 ± 20.58	276.42 ± 23.03
5	amph + BP 1.0/sal	263.42 ± 21.95	304.25 ± 25.35	350.83 ± 29.24	253.00 ± 21.08	292.88 ± 24.41
6	amph + BP 2.0/sal	337.92 ± 22.21	394.58 ± 29.62	369.75 ± 22.86	384.25 ± 21.85	371.63 ± 24.13
	Treatment	Drug session				
		1	2	3	4	Average
1	amph/sal	837.25 ± 69.77	864.00 ± 72.00	744.33 ± 62.03	858.33 ± 71.53	825.98 ± 68.83
2	amph/BP 0.5	798.82 ± 66.58	742.00 ± 61.83	828.25 ± 69.02	855.08 ± 71.26	806.06 ± 67.17
3	amph/BP 1.0	864.75 ± 72.06	744.58 ± 62.05	787.67 ± 65.64	932.83 ± 77.74	832.46 ± 69.37
4	amph/BP 2.0	853.92 ± 71.16	887.75 ± 73.98	817.00 ± 68.08	783.08 ± 65.26	835.44 ± 69.62
5	amph + BP 1.0/sal	799.67 ± 66.64	781.58 ± 65.13	773.75 ± 64.48	797.42 ± 66.45	788.10 ± 65.68
6	amph + BP 2.0/sal	540.25 ± 59.16	586.17 ± 71.52	636.17 ± 78.59	663.58 ± 77.97	606.54 ± 71.81

amph, amphetamine; BP, BP 897; sal, saline; SEM, standard error of the mean.

cocaine-CPP when administered prior to the conditioning sessions.

Ashby *et al.* (2003) and Vorel *et al.* (2002) found that systemic administration of SB-277011 blocked not only the expression, but also the establishment, of a heroin- or cocaine-CPP in rats. Durate *et al.* (2003) reported that BP 897 blocked both the acquisition and expression of a cocaine-CPP but had no effect on a morphine- or food-CPP. These results were surprising given the findings of the current study, as well as those of Gyertyan and Gal (2003) that D_3 receptor-preferring agents, including SB-277011, failed to affect the establishment of place conditioning based on psychomotor stimulants. These conflicting findings await resolution.

Although BP 897 and SB 277011-A are D_3 receptor-preferring agents, they also affect other receptors, including the D_2 dopamine receptor. This makes it difficult to attribute unequivocally the effect of one of these agents to a specific action at a specific receptor subtype. The specificity of some D_3 receptor-preferring agents was also brought into question by the observation that those agents remained effective in tests of physiological and unconditioned behavioural responses in D_3 receptor knockout mice (Boulay *et al.*, 1999). Although results with mutant mice must be viewed with caution, because compensatory developmental changes may alter the function of neurotransmitter systems, the results also suggest caution in attributing the observed effects of a non-specific pharmacological agent to a particular receptor.

Past studies examining DA antagonists, including haloperidol (Spyraki *et al.*, 1982), sulpiride, metoclopramide (Hiroi and White, 1991) or pimozide (Beninger and Hahn, 1983), have shown disruption in the acquisition, but not expression, of amphetamine-conditioned behaviours. Hiroi and White (1991) reported attenuation of the acquisition of an amphetamine-CPP in rats pretreated with the D_2-preferring agents metoclopramide or sulpiride, at doses that did not affect expression. However, they also reported that at higher doses these agents did indeed attenuate expression. Perhaps the higher doses that affected expression also affected D_3 receptors, making the results consistent with other reports that D_3 receptor-preferring antagonists block expression of conditioned responses. The use of non-selective compounds (with respect to D_2 versus D_3 receptors) in the past makes it difficult to draw conclusions regarding the role of D_2 receptors in expression of conditioned responses. Clearly, further studies employing more selective D_2 compounds are needed before we begin to delineate effectively the roles of D_2 and D_3 receptors in behaviours under the control of unconditioned versus conditioned rewards.

Phillips and colleagues have studied the behavioural effects of centrally administered D_3 agents (Hitchcott *et al.* 1997; Hitchcott and Phillips, 1998a, b; Phillips *et al.*, 2002a, b). Hitchcott and Phillips (1998b) found that intra-amygdala administration of the mixed D_3/D_2 receptor agonist 7-hydroxy-dipropylaminotetralin (7-OH-DPAT), but not the D_1 receptor agonist SKF 38393 or the D_2 receptor agonist quinpirole, enhanced the Pavlovian association of a tone or light with a 10% sucrose solution. This enhancement was manifested as an increased rate of acquisition of discriminated approach behaviour. Intra-amygdala administration of the D_3 receptor-preferring antagonist nafadotride blocked amphetamine-enhanced discriminated approach to a 10% sucrose solution (Phillips *et al.*, 2002a). This may provide evidence that DA D_3 receptors in the amygdala are important for reward.

Few studies have examined the effects of BP 897 administered centrally. Aujla and Beninger (2004) found

that BP 897 (1.0 µg/0.5 µl/side) injected into the basolateral amygdala (BLA) or NAc attenuated conditioned activity based on amphetamine, but had no effect with given in conditioning sessions. Le Foll *et al.*(2002) found that i.p. administration of BP 897 in cocaine cue-conditioned mice inhibited c-*fos* expression in the ventral tegmental area (VTA) while activating expression in the amygdala. No changes were seen in these structures in mice that received saline–cue pairings. Nor were changes seen in the NAc (core or shell), caudate-putamen, bed nucleus of the stria terminalis, hippocampus (CA1, CA2, CA3), or the paraventricular nucleus of the hypothalamus. These, and the behavioural findings, suggest that BP 897 may affect amphetamine- and cocaine-conditioned cues via the VTA–NAc–amygdala circuitry.

BP 897 is a partial agonist *in vitro* and acts as an agonist or antagonist *in vivo* (Pilla *et al.*, 1999), making it difficult to infer its relevant action for the attenuated expression of CPP observed here. However, Pilla *et al.* (1999) and Di Ciano *et al.* (2003), respectively using BP 897 or the somewhat more D_3 receptor-preferring antagonist SB-277011-A, observed similar blocking effects on responding for a cocaine cue. Le Foll *et al.* (2002) found similar blocking effects of BP 897 and SB-277011-A on the expression of cocaine-conditioned activity. These results may provide evidence for a role for D_3 receptors in responding to conditioned cues.

The current results are consistent with the notion that BP 897 would be a potentially effective treatment for preventing drug relapse by reducing the motivational properties of conditioned stimuli that have become strongly associated with drug taking (Le Foll *et al.*, 2000). People, locations, or drug-related paraphernalia that reliably predict drug administration may stimulate relapse. The inability of BP 897 to support self-administration (Pilla *et al.*, 1999) indicates that this agent does not have a high abuse liability. Although the selectivity of available agents remains relatively low, the present data suggest that D_3 receptors may mediate the behavioural effects of conditioned stimuli.

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References

Ashby CRJ, Paul M, Gardner EL, Heidbreder CA, Hagan JJ (2003). Acute administration of the selective D3 receptor antagonist SB-277011A blocks the acquisition and expression of the conditioned place preference response to heroin in male rats. *Synapse* **48**:154–156.

Aujla H, Beninger RJ (2004). Intra-BLA or intra-NAc infusions of the dopamine D3 receptor partial agonist, BP 897 block intra-NAc amphetamine conditioned activity. *Behav Neurosci* **118**:1324–1330.

Aujla H, Sokoloff P, Beninger RJ (2002). A dopamine D3 receptor partial agonist blocks the expression of conditioned activity. *Neuroreport* **13**:173–176.

Beninger RJ, Hahn BL (1983). Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. *Science* **220**:1304–1306.

Beninger RJ, Miller R (1998). Dopamine D1-like receptors and reward-related incentive learning. *Neurosci Biobehav Rev* **22**:335–345.

Boulay D, Depoortere R, Rostene W, Perrault G, Sanger DJ (1999). Dopamine D3 receptor agonists produce similar decreases in body temperature and locomotor activity in D3 knock-out and wild-type mice. *Neuropharmacology* **38**:555–565.

Breese GR, Cooper BR (1974). Proceedings: Evidence for a dopaminergic involvement in the maintenance of self-stimulation. *Psychopharmacol Bull* **10**:45–46.

Brockwell NT, Ferguson DS, Beninger RJ (1996). A computerized system for the simultaneous monitoring of place conditioning and locomotor activity in rats. *J Neurosci Methods* **64**:227–232.

Cervo L, Carnovali F, Stark JA, Mennini T (2003). Cocaine-seeking behavior in response to drug-associated stimuli in rats: involvement of D3 and D2 dopamine receptors. *Neuropsychopharmacology* **28**:1150–1159.

Di Ciano P, Underwood RJ, Hagan JJ, Everitt BJ (2003). Attenuation of cue-controlled cocaine-seeking by a selective D3 dopamine receptor antagonist SB-277011-A. *Neuropsychopharmacology* **28**:329–338.

Durate C, Lefebvre C, Chaperon F, Hamon M, Thiebot MH (2003). Effects of a dopamine D3 receptor ligand, BP 897, on acquisition and expression of food-, morphine-, and cocaine-induced conditioned place preference, and food seeking behavior in rats. *Neuropsychopharmacology* **28**:1903–1915.

Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann NY Acad Sci* **985**:233–250.

Gyertyan I, Gal K (2003). Dopamine D3 receptor ligands show place conditioning effect but do not influence cocaine-induced place preference. *Neuroreport* **14**:93–98.

Hiroi N, White NM (1991). The amphetamine conditioned place preference: differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. *Brain Res* **552**:141–152.

Hitchcott PK, Phillips GD (1998a). Double dissociation of the behavioural effects of R(+) 7-OH-DPAT infusions in the central and basolateral amygdala nuclei upon Pavlovian and instrumental conditioned appetitive behaviours. *Psychopharmacology (Berl)* **140**:458–469.

Hitchcott PK, Phillips GD (1998b). Effects of intra-amygdala R(+) 7-OH-DPAT on intra-accumbens d-amphetamine-associated learning. I. Pavlovian conditioning. *Psychopharmacology (Berl)* **140**:300–309.

Hitchcott PK, Bonardi CM, Phillips GD (1997). Enhanced stimulus–reward learning by intra-amygdala administration of a D3 dopamine receptor agonist. *Psychopharmacology (Berl)* **133**:240–248.

Le Foll B, Schwartz JC, Sokoloff P (2000). Dopamine D3 receptor agents as potential new medications for drug addiction. *Eur Psychiatry* **15**:140–146.

Le Foll B, Frances H, Diaz J, Schwartz JC, Sokoloff P (2002). Role of the dopamine D3 receptor in reactivity to cocaine-associated cues in mice. *Eur J Neurosci* **15**:2016–2026.

Levant B (1998). Differential distribution of D3 dopamine receptors in the brains of several mammalian species. *Brain Res* **800**:269–274.

Phillips AG, Brooke SM, Fibiger HC (1975). Effects of amphetamine isomers and neuroleptics on self-stimulation from the nucleus accumbens and dorsal noradrenergic bundle. *Brain Res* **85**:13–22.

Phillips GD, Harmer CJ, Hitchcott PK (2002a). Blockade of sensitisation-induced facilitation of appetitive conditioning by post-session intra-amygdala nafadotride. *Behav Brain Res* **134**:249–257.

Phillips GD, Harmer CJ, Hitchcott PK (2002b). Isolation rearing-induced facilitation of Pavlovian learning: abolition by postsession intra-amygdala nafadotride. *Physiol Behav* **76**:677–684.

Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermuth CG, *et al.* (1999). Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. *Nature* **400**:371–375.

Robertson A, Mogenson GJ (1978). Evidence for a role for dopamine in self-stimulation of the nucleus accumbens of the rat. *Can J Psychol* **32**:67–76.

Rolls ET, Rolls BJ, Kelly PH, Shaw SG, Wood RJ, Dale R (1974). The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. *Psychopharmacology (Berl)* **38**:219–230.

Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC (1990). Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature* **347**:146–151.

Spyraki C, Fibiger HC, Phillips AG (1982). Dopaminergic substrates of amphetamine-induced place preference conditioning. *Brain Res* **253**:185–193.

Tzschentke TM (1998). Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog Neurobiol* **56**:613–672.

Vorel SR, Ashby CR Jr, Paul M, Liu S, Hayes R, Hagan JJ, *et al.* (2002). Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci* **22**:9595–9603.