



Published in final edited form as:

*Brain Res Brain Res Rev.* 2005 July ; 49(1): 77–105. doi:10.1016/j.brainresrev.2004.12.033.

## The role of central dopamine D<sub>3</sub> receptors in drug addiction: a review of pharmacological evidence

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### Abstract

The cDNA for the dopamine D<sub>3</sub> receptor was isolated and characterized in 1990. Subsequent studies have indicated that D<sub>3</sub> receptors, as well as D<sub>3</sub> receptor mRNA, are primarily localized in limbic regions in mammals. This finding led to the postulate that D<sub>3</sub> receptors may be involved in drug dependence and addiction. However, this hypothesis has been difficult to test due to the lack of compounds with high selectivity for central D<sub>3</sub> receptors. The interpretation of results from studies using mixed D<sub>2</sub>/D<sub>3</sub> agonists and/or antagonists is problematic because these agents have low selectivity for D<sub>3</sub> over D<sub>2</sub> receptors and it is likely that their actions are primarily related to D<sub>2</sub> receptor antagonism and possibly interaction with other neurotransmitter receptors. Currently, with the synthesis and characterization of new highly selective D<sub>3</sub> receptor antagonists such as SB-277011-A this difficulty has been surmounted. The purpose of the present article is to review, for the first time, the effects of various putative D<sub>3</sub> receptor selective compounds in animal models of drug dependence and addiction. The results obtained with highly selective D<sub>3</sub> receptor antagonists such as SB-277011-A, SB-414796, and NGB-2904 indicate that central D<sub>3</sub> receptors may play an important role in drug-induced reward, drug-taking, and cue-, drug-, and stress-induced reinstatement of drug-seeking behavior. Provided these results can be extrapolated to human drug addicts, they suggest that selective DA D<sub>3</sub> receptor antagonists may prove effective as potential pharmacotherapeutic agents to manage drug dependence and addiction.

### Keywords

Addiction; Brain stimulation reward; Conditioned place preference; Dopamine D<sub>3</sub> receptors; SB-277011-A; Self-administration

## 1. Introduction: drug addiction, the mesolimbic DA system, and the DA D<sub>3</sub> receptor

Drug addiction is a dynamic phenomenon characterized by several key stages: (1) initiation or acquisition of drug-taking, (2) compulsive drug taking, and (3) drug taking coupled with a marked narrowing of the behavioral repertoire. The behavioral progression typically ends with excessive drug intake, loss of control over intake, and vulnerability to relapse [156]. One of the main challenges in drug dependence research is to understand the psychobiological dysregulation, and by extension, the molecular, cellular, and system processes that underlie these various phases.

In order to assess the neuroadaptations occurring within the brain reward systems in response to acute and repeated exposure to drugs of abuse, one must first understand the neurobiological bases of drug reward [183]. Consequently, molecular and cellular approaches have emphasized differences in the primary sites of action of drugs of abuse [52]. In contrast, the neural systems approach has explored the possible commonalities of the effects of such drugs [213]. The major focus of most of these investigations has been the mesocorticolimbic dopamine (DA) system originating from the ventral tegmental area (VTA) and projecting towards a wide range of limbic and telencephalic structures including the olfactory tubercle, the amygdala, frontal and limbic cortices, especially the medial prefrontal cortex (mPFC), and the nucleus accumbens (NAc). The NAc occupies a prominent position in the ventral striatum and is a main target of the mesotelencephalic DA system. As such, DA neurotransmission in the NAc provides the framework for theories exploring the chemoarchitectural substrates of reward and motivation, including aspects of drug addiction.

The role of mesolimbic DA in general reinforcement processes clearly pointed towards DA receptors as potential targets for the study of drug consumption and craving. After the cloning of the D<sub>1</sub> and D<sub>2</sub> receptors [39,204,315] several additional low-abundance DA receptors were identified. These new subtypes included the D<sub>3</sub> and D<sub>4</sub> receptors, which are homologous to the D<sub>2</sub> receptor, and the D<sub>5</sub> receptor, which is homologous to the D<sub>1</sub> receptor [273,286,292]. A growing body of evidence suggests strongly that the DA D<sub>3</sub> receptor is significantly involved in mechanisms of drug dependence and abuse [6,10,41,43,84,131,167,295]. These findings have underlined the need for selective tools to investigate the role of the DA D<sub>3</sub> receptor in drug dependence. The present review will not cover molecular biological (gene organization, receptor synthesis, receptor isoforms, and protein structure) or cellular signaling mechanisms associated with the DA D<sub>3</sub> or other DA receptor subtypes (see [175]), but will specifically focus on the rationale for the use of selective DA D<sub>3</sub> receptor antagonists as potential pharmacotherapeutic agents to manage drug dependence and addiction. The review will start with a discussion of the selective distribution of the D<sub>3</sub> receptor in the mesolimbic DA system. Functional pharmacological aspects of different DA D<sub>3</sub> and mixed D<sub>3</sub>/D<sub>2</sub> receptor agonists and antagonists will then be summarized in the context of drug addiction paradigms. Finally, potential sites of action of DA D<sub>3</sub> receptor antagonists in the brain will be discussed.

## 2. Localization of DA D<sub>3</sub> receptors

The DA D<sub>3</sub> receptor was initially cloned from a rat cDNA library by using probes derived from the DA D<sub>2</sub> receptor sequence [273]. The cloning of the human D<sub>3</sub> receptor was reported thereafter [112], followed by the murine D<sub>3</sub> receptor [100]. Molecular neurobiology techniques permitted the study of the D<sub>3</sub> receptor in vitro by transfection in cells that do not normally express DA receptors. Molecular methods also allowed the study of receptor messenger ribonucleic acid (mRNA) in the brain.

### 2.1. Rodent DA D<sub>3</sub> receptor localization under basal condition

The greatest densities of D<sub>3</sub> mRNA in rat brain are found primarily in limbic brain areas such as the NAc (rostral pole and parts of shell), islands of Calleja, and olfactory tubercle [30,66,77,78,162,197,233,273]. Other brain areas reported to contain high levels of D<sub>3</sub> mRNA include the medial and ventral lateral geniculate nuclei, mammillary nucleus, magnocellular preoptic nucleus, lateral substantia nigra pars compacta, dorsal cochlear nuclei, Purkinje cell layer of the vestibulocerebellum, paracentral thalamic nucleus, bed nucleus of the stria terminalis (BNST), and vertical limb of the diagonal band of Broca [30,77,197]. Bouthenet et al. [30] have reported moderate levels of D<sub>3</sub> mRNA in the amygdala, ventral pallidum, various thalamic and hypothalamic nuclei, superior colliculus, inferior olivary nucleus, and nucleus of the horizontal limb of the diagonal band of Broca. Transcripts for the D<sub>3</sub> receptor are located in the mesencephalic areas rich in DA cell bodies [77,78,282]. The restricted localization of the D<sub>3</sub> receptor has led to the hypothesis that it may play an important role in emotion, cognition, and addiction [117,167,231,232,253,273,275].

In vitro homogenate and autoradiographic studies indicate that DA D<sub>3</sub> receptors are expressed in highest densities in the islands of Calleja, olfactory bulb, NAc, and intermediate lobe of the pituitary [20,27,106,107,117,162, 173,177,179,182,252,258,282] (for reviews, see Refs. [175,258]). The lateral aspect of the substantia nigra pars compacta and the molecular layer of the vestibulocerebellum also contain moderate levels of D<sub>3</sub> receptors.

### 2.2. Rodent DA D<sub>3</sub> receptor localization following drug exposure

DA D<sub>3</sub> mRNA and receptors are increased in cocaine cue conditioned locomotion [168]. A recent series of experiments has also shown that termination of a cocaine self-administration regimen increases DA D<sub>3</sub> binding over time in the NAc core and ventral caudate–putamen, an adaptive change that may occur through regulatory responses to an increase in phasic DA levels associated with cocaine-taking and -seeking behavior [212]. In addition, nicotine-induced conditioned locomotion [169] and nicotine behavioral sensitization [170] are both associated with significant increases in D<sub>3</sub> receptor binding and mRNA levels in the NAc shell without altering D<sub>1</sub> or D<sub>2</sub> receptor mRNA in the NAc shell or core subregions. Furthermore, twice daily morphine administration over 8 consecutive days with an escalating dosing regimen starting at 10 mg/kg was shown to produce a significant increase in D<sub>3</sub> receptor mRNA in the caudate–putamen and ventral midbrain, including the substantia nigra and VTA. Morphine also produced a 25% decrease in D<sub>2</sub> receptor mRNA in the caudate–putamen, but no alterations were seen in mRNA levels related to tyrosine hydroxylase or the DA transporter [278].

### 2.3. Human DA D<sub>3</sub> receptor localization under basal condition

Expression of DA D<sub>3</sub> receptor mRNA in the human brain follows a similar pattern as in the rodent brain [120,162, 194,287]. High levels are present in the islands of Calleja, ventral striatum/NAc, dentate gyrus, and striate cortex. Low to moderate densities are present in the caudate–putamen, anterior and medial thalamic nuclei, amygdala, hippocampal CA region, cortical regions (particularly the anterior cingulate and subcallosal gyrus), lateral geniculate body, substantia nigra pars compacta, locus ceruleus, and median raphé. Receptor binding data also indicate the presence of D<sub>3</sub> receptors in the NAc, internal globus pallidus, ventral pallidum, septum, islands of Calleja, amygdala, and VTA [120,124,132,162,205]. Interestingly, significant inter-species differences have been reported in the distribution of D<sub>3</sub> receptors [176]. For example, although rats, mice, guinea pigs, and humans show similar distributions of D<sub>3</sub> sites in the basal ganglia and limbic forebrain, notable differences are typically observed in hypothalamic, thalamic, and mesencephalic brain areas. Furthermore,

the detection of D<sub>3</sub> sites in the vestibulocerebellum of the rat, but not other species suggests a possible role of DA D<sub>3</sub> receptors in the control of posture, muscle tone, or eye movements in the rat.

#### 2.4. Human DA D<sub>3</sub> receptor localization following drug exposure

Postmortem studies using [<sup>3</sup>H]-(+)-7-OH-DPAT have shown an increase in the number of D<sub>3</sub> receptors in the NAc [190,256] and specific areas of the striatum and substantia nigra [281] in cocaine overdose fatalities compared to drug-free and age-matched controls. A significant elevation in the levels of D<sub>3</sub> receptor mRNA of human cocaine fatalities has also been reported [256] but was not corroborated by another study [195]. The discrepancy between these two studies might be related to the different methods used to determine levels of D<sub>3</sub> receptor mRNA (reverse transcription-polymerase chain reaction (RT-PCR) [256] vs. in situ hybridization [195]). A human postmortem study comparing DA receptor density between smokers and nonsmokers revealed no significant differences in D<sub>3</sub> receptors [63]. In that study, analysis of groups and areas for D<sub>3</sub> receptor binding in the striatum indicated a significant difference between areas, but no difference between smokers, exsmokers and nonsmokers was observed and there was no interaction between groups and areas. However, [<sup>3</sup>H]-7-OH-DPAT binding was focused mainly on the putamen and caudate rather than the NAc. A recent study measured the expression of dopamine D<sub>3</sub> receptor mRNA in peripheral blood lymphocytes by real-time polymerase chain reaction in smokers, former smokers, and nonsmoking control subjects [69]. The results of this study revealed a significant reduction in DA D<sub>3</sub> receptor mRNA expression in smokers, but not former smokers compared with controls. Furthermore, the expression of DA D<sub>3</sub> receptor mRNA in smokers was negatively correlated with daily number of cigarettes, suggesting a selective inhibiting effect of smoking on the expression of DA D<sub>3</sub> receptor mRNA. Additional studies looking at the density of DA D<sub>3</sub> receptors in smokers vs. nonsmokers are clearly warranted.

The above findings suggest that the distribution pattern of DA D<sub>3</sub> receptors in both rodent and human brain is compatible with a major role in emotion, cognition, and processing of motor and sensory information. Postmortem and preclinical studies point to the possibility that chronic abuse of cocaine, nicotine, and opioids may be associated with an adaptive change in D<sub>3</sub> receptors.

### 3. In vitro pharmacological characterization of DA D<sub>3</sub> ligands

A number of agonists and antagonists have been used to characterize the pharmacology of DA D<sub>3</sub> receptors in various expression systems and in the brain. However, results generated from these studies vary considerably and seem to be dependent upon the expression system or tissue, the radioligand, and the in vitro assay conditions used (for a detailed review, see Ref. [175]). For example, the observed D<sub>3</sub> selectivity of several DA agonists may directly result from the use of in vitro conditions that disfavor the high-affinity conformation of the D<sub>2</sub> receptor such as the inclusion of Na<sup>+</sup> in some in vitro assay systems [40,180]. The greatest D<sub>2</sub>/D<sub>3</sub> selectivity with [<sup>3</sup>H]-7-OH-DPAT and [<sup>3</sup>H]-PD128907 can also be obtained in the absence of Mg<sup>2+</sup> and the presence of EDTA [40]. Studies have shown that although selective labeling of putative D<sub>3</sub> sites may be reasonably obtained using [<sup>3</sup>H]-PD128907 or [<sup>3</sup>H]-7-OH-DPAT, labeling of the D<sub>2</sub> site is also observed [20,114,250] as well as labeling of  $\sigma$  [250,296] and 5-HT<sub>1A</sub> receptors [72,198] in rat brain. In our hands, however, [<sup>3</sup>H]-7-OH-DPAT binding to rat brain slice preparations can be fully displaced by the highly selective DA D<sub>3</sub> receptor antagonist SB-277011-A, at doses predicted by the affinity values of [<sup>3</sup>H]-7-OH-DPAT and SB-277011-A for rat D<sub>2</sub> and D<sub>3</sub> receptors [182,229], suggesting that appropriate conditions can be chosen to favor preferential [<sup>3</sup>H]-7-OH-DPAT binding to D<sub>3</sub> receptors in receptor auto-radiography experiments (see Fig. 1 for further details).

In addition to radioligand binding studies, several functional assays including induction of Chinese hamster ovary (CHO) cell mitogenesis, melanocyte aggregation, or extracellular acidification rates in the microphysiometer assay have not only established the agonist or antagonist activity of a variety of DA compounds at the D<sub>3</sub> receptor, but have also contributed to determining their D<sub>2</sub>/D<sub>3</sub> selectivity. In contrast with the significant DA D<sub>3</sub> selectivity reported in some binding studies, agonists such as DA, PD128907, 7-OH-DPAT, quinelorane, and (+)-UH232 exhibited only modest, if any, D<sub>3</sub> selectivity in these functional tests [56,225,226] (for a direct comparison of selectivities obtained from radioligand binding vs. functional assays in CHO cells using the cytosensor microphysiometer, the reader is referred to Ref. [60]).

Overall, these findings clearly demonstrate that the rank order of potencies and selectivities in functional assays is not equivalent to the rank order of radioligand binding affinities and selectivities. These results further emphasize the need to consider both radioligand binding affinities and functional potencies as well as intrinsic activities in order to reliably interpret behavioral effects mediated by DA D<sub>2</sub> and D<sub>3</sub> receptors. Furthermore, they also further underline the need for caution in the use of in vitro binding data in the interpretation of in vivo or in vitro functional studies.

#### 4. Role of DA D<sub>3</sub> receptors in drug addiction: studies with mixed DA D<sub>2</sub>/D<sub>3</sub> receptor agonists

The mixed D<sub>2</sub>/D<sub>3</sub> agonists 7-OH-DPAT [41,42,102,219], quinpirole [41], quinelorane [43,219], pramipexole [43], and PD128907 [43] have all been shown to decrease cocaine self-administration in rats. However, the same mixed D<sub>2</sub>/D<sub>3</sub> agonists have also led to discrepant findings in a wide range of paradigms. For example, 7-OH-DPAT (0.1 mg/kg) inhibits cocaine-seeking behavior as assessed by the conditioned place preference (CPP) paradigm [150] but reinstates intravenous (iv) cocaine self-administration behavior at doses of 3 and 10 mg/kg [257]. In contrast, Khroyan et al. [151] found that neither 7-OH-DPAT (0.01–0.1 mg/kg) nor PD128907 (0.01–0.1 mg/kg) alter cocaine-triggered reinstatement of drug-seeking behavior. Furthermore, 7-OH-DPAT (2.5–74 µg/kg) does not significantly alter brain stimulation reward (BSR) maintained by electrodes in the lateral hypothalamus in rats [128], and 7-OH-DPAT (0.05 mg/kg) given subcutaneously (sc) does not block the development of sensitization to cocaine [191]. However, 7-OH-DPAT can partially substitute for cocaine in the drug discrimination paradigm [1,105,146,161,208,269,280].

These mixed in vivo findings clearly demonstrate that the effect of the aforementioned mixed D<sub>2</sub>/D<sub>3</sub> agonists (see Table 1) in drug addiction paradigms might be related to (1) their lack of selectivity for D<sub>3</sub> over D<sub>2</sub> receptors and/or (2) their ability to have incentive value per se. In support of the first argument (lack of selectivity) are the findings described in the previous section (i.e., radioligand binding studies vs. in vitro functional assays). In addition to lack of D<sub>3</sub> receptor selectivity under in vitro assay conditions, both 7-OH-DPAT and PD128907 may activate D<sub>2</sub> receptors in vivo in rats as a function of the doses used in different behavioral paradigms [2,19,36,71,73,95,146,159,180,181,203,228,293]. For example, behavioral characterizations of both 7-OH-DPAT and PD128907 up to 10 mg/kg revealed U-shaped dose–response curves for both compounds [2,71,228], suggesting activation of D<sub>3</sub> receptors at low doses and increasing D<sub>2</sub> receptor occupancy at higher doses. This hypothesis is further supported by studies based upon D<sub>2</sub> receptor protection from *N*-ethoxycarbonyl-2-ethoxyl-1,2-dihydro-quinilone (EEDQ) alkylation, suggesting that 7-OH-DPAT doses below 0.3 mg/kg are devoid of significant D<sub>2</sub> receptor occupancy [181]. Similarly, studies using DA D<sub>3</sub> knockout mice showed that intraperitoneal (ip) doses of PD128907 in the range of 0.03–0.1 mg/kg affect DA release in wild type, but not knockout mice, suggesting D<sub>3</sub>-mediated effects of PD128907 when given at sufficiently low dose



[314]. Furthermore, 7-OH-DPAT and PD128907 doses below 10 µg/kg have been reported to produce inhibition of novelty-stimulated locomotion in wild type, but not in D<sub>3</sub> receptor knockout mice [227]. All other D<sub>3</sub> knockout studies using 7-OH-DPAT or PD128907 doses at least 10-fold higher reported that neither 7-OH-DPAT nor PD128907 inhibit locomotion through selective D<sub>3</sub> receptor stimulation [28,29], and hence concluded that locomotor inhibitory effects of 7-OH-DPAT are mediated through D<sub>2</sub> autoreceptors or other receptors.

In support of the second argument (incentive value) is that 7-OH-DPAT alone (at 5 mg/kg [187]) or PD128907 alone (at 1 mg/kg [148]) have been reported to produce a significant CPP (however, see Refs. [147,149,150] for contrary findings). Furthermore, 7-OH-DPAT at 0.03 mg/kg [147] or at 0.05–0.1 mg/kg [121] has been reported to produce conditioned place aversion (CPA), as does PD128907 at 1 mg/kg sc [121]. It has also been shown that 7-OH-DPAT can attenuate the CPP response to morphine [245], *D*-amphetamine [149], and cocaine [150] in rats. However, evidence from Ukai et al. [290] indicates that administration of *R*(+)-7-OH-DPAT (0.001–0.1 mg/kg sc) produces an amnesic effect in the passive avoidance learning model in mice, and Smith et al. [270] have demonstrated that systemic administration of 7-OH-DPAT (6 or 25 µg/kg) induces cognitive impairment in the marmoset. Consequently, one cannot rule out the possibility that 7-OH-DPAT may interfere with the animals' association of the appetitive value of these agents with the appropriate cues.

Together, these findings clearly indicate that the degree of functional selectivity of mixed D<sub>2</sub>/D<sub>3</sub> agonists in recombinant systems is too low to allow meaningful discrimination *in vivo* between D<sub>2</sub> and D<sub>3</sub> receptors. The significant controversy around the outcome of *in vivo* studies using mixed DA D<sub>2</sub>/D<sub>3</sub> agonists relates essentially to their lack of selectivity, but also to the possibility that these agents have intrinsic rewarding properties or produce nonspecific aversive effects.

## 5. Role of DA D<sub>3</sub> receptors in drug addiction: studies with the partial DA D<sub>3</sub> receptor agonist BP-897

A series of *in vivo* studies assessed the efficacy of the partial DA D<sub>3</sub> receptor agonist BP-897 in animal models of drug addiction. In 1999, Pilla and colleagues [224] demonstrated that administration of BP-897 (0.05, 0.5, and 1 mg/kg) produces a significant dose-dependent decrease in the number of responses for cocaine in the first, but not the second interval of a second-order schedule of reinforcement without having intrinsic rewarding effects. In support of those findings [224], recent evidence suggests that BP-897 (1 mg/kg) can reduce cocaine-seeking behavior induced by the presentation of stimuli associated with and predictive of cocaine availability after a period of extinction and in the absence of cocaine itself [50]. However, it must be noted that, in contrast with the findings of Pilla et al. [224], a recent report found that, similar to *ip* administration of the D<sub>1</sub> receptor antagonist SCH-23390 (0.1 and 0.2 mg/kg) or oral (*po*) administration of the D<sub>2</sub> receptor antagonist haloperidol (0.2 and 0.5 mg/kg), BP-897 (1 mg/kg *ip*) increased cocaine self-administration under a continuous reinforcement schedule [102].

BP-897 (0.3, 1, or 3 mg/kg *ip*) reduces cocaine cue-induced hyperlocomotion in Swiss-Webster mice [168] as well as nicotine-induced conditioned locomotion [169] and nicotine-induced behavioral sensitization in rats [170]. Aujla et al. [12] also showed that BP-897 (1 mg/kg) blocked the expression of conditioned locomotor activity to amphetamine (2 mg/kg) in male Wistar rats without altering the acquisition of conditioning or the locomotor activating effect of amphetamine.

BP-897 significantly decreases the discriminative stimulus effects of *D*-amphetamine and cocaine [21] and attenuates the expression and acquisition of the CPP response to cocaine without altering the acquisition or expression of the CPP response to food or morphine [88]. However, BP-897 alone produced CPA, a finding congruent with that of Gyertyán and Gál [121], and may also have anxiolytic properties [246].

A recent paper by Campiani et al. [44] reported the pharmacological evaluation of a series of novel arylalkylpiperazine structures related to BP-897 as well as BP-897 itself. BP-897 (1 mg/kg) significantly reduced the number of active lever presses by male Sprague–Dawley rats following re-exposure to cocaine-associated stimuli. In contrast, *compound 5q* (*N*-[4-[4-(2,4-dichlorophenyl)piperazin-1-yl]butyl]-5-chloroindole-2-carboxamide), a selective DA *D*<sub>3</sub> receptor partial agonist ( $K_i D_2 > 10000$  nM;  $K_i D_3 = 0.38 \pm 0.005$  nM;  $K_i 5-HT_{1A} > 10000$  nM) did not significantly alter cocaine-seeking behavior produced by environmental cues previously associated with cocaine self-administration. The explanation for the difference in the behavioral effects between these compounds remains to be elucidated.

It has been hypothesized that BP-897 exerts its anti-addictive actions via a selective partial agonism at *D*<sub>3</sub> receptors. However, antagonism at *D*<sub>3</sub> receptors and/or activity at other receptors might also explain some of the *in vivo* data. In support of the first argument (partial agonism vs. antagonism at *D*<sub>3</sub> receptors) are pharmacological data (forskolin-induced increase in cAMP) indicating that in NG 108-15 cells expressing human *D*<sub>3</sub> receptors, BP-897 behaves as a partial agonist compared to DA (59%) [224]. Similarly, in the mitogenesis assay, the maximum response elicited by BP-897 was 55% of that elicited by the full agonist quinpirole [23,224]. In cells expressing *D*<sub>2</sub> receptors, BP-897 alone does not inhibit cAMP accumulation or elicit mitogenesis [224]. However, it reversibly antagonizes quinpirole-induced mitogenesis, but only at concentrations significantly greater than those required for *D*<sub>3</sub> receptor stimulation [224]. Thus, based on the results obtained by Pilla et al. [224], BP-897 can be classified as a partial *D*<sub>3</sub> receptor agonist. However, recent evidence from studies using microphysiometry shows that in CHO-K1 cells transfected with human *D*<sub>2</sub> and *D*<sub>3</sub> receptors, BP-897 behaves as a full antagonist at both DA *D*<sub>2</sub> ( $pK_b = 8.05$ ) and *D*<sub>3</sub> ( $pK_b = 9.43$ ) receptors [305]. In addition, in CHO cells transfected with human *D*<sub>3</sub> receptors, BP-897 does not stimulate *D*<sub>3</sub> receptors and displays antagonistic effects in a [<sup>35</sup>S]-GTPγS binding assay in cells expressing human *D*<sub>3</sub> receptors [302]. Clearly, different results in the intrinsic activity of partial agonists can be obtained using different assay systems. The observed efficacy of partial agonists could be related to differences in the level of receptor reserve and efficiency of functional coupling. Wood et al. [305] identified BHT920 as a full agonist, but the same compound was identified as only a partial agonist by Pilla et al. [224]. There are also distinct differences between the microphysiometry and mitogenesis assays that are worth noting. The mitogenesis assay requires sustained activation that can be complicated by desensitization and stability of the agonists. The microphysiometry assay involves measurements carried out in real time. The response observed in the microphysiometry assay is likely a direct consequence of activation of *D*<sub>3</sub> receptors whereas the response seen in the mitogenesis assay represents an adaptation of the cell to continuous receptor activation and may be complicated by the presence of endogenous receptors and regulators. Finally, in anesthetized rats, *in vivo* extracellular recording demonstrated that *iv* administration of BP-897 (maximum dose of 8.2 mg/kg) did not significantly alter the firing rate of spontaneously active substantia nigra pars compacta (A9) DA neurons, but did antagonize quinpirole-induced inhibition of firing of these neurons with an ED<sub>50</sub> of 1.1 mg/kg [302]. Taken together, these results suggest that BP-897 may also exert antagonist actions at the DA *D*<sub>3</sub> receptor and that one cannot exclude the possibility that BP-897's antagonism of quinpirole's action is partly related to antagonism at DA *D*<sub>2</sub> receptors.

In support of the second argument (cross-selectivity profile) are data showing that BP-897 has affinity for other neurotransmitter receptors (for a detailed review on BP-897, the reader is referred to Ref. [103]). BP-897 shows moderate affinity for  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors ( $K_i = 60$  and  $83$  nM, respectively), 5-HT<sub>1A</sub> ( $K_i = 84$  nM), and DA D<sub>2</sub> receptors ( $K_i = 61$  nM) [224] (see also Ref. [44]). BP-897 also displays potent antagonistic action at 5-HT<sub>2A</sub> and  $\alpha_1$ -adrenergic receptors (M.J. Millan, personal communication). The interaction with 5-HT<sub>2A</sub> receptors may be important as a recent study in rats indicates that the 5-HT<sub>2A</sub> receptor antagonist M100,907 attenuates the ability of a priming injection of cocaine to reinstate lever pressing [101]. Thus, the effect of BP-897 in some animal models of addiction could be partially related to its antagonist action at 5-HT<sub>2A</sub> receptors. Finally, a recent study reported that the  $K_i$  of BP-897 for human D<sub>4</sub> receptors is 39 nM and the human D<sub>4</sub>/D<sub>3</sub> ratio is 28 [23].

Altogether, both in vitro and in vivo data suggest that BP-897 may act as a D<sub>3</sub> receptor agonist or antagonist. In addition, one cannot rule out the possibility that part of BP-897's action is mediated by interaction with other receptors.

## 6. Role of DA D<sub>3</sub> receptors in drug addiction: studies with mixed DA D<sub>2</sub>/D<sub>3</sub> receptor antagonists

A number of compounds were originally reported to be selective D<sub>3</sub> receptor antagonists, including (+)-AJ-76 [273,274], (+)-UH-232 [273,274], U99194A [122], nafadotride [248], GR103691 [206], and DS-121 [153]. However, evidence from a variety of studies indicates that these compounds either lack sufficient in vitro and/or in vivo selectivity or interact with other receptors and therefore cannot be characterized as selective D<sub>3</sub> receptor antagonists (see Table 1). For example, the in vitro selectivity of (+)-UH-232, (+)-AJ-76, nafadotride, and U99194A for D<sub>3</sub>/D<sub>2</sub> is only 4–8, 2–6, 6–9, and 10–20-fold, respectively [118,175,272,298,307]. Functional and/or behavioral studies suggest that the aforementioned pharmacological agents produce effects associated with D<sub>2</sub> receptor antagonism. For example, systemic administration of (+)-UH-232, (+)-AJ-76, and nafadotride can induce catalepsy and increase prolactin levels in rats [11]. The acute administration of U-99194A, nafadotride, and (+)-UH-232 significantly increases DA turnover in the striatum, NAc, frontal cortex and olfactory tubercle [11]. Levant and Vansell [178] also examined the in vivo occupancy of D<sub>2</sub> receptors by nafadotride (0.1–10 mg/kg ip) in the EEDQ assay. Their results indicate that D<sub>2</sub> receptor antagonism contributes to the pharmacological actions of nafadotride at sc doses above 1 mg/kg and ip doses above 3 mg/kg. A detailed summary of the main behavioral pharmacology of DS-121, nafadotride, U99194, S14297, and PD152255 can be found in Table 2.

## 7. Role of DA D<sub>3</sub> receptors in drug addiction: studies with selective DA D<sub>3</sub> receptor antagonists—SB-277011-A

Radioligand binding studies have shown that SB-277011-A is a selective DA D<sub>3</sub> receptor antagonist with high affinity for the human ( $pK_i$  7.95) and rat ( $pK_i$  7.97) cloned DA D<sub>3</sub> receptor. The ratio of the in vitro D<sub>3</sub>/D<sub>2</sub> affinity of SB-277011-A for human and rat is 120 and 80, respectively [229]. SB-277011-A has a 100-fold selectivity over 66 other receptors, enzymes, and ion channels [229]. SB-277011-A is a potent and competitive antagonist, with  $pK_b$  8.4 (4 nM) in the microphysiology in vitro functional assay using human cloned DA D<sub>3</sub> receptors expressed in CHO cells, and it maintains selectivity with respect to DA D<sub>2</sub> receptors ( $pK_b$  6.5). SB-277011-A has also been shown to readily penetrate the rat brain with a steady-state brain/ plasma ratio of 3.6:1 [229,283]. In the rat, SB-277011-A has an



oral bioavailability of 43%, shows low clearance, and a half-life of 2.0 h. The drug appears to be metabolized by the liver enzyme hepatic aldehyde oxidase [16].

The effects of SB-277011-A per se in in vivo behavioral models are summarized in Table 3. SB-277011-A is devoid of typical DA D<sub>2</sub>/D<sub>3</sub> receptor antagonist effects and does not show proconvulsant activity. Only very high doses of SB-277011-A (above 90 mg/kg po), which are significantly higher than those showing efficacy in models of addiction, produce weak sedative-like actions in the mouse Irwin test and impair performance in the rat rotarod test. In vivo brain microdialysis data indicate that administration of SB-277011-A (2.8 mg/kg po) reverses the decrease in extracellular DA levels produced by quinlorane (D<sub>2</sub>/D<sub>3</sub> agonist) in the NAc, but not the dorsal striatum, a regional selectivity consistent with the distribution of DA D<sub>3</sub> receptors in the rat brain [229]. A single ip administration of 10 mg/kg of SB-277011-A significantly increases extracellular levels of DA, norepinephrine (NE), and acetylcholine (ACh) in the anterior cingulate cortex in freely moving rats [160]. It should be pointed out that SB-277011-A does not produce a functional antagonism of D<sub>2</sub> receptors in vivo as, unlike D<sub>2</sub> receptor antagonists, its systemic administration in rats does not (1) elicit catalepsy at doses that exhibit anti-addiction action [229,295]; (2) produce a rightward shift in brain stimulation reward curve [229]; (3) increase plasma prolactin levels [295]; (4) inhibit spontaneous or stimulant-induced locomotion [295]; (5) antagonize the action of quinpirole in the dorsal striatum, a brain region with a high density of D<sub>2</sub> receptors [295]; (6) increase DA levels in the striatum [295]; and (7) increase cocaine self-administration under a schedule of continuous reinforcement ([84,102,295]; see Section 7.4).

The following subsections will summarize the effects of SB-277011-A in animal models of drug addiction (see also Table 4).

### **7.1. Effect of SB-277011-A on nicotine self-administration and nicotine-triggered relapse to nicotine-seeking behavior**

Andreoli et al. [6] examined the effect of SB-277011-A on self-administration of nicotine (0.03 mg/kg) using an FR-1/FR-2 schedule in male Wistar rats. SB-277011-A (3 or 10 mg/kg ip) did not affect the number of infusions/h or the number of active lever presses/h compared with the vehicle group at any dose tested. SB-277011-A also failed to modify the number of inactive lever presses/h. The effect of SB-277011-A was also examined on noncontingent nicotine-triggered (0.15 mg/kg) reinstatement of extinguished responding on an operant lever, the depression of which previously resulted in iv nicotine infusions, 24 h after cessation of the self-administration of nicotine [6]. While acute administration of nicotine (0.15 mg/kg sc) produced a significant increase in nicotine-paired lever presses in the vehicle/nicotine group compared with the vehicle/saline control group, SB-277011-A (3 and 10 mg/kg ip) produced a significant reduction in nicotine-paired lever presses compared to the vehicle/nicotine group. No significant changes in the number of inactive lever presses were seen during the noncontingent nicotine priming component of the experiment, suggesting a specific effect of SB-277011-A on drug-triggered drug-seeking behavior. These data suggest that SB-277011-A attenuates nicotine-triggered reinstatement of nicotine-seeking behavior without affecting stable maintenance of nicotine self-administration per se.

### **7.2. Effect of SB-277011-A on nicotine- and cocaine-induced enhancement of brain stimulation reward**

The effects of SB-277011-A on nicotine-induced enhancement of BSR in male Long-Evans rats were also examined [45]. Rats were trained to lever press for BSR of the medial forebrain bundle at the level of the lateral hypothalamus and tested on a rate-frequency curve-shift brain reward paradigm. Administration of nicotine (0.5 mg/kg ip) robustly shifted BSR curves to the left, lowering brain reward thresholds by approximately 25%.

Acute administration of SB-277011-A (3 and 6 mg/kg ip), given 1 h prior to BSR testing, failed to alter nicotine-enhanced BSR. However, 12 mg/kg of SB-277011-A significantly attenuated (70%) nicotine-induced enhancement of BSR. These data suggest that DA D<sub>3</sub> receptors play an important role in mediating nicotine-enhanced brain reward.

Administration of SB-277011-A (3 mg/kg ip), given 30 min prior to BSR testing, also completely blocked the robust enhancement of BSR produced by cocaine (2 mg/kg ip) in rats [295]. This effect cannot be attributed to a D<sub>3</sub> receptor antagonist-induced diminution of brain reward, as SB-277011-A alone did not significantly alter BSR thresholds at doses up to 12 mg/kg.

### **7.3. Effect of SB-277011-A on acquisition and expression of cocaine-induced conditioned place preference (CPP)**

Acute systemic administration of SB-277011-A at all doses tested (0.3, 1, 3, and 10 mg/kg), 30 min prior to each administration of cocaine during the CPP acquisition phase, produced a significant blockade of the acquisition of cocaine-induced CPP [295]. This finding cannot be attributed to a D<sub>3</sub>-antagonist-induced place aversion, as SB-277011-A by itself produced neither a significant place preference nor a significant place aversion at doses up to 10 mg/kg. The finding that SB-277011-A by itself produces neither preference nor aversion was recently confirmed using oral doses of SB-277011-A (5 and 20 mg/kg po) [121]. A single injection of 1, 3, or 10 mg/kg ip of SB-277011-A, 30 min prior to behavioral testing, also produced a significant blockade of the expression of cocaine-induced CPP [295]. Finally, daily ip administration of SB-277011-A (3 mg/kg) for 14 days prior to testing for expression of cocaine-induced CPP produced a robust blockade of the expression of cocaine-induced CPP [295]. It should also be noted that acute administration of SB-277011-A (10 mg/kg ip) did not block the expression of food-induced CPP [295].

In contrast to our CPP findings with SB-277011-A [295], Gyertyán and Gál [121] have reported that administration of 5 or 20 mg/kg po of SB-277011-A (30 min prior to cocaine administration) did not significantly alter the acquisition of a CPP response to cocaine (10 mg/kg ip) in male Sprague–Dawley rats. The reason for the difference between our findings and those of Gyertyán and Gál [121] is unknown, although there were significant differences in methodology including (1) preconditioning the animals to the CPP apparatus vs. no preconditioning; (2) time period of 4 h between the administration of saline and cocaine vs. 24 h; (3) SB-277011-A administered via the po vs. ip route; and (4) SB-277011-A suspended in 5% Tween 80 vs. 2% methylcellulose.

### **7.4. Effect of SB-277011-A on cocaine self-administration and cocaine-triggered relapse to cocaine-seeking behavior**

Acute administration of SB-277011-A (3, 10, and 12 mg/kg ip) did not affect stable maintenance of cocaine self-administration under a continuous reinforcement schedule [84,295]. These findings were also recently confirmed by Gál and Gyertyán [102] who showed that acute administration of SB-277011-A (5 and 20 mg/kg po) does not affect cocaine self-administration under continuous reinforcement. In contrast, the same study showed that both the DA D<sub>1</sub> receptor antagonist SCH-23390 (0.1 and 0.2 mg/kg ip) and the DA D<sub>2</sub>-preferring receptor antagonist haloperidol (0.2 and 0.5 mg/kg po) produced a compensatory increase in lever pressing, of the type classically known to be produced by DA antagonists [110,311]. Finally, the mixed D<sub>2</sub>/D<sub>3</sub> agonists PD-128907 (1 mg/kg sc) and 7-OH-DPAT (0.1 and 0.5 mg/kg sc) produced a significant decrease in lever pressing for cocaine. Interestingly, the same study showed that BP-897 (1 mg/kg ip) significantly increased cocaine self-administration under a continuous reinforcement schedule, suggesting that this effect of BP-897 at a dose of 1 mg/kg is unlikely to be mediated through an action

at DA D<sub>3</sub> receptors. In addition to the findings of Gál and Gyertyán [102], it has been shown that cocaine self-administration is increased in a manner suggestive of a reduction in the reinforcing effects of the drug following administration of the nonselective D<sub>2</sub>/D<sub>3</sub> or D<sub>1</sub>/D<sub>2</sub> receptor antagonists YM-09–151-2 [37,279], spiperone [62,137], sulpiride, metoclopramide, thioridazine, chlorpromazine, haloperidol, pimozide, or alpha-flupentixol [238,239].

Although SB-277011-A did not alter the self-administration of cocaine or nicotine in animals under FR-1 reinforcement, we have seen that it does attenuate the CPP and enhanced BSR produced by cocaine and nicotine. There is evidence suggesting that the nigrostriatal dopaminergic system plays an important role in habit formation, allowing animals to acquire and maintain performance [142]. Since, as previously mentioned, the nigrostriatal system is virtually devoid of D<sub>3</sub> receptors, it is possible that the inability of SB-277011-A to affect the self-administration of cocaine and nicotine is related to the relative lack of D<sub>3</sub> receptors in the nigrostriatal system. However, this hypothesis remains to be tested. An alternative hypothesis, supported by our findings of inhibition of cocaine self-administration by SB-277011-A when the cocaine reinforcement schedule is changed from FR-1 to higher FR ratios (see below), is that drug reinforcement on an FR-1 ratio constitutes too powerful a reinforcer for D<sub>3</sub> receptor antagonism to overcome.

A single noncontingent iv injection of 1 mg/kg cocaine produced robust reinstatement of extinguished operant behavior previously reinforced by iv cocaine injections. Acute pretreatment with SB-277011-A produced a dose-dependent attenuation of this cocaine-triggered reinstatement of extinguished cocaine-seeking behavior [295]. Importantly, SB-277011-A (3, 6, or 12 mg/kg) alone did not trigger reinstatement of cocaine seeking. Finally, over the dose range tested, SB-277011-A did not affect responses on the inactive lever.

### 7.5. Effect of SB-277011-A on cue-controlled cocaine-seeking behavior

The effect of SB-277011-A was also tested against cocaine-seeking behavior using second-order schedules of cocaine reinforcement, which provide an animal model of cue-controlled drug-seeking both prior to and after cocaine has been self-administered [84]. SB-277011-A (0.3, 3, 10, 20, and 30 mg/kg ip) produced a dose-dependent decrease in cocaine-seeking behavior maintained by a cocaine-associated conditioned reinforcer in both the first (drug-free) test interval and also following self-administration of cocaine (second interval) [84]. At higher doses, SB-277011-A also increased the latency to receive the first conditioned stimulus (CS) presentation and cocaine infusion, thereby decreasing the number of cocaine infusions self-administered under the second-order schedule of reinforcement. The decreased responding during the first and second intervals produced by pretreatment with SB-277011-A can be explained as an attenuation of the impact of the conditioned reinforcing properties of the drug-paired stimulus. Furthermore, the increase in latency to the first presentation of the contingent CS and the first cocaine infusion suggests that the decrease in cocaine intake under the second-order schedule is related to a decreased motivation to respond for cocaine. This suggestion is further strengthened by the observation that cocaine self-administration under an FR-1 schedule of reinforcement was not altered by SB-277011-A. Finally, the selectivity of D<sub>3</sub> receptors in mediating cuecontrolled drug-seeking was further supported by the finding that SB-277011-A had no effect on responding for sucrose under similar second-order reinforcement.

Similar findings were reported in a model using male Sprague–Dawley rats trained to self-administer cocaine, while simultaneously establishing discriminative stimuli associated with, and predictive of, cocaine availability or nonavailability [51]. When given in doses

ranging from 3 to 30 mg/kg ip, SB-277011-A decreased responding produced by re-introduction of cocaine-associated cues in a dose-dependent manner.

### **7.6. Effect of SB-277011-A on cocaine self-administration as determined by varying fixed-ratio and progressive-ratio reinforcement**

The effect of SB-277011-A on cocaine self-administration under both fixed-ratio (FR) and progressive-ratio (PR) schedules of reinforcement in male Long–Evans rats was also examined [111]. The administration of SB-277011-A (3–24 mg/kg ip) did not significantly alter cocaine self-administration (0.75 mg/kg/injection) reinforced under an FR-1 schedule. However, SB-277011-A (24 mg/kg ip) produced a significant decrease in cocaine self-administration when (1) the unit dose of cocaine was decreased from 0.75 to 0.125–0.5 mg/kg, or (2) the work demand for cocaine was increased from an FR1 to FR10 schedule. Under a PR reinforcement schedule, SB-277011-A (6–24 mg/kg) produced a significant dose-dependent lowering of the PR breakpoint for cocaine self-administration. Furthermore, the 24 mg/kg dose significantly shifted the cocaine (0.25–1 mg/kg) dose–response breakpoint curve to the right. Finally, when SB-277011-A was substituted for cocaine in an FR schedule, it did not maintain cocaine self-administration behavior. Overall, these results indicate that antagonism of D<sub>3</sub> receptors by SB-277011-A significantly inhibits acute cocaine-induced reinforcement in an FR schedule following a reduction in reinforcement potency or an increase in work requirement. Why SB-277011-A significantly attenuates cocaine self-administration when the unit dose of cocaine is decreased or the FR reinforcement schedule is increased from 1 to 10 remains unknown. Compared with the amount of cocaine administered in other paradigms such as BSR and CPP, animals readily self-administer a significantly larger amount of cocaine under a continuous FR1 schedule for a high unit dose of cocaine. Therefore, it is possible that the high cocaine intake might produce increases in extracellular DA which (by competitive inhibition produced by SB-277011-A binding to the D<sub>3</sub> receptor) are too large for SB-277011-A to overcome. This hypothesis is partially supported by a study indicating a positive correlation between the amount of cocaine self-administered and extracellular NAc DA levels [220], and by the fact that the affinity of the D<sub>3</sub> receptor for DA is greater than that of all other DA receptor subtypes. One may also suggest that, given the half-life of SB-277011-A (2 h) vs. the half-life of cocaine (20–40 min), SB-277011-A attenuates the “rush” effects induced by cocaine, and also possibly the negative compensatory effects that quickly follow the acute positive effects. Finally, it should also be noted that the FR1 schedule of reinforcement is useful for exploring patterns of rate of drug intake. However, the use of an FR1 schedule is less appropriate to assess changes in the reinforcing effects of drugs of abuse. In fact, rate of drug self-administration may be insensitive to changes in reinforcing efficacy and, even if changes are observed, there is little theoretical basis for interpreting these changes. The FR approach was mainly designed to explore how behavior changed when the contingencies between stimulus and response were altered; these procedures were not designed to estimate the magnitude of a reinforcer. Thus, FR responding is the equivalent to the rate of consumption and therefore corresponds to the rate of drug intake. This rate, however, is an ambiguous measure of drug efficacy. Since the PR breakpoint is an index of the relative strength of a reinforcer independent of response rate [8,135, 136,247], the shift in PR breakpoint produced by SB-277011-A indicates that SB-277011-A decreases the reinforcing value of cocaine in rats. Together, we conclude that SB-277011-A not only inhibits cocaine-induced incentive motivation and reinstatement, but also attenuates cocaine’s rewarding efficacy.

### **7.7. Effect of SB-277011-A on stress-triggered relapse to cocaine-seeking behavior**

One of the factors that can lead to relapse to drug use is exposure to stress. It has been well established in both animals [3,38,92,165,259–263,266,284] and humans [157,267,268] that

exposure to stressors can produce reinstatement of self-administration of addictive drugs and/ or drug-seeking behavior. Furthermore, studies in rats have indicated that morphine or cocaine CPP can be reactivated by footshock stress following drug-free periods [184,185,296]. Stressors such as food deprivation [265] and induction of a stress-like state by corticotropin-releasing factor (CRF) administration [261] reinstate heroin seeking in rats. As noted above, we have shown that acute administration of SB-277011-A significantly attenuates cocaine-induced reinstatement of cocaine-seeking behavior [295]. More recently, we have examined the effect of SB-277011-A on stress-induced reinstatement of cocaine seeking [310]. Administration of SB-277011-A (3–12 mg/kg ip) produced a dose-dependent decrease in the reinstatement of cocaine-seeking behavior produced by footshock stress. Furthermore, SB-277011-A microinjected intracranially into the NAc bilaterally (1.5 µg/0.5 µl/side) completely blocked stress-induced reinstatement of cocaine seeking, but micro-injections into the dorsal neostriatum failed to affect stress-triggered reinstatement. The SB-277011-A-induced attenuation of stress-induced relapse to cocaine-seeking would appear not to be the result of anxiolytic and/or analgesic action since (1) SB-277011-A is inactive in paradigms that are used as screens for anxiolytic agents, and (2) SB-277011-A, compared to vehicle-treated animals, did not significantly alter avoidance behaviors such as foot flicking, foot withdrawal, or jumping following the administration of intermittent footshock stimuli (Z.-X. Xi et al. unpublished observations; also see Ref. [260]).

### **7.8. Effect of SB-277011-A on ethanol self-administration and relapse to ethanol-seeking behavior**

We have examined the effect of SB-277011-A on the intake of ethanol in ethanol-preferring (P) and non-ethanol-preferring (NP) rats [235]. A single administration of SB-277011-A (3 mg/kg po) did not significantly alter ethanol intake in P or NP rats compared to vehicle-treated rats. However, compared to vehicle-treated animals, a single po administration of 10 or 30 mg/kg of SB-277011-A significantly decreased ethanol intake in P rats, and a single po administration of 30 mg/kg of SB-277011-A significantly decreased ethanol intake in both P and NP rats.

We also examined the effect of a single ip injection of 10, 20, or 30 mg/kg of SB-277011-A, and its vehicle, on the number of oral ethanol reinforcements and ethanol intake in adult male C57BL/6N mice [7]. Acute administration of either 10 or 20 mg/kg ip of SB-277011-A did not significantly alter oral ethanol self-administration compared to vehicle-treated animals. However, a single administration of 30 mg/kg ip of SB-277011-A significantly decreased the number of reinforcements (by 71%) and the amount of ethanol consumed (by 72%) compared to vehicle-treated animals.

In contrast to our findings, the mixed D<sub>2</sub>/D<sub>3</sub> receptor antagonist U99194 enhances ethanol CPP but does not affect oral alcohol self-administration in Swiss–Webster mice [31,32]. In contrast, U99194 fails to alter ethanol CPP in DBA/2J mice [86]. Moreover, Narita et al. [209] reported that in D<sub>3</sub> receptor knockout mice, physical dependence to ethanol is increased, although another study indicates that deleting the D<sub>3</sub> receptor in C57BL/6J mice does not significantly alter the rewarding effects of ethanol as assessed by operant ethanol self-administration [33]. These findings are in direct contrast to our data indicating that selective antagonism at D<sub>3</sub> receptors by SB-277011-A significantly decreases the intake of ethanol by rats and mice compared to animals treated with vehicle. The discrepant findings with D<sub>3</sub> receptor knockout studies might be explained by changes during the development of the genetically modified animal to compensate for the absence of the D<sub>3</sub> receptor. In support of this suggestion are findings that haloperidol-treated animals acquire ethanol CPP normally [234] whereas DA D<sub>2</sub> receptor knockout mice fail to acquire the CPP response [65]. These findings demonstrate that the behavioral effects produced by a receptor antagonist are not always compatible with those produced by genetically deleting the



receptor at which the antagonist acts. For a detailed review on the role of DA D<sub>3</sub> receptors in the addictive properties of ethanol, the reader is referred to Ref. [131].

Using a new model of relapse to ethanol-seeking behavior in mice that we have recently developed [189], we have found that noncontingent ethanol administration or ethanol-associated cues can robustly reinstate ethanol-seeking behavior in mice behaviorally extinguished from their previous ethanol self-administration behavior. Acute pretreatment with SB-277011-A (10, 20, and 30 mg/kg ip) produced a dose-dependent attenuation of reinstatement of extinguished ethanol-seeking behavior [189].

### 7.9. Effect of SB-277011-A on opiate-induced conditioned place preference (CPP)

We have recently shown that the administration of 10 mg/kg ip of SB-277011-A significantly attenuates the acquisition and expression of the CPP response to 1.5 mg/kg ip of heroin in adult male Sprague–Dawley rats [10]. As previously discussed, SB-277011-A alone does not produce place preference or aversion or shift the BSR curve, suggesting that the effect of SB-277011-A on heroin CPP cannot be related to SB-277011-A itself producing reward or aversion. In contrast, others report that the incentive motivating effect of morphine is significantly enhanced in D<sub>3</sub> receptor knockout mice ([210], but see discussion above).

### 7.10. Summary of effects of SB-277011-A on addictive drug action

The effects of SB-277011-A in several animal models of drug addiction are summarized in Table 4. Together, these findings indicate that SB-277011-A can reduce cocaine-, nicotine-, ethanol-, and heroin-seeking behaviors. These effects are most likely related to the selective antagonism of D<sub>3</sub> receptors, as SB-277011-A is a selective high affinity D<sub>3</sub> receptor antagonist. In addition, the effects of SB-277011-A are unlikely to result from (1) SB-277011-A producing aversive effects as it does not produce a dysphoric shift in the BSR curve and does not produce CPA, or (2) SB-277011-A producing a rewarding/reinforcing effect as it does not produce a significant left shift of the BSR curve, is not self-administered, and does not produce CPP. SB-277011-A completely blocked the acquisition and expression of the CPP to cocaine. Since the acquisition phase involves storage and encoding of contextual stimuli, and the expression phase involves retrieval of memories of contextual stimuli, it is possible that SB-277011-A may block CPP by interfering with various aspects of encoding and retrieving memories. However, SB-277011-A does not appear to alter memory (as measured using a delayed nonmatched position test, D. Jones and J.J. Hagan, personal communication). Furthermore, acute administration of SB-277011-A significantly increases ACh levels in the anterior cingulate cortex [160] and reverses scopolamine-induced memory deficits as assessed by the threechoice point water labyrinth test [163]. Both of these effects would be expected to improve rather than to interfere with memory. Finally, SB-277011-A does not produce catalepsy or significantly alter locomotor activity [229] at the doses used for the BSR, reinstatement, and CPP experiments, suggesting that the effects observed in these paradigms were not due to interference with normal locomotion/coordination.

The minimum effective dose of SB-277011-A to attenuate cocaine-induced CPP (0.3 mg/kg) was significantly lower than the minimum effective dose to attenuate cocaine-triggered reinstatement (6 mg/kg). This difference could be related to the fact that the reinstatement-triggering dose of cocaine (1 mg/kg iv) may have been significantly supra-threshold (see, e.g., Ref. [76]) and therefore more difficult to overcome. Another explanation could be that cocaine-induced CPP is fundamentally more sensitive to D<sub>3</sub> antagonism than cocaine-induced reinstatement. In this regard, the absence of SB-277011-A dose-dependence in blocking cocaine-induced CPP within the dose range used in the reported experiments may

be relevant; dose dependence may exist at lower doses. Similarly, it is possible that cocaine-associated cue-induced increases in forebrain DA are substantially lower than cocaine-induced increases [35,109], and perhaps easier for D<sub>3</sub> antagonism to surmount.

The different experimental animal paradigms described in previous sections of the present review and summarized in Table 4 each have unique relevance for different aspects of human cocaine addiction. BSR presumably measures the direct rewarding properties of addictive drugs and may come closest to modeling the drug-induced subjective “high”. CPP presumably measures drug-seeking behavior specifically evoked by the incentive salience [24,25,85, 138,285] acquired by environmental cues after repeated association with an addictive drug. Reinstatement presumably measures drug-seeking behavior specifically evoked by re-exposure to drugs, cues, or stressors after behavioral extinction and pharmacological detoxification. The present data suggest that selective DA D<sub>3</sub> antagonism may hold highest promise for attenuating cue-evoked relapse to addictive drug use. To date, few other potential pharmaco-therapies have been found which block cue-triggered reinstatement (see, however, [75]). Therefore, a relatively unique therapeutic utility may exist for selective DA D<sub>3</sub> antagonists.

Our results are also the first to show that the acute systemic administration of a potent and highly selective brain penetrant D<sub>3</sub> receptor antagonist significantly decreases stress-induced reinstatement to iv drug-seeking behavior. We therefore suggest that D<sub>3</sub> receptors in the brain are involved in mediating/modulating stress-induced relapse. This suggestion is novel, as stress-triggered relapse has heretofore appeared to be predominantly mediated by noradrenergic and CRF neurotransmitter mechanisms (for reviews, see Refs. [223,262,264,266]). Importantly, however, a role for DA has not been ruled out. For example, acute stress rapidly activates DA neurons in the VTA [144] and increases DA release in the NAc [143,260,289] and mPFC [277,312]. Stress-induced elevation of NAc DA correlates temporally with reinstatement of heroin seeking [259]. Stress appears to stimulate NAc DA release by activating an excitatory projection from the mPFC to glutamate receptors on VTA DA neurons [203]. In addition, stress may also activate mesolimbic DA via CRF release in the midbrain and amygdala [262]. Intracerebroventricular infusion of CRF mimics stress-induced heroin seeking [261] and enhances DA release in the hypothalamus and mPFC [164], although CRF effects on DA release in the NAc have not been reported. Finally, it has been postulated that DA may play an indirect/modulatory role in footshock stress-induced reinstatement [262,266]. Overall, it is likely that multiple neurochemical and anatomical substrates are involved in stress-induced relapse. While our findings with NAc microinjections of SB-277011-A suggest that the NAc may be involved in stress-triggered relapse, there is an important caveat. The NAc is close to the BNST, a region implicated in stress-triggered relapse [262,266,284]. The latency between microinjections and testing in the experiments described in the present review appears sufficient for diffusion of SB-277011-A from NAc to BNST. As discussed earlier, the BNST is a brain area that has a moderate to high density of D<sub>3</sub> receptor mRNA, although this area seems to have few or no D<sub>3</sub> receptors as ascertained by radioligand binding studies. Thus, additional studies are needed to localize the intracerebral site of action for SB-277011-A's protective effects against stress-triggered reinstatement of drug-seeking behavior.

## 8. Role of DA D<sub>3</sub> receptors in drug addiction: further confirmation with similar and structurally diverse selective D<sub>3</sub> receptor antagonists

Confirmation that it is D<sub>3</sub> receptor blockade that is important in mediating the effects of SB-277011-A is provided by reports that structurally dissimilar D<sub>3</sub> receptor antagonists possess similar in vivo properties. Recent studies have shown that *trans*-3-(2-(4-((3-(3-(5-

methyl-1,2,4-oxadiazolyl)phenyl)carboxamido)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzapine (SB-414796), another potent and selective DA D<sub>3</sub> receptor antagonist, can also block the expression of cocaine-induced CPP [186]. Furthermore, the effect of the selective D<sub>3</sub> receptor antagonist NGB-2904 [236,313] has recently been examined in animal models of addiction [309]. It has been reported that, using baculovirus expression of rat DA receptors in vitro, the selectivity of NGB-2904 for D<sub>3</sub> vs. D<sub>2</sub> is 830 as determined by D<sub>2</sub> and D<sub>3</sub> receptor binding and use of the radioligand [<sup>125</sup>I]-IABN [214]. NGB-2904 was also shown to be a functional antagonist in the mitogenesis assay using human D<sub>3</sub>-transfected CHO cells [236]. It was found that in male Long–Evans rats, acute ip administration of NGB-2904 (1) dose-dependently (0.1, 1, or 5 mg/kg) attenuated iv cocaine self-administration maintained by an FR-2 schedule of reinforcement; (2) significantly reduced motivation for cocaine reward (1 or 5 mg/kg), manifested as a significant reduction in progressive-ratio breakpoint for iv cocaine self-administration; and (3) inhibited cocaine-triggered reinstatement of cocaine-seeking behavior in a dose-dependent manner [309]. The inhibitory effect of NGB-2904 on cocaine-taking and cocaine-seeking behavior was prolonged (2–3 days) after a single ip injection. This phenomenon may result from lipid sequestration of NGB-2904, which is highly lipophilic (clogD = 6.94). Importantly, NGB-2904 (1 mg/kg/infusion) cannot by itself maintain iv self-administration when substituted for cocaine. Finally, when tested over a broad dose range (0.1–10 mg/kg), NGB-2904 alone had no significant effects on rat locomotor behavior.

Together, the results obtained with the selective DA D<sub>3</sub> receptor antagonists SB-414796 [186], NGB-2904 [309], and *compound 5p* (*N*-[4-[4-(2,4-dichlorophenyl)piperazin-1-yl]butyl]indole-2-carboxamide) [44] all confirm our previous findings with SB-277011-A and further strengthen the hypothesis that central D<sub>3</sub> receptors play an important role in the rewarding and incentive motivating effects of cocaine.

Other compounds have been reported to exhibit high in vitro selectivity for D<sub>3</sub> receptors whose anti-addiction profiles remain to be characterized. As two previous excellent reviews by Crider and Scheideler [64] and by Hackling and Stark [123] have been published on the medicinal chemistry and selectivity of various compounds for the D<sub>3</sub> receptor, we will only discuss the profiles of some recently synthesized compounds that may be worth examining in models of addiction.

Using [<sup>3</sup>H]-antagonist radioligands, it has been reported that 2-(3-[4-(2-*tert*-butyl-6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-propyl-sulfanyl)-<sup>3</sup>H-pyrimidin-4-one fumarate (A-437203) has D<sub>2S</sub>/D<sub>3</sub> and D<sub>2L</sub>/D<sub>3</sub> receptor selectivity ratios of 45 and 120, respectively, using HEK293 cells transfected with human D<sub>2</sub> and D<sub>3</sub> receptors [291] (see also Ref. [53]). Functional studies in cellular systems transfected with human D<sub>3</sub> receptors indicate that A-437203 lacks intrinsic activity at the D<sub>3</sub> receptor but antagonizes agonist-induced actions with p*K* values of 9 and 7.5 [291]. This compound does not produce catalepsy at doses as high as 464 mg/kg po. Systemic administration of A-437203 induces *c-fos* expression in the NAc and islands of Calleja, an effect reported for other selective D<sub>3</sub> receptor antagonists, and blocks the quinpirole-induced decrease of extracellular DA in the mPFC and NAc [87]. Furthermore, chronic administration of A-437203 for 21 days produces a significant and selective decrease in the number of spontaneously active VTA DA neurons in anesthetized rats [85], a finding similar to that reported for SB-277011-A [9].

The compound 3aR, 9bS-*N*-[4-(8-cyano-1,3a,4,9b-tetrahydro-<sup>3</sup>H-benzopyrano[3,4]pyrrole-2-yl)-butyl]-(4-phenyl) benzamide (S33084) has been reported to be a selective D<sub>3</sub> receptor antagonist [67,68,90,200,201] with more than 200-fold selectivity compared to 40 other binding sites [200]. Binding studies using cloned human D<sub>3</sub> and D<sub>2</sub> receptors indicate that the D<sub>2</sub>/D<sub>3</sub> receptor selectivity ratios using [<sup>125</sup>I]-iodosulpiride and

[<sup>3</sup>H]-spiperone are 120 and 125, respectively [200]. S33084 also exhibits high selectivity for cloned and native rat D<sub>3</sub> receptors [68]. S33084 alone does not significantly modify [<sup>35</sup>S]GTPγS binding at human D<sub>3</sub> receptors [200]. In addition, S33084 does not activate the ERK1 and ERK2 species of MAP kinase in CHO cells transfected with human D<sub>3</sub> receptors, but antagonizes the induction of MAP by DA [200]. The pA<sub>2</sub> value of S33084 to antagonize the stimulation of D<sub>3</sub> receptors by DA is 9.69. S33084 has low affinity for a number of other neuro-transmitter receptors, including D<sub>1</sub> and D<sub>4</sub> receptors [200]. Behavioral studies in rats indicate that S33084 does not induce catalepsy, significantly alter locomotor responses to amphetamine or cocaine, or antagonize methylphenidate-induced gnawing [201]. Furthermore, S33084 does not increase prolactin secretion in rats [201]. Thus, these functional studies suggest that S33084 is not a D<sub>2</sub> receptor antagonist. Similarly, the compound 2(R,S)-(di-n-propylamino)-6-(4-methoxyphenylsufonyl methyl)-1,2,3,4-tetrahydronaphthalene (GR218,231) [207] is a selective hD<sub>3</sub> vs. hD<sub>2</sub> receptor antagonist with hD<sub>2</sub>/hD<sub>3</sub> receptor selectivity ratios using [<sup>125</sup>I]-sulpiride and [<sup>3</sup>H]-spiperone of 60 and 100, respectively, and a neurochemical profile similar to that of S33084 [200,201].

A series of studies published by Austin and colleagues reports the synthesis of various novel compounds with excellent in vitro selectivity for D<sub>3</sub> vs. D<sub>2</sub> receptors. A novel substituted 1,2,3,4-tetrahydroisoquinoline with a 7-CF<sub>3</sub>SO<sub>2</sub>O substituent and a 3-indolylpropenamido group has a D<sub>2</sub>/D<sub>3</sub> receptor selectivity ratio of 150 as determined in CHO cells transfected with human D<sub>2</sub> and D<sub>3</sub> receptors [13]. A 2,3,4,5-tetrahydro-1*H*-3-benzazepine derivative ("compound 20") has a 130-fold selectivity for D<sub>3</sub> vs. D<sub>2</sub> receptors [14]. In addition, a 5-substituted-2,3-dihydro-1*H*-isoindole has at least 100-fold selectivity for D<sub>3</sub> receptors over other aminergic receptors [15].

Recently, it has been reported that the benzothiophenes designated FAUC346 and FAUC365 have high affinity for human D<sub>3</sub> receptors, with K<sub>i</sub> values of 0.23 and 0.5 nM, respectively [23]. The hD<sub>2L</sub>/hD<sub>3</sub> receptor selectivity ratios for FAUC346 and FAUC365 are 380 and 7200, respectively. In the mitogenesis assay in CHO cells transfected with hD<sub>3</sub> receptors, FAUC346 displayed partial agonist action whereas FAUC365 lacked intrinsic action, suggesting that it is a D<sub>3</sub> receptor antagonist. The compounds designated 1c, 3a, 3b, 3e, and 3f have hD<sub>2L</sub>/hD<sub>3</sub> receptor selectivity ratios of 72, 100, 210, 93, and 170, respectively [23].

Wright et al. [306] reported the synthesis of benzimidazole derivatives, one of which, 3-[4[1-[4-[2-[4-(3-diethylamino-propoxy)phenyl]-benzimidazol-1-yl-butyl]-1*H*-benzimidazol-2-yl]-phenoxy]propyl]diethylamide (PD 58491), was found to be a selective D<sub>3</sub> receptor antagonist. A subsequent study, using CHO cells transfected with human D<sub>3</sub> and D<sub>2L</sub> receptors, indicated that PD 58491 has a D<sub>2</sub>/D<sub>3</sub> receptor selectivity ratio of 120 [300]. PD 58491 antagonized the quinpirole-induced stimulation of [<sup>3</sup>H]-thymidine uptake in CHOpro-5 cells but lacked significant intrinsic activity by itself [300]. PD 58491 only partially blocked the decrease in DA synthesis in the striatum and mesolimbic system of rats produced by the putative selective D<sub>3</sub> receptor agonist PD 128907. This finding may be related to stimulation of D<sub>2</sub> autoreceptors by PD 128907, and PD 58491 would not antagonize this action, a hypothesis congruent with studies suggesting that PD 128907 can activate D<sub>2</sub> receptors in the rat brain. It was also hypothesized that there may be a high presynaptic receptor reserve of D<sub>3</sub> receptors, although this must still be determined.

Park et al. [216] have reported that the compound 1-(2-ethoxy-phenyl)-4-[3-(3-thiophen-2-yl)-isoxaolin-5-yl]-propyl]-piperazine (KCH-1110) has an in vitro hD<sub>3</sub>/hD<sub>2</sub> ratio of 90. However, it is likely that this compound is an antagonist at D<sub>2</sub> receptors in vivo as it significantly (1) decreases basal locomotor activity in mice at doses of 2.5 and 5 mg/kg; (2) antagonizes apomorphine-induced climbing in mice; (3) increases serum prolactin levels in rats at a dose of 10 mg/kg; (4) antagonizes 7-OH-DPAT-induced hyperthermia in mice; and

(5) induces catalepsy, albeit mild, at 30 mg/kg. These effects are generally indicative of D<sub>2</sub> receptor antagonism. In addition, these effects of KCH-1110 are not seen after the administration of high doses of SB-277011-A [229]. The authors did not examine the effect of KCH-1110 against drugs of abuse in animal models of addiction (e.g., self-administration, CPP, reinstatement). Interestingly, the pre-treatment of mice with 1 mg/kg of KCH-1110 significantly attenuated cocaine-induced hyperlocomotion. However, there is no significant correlation between a compound's efficacy to increase locomotor activity and its abuse potential. Finally, it should be noted that Park et al. [216] did not report whether KCH-1110 interacted with other CNS receptors to any significant degree.

## 9. Conclusions

The two compounds that have been systematically tested in animal models of drug addiction are the partial DAD<sub>3</sub> receptor agonist BP-897 and the selective DA D<sub>3</sub> receptor antagonist SB-277011-A (see Table 4). The sites of action of SB-277011-A and BP-897 in the CNS remain to be elucidated. There is considerable evidence that DA plays an important role in the addictive properties of drugs of abuse (for reviews, see Refs. [22,34,96–98,104,138,171,237,242,303,304]). Indeed, virtually all abusable substances activate the mesolimbic DA system [46,47,79,139,140,220,240,288] (for reviews, see Refs. [104,155]). However, the concept that the mesolimbic DA system simply encodes hedonic tone has been called into question. Analysis of response patterns of single DA neurons to reward presentation has led Schultz and colleagues to suggest that mesolimbic DA may be more involved in prediction of reward and the use of such information to strengthen behaviors and increase their future likelihood. Schultz and colleagues have suggested that the DA signal may constitute an alert message about reward prediction error that rapidly informs postsynaptic structures about unexpected rewards or reward omissions, without detailed information about the nature of the reward per se. The advantage of such a reward alert signal would be to allow rapid behavioral reactions towards rewarding stimuli, while the exact nature of the reward would be evaluated by slower systems during the approach behavior to the rewarding stimulus (for a recent review, see Ref. [251]). On the other hand, Wise and colleagues have argued compellingly for a crucial role for meso-accumbens DA in the actual mediation of reward—if not a final common path for all rewards, at least an intermediate common path for most rewards [303], and we [104] and others [34,46,79,139,140,220,288] have argued that elevation of brain DA constitutes a neurochemical substrate of the reward produced by addictive drugs (and by drug-associated environmental cues; see e.g., Refs. [82,109,141]), not merely a correlate.

The circuitry that mediates reinstatement of drug-seeking behavior is complex [4,5,26,116,118,131,177,211,218,270, 301,303], but key elements involve DA mechanisms. For example, the presentation of a drug-associated CS to animals can induce large conditioned increases in NAc DA [82,141], suggesting that DA in the NAc is involved in cue-controlled drug seeking [308] through interactions with limbic afferents to the NAc [81,83]. Cue incentive properties [24,242] appear mediated by hippocampal and amygdaloid mechanisms [55,152,196]. The amygdala plays an important role [94], particularly in drug-enhanced stimulus–reward associations [127,243] which may, in conjunction with enhanced stimulus–response associations [79], underlie drug craving and compulsive drug taking at the human level [80,215]. Lesions of the central amygdala (CeA) or infusion of 7-OH-DPAT into this brain area can attenuate the acquisition of a Pavlovian approach response [133,134, 217] and can impair the enhancement of instrumental behavior by presentation of a Pavlovian CS [125,126]. Interestingly, lesions of the basolateral amygdala (BLA) can impair the acquisition of cocaine seeking under a second-order schedule [301]. In addition, reversible inactivation of the BLA by lidocaine can block both the acquisition and expression of the response-maintaining properties of a CS under both second-order and



reinstatement conditions [119,145,158]. Recent studies have also shown that direct microinfusion of  $D$ -amphetamine into the BLA can potentiate cue-triggered relapse to cocaine seeking in a dose-dependent manner without affecting extinction responding [166]. Furthermore, electrical or chemical stimulation of the BLA can reinstate cocaine-seeking behavior following behavioral extinction of the cocaine-seeking habit [129], as can electrical stimulation of the hippocampus, another brain structure implicated in the storage and retrieval of memories underlying the cue-incentive properties of addictive drugs [294]. Within the amygdala, direct infusion of the nonselective muscarinic receptor antagonist scopolamine into the BLA during the acquisition of conditioned pairing of a light/tone stimulus with cocaine self-administration can also disrupt cocaine-seeking behavior maintained by the cocaine-associated cues [255]. In contrast, the same scopolamine treatment given just prior to the reinstatement test fails to affect conditioned cue-induced relapse to cocaine seeking [255]. Reversible inactivation of the BLA, anterior cingulate cortex, or prelimbic cortex just prior to the reinstatement test impairs the ability of a light/tone stimulus to reinstate extinguished lever pressing for cocaine-paired stimuli [193]. These results are congruent with the finding that neural activity in the VTA, anterior cingulate cortex, NAc core, and ventral pallidum is necessary for cocaine-induced reinstatement of drug-seeking behavior [192]. It has also been shown that stress-induced relapse may be mediated by the BNST and CeA [93,173,264].

Such findings as those noted above point toward an important role of the BLA in stimulus–reward associations that mediate cue-triggered reinstatement of cocaine-seeking behavior. Enhanced monoaminergic tone in the BLA appears to increase the motivational properties or salience of cocaine-associated cues during reinstatement of cocaine-seeking behavior, whereas inactivation of the BLA produces the reverse effect. The CeA may mediate conditioned increases in DA measured in the NAc following the noncontingent presentation of a CS [82,141] perhaps via projections to the VTA [218] and seems to play a key role in stress-triggered relapse to cocaine-seeking behavior. Finally, the anterior cingulate cortex seems to serve as a common link in the neural circuitry underlying reinstatement of drug-seeking behaviors, perhaps because the anterior cingulate cortex is critically involved in the discrimination of multiple stimuli on the basis of their association with reward [48], in shifting away from spatial locations previously associated with reward (response perseveration), attention, and the ability to adequately plan actions involved in fear responding (for a complete review, see Ref. [130]). Thus, these results point towards the anterior cingulate cortex as a key component involved in the temporal patterning of behavioral sequences.

Given that SB-277011-A is effective in attenuating the action of a number of addictive drugs in various paradigms, one might hypothesize that (1) the cue-, drug-, and stress-induced reinstatement circuits may, in fact, have a common final pathway and that the efficacy of SB-277011-A is due to blockade of  $D_3$  receptors in this pathway, and/or (2)  $D_3$  receptors are located at critical junctions in the pathways involved in cue-, drug-, and stress-induced reinstatement. Indeed, DA  $D_3$  receptors are present in moderate to high densities in the amygdala, NAc, VTA, BNST, and mPFC. In a recent series of pharmacological magnetic resonance imaging (MRI) experiments, we have shown that pretreatment with SB-277011-A, at a dose behaviorally effective against drug-seeking, potentiates the rapid relative cerebral blood volume (rCBV) response to amphetamine in regions including, but extending beyond, the  $D_3$ -rich areas, while SB-277011-A itself produced only limited activation and gradual rCBV changes commensurate with its pharmacokinetics [254]. Importantly, the regions showing increased rCBV due to SB-277011-A alone did not correspond to the foci of dense  $D_3$  receptor distribution and thus did not coincide with those foci showing a potentiated response to amphetamine. SB-277011-A itself produced focal bilateral activation in the entorhinal cortex, lateral globus pallidus, and CeA. The pattern of potentiation was

more widespread and included the NAc, islands of Calleja, anterior cingulate and retrosplenial cortices, thalamus, dorsal striatum, BNST, and ventral subiculum. These findings suggest that the efficacy of selective DA D<sub>3</sub> receptor antagonists in attenuating reinstatement of drug-seeking behavior may in fact proceed via increased activity in both the extended amygdala and the mesolimbic DA system. Additional studies must be conducted in order to determine the specific brain areas involved in the effects of SB-277011-A in the CPP, BSR, and reinstatement paradigms. Studies examining the effect of SB-277011-A microinjections into areas such as the amygdala, VTA, NAc, and anterior cingulate cortex are warranted and have been initiated.

## Acknowledgments

We thank Sharon Buie for assistance with manuscript preparation and Arlene C. Pak and Jeremy Gilbert for helpful comments, criticisms, and assistance with reference citations.

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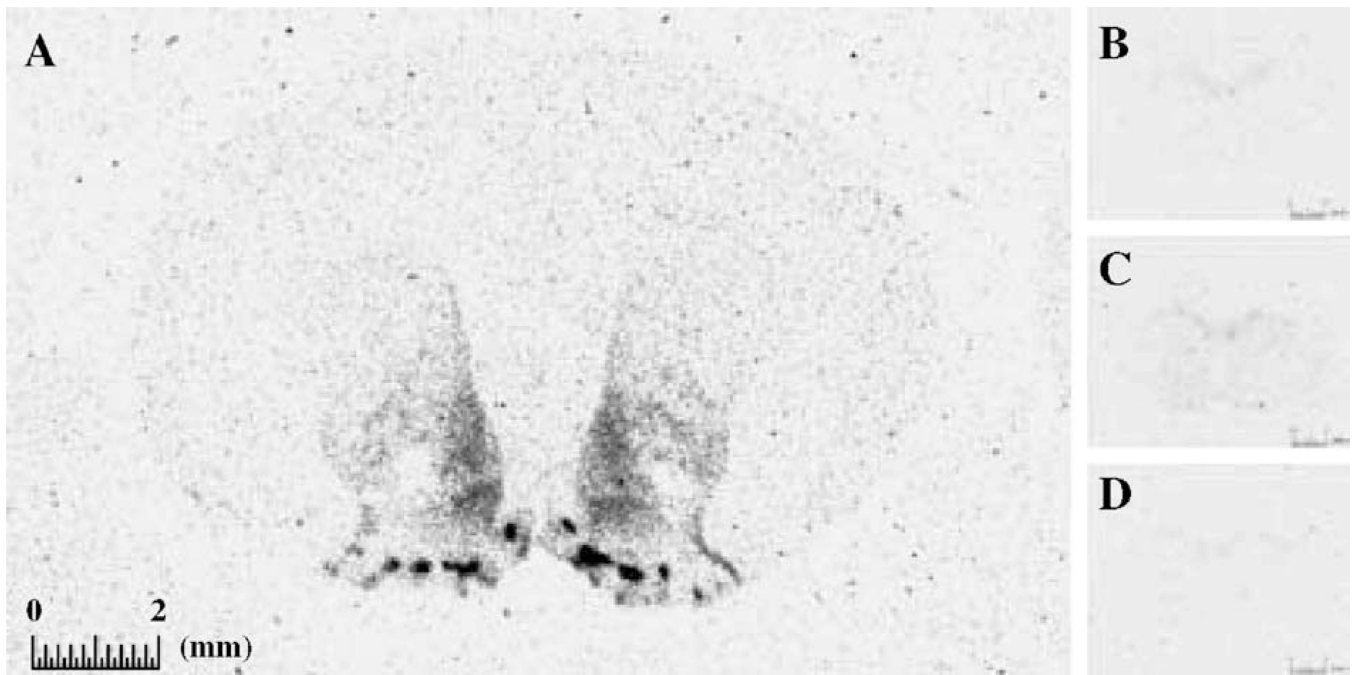


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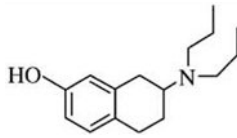
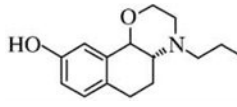
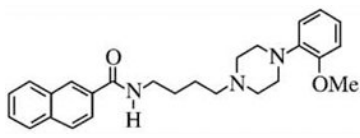
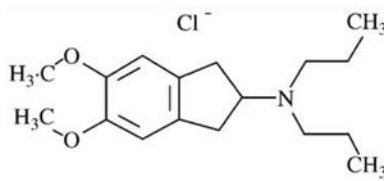
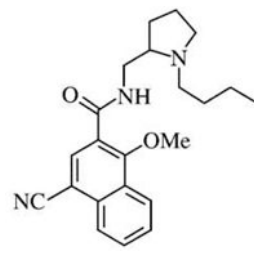
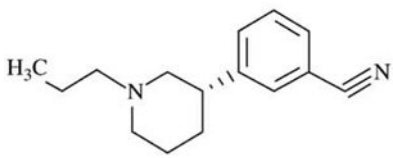


**Fig. 1.** Distribution of D<sub>3</sub> receptors in rat brain, as revealed by [<sup>3</sup>H]-7-OH-DPAT autoradiography—displacement with the selective DA D<sub>3</sub> receptor antagonist SB-277011. Coronal rat brain sections (at +1.70 mm from Bregma) were incubated in the presence of 0.5 nM [<sup>3</sup>H]-7-OH-DPAT for 60 min at room temperature. (A) Total binding; (B) nonspecific binding, in the presence of 1 μM dopamine; (C) binding in the presence of 100 nM SB-277011-A; (D) binding in the presence of 1 μM SB-277011-A. Calibration bars correspond to 2 mm. Incubation with [<sup>3</sup>H]-7-OH-DPAT was performed in the presence of 1 mM EDTA, in order to abolish the radioligand binding to D<sub>2</sub> receptors without affecting that to D<sub>3</sub> receptors, as demonstrated in transfected cell lines [182]. The specificity of the radioligand binding to D<sub>3</sub> receptors was confirmed by the distribution of [<sup>3</sup>H]-7-OH-DPAT binding sites, in line with that of D<sub>3</sub> mRNA [30] and by displacement with the selective D<sub>3</sub> antagonist SB-277011-A. As predicted by the affinity values of [<sup>3</sup>H]-7-OH-DPAT and SB-277011-A for rat D<sub>2</sub> and D<sub>3</sub> receptors [182,229], 0.5 nM [<sup>3</sup>H]-7-OH-DPAT binding was inhibited by 80% and 100% by 100 nM and 1 μM SB-277011-A, respectively.



**Table 1**

Representative DA D<sub>2</sub>/D<sub>3</sub> receptor agonists and antagonists, the partial agonist BP-897, and selective DA D<sub>3</sub> receptor antagonists<sup>a</sup>

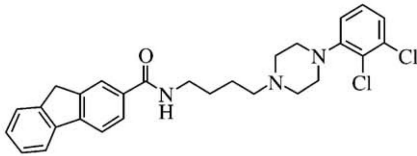
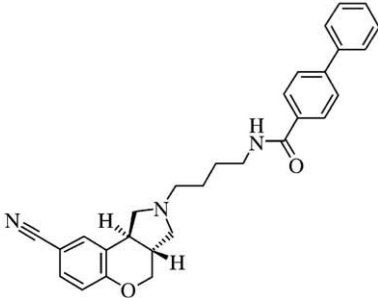
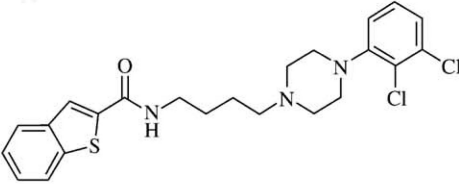
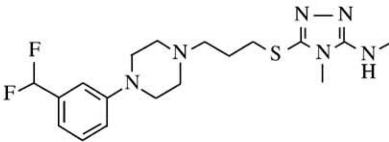
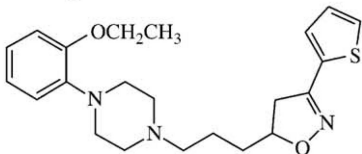
| Ligand Name  | K <sub>i</sub> hD <sub>2</sub> (nM)      | K <sub>i</sub> hD <sub>3</sub> (nM)      | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios     | Chemical structure  |
|--|--|--|--|---|
| <i>Mixed DA D<sub>2</sub>/D<sub>3</sub> agonists</i>   |  |  |  |   |
| <i>7-OH-DPAT</i> <sup>b</sup>                          | [ <sup>125</sup> I]-iodosulpiride = 92   | [ <sup>3</sup> H]-PD128907 = 0.34        | [ <sup>3</sup> ]-PD128907 = 302                          |    |
|  |  | [ <sup>3</sup> H]-S14297 = 1             | [ <sup>3</sup> H]-S14297 = 103                           |   |
|  |  | [ <sup>125</sup> I]-iodosulpiride = 2.2  | [ <sup>125</sup> I]-iodosulpiride = 47                   |   |
| <i>PD 128907</i> <sup>c</sup>                          | [ <sup>125</sup> I]-iodosulpiride = 339  | [ <sup>3</sup> H]-PD128907 = 1.33        | [ <sup>3</sup> H]-PD128907 = 340                         |    |
|  |  | [ <sup>3</sup> H]-S14297 = 1.31          | [ <sup>3</sup> H]-S14297 = 345                           |   |
|  |  | [ <sup>125</sup> I]-iodosulpiride = 1.9  | [ <sup>125</sup> I]-iodosulpiride = 239                  |   |
| <i>Partial DA D<sub>3</sub> agonist</i>                |  |  |  |   |
| <i>BP-897</i> <sup>d</sup>                             | [ <sup>125</sup> I]-iodosulpiride = 61   | [ <sup>125</sup> I]-iodosulpiride = 0.92 | [ <sup>125</sup> I]-iodosulpiride = 66                   |    |
| <i>Mixed DA D<sub>2</sub>/D<sub>3</sub> antagonist</i> |  |  |  |   |
| <i>U 99194-A</i> <sup>e</sup>                          | [ <sup>125</sup> I]-iodosulpiride = 2281 | [ <sup>3</sup> H]-PD128907 = 160         | [ <sup>3</sup> H]-PD128907 = 14                          |  |
|  |  | [ <sup>3</sup> H]-S14297 = 180           | [ <sup>3</sup> H]-S14297 = 13                            |   |
|  |  | [ <sup>125</sup> I]-iodosulpiride = 223  | [ <sup>125</sup> I]-iodosulpiride = 10                   |   |
| <i>Nafadotride</i> <sup>f</sup>                        | [ <sup>125</sup> I]-iodosulpiride = 5    | [ <sup>3</sup> H]-PD128907 = 0.52        | [ <sup>3</sup> H]-PD128907 = 9                           |  |
|  |  | [ <sup>3</sup> H]-S14297 = 0.88          | [ <sup>3</sup> H]-S14297 = 6                             |   |
|  |  | [ <sup>125</sup> I]-iodosulpiride = 0.81 | [ <sup>125</sup> I]-iodosulpiride = 6                    |   |
| <i>DS 1218</i> <sup>g</sup>                            | [ <sup>3</sup> H]-spiperone = 1140       | [ <sup>3</sup> H]-spiperone = 249        | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 4 |  |

| Ligand Name                   | K <sub>i</sub> hD <sub>2</sub> (nM)     | K <sub>i</sub> hD <sub>3</sub> (nM)   | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios   | Chemical structure |
|-------------------------------|---|---|--|--------------------|
| <i>(+)-AJ 76<sup>h</sup></i>  | [ <sup>125</sup> I]-iodosulpiride = 155 | [ <sup>3</sup> H]-PD128907 = 26<br>[ <sup>3</sup> H]-S14297 = 34<br>[ <sup>125</sup> I]-iodosulpiride = 70    | [ <sup>3</sup> H]-PD128907 = 6<br>[ <sup>3</sup> H]-S14297 = 5<br>[ <sup>125</sup> I]-iodosulpiride = 2    |                    |
| <i>R=H</i>                    |   |   |  |                    |
| <i>(+)-UH-232<sup>i</sup></i> | [ <sup>125</sup> I]-iodosulpiride = 28  | [ <sup>3</sup> H]-PD128907 = 3.3<br>[ <sup>3</sup> H]-S14297 = 5.4<br>[ <sup>125</sup> I]-iodosulpiride = 7   | [ <sup>3</sup> H]-PD128907 = 8<br>[ <sup>3</sup> H]-S14297 = 5<br>[ <sup>125</sup> I]-iodosulpiride = 4    |                    |
| <i>R=propyl</i>               |   |   |  |                    |
| <i>S 14297<sup>j</sup></i>    | [ <sup>125</sup> I]-iodosulpiride = 297 | [ <sup>3</sup> H]-PD128907 = 4.9<br>[ <sup>3</sup> H]-S14297 = 7.4<br>[ <sup>125</sup> I]-iodosulpiride = 13  | [ <sup>3</sup> H]-PD128907 = 61<br>[ <sup>3</sup> H]-S14297 = 40<br>[ <sup>125</sup> I]-iodosulpiride = 23 |                    |
| <i>GR 103691<sup>k</sup></i>  | [ <sup>125</sup> I]-iodosulpiride = 24  | [ <sup>3</sup> H]-PD128907 = 0.4<br>[ <sup>3</sup> H]-S14297 = 0.4<br>[ <sup>125</sup> I]-iodosulpiride = 0.4 | [ <sup>3</sup> H]-PD128907 = 60<br>[ <sup>3</sup> H]-S14297 = 60<br>[ <sup>125</sup> I]-iodosulpiride =    |                    |

*Selective DA D<sub>3</sub> antagonists*

|                                |   |   |  |  |
|--------------------------------|---|---|--|--|
| <i>SB-277011-A<sup>l</sup></i> | [ <sup>125</sup> I]-iodosulpiride<br>pK <sub>i</sub> = 5.98 | [ <sup>125</sup> I]-iodosulpiride<br>pK <sub>i</sub> = 7.95 | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 120 |  |
| <i>SB-414796<sup>m</sup></i>   | [ <sup>125</sup> I]-iodosulpiride<br>pK <sub>i</sub> = 6.4  | [ <sup>125</sup> I]-iodosulpiride<br>pK <sub>i</sub> = 8.4  | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 100 |  |

R<sup>1</sup> = MeSO<sub>2</sub>;  
R<sup>2</sup> = 3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl

| Ligand Name                 | K <sub>i</sub> hD <sub>2</sub> (nM)  | K <sub>i</sub> hD <sub>3</sub> (nM)  | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios  | Chemical structure  |
|-----------------------------|--|--|---|---|
| <i>NGB-2904<sup>d</sup></i> | [ <sup>125</sup> I]-IABN = 911   | [ <sup>125</sup> I]-IABN = 1.1   | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 830  |    |
| <i>S33084<sup>o</sup></i>   | [ <sup>125</sup> I]iodosulpride; pK <sub>i</sub> = 7.54<br>[ <sup>3</sup> H]spiperone; pK <sub>i</sub> = 7.28<br>[ <sup>35</sup> S]GTPγS; pK <sub>b</sub> = 7.75 | [ <sup>125</sup> I]iodosulpride; pK <sub>i</sub> = 9.59<br>[ <sup>3</sup> H]spiperone; pK <sub>i</sub> = 9.40<br>[ <sup>35</sup> S]GTPγS; pK <sub>b</sub> = 9.61 | [ <sup>125</sup> I]iodosulpride = 120<br>[ <sup>3</sup> H]spiperone = 125<br>[ <sup>35</sup> S]GTPγS = 66 |    |
| <i>FAUC 363<sup>p</sup></i> | [ <sup>3</sup> H]spiperone = 3600  | [ <sup>3</sup> H]spiperone = 0.5   | D <sub>2L</sub> :D <sub>3</sub> K <sub>i</sub> ratios =   |    |
| <i>A-437203<sup>q</sup></i> | K <sub>i</sub> D <sub>2L</sub> = 348   | K <sub>i</sub> = 29  | D <sub>2L</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 120   |  |
| <i>KCH 1110<sup>r</sup></i> | [ <sup>3</sup> H]-spiperone = 118.8  | [ <sup>3</sup> H]-spiperone = 1.28   | D <sub>2</sub> :D <sub>3</sub> K <sub>i</sub> ratios = 90   |  |

<sup>a</sup>D<sub>2</sub>:D<sub>3</sub>K<sub>i</sub> ratios are shown for different radioligands.

<sup>b</sup>See Ref. [11].

<sup>c</sup>See Ref. [11].

<sup>d</sup>See Ref. [224].

<sup>e</sup>See Ref. [11].

<sup>f</sup>See Ref. [11].

<sup>g</sup>See Ref. [276].

<sup>h</sup>See Ref. [11].

<sup>i</sup>See Ref. [11].

<sup>j</sup>See Ref. [11].

<sup>k</sup>See Ref. [11].

<sup>l</sup>See Ref. [229].

<sup>m</sup>See Ref. [186].

<sup>n</sup>See Refs. [236,313].

<sup>o</sup>See Ref. [201].

<sup>p</sup>See Ref. [23].

<sup>q</sup>See Ref. [291].

<sup>r</sup>See Ref. [216].

Table 2

Effect of mixed D<sub>2</sub>/D<sub>3</sub> receptor antagonists in animal models of drug addiction<sup>a</sup>

| Compound name | D <sub>2</sub> :D <sub>3</sub> selectivity | Paradigm   | Dose (mg/kg) and route of administration   | Main finding                                   | Reference  |       |
|---------------|--|--|--|--|--|-------|
| DS-121        | 3–5  | Cocaine-induced locomotor activity in cocaine tolerant rats  | 0–7 (ip)   | Potentiation                                   | [91]   |       |
|               |  | Spontaneous locomotor activity                               | 3.3–13.3 (sc)<br>Intra-NAc (0.05–53 µg/side)<br>Intra-VTA (0.05–53 µg/side)<br>ICV bilateral (66.3 µg/side)  | Increase<br>No effect<br>No effect<br>Increase | [153]  |       |
|               | CPP  | BSR  | Discriminative stimulus properties of amphetamine (0.5 mg/kg) and cocaine (5 mg/kg)  | 3.3–13.3 (sc)                                  | Place preference   | [153] |
|               |  |  |  | 3.3–13.3 (sc)                                  | No effect  | [153] |
|               |  |  |  | 3.5–14 (sc)                                    | Increase in amphetamine-like and cocaine-like responding                   | [58]  |
|               | Cocaine self-administration                | Progressive ratio breakpoint for cocaine self-administration | Extracellular levels of DA in dorsal striatum  | 3–10 (sc)                                      | Decrease   | [238] |
|               |  |  |  | 15 (ip)  | Decrease   | [154] |
|               |  |  |  | 15 (ip)  | Increase   | [154] |
|               | Nafadotride                                | 6–9  | Development of amphetamine sensitization<br>Expression of cocaine sensitization<br>Cocaine self-administration under FR-5<br>Cue-induced cocaine-seeking behavior<br>Apomorphine- and 7-OH-DPAT-induced reinstatement of food-seeking behavior | 25 µg/kg (sc)                                  | Potentiation of cocaine-induced increase in striatal DA levels<br>Decrease | [230] |
|               |  |  |  | 0.4 (ip)                                       | Potentiation   | [99]  |
| 1–3 (sc)      |  |  |  | Increase                                       | [43]   |       |
| 1 (ip)        |  |  |  | Decrease                                       | [299]  |       |
| 1 (ip)        |  |  |  | Decrease                                       | [89]   |       |

No effect on food-primed food seeking



| Compound name | D <sub>2</sub> :D <sub>3</sub> selectivity | Paradigm  | Dose (mg/kg) and route of administration | Main finding   | Reference        |
|---------------|--|---|--|--|------------------|
|               |  | Sensitization-induced facilitation of appetitive conditioning                           | Intra-amygdala (20 µmol/ml; 0.5 µl/side) | Retardation of conditioned response                                | [221]            |
|               |  | Isolation rearing-induced facilitation of Pavlovian learning                            | Intra-amygdala (20 µmol/ml; 0.5 µl/side) | Abolition of acquisition of Pavlovian-conditioned approach         | [222]            |
|               |  | Spontaneous locomotor activity  | 0.1–1 (sc)                               | Increase   | [248]            |
|               |  | Morphine (10 mg/kg)-induced hyperactivity   | 0.75–3 (ip)                              | Increase   | [70]             |
|               |  | MK-801-induced hyperactivity  | 0.3–1 (sc)                               | Blockade at 1 mg/kg  | [61]             |
|               |  | Climbing behavior in mice   | 0.3 and 1 (ip)                           | Blockade   | [174]            |
|               |  | Conditioned reaction time   | 0.1–1 (sc)                               | Increase   | [248]            |
|               |  | Catalepsy   | 0.1, 0.3, and 1 (sc)                     | Increased number of delayed responses at 1 mg/kg                   | [271]            |
|               |  | DA turnover in dorsal striatum  |  | AD <sub>50</sub> = 16.4 (sc) <sup>b</sup>                          | [11]             |
|               |  | Plasma prolactin levels   |  | AD <sub>50</sub> = 0.5 (sc) <sup>c</sup>                           | [11]             |
|               |  | Social interaction  |  | MED = 0.16 (sc) <sup>d</sup>                                       | [11]             |
| U99194        | 10–15                                      |   | 20 and 40 (sc)                           | Increase   | [244]            |
|               |  | Spontaneous locomotor activity and rearing  | 5 and 10 (sc)                            | Increase   | [108]            |
|               |  | Spontaneous and morphine-induced locomotor activity                                     | 20 and 40 (sc)                           | Decrease   | [49,244,249,298] |
|               |  | Development of amphetamine sensitization  | 20 (ip)                                  | Increase and blockade of morphine (20 mg/kg)-induced hyperactivity | [188]            |
|               |  | Discriminative stimulus properties of 7-OH-DPAT (0.01–1 mg/kg) or PD128907 (0.03 mg/kg) | ICV (20 µg × 7 days)                     | Decrease   | [54]             |
|               |  | Amphetamine-induced enhancement of BSR  | 2.5–20 (sc)                              | No effect/partial blockade   | [57,105]         |
|               |  | Discriminative stimulus properties of amphetamine (1 mg/kg) and cocaine (5 mg/kg)       | 5–20 (sc)                                | Potentiation   | [74]             |
|               |  | Cocaine CPP   | 10–40 (sc)                               | Increase   | [49]             |
|               |  | Ethanol CPP   | 12 and 24 (sc)                           | No effect  | [18,19]          |
|               |  |   | 10 and 20 (ip)                           | No effect<br>Place preference per se                               | [121]            |
|               |  |   |  | No effect  | [86]             |
|               |  |   |  | Enhancement  | [31,32]          |

| Compound name | D <sub>2</sub> :D <sub>3</sub> selectivity | Paradigm   | Dose (mg/kg) and route of administration              | Main finding   | Reference    |
|---------------|--|--|---|--|--------------|
|               |  | Oral ethanol self-administration   | 10 and 20 (ip)  | No effect  | [31,32]      |
|               |  | Amphetamine (2.5 mg/kg)-induced contralateral rotation in 6-OHDA-lesioned rats | 5, 10, and 20 (sc)                                    | >98% DA depletion (ipsilateral rotations):<br>no effect<br>80–97% DA depletion (contralateral rotations): blockade | [241]        |
|               |  | Drug discrimination  | 5–35 (sc)   | Generalization to UH-232, scopolamine, trihexyphenidyl, and clozapine  | [115]        |
|               |  | Catalepsy  |   | AD <sub>50</sub> > 40 (sc) <sup>e</sup>  | [11]         |
|               |  | DA turnover in dorsal striatum   |   | AD <sub>50</sub> = 6.9 (sc) <sup>f</sup>   | [11]         |
|               |  | Plasma prolactin levels  |   | MED = 40 (sc) <sup>g</sup>   | [11]         |
| S 14297       | 23–61                                      | Catalepsy  |   | AD <sub>50</sub> > 20 (sc) <sup>h</sup>  | [11,113,199] |
|               |  | Plasma prolactin levels  |   | MED > 40 (sc) <sup>i</sup>   | [11]         |
|               |  | Discriminative stimulus properties of U99194                                   | 3–8 (sc)  | Partial substitution (66%)   | [17]         |
|               |  | Spontaneous locomotor activity   | ED <sub>50</sub> = 15.4 (ip)                          | Decrease   | [62]         |
|               |  | Amphetamine-induced locomotor activity   | ED <sub>50</sub> > 30 (sc)                            | No effect  |              |
| PD152255      | 40–50                                      |  | 1, 3, and 10 (ip)                                     | Decrease   |              |
|               |  | Discriminative stimulus properties of U99194                                   | 1, 3, and 10 (sc)                                     | No effect  | [62]         |
|               |  |  | 1–3 (ip)<br>Suppression of responding at higher doses | No generalization  | [17]         |

<sup>a</sup>For a detailed ethologically based approach comparing the ethograms of U99194A, GR103691, and nafadotride, the reader is referred to Ref. [59].

<sup>b</sup>AD50 was defined as the dose required for the induction of a half-maximal response (equivalent to 15 s).

<sup>c</sup>AD50 was defined as an increase in DOPAC:DA ratios to 150% relative to vehicle values.

<sup>d</sup>MED was defined as the lowest dose significantly different ( $P < 0.05$ ) from vehicle control values.

<sup>e</sup>AD50 was defined as the dose required for the induction of a half-maximal response (equivalent to 15 s).

<sup>f</sup>AD50 was defined as an increase in DOPAC:DA ratios to 150% relative to vehicle values.

$g_{\text{MED}}$  was defined as the lowest dose significantly different ( $P < 0.05$ ) from vehicle control values.

$h_{\text{AD50}}$  was defined as the dose required for the induction of a half-maximal response (equivalent to 15 s).

$l_{\text{MED}}$  was defined as the lowest dose significantly different ( $P < 0.05$ ) from vehicle control values.

**Table 3**Effects of SB-277011-A alone in various pharmacology models<sup>a</sup>

| <b>Experimental paradigm</b>                              | <b>Doses</b>    | <b>Main finding</b>   |
|---|-----------------|---|
| Spontaneous locomotor activity                            | 0–42.3 mg/kg po | No effect   |
| Amphetamine-induced locomotor activity                    | 0–51.3 mg/kg po | No effect   |
| Phencyclidine-induced locomotor activity                  | 0–51.3 mg/kg po | No effect   |
| Apomorphine-induced climbing in mice                      | 0–42 mg/kg po   | No effect   |
| Quinelorane-induced locomotor hypoactivity                | 0–41 mg/kg po   | No effect   |
| Quinelorane-induced reversal of amphetamine hyperactivity | 0–41 mg/kg po   | No effect   |
| Quinpirole-induced deficit in prepulse inhibition         | 0–41 mg/kg po   | No effect   |
| Apomorphine-induced deficit in prepulse inhibition        | 0–41 mg/kg po   | No effect   |
| Differential reinforcement of low response rates          | 0–27.5 mg/kg po | No effect   |
| Catalepsy   | 0–78.8 mg/kg po | No effect   |
| Haloperidol-induced catalepsy                             | 0–41 mg/kg po   | No effect   |
| Serum prolactin levels                                    | 0–93 mg/kg po   | No effect   |
| Rotarod performance                                       | 0–91.8 mg/kg po | No effect, except 91.8 mg/kg dose producing impairment in performance |
| Maximal electroshock seizure threshold                    | 0–92 mg/kg po   | No effect   |
| Mouse Irwin profile                                       | 0–91.8 mg/kg po | No effect, except 91.8 mg/kg dose producing weak sedative-like effect |
| Delayed nonmatching test                                  | 0–41 mg/kg po   | No effect   |

<sup>a</sup>See Ref. [229].

**Table 4**

Effect of SB-277011-A in animal models of drug addiction

| <b>Behavioral paradigm</b>  | <b>Doses</b>                       | <b>Main finding</b> | <b>Reference</b> |
|---|------------------------------------|---------------------|------------------|
| Nicotine self-administration (FR-1/FR-2)                                  | 3–10 mg/kg ip                      | No effect           | [6]              |
| Nicotine-triggered relapse to nicotine seeking                            | 3–10 mg/kg ip                      | Blockade            | [6]              |
| Nicotine-induced enhancement of brain stimulation reward                  | 3, 6, and 12 mg/kg ip              | Blockade            | [111]            |
| Nicotine-conditioned locomotor activity                                   | 10 mg/kg ip                        | Blockade            | [169]            |
| Cocaine self-administration (FR-1)  | 3, 6, and 12 mg/kg ip              | No effect           | [295]            |
|   | 5 and 20 mg/kg po                  | No effect           | [102]            |
| Cocaine-induced enhancement of brain stimulation reward                   | 3, 6, and 12 mg/kg ip              | Blockade            | [295]            |
| Acquisition of cocaine-induced conditioned place preference               | 0.3, 1, 3, and 10 mg/kg ip         | Blockade            | [295]            |
| Expression of cocaine-induced conditioned place preference                | 0.3, 1, 3, and 10 mg/kg ip         | Blockade            | [295]            |
| Expression of food-induced conditioned place preference                   | 10 mg/kg ip                        | No effect           | [295]            |
| Cocaine-triggered relapse to cocaine seeking                              | 3, 6, and 12 mg/kg ip              | Blockade            | [295]            |
| Cue-triggered relapse to cocaine seeking                                  | 3, 10, and 30 mg/kg ip             | Blockade            | [51]             |
| Cue-controlled cocaine seeking (2nd order reinforcement schedule)         | 0.3, 1, 3, 10, 20, and 30 mg/kg ip | Blockade            | [84]             |
| Sucrose self-administration under 2nd order reinforcement schedule        | 0.3, 1, 3, 10, 20, and 30 mg/kg ip | No effect           | [84]             |
| Cocaine self-administration under FR-10 and PR schedules of reinforcement | 3, 6, 12, and 24 mg/kg ip          | Blockade            | [111]            |
| Stress-induced relapse to cocaine seeking                                 | 3, 6, and 12 mg/kg ip              | Blockade            | [310]            |
|   | 1.5 µg/0.5 µl/side NAc             | Blockade            |                  |
|   | 1.5 µg/0.5 µl/side dorsal Striatum | No effect           |                  |
| Ethanol intake in ethanol-preferring vs. nonpreferring rats               | 3, 10, and 30 mg/kg ip             | Blockade            | [235]            |
| Oral ethanol self-administration  | 10, 20, and 30 mg/kg ip            | Blockade            | [7]              |
| Relapse to ethanol seeking  | 10, 20, and 30 mg/kg ip            | Blockade            | [189]            |
| Expression of heroin-induced conditioned place preference                 | 10 mg/kg ip                        | Blockade            | [10]             |