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Current perspectives on selective dopamine D_3 receptor antagonists as pharmacotherapeutics for addictions and related disorders

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Abstract

Repeated exposure to drugs of abuse produces long-term molecular and neurochemical changes that may explain the core features of addiction, such as the compulsive seeking and taking of the drug, as well as the risk of relapse. A growing number of new molecular and cellular targets of addictive drugs have been identified, and rapid advances are being made in relating those targets to specific behavioral phenotypes in animal models of addiction. In this context, the pattern of expression of the dopamine (DA) D_3 receptor in the rodent and human brain and changes in this pattern in response to drugs of abuse have contributed primarily to direct research efforts toward the development of selective DA D_3 receptor antagonists. Growing preclinical evidence indicates that these compounds may actually regulate the motivation to self-administer drugs and disrupt drug-associated cue-induced craving. This report will be divided into three parts. First, preclinical evidence in support of the efficacy of selective DA D_3 receptor antagonists in animal models of drug addiction will be reviewed. The effects of mixed DA D_2/D_3 receptor antagonists will not be discussed here because most of these compounds have low selectivity at the D_3 versus D_2 receptor, and their efficacy profile is related primarily to functional antagonism at D_2 receptors and possibly interactions with other neurotransmitter systems. Second, major advances in medicinal chemistry for the identification and optimization of selective DA D_3 receptor antagonists and partial agonists will be analyzed. Third, translational research from preclinical efficacy studies to so-called proof-of-concept studies for drug addiction indications will be discussed.

Keywords

addiction; dopamine; D_3 receptor; impulse control disorder; polymorphisms; proof of concept; selective antagonists

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Conflicts of interest
The authors declare no conflicts of interest.

Part I: Evidence in support of the efficacy of selective DA D_3 receptor antagonists in animal models of drug addiction

Rationale

Recent advances in addiction research are revealing long-lasting changes in the brains of individuals addicted to drugs and are supporting the concept of addiction as a disease of the brain with the recruitment of specific neural networks, the progressive adaptation of molecular and cellular mechanisms, and the association of drug use with environmental cues. This perspective on addictive disorders casts a new light on the extent and nature of the brain changes caused by chronic drug abuse, their effect on the neural substrates of self-control, and the biological and environmental factors that might confer increased vulnerability to these effects. This new perspective also affects the translational value of preclinical animal models, and the discovery and optimization of novel pharmacotherapeutic approaches.

The selective distribution of the dopamine (DA) D_3 receptor (for a schematic representation of key distribution patterns of the D_3 receptor in the mouse brain, see Fig. 1) onto key neurocircuits that underlie the processing of motivationally relevant events has made this target a main focus of significant drug discovery efforts over the last decade.[1–15] First, high levels of DA D_3 receptor mRNA are present in the mesolimbic DA system that originates in the ventral tegmental area (VTA) and projects toward limbic forebrain regions, including the "extended amygdala," which is comprised of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and the shell subregion of the nucleus accumbens (NAc shell). This system appears to play a rheostatic role in the learning of the motivational significance of a stimulus and has been directly associated with the binge, intoxication stage of addiction.[16,17] Second, DA D_3 receptor mRNA is found in the medial prefrontal cortex (mPFC)–NAc–ventral pallidum loop that plays an important role in drug-,[16,18] cue-,[16,19] and stress[16,20]-induced reinstatement of drug-seeking behavior (craving stage). Third, DA D_3 receptor mRNA is also found in the ventral striatal, ventral pallidal, thalamic, and orbitofrontal loops, which are implicated in drug-seeking and compulsive behaviors.[16,17] Fourth, recent positron emission tomography studies showed that [^{11}C](+)-PHNO ([^{11}C](+)-4-propyl-3,4,4*a*,5,6,10*b*-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol), a mixed D_3/D_2 receptor agonist, produces preferential uptake in the ventral striatum and globus pallidus of humans and baboons compared to radiolabeled D_2 receptor antagonists (such as [^{11}C]raclopride) or other D_2 receptor agonists (such as [^{11}C]NPA((–)-*N*-[^{11}C]propyl-norapomorphine)) that show preferential uptake in the dorsal striatum.[21–23] Furthermore, the specific binding of [^{11}C](+)-PHNO in the globus pallidus of baboons was inhibited by the partial D_3 receptor agonist BP 897 (*N*-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]naphthalene-2-carboxamide) to a greater extent than that of [^{11}C]raclopride, suggesting that the D_3 receptor contribution to the specific binding signal of [^{11}C](+)-PHNO is higher than that of [^{11}C]raclopride.[21]

In addition to the restricted high-density localization of the D_3 receptor in neurocircuits that play an important role in emotional and cognitive functions including behaviors controlled by the presentation of drug-associated cues, enhanced expression of DA D_3 mRNA and receptors has also been reported in the rodent brain after acute, subchronic, or chronic exposure to cocaine,[24,25] nicotine,[26,27] morphine,[28] and alcohol.[29] An increase in the number of D_3 receptors in the ventral striatum has been corroborated by human postmortem [^{3}H]-7-OH-DPAT binding studies performed on cocaine overdose fatalities,[30–33] but changes in the density of D_3 receptors have not been observed in the putamen and caudate of smokers compared to nonsmokers.[34] Preliminary findings also indicate that the expression of DA D_3 receptor mRNA in peripheral blood lymphocytes is negatively correlated with

daily number of cigarettes in smokers versus nonsmokers[35] and is associated with Cloninger's personality trait of persistence (i.e., maintenance of behavior without or with rare reinforcement).[36]

Effects of selective DA D_3 receptor antagonists in animal models of drug addiction

Translation of preclinical efficacy data on a compound prior to testing in a full-scale clinical trial is particularly challenging in the drug addiction area. The predictive value of animal paradigms has been hampered by the absence of effective medications with which to validate those models. Notwithstanding these limitations, animal models of addiction that have face validity, reliability, and construct validity do exist for several elements of the addiction syndrome. In this section we will review data showing that highly potent and selective DA D_3 receptor antagonists, such as **SB-277011A** (*trans-N*-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2yl)ethyl] cyclo-hexyl]-4-quinolininecarbo-xamide)[37–39], **SB-414796** (*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-benzazepine)[40], **Compound 35** (7-(1,3-dimethyl-1*H*-pyrazol-5-yl)-3-(3-{[4-methyl-5-(2-methyl-5-quinolinyl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine)[41], and **NGB 2904** ([*N*-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-9*H*fluorene-2-carboxamide])[42] have efficacy in preclinical paradigms assessing the behavioral effects induced by nicotine, cocaine, alcohol, methamphetamine, and heroin. In the following subsections we will show how gradual increase in our understanding of the *in vivo* effects of these compounds guided medicinal chemistry efforts, which will be described in detail in Part II.

Measurement of the direct rewarding properties of addictive drugs: brain stimulation reward—

Brain stimulation reward (BSR), also referred to as intracranial self-stimulation, is a procedure during which steady rates of lever-pressing behavior in rats can be maintained if brief electrical stimulation of the medial forebrain bundle or other rewarding brain sites follows the operant behavior. The rate–frequency procedure typically involves the generation of a stimulation–response function and provides a frequency threshold measure. The frequency of the stimulation is varied, and the subject's response rate is measured as a function of frequency. The relationship between response rate and pulse frequencies yields a sigmoidal rate–frequency curve. Lateral shifts along the pulse frequency axis in the rate–frequency curve are a selective measure of reward, while vertical shifts provide information on motor/performance capacity. Thus, an increase in the level of BSR current required to maintain lever-pressing (i.e., a rightward shift along the pulse frequency axis in the rate–frequency curve paradigm) is taken as evidence of decreased sensitivity to brain reward. Conversely, almost all drugs of abuse will lower the brain stimulation threshold or produce a leftward shift in the rate–frequency curve paradigm.

Acute administration of SB-277011A in rats significantly and dose-dependently attenuated the enhancement of BSR produced by cocaine,[43] nicotine,[44] methamphetamine,[45] and tetrahydrocannabinol[46] without altering BSR thresholds when administered alone. These findings were recently corroborated by using NGB 2904 in cocaine-, nicotine-, methamphetamine-, and heroin-induced enhanced BSR.[13,47]

Measurement of incentive motivation or drug-seeking behavior evoked by cues previously paired with drugs

Cue-conditioned locomotor activity: Cue-conditioned locomotor activity is based on Pavlovian conditioning. In this procedure, rats are typically injected with a drug and immediately placed in individual locomotor activity cages (experimental environment), which the animals presumably perceive as an environment distinct from their home

environment. The procedure is repeated once a day for 4–5 days and locomotor responses are recorded during each session. Upon repeated administration of the drug in the experimental environment, a progressive behavioral sensitization develops, which is typically reflected by a progressive enhancement of the locomotor response to the drug. This phenomenon is also referred to as context-dependent behavioral sensitization and may have a role in the development of compulsive drug-seeking behaviors.[48]

Rats subjected to nicotine-associated cue-conditioned locomotor activity and subsequently exposed to the nicotine-paired environment were shown to exhibit locomotor hyperactivity without any nicotine injection before reexposure; this effect was also associated with a significant increase in D_3 receptor binding in the shell of the NAc.[26,27] SB-277011A significantly blocked the expression of nicotine-paired cue-induced locomotor hyperactivity.[27,44] Similarly, SB-277011A significantly attenuated cocaine cue-conditioned locomotor activity in mice repeatedly receiving cocaine in a particular environment distinct from home-cages and showing hyperlocomotion after subsequent exposure to the cocaine-paired environment.[24]

Conditioned place preference: The conditioned place preference (CPP) paradigm relies on the phenomenon of secondary conditioning in which a neutral stimulus that has been paired with a reward acquires the ability to serve as a reward itself. Consequently, a drug treatment and its presumed internal effects are paired with the external neutral stimuli of a particular environment. If during a subsequent test the animal increases the time that it spends approaching and maintaining contact with the stimuli in that environment, it is inferred that the drug treatment was rewarding.

Using an unbiased CPP procedure (i.e., no *a priori* preferences for either chamber of the CPP apparatus prior to CPP training, and no *a posteriori* preferences for either chamber after vehicle exposure in both CPP compartments on the CPP training days), the acute systemic administration of SB-277011A prior to each administration of cocaine during the CPP acquisition phase was shown to produce a significant blockade of the *acquisition* or *development* of cocaine-induced CPP.[43] Daily systemic administration of SB-277011A for 14 days prior to testing for expression of cocaine-induced CPP produced a significant blockade of the expression of cocaine-induced CPP.[43] Acute administration of SB-277011A prior to behavioral testing also produced a significant blockade of the *expression* of cocaine-,[43,49] nicotine-,[44] and heroin[50]-induced CPP. SB-277011A by itself produced neither preference nor aversion[43,44,51] and failed to alter the expression of food-induced CPP.[43] The acute effects of SB-277011A on the expression of cocaine- and nicotine-induced CPP have been confirmed by using other selective DA D_3 receptor antagonists, such as SB-414796[40] and Compound 35.[41]

Drug self-administration—More than 20 psychoactive drugs that are abused by humans have also been found to act as reinforcers in rats, thus supporting the hypothesis that drug self-administration in animals may be a reliable predictor of abuse liability in humans. A major focus of preclinical research on drug self-administration has been to examine the variables (behavioral and pharmacological) that modify this behavior. Consequently, different reinforcement contingencies have led to variants of the core self-administration model.

Measurement of patterns of rate of drug intake (low fixed-ratio schedules): In low fixed-ratio (FR) schedules of reinforcement, the response requirements for each drug infusion are set at a fixed number. Within a range of drug doses that maintain stable responding, animals will typically increase their response rate as the unit dose is decreased but will reduce their rate of self-administration when the unit dose is increased. Low FR

schedules of reinforcement are useful for exploring patterns of rate of drug intake, which are an ambiguous measure of drug efficacy, but are less appropriate to assess changes in the reinforcing effects of drugs of abuse.

SB-277011A[52,53] or NGB 2904[13,47] failed to significantly alter cocaine self-administration under low FR schedules of reinforcement. Similarly, SB-277011A[54] and Compound 35[41] failed to affect nicotine self-administration under low FR conditions.

Measurement of the relative strength of a reinforcer independent of response rate (progressive ratio schedules): During progressive-ratio (PR) schedules of reinforcement rats must complete increasing FR response requirements to obtain a reinforcer (here the drug). The essential feature of the PR schedule is that the response requirement continues to increase until responding ceases altogether and the reinforcer is no longer obtained. The final ratio completed is termed “breaking point” or “breakpoint.” Because the PR breakpoint is an index of the relative strength of a reinforcer independent of response rate, one assumes that a shift in PR breakpoint produced by a pharmacological agent indicates that the latter decreases the reinforcing value of the drug.

Under a PR reinforcement schedule, both SB-277011A[52] and NGB 2904[13,47] produced a significant dose-dependent lowering of the PR breakpoint for cocaine self-administration. Furthermore, both compounds significantly shifted the cocaine dose–response breakpoint curve to the right. These effects were recently confirmed in a study showing that a high dose of SB-277011A significantly decreased nicotine self-administration, but not food-maintained behavior under a PR schedule of reinforcement.[55] SB-277011A also produced a significant decrease in cocaine self-administration when the unit dose of cocaine was decreased or when the work demand for cocaine was increased from an FR1 to FR10 schedule.[52]

Measurement of the effect of the conditioned reinforcing properties of the drug-paired stimulus (second-order schedules): Second-order schedules of drug reinforcement provide an animal model of cue-controlled drug-seeking prior to *and* after the drug has been self-administered. One of the main advantages of second-order schedules of reinforcement is that responding for the drug can be maintained for extended periods prior to actual drug infusion. Furthermore, this model is not contaminated by cumulative drug effects. Decreased responding during the first and second intervals produced by treatment with a pharmacological agent is typically explained as an attenuation of the effect of the conditioned reinforcing properties of the drug-paired stimulus. A concomitant increase in latency to the first presentation of the contingent conditioned stimulus and the first cocaine infusion may suggest that the decrease in drug intake under the second-order schedule is related to a decreased motivation to respond for that drug.

SB-277011A produced a dose-dependent decrease in cocaine-seeking behavior maintained by a cocaine-associated conditioned reinforcer in both the first drug-free interval and after the second cocaine self-administration interval.[56] SB-277011A also increased the latency to receive the first conditioned stimulus presentation and cocaine infusion, thereby decreasing the number of cocaine infusions self-administered under the second-order schedule of reinforcement. The selectivity of D_3 receptors in mediating cue-controlled drug seeking was further supported by the finding that SB-277011A had no effect on responding for sucrose under similar second-order reinforcement. A recent study using the same second-order schedule of reinforcement also showed that SB-277011A infused directly into the basolateral amygdala (BLA), but not into the dorsal striatum or NAc shell, decreased cocaine-seeking maintained by conditioned reinforcers.[57]

Oral alcohol self-administration: The intravenous (i.v.) self-administration of alcohol is difficult to sustain in rodents. Accordingly, a relatively simple method to measure alcohol consumption in rodents is to provide the animals with a choice between a bottle containing a given percentage of alcohol and another bottle containing water. The proportion of alcohol intake relative to total fluid intake is then calculated as a preference ratio.

SB-277011A produced a significant attenuation in alcohol preference, intake, and lick responses in a two-bottle choice paradigm that monitored alcohol consumption in alcohol-preferring (P) versus nonpreferring (NP) rats[58] without producing locomotor side effects, as indicated by stable lick response-volume ratios and lick response time distributions.[58]

Reinstatement of drug-seeking behavior—In the self-administration version of the reinstatement model animals are typically trained to respond for a drug by pressing a lever. After extinction of responding, nonreinforced pressing on the drug-associated lever is induced by reexposure to the drug itself (drug-triggered reinstatement), exposure to environmental cues that had been previously associated with drug-taking (cue-triggered reinstatement), or stressors (stress-triggered reinstatement).

Drug-triggered reinstatement: SB-277011A was shown to significantly reduce reinstatement of cocaine seeking triggered by a single, noncontingent cocaine injection without affecting food-triggered reinstatement of food-seeking behavior.[43] Recent studies have confirmed these results with NGB 2904, which produced a significant attenuation of cocaine triggered reinstatement of cocaine seeking without affecting sucrose-plus-sucrose-cue-triggered reinstatement of sucrose-seeking behavior.[13,47] Both SB-277011A[54] and Compound 35[41] also significantly attenuated the noncontingent nicotine-triggered reinstatement of extinguished responding on a lever that was previously associated with the i.v. infusion of nicotine.

Cue-triggered reinstatement: Pretreatment with SB-277011A[59] or NGB 2904[13,47,59] dose-dependently decreased cocaine cue-induced reinstatement of cocaine-seeking behavior without altering inactive lever responding during reinstatement testing. These findings were confirmed for SB-277011A in a reinstatement model where animals with stable cocaine self-administration behavior were exposed to all the environmental and reinforcement-contingent discrete cues associated with previous cocaine intake in a single extinction session after a 3-week abstinence period.[60] The same study also clearly showed that SB-277011A did not alter cue-controlled sucrose-seeking behavior.[60] In a model of extinction/reinstatement in which cocaine-associated cues induce a robust and enduring drug-seeking behavior in abstinent rats as measured by the recovery of extinguished responding at a previous drug-paired lever,[61–63] SB-277011A[64] and another selective DA D_3 receptor antagonist, (*N*-[4-[4-(2,4-dichlorophenyl)piperazin-1-yl]butyl]indole-2-carboxamide),[65] produced a significant dose-dependent decrease in responding produced by reintroduction of cocaine-associated cues. In addition, SB-277011A, at a dose that reduced cocaine seeking, did not alter conditioned reinstatement of seeking behavior triggered by cues associated with sucrose pellets.[64] The acute administration of SB-277011A also significantly reduced cue-induced reinstatement of alcohol-seeking behavior in rats[29] and mice.[66] The latter finding was recently reconfirmed by using Compound 35.[41]

Stress-triggered reinstatement: In addition to reexposure to the drug itself or reexposure to environmental stimuli that had been previously associated with drug taking, exposure to stressors can also produce reinstatement of drug self-administration and/or drug-seeking behavior.[67] Administration of SB-277011A produced a dose-dependent decrease in the reinstatement of cocaine-seeking behavior induced by foot-shock stress.[68] Furthermore, bilateral microinjection of SB-277011A directly into the NAc, but not the dorsal striatum,

significantly blocked stress-induced reinstatement of cocaine seeking.[68] These results point toward a key role of DA D_3 receptors in the NAc in stress-induced reinstatement of cocaine-seeking behavior.

Alcohol deprivation effect: One of the main criteria to define relapse to alcohol-taking is that levels of ethanol consumption must be resumed to equal or greater levels than those measured prior to abstinence. The alcohol deprivation effect is observed after reexposure to alcohol after a period of alcohol deprivation and measured as a transient increase in the ratio of alcohol/total fluid intake and voluntary intake of alcohol solutions over baseline drinking conditions.[69] SB-277011A produced a dose-dependent reduction in the alcohol deprivation effect in long-term alcohol drinking Wistar rats.[29]

Functional connectivity using pharmacological magnetic resonance imaging—The recent combination of pharmacological treatment with functional magnetic resonance imaging (fMRI), also referred to as pharmacological MRI (phMRI), provides a new method to identify functional changes sequentially over real time in response to the acute, subchronic, or chronic administration of drugs. The classical univariate analysis of phMRI data emphasizes the specialization of function within different brain areas (also referred to as functional segregation). However, brain functional processes rely on efficient information flow within widely distributed and highly integrated neuronal networks, and drug effects may be partly explained by disrupted connectivity. The recent application of multivariate approaches to the analysis of phMRI time-series can provide insight into the functional integration of the brain and into changes in inter-regional interactions in response to drug treatment.

A recent preclinical phMRI study that used inter-subject functional connectivity analyses of phMRI responses to d-amphetamine showed that selective antagonism at DA D_3 receptors via acute SB-277011A treatment produced a reversed correlation between responses in the VTA and the dorsal thalamus, and a reduced correlation between the VTA and ventral striatum.[70] These findings suggest that a modified functional connectivity within a circuit that is a key substrate in the so-called reward system may play an important role in the efficacy of selective DA D_3 receptor antagonists in attenuating drug-seeking behavior.

Effects of selective DA D_3 receptor antagonists in animal models of highly palatable food intake

Overeating of highly palatable food, like drug addiction, is linked to repeated exposure to powerful reinforcers that activate common brain circuits involved in reward, motivation, and decision making.[71] Recent evidence shows that some eating disorders may actually fall into the category of impulse control disorders. People suffering from impulse control disorders typically show a greater tendency to choose small, immediate rewards (e.g., drugs or money) over larger, delayed rewards,[72–75] and discount their hedonic stimuli of choice faster than they do monetary rewards of equal value.[76]

Although the effects of selective DA D_3 receptor antagonists in paradigms investigating changes in responding for delayed or intermittent reinforcement[77,78] remains to be fully characterized, a recent study showed that SB-277011A significantly reduced food self-administration in obese Zucker rats.[79] These findings indicate that selective DA D_3 receptor antagonists may also have some potential in the treatment of impulsive food intake and food craving.

Potential confounding factors in the efficacy of selective DA D_3 receptor antagonists in animal models of addictive behaviors

Locomotor impairment—Highly selective DA D_3 receptor antagonists do not exhibit functional antagonism at DA D_2 receptors. Thus, one may hypothesize that a proportionally high degree of D_3 versus D_2 receptor blockade is predictive of a low potential for locomotor side effects that could confound the outcome of animal models of addictive behaviors. This assumption is supported by preclinical data showing that, in contrast to DA D_2 receptor antagonists, selective DA D_3 receptor antagonists: (1) do not affect spontaneous or stimulant-induced locomotion; (2) do not affect motor coordination; (3) do not elicit catalepsy; (4) do not increase serum prolactin levels, and (5) do not increase DA levels in the striatum.[5,38] Recent data also show that both SB-277011A and S33084 ([(3aR,9bS)-*N*[4-(8-cyano-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[3,4-c]pyrrole-2-yl)-butyl](4-phenyl)benzamide]), another selective DA D_3 receptor antagonist, actually reduce haloperidol-induced catalepsy.[80–82]

Memory impairment—One may argue that because several preclinical paradigms that assessed the efficacy of selective DA D_3 receptor antagonists (e.g., cue-induced locomotor activity, CPP, reinstatement of drug-seeking behavior) presumably involve encoding and storage of cue-induced associations, as well as memory retrieval of such associations, the efficacy of these selective antagonists might be mediated by interference with general aspects of memory storage and retrieval. This possibility, however, is unlikely in the light of recent findings. First, selective DA D_3 receptor antagonists significantly increase extracellular levels of acetylcholine in frontocortical regions.[83–85] Acetylcholine plays an important role in various domains of cognition, such as attention, learning, and memory,[86] and cortical acetylcholine levels increase when demands on attentional processing are high.[87] Second, the lack of D_3 receptors (knockout studies) actually enhances performance in set-shifting/reversal phases of a cognitive task.[88] Third, selective DA D_3 receptor antagonists significantly improve drug-induced learning deficits without altering the normal learning process in nonimpaired rats,[89] and improve social recognition in rats after either systemic administration[85] or local microin-fusion into the mPFC (cingulate and infralimbic subterritories).[90]

Despair, helplessness, and anhedonia—One may also argue that selective DA D_3 receptor antagonists alter mood states. This argument, again, seems unlikely because selective DA D_3 receptor antagonists, in contrast with DA D_2 receptor antagonists,[91] enhance social interaction[92] and reduce responding to aversively conditioned stimuli.[93] Furthermore, recent studies have shown that D_3 receptorknockoutmicehavenoimpairmentinanimal models of despair, helplessness, and anhedonia.[94]

Abuse liability—One could also argue that selective DA D_3 receptor antagonists can be self-administered and carry abuse liability *per se*. However, when SB-277011A was substituted for cocaine in an FR schedule, it did not maintain cocaine self-administration behavior.[52] Similarly, substitution tests with NGB 2904 in rats already experienced and displaying behaviorally stable cocaine self-administration under FR2 reinforcement conditions clearly showed that NGB 2904 does not sustain a stable pattern of self-administration as reflected by gradual extinction that was identical to that seen when saline was substituted for cocaine.[13,47] Finally, NGB 2904 did not substitute for cocaine in a drug discrimination task in the rhesus monkey and failed to attenuate the discriminative stimulus properties of cocaine.[95]

Possible role of the DA D_3 receptor in specific neurocircuits

Summary of the "what"—The preclinical models used to assess the efficacy of selective DA D_3 receptor antagonists have shown that these compounds do not affect the primary reinforcing effects of drugs of abuse, but rather regulate the motivation to self-administer drugs under schedules of reinforcement that require an increase in work demand. In addition, selective antagonism at DA D_3 receptors appears to disrupt significantly the responsiveness to drug-associated stimuli that play a key role in reinstatement of drug-seeking behavior triggered either by reexposure to the drug itself, reexposure to environmental cues that had been previously associated with drug-taking behavior, or stress (Fig. 2). Impulsive food intake and food craving might also be a new potential therapeutic indication for selective DA D_3 receptor antagonists. The data collected thus far also confirm the lack of effect of selective DA D_3 receptor antagonists on low FR drug self-administration. Furthermore, their effects appear to be specific to drugs of abuse without producing a state of general, undifferentiated "anhedonia" as evidenced by a lack of effect on food-maintained PR schedules, expression of food CPP, second-order schedules for sucrose, food or sucrose-triggered reinstatement, or cue-controlled sucrose seeking. Finally, selective DA D_3 receptor antagonists do not produce impairment in locomotor activity, memory and mood, and do not seem to have abuse liability.

Possible "where" and "how"—Although the distribution of the DA D_3 receptor has been well characterized in many species, its role in specific brain regions or within neural networks remains largely unknown. However, recent studies using local microinfusion of selective DA D_3 receptor antagonists may provide new insight into the key networks that might mediate the efficacy of these compounds in animal models of addiction.

First, bilateral microinfusion of SB-277011A into the NAc (1.5 μg/0.5 μL/side), but not the dorsal neostriatum, was reported to completely block footshock stress–induced reinstatement of cocaine seeking.[68] Acute stress activates DA neurons in the VTA[96] and increases DA outflow in the NAc[97–99] and mPFC,[100,101] possibly by activating an excitatory projection from the mPFC to glutamate receptors on VTA DA neurons[102] and/or via corticotropin releasing factor release in the midbrain and amygdala.[103] Finally, inhibition of the central extended amygdala, which includes the central nucleus of the amygdala, ventral bed nucleus of the stria terminalis, and NAc shell, but also the VTA and motor circuits (including the dorsal prefrontal cortex, NAc core, and ventral pallidum) significantly reduced the ability of footshock stress to reinstate lever pressing previously associated with cocaine self-administration.[104] In contrast, inhibition of the BLA, mediodorsal nucleus of the thalamus, or the ventral prefrontal cortex had no effect on stress-induced reinstatement of cocaine-seeking behavior.[104] Additional studies are needed to further refine the central extended amygdala sites of action that mediate the protective effects of SB-277011A against stress-triggered reinstatement of drug-seeking behavior.

Second, SB-277011A infused directly into the BLA (2–4 μg/0.3 μL/side), but not into the dorsal striatum or NAc shell, was also reported to decrease cocaine seeking maintained by a second-order schedule of reinforcement,[57] thus suggesting a key role of DA D_3 receptors in the BLA in stimulus–reward associations that mediate cue-triggered reinstatement of cocaine-seeking behavior. Enhanced monoaminergic tone in the BLA has been previously shown to increase the motivational properties or salience of cocaine-associated cues during reinstatement of cocaine-seeking behavior,[105,106] whereas inactivation of the BLA produces the reverse effect.[107–110] Spontaneous recovery of cocaine seeking[111] and consolidation of drug-conditioned stimulus associations into long-term memories that, in turn, drive cocaine seeking during relapse[112,113] seem to depend upon the integrity of the BLA. Recent studies also point toward an important role of cue-selective neurons in the BLA, which are essential

to the expression of the reversal-learning deficit observed in cocaine-treated rats.[114] The question of whether or not D_3 receptors are expressed on those neurons and to what extent D_3 receptors contribute to the regulation of decision-making deficits in reversal-learning tasks and complex gambling variants remains to be fully investigated.

Third, direct microinfusion of the selective DA D_3 receptor antagonists S33084 (0.04–2.5 μg/side) and SB-277011A (0.16–2.5 μg/side), into the cingulate and infralimbic subterritories of the mPFC, but not into the NAc or dorsal striatum, was recently shown to reverse a delay-induced deficit of social recognition in rats.[90] These findings suggest a possible role of D_3 receptors located in the mPFC in the modulation of working memory and attentional processes. In contrast to rodents, the DA D_3 receptor is expressed on Von Economo neurons[115] located in the anterior cingulate and frontoinsular cortices[116] of humans, great apes, and whales.[117,118] Recent functional imaging studies have shown that frontoinsular cortex and anterior cingulate cortex are activated when subjects experience social emotions.[119–122] Smokers with brain damage involving frontoinsular cortex are more likely to undergo a significant disruption of smoking behavior, characterized by the ability to immediately quit smoking, without relapse, and without persistence of craving.[123] The question of whether DA D_3 receptors on Von Economo neurons in the frontoinsular and anterior cingulate cortices are implicated in this process remains unanswered.

Altogether these findings suggest that the efficacy of selective DA D_3 receptor antagonists in animal models of addiction might be directly mediated by D_3 receptors located at critical junctures in three main pathways: (1) stress-induced reinstatement of drug-seeking behavior in the NAc Shell; (2) stimulus–reward associations mediating cue-triggered reinstatement of drug seeking in the BLA, and (3) working memory and attentional processes in the mPFC (Fig. 3). Additional studies are now required to further refine this functional mapping and posit new working hypotheses.

Polymorphisms at the DA D_3 receptor and addictive behaviors

The DA D_3 receptor gene is located on chromo-some 3q13.3; its coding sequence consists of six exons that are distributed over 40,000 base pairs. The most commonly studied polymorphism at the DA D_3 receptor gene is the Ser^9Gly (*Bal*I/*Msc*I) that is located at amino acid position 9 of the N-terminal extracellular domain of the receptor.[124] The Ser^9 variant is also referred to as allele 1, and the Gly^9 variant as allele 2. Disparate findings have been reported regarding the possible relationship between polymorphisms at the DA D_3 receptor gene and addictive behaviors.

The presence of the glycine allele at the Ser^9Gly polymorphism has been associated with the time to first cigarette of the day as well as with the Heaviness of Smoking Index.[125] A recent study also suggests that the single-nucleotide polymorphism, rs6280, is associated with nicotine dependence as measured by smoking quantity, the Heaviness of Smoking Index, and the Fagerström Test for Nicotine Dependence.[126]

Early studies suggested an increased frequency of allele 1 in a subgroup of alcohol-dependent patients with delirium.[127] These findings were corroborated by another study showing an association between alcohol-dependent patients with the heterozygous 1–2 genotype and higher novelty-seeking scores as measured by the Tridimensional Personality Questionnaire compared to patients with the 1–1 genotype.[128] Similarly, alcohol-dependent patients with above-median values for cognitive impulsiveness were more frequently heterozygous compared to both alcohol-dependent patients with lower impulsiveness and healthy controls.[129] In contrast, several studies have reported a lack of association between alcohol dependence and the *Bal*I polymorphism at the DA D_3 receptor gene.[130–135]

There is currently no clear evidence in support of an association between the *Bal*I polymorphism at the DA D_3 receptor gene and cocaine dependence.[136–138]

Opiate-dependent patients with high sensation-seeking scores were found to be more frequently homozygotes for both alleles than patients with low sensation-seeking scores or controls.[139] However, other studies were unable to find any significant association between the *Bal*I polymorphism at the DA D_3 receptor gene and heroin addiction.[140,141]

Finally, a recent study indicated that three DA D_3 receptor genotypes share higher association with the hyperactive/impulsive symptom scale of attention deficit–hyperactivity disorder.[142] The *Bal*I polymorphism at the DA D_3 receptor gene was also associated with impulsivity and some psychopathological traits of attention deficit–hyperactivity disorder specifically related to violent behavior.[143] A few isolated reports also found an association between (1) the *Bal*I polymorphism and novelty seeking in bipolar patients[144] and (2) homozygosity and substance abuse in schizophrenia.[145]

Altogether these findings suggest that the *Bal*I polymorphism at the DA D_3 receptor gene does not seem to influence directly the risk of drug addiction *per se* but appears to influence personality traits, such as novelty seeking and impulsiveness, which have been reported to predict later alcoholism[146] and relapse rate in detoxified alcoholics.[147] Clearly, additional studies and replications are needed in order to assess the relevance of genetic variants in the DA D_3 receptor gene for novelty seeking and impulsiveness, which in turn may serve as vulnerability factors for addictive behaviors.

Part II: Major advances in medicinal chemistry for the identification and optimization of selective DA D_3 receptor antagonists

Prototypic D_3 receptor antagonist template

In Part I, the rationale for targeting DA D_3 receptors for development as medications to treat addiction is described in detail. Furthermore, the evaluation of the prototypic D_3 receptor antagonists SB-277011A and NGB 2904 in many animal models of drug abuse and addiction have provided further incentive to move forward in the discovery and development of novel and selective D_3 receptor antagonists. To this end, SB-277011A and NGB 2904 have served as templates for the design of most high-affinity and selective D_3 receptor antagonists, to date. As described previously, both of these compounds bind with low nanomolar (nM) affinity to D_3 receptors and are selective over the other D_2-family receptor subtypes (D_2 and D_4) by varying degrees, depending on the radioligand binding or functional assays used for comparison. In addition, significant chemical modification of these templates has resulted in D_3 receptor antagonists that are not only highly selective over the D_2 and D_4 receptor subtypes but most or all central nervous system receptors and transporters tested. Some of these D_3-selective antagonists have been evaluated in >100 biological as-says and represent the most selective D_3 antagonists reported to date.[5,9]

Although high binding affinity for D_3 receptors may be achieved with a large number of structurally related molecules, >100-fold binding selectivity for D_3 over D_2 receptors remains tied to an extended molecule with aryl substituents at each terminus. Thus far, despite extensive exploration of the D_3 antagonist pharmacophore, achieving the desired pharmacological profile while obtaining “druglike” physical properties remains a challenge for the field. Indeed, *in vivo* studies with both SB-277011A and NGB 2904 have been complicated by their respective high lipophilicities and poor water solubility. Further, the physical consequences of their large molecular weights (438.6 and 494.5, respectively) and cLogP values of 4.8 and 6.7 (determined with ChemDraw Ultra 11.0) respectively, may also

contribute to the need for higher doses/concentrations for *in vivo* investigation than would be predicted based on their D_3 receptor antagonist potencies, *in vitro*.

In the next section, the structure–activity relationships (SAR) of the DA D_3 receptor antagonists are described in detail. In addition to binding affini-ties and selectivities for D_3 receptors, intrinsic activity of the resulting compounds will also be discussed, as this has been a topic of great interest and controversy, in terms of medication development. Although the primary focus of this review is on D_3 receptor antagonists, D_3 partial agonists have also been reported. These partial agonists share significant SAR with the antagonists, exemplified by the prototypic D_3 partial agonist BP 897. Thus, these compounds and inclusion of the most recent medicinal chemistry toward novel partial agonists that depart from the traditional phenylpiperazine template is described in the third section, although significant preclinical evaluation of these compounds remains to be reported. All compounds described throughout this Part II are denoted in both the text and the figures as their original code or compound number from the primary papers, for easy cross-reference.

In the fourth section, the evolution of drug design that goes beyond SAR and incorporates structural elements to improve bioavailability, reduce metabolism, and eliminate potential toxicity is detailed. In this part, four drug classes are highlighted as they illustrate the evolving drug design, synthesis, and preclinical evaluation of the D_3 receptor antagonists and partial agonists, thus far. Further, significant biological evaluation, especially with the GlaxoSmithKline compounds, has led to design features that optimize all pharmacological properties of these agents, which ultimately led to clinical candidates that will be discussed in Part III.

Structure–activity relationships for D_3 receptor antagonists

Extensive SAR have been described for the D_3 receptor antagonists in many primary papers and reviews. Several comprehensive reviews[9,148] of the most popular class of D_3 receptor antagonists, the 4-phenylpiperazines, have been recently published and reiteration of these will not be discussed in this review. Rather, a summary of SAR is described in detail below with selected examples from the primary literature.

In general, in order to obtain high (<10 nM) binding affinity at D_3 receptors and either a D_3 antagonist or partial agonist functional profile, and to approach or exceed >100-fold selectivity over the D_2 receptor subtype, the following SAR has been deduced and is illustrated in Figure 4.

1. An extended aryl amide is sufficient, but not necessary for high-affinity binding at D_3; however, if it is replaced with a smaller aryl ring system or an alkyl substituent, D_2 affinity is regained and D_3/D_2 selectivity is consequently reduced.[149,150] Addition of heteroatoms into the extended aryl ring system serves to preserve the necessary steric bulk while reducing lipophilicity. For example, heteroaromatic analogues of NGB 2904 were prepared to maintain or improve D_3 binding affinity and D_3 selectivity while reducing lipophilicity by several orders of magnitude.[150,151]
2. The amide linker is a convenient synthon for convergent synthesis but is not necessary for high D_3 affinity and selectivity.[15,41] Nevertheless, a bioisosteric replacement, such as an oxazole, appears to provide optimal D_3 binding,[41] suggesting that the amide serves as more than a spacer in these molecules and probably provides additional hydrogen bonding interactions at the binding site.
3. The linking chain between the aryl amide and the amino terminus must be a certain length to optimize D_3 affinity and selectivity. The simple saturated butyl chain

(e.g., NGB 2904) provides the optimal chain length, but further improvement in D_3 selectivity can be obtained by rigidifying this linker via an olefin (preferably *trans*, e.g., PG01037) or a *trans* cyclohexyl ring (SB-277011A). In addition, functionalizing this alkyl linking chain with an OH group, preferably in the 3-position, serves to retain or further improve binding affinity and D_3 receptor selectivity.[151–153] However, increasing the steric bulk in this position on the linking chain significantly reduces D_3 receptor binding affinity, suggesting there is little steric space to accommodate these larger substituents.[151] Moreover, enantioselectivity at this position has recently been demonstrated with PG648, where the *R*-enantiomer is ~15-fold selective at D_3 over the *S*-enantiomer and interestingly, this enantioselectivity is not as pronounced at D_2 receptors (less than twofold), suggesting critical amino acid residue differences between D_2 and D_3 in this region of the binding pocket.[153]

4. A terminal aryl ring system that is sterically extended and adds lipophilicity, e.g., 5-CN isoquinoline of SB-277011A or the 2,3-diClphenylpiperazine of NGB 2904 or PG01037 series significantly improves selectivity over D_2 and other receptors, such as serotonin (5-HT). The2-OCH_3-phenylpiperazineisacommonly used synthon, from the D_3 partial agonist BP 897. Unfortunately, selectivity over D_2 and several 5-HT receptor subtypes is reduced when thisarylterminusisused,althoughthereduced lipophilicity it provides, compared to the 2,3-diCl-phenylpiperazine is an advantage.[151–153]

The essential structural elements that result in both high-affinity and selective D_3 ligands have now been established for the D_3 receptor pharmacophore, exemplified by the prototypic antagonists described. However, when tested in *in vitro* models of intrinsic activity, these compounds can range from being D_3 receptor antagonists to nearly full agonists, depending on the assay used.[8] The classic example of this is BP 897, which was originally reported to be a partial agonist in several *in vitro* assays, but later reported to be an antagonist in others.[154–156] Because its behavioral actions in many models of addiction are not typically different (see, however, significant differences in dose–response curves) from other D_3 receptor antagonists, such as SB-277011A and NGB 2904, the translation of intrinsic activity, as measured in cells expressing cloned human D_3 receptors, has not been a reliable predictor of behavior in animal models of addiction. This may be a result of functional selectivity,[157] but this concept in the D_3 receptor field is still in its infancy. Moreover, tractable SAR that predicts intrinsic activity in this class of compounds has remained elusive.

Hybrid molecule approach to D_3 partial agonists

One approach to specifically design D_3 partial agonists has been to synthesize molecules that incorporate elements of both D_3-preferential agonists and antagonists in an attempt to improve D_3 selectivity and affect intrinsic activity of the resulting compounds from antagonists to partial or full D_3 agonists. As described above, discernible SAR for intrinsic activity has not been elucidated in the prototypic D_3 receptor antagonist class of compounds, and compounds with very similar structures may show antagonist or partial agonist activity in various *in vitro* assays. Hence, in this pursuit and after success in a series of hexahydropyrazinoquinoline hybrids, Wang *et al.* have recently published a series of pramipexole derivatives, the best of which is shown as compound **6** in Figure 5 with a K_i = 0.4 mM at D_3 and K_i = 330 nM at D_2 receptors.[158] These compounds not only showed excellent D_3 receptor selectivity but were also water soluble, eliminating this as a problem for further *in vivo* pharmacological evaluation. Although compound **6** and the other analogues were not evaluated for intrinsic activity *in vitro*, **6** was tested in an *in vivo* model of D_3 receptor mediated yawning in rats.[159–161] The lack of effectiveness in either inducing

yawning (D_3 agonist effect) or blocking yawning induced by pramipexole left its intrinsic efficacy *in vivo,* in question. The strong possibility that this molecule has poor bioavailability underscores the frustration researchers in this field have experienced with identifying D_3-mediated behaviors and relating those to intrinsic efficacy.

Dutta *et al.*[162] have also undertaken the hybrid molecule approach wherein the D_3 agonist portion of the molecule was based on either 5-OH aminotetralin pharmacophore or the D_3-preferential agonist pramipexole (Fig. 5). As in the previously described molecules, the N-propyl group was retained; however, the butylamide linking chain was replaced with the significantly shorter ethyl linker to an aryl-substituted piperazine (e.g., Fig. 5).[162] Although in this series, D_3 over D_2 receptor binding selectivity is significantly <100, SAR divergence from the prototypic D_3 receptor antagonists is also noticeable. In addition to the shorter alkyl linker, the 2,3-diCl-phenylpiperazine is not more potent or selective for D_3 than the unsubstituted phenylpiperazine. These compounds were reported to be partial agonists in the [^{35}S]-GTPγS stimulation binding assay in CHO and AtT-20 cells expressing cloned hD_3 or hD_2s receptors, respectively.[162] Long lasting increases in contralateral rotation in 6-OHDA unilaterally lesioned rats was suggested to be due to D_3 receptor stimulation. When the arylpiperazine was extended to the biphenyl, the resulting compound (-) **34** was reported to be a highly potent and selective full D_3 receptor agonist that also stimulated contralateral rotation in this model,[162] although additional behavioral testing is warranted to further characterize the mechanism underlying behaviors elicited by these compounds. In addition, enantioselectivity was demonstrated in this series at both D_3 and D_2 receptors.

Additional SAR generated with a third hybrid molecule set based on octahydrobenzo (g or f) quinolines has lead to the generation of a pharmacophoric model that emphasizes the importance of the piperazine ring in these structures, but also demonstrates a unique pharmacophore for these hybrid molecules as compared to the more prototypic antagonists and partial agonists described above.[163] Other examples of these hybrid molecules have been recently described with varying efficacies *in vitro* (FAUC 460 in Fig. 5).[163,164]*In vivo* testing of these agents in models of D_3-mediated behavior as well as addiction will be essential to determine if these intrinsic activities observed *in vitro* translate to behaviors *in vivo* and further what is most favorable for medication development.

Design evolution for *in vivo* investigation of selected D_3 receptor antagonists

The evolution of selective D_3 drug design has been recently described in detail[9] for the class, as a whole. In this section the design strategy for four selected and evolving series of compounds will be described and their preclinical evaluation to date, summarized. The goal to drug design is uniform across laboratories, which is to obtain high-affinity and selective D_3 receptor antagonists or partial agonists that are bioavailable and thus will serve as *in vivo* tools to elucidate the role of the D_3 receptor in drug addiction (and other neuropsychiatric disorders, such as schizophrenia) and to ultimately develop a medication for clinical use. In each case, the structural template is slightly different, the evaluation process is elaborate and dependent on the research environment (e.g., industry versus academic labs) and the results are extremely exciting, if not absolutely confirmatory.

Drug design for improved bioavailability—The SAR described in the preceding has been evolving for more than a decade to ultimately result in the discovery of many high-affinity and selective D_3 receptor antagonists and partial agonists, across laboratories. However, in order to achieve these pharmacological properties, drug molecules that have suboptimal physical properties for *in vivo* investigation, such as poor water solubility, undesirable pharmacokinetics (PK), predicted metabolism or other untoward side effects that are unrelated to D_3 receptor binding have resulted. These factors have precluded many

compounds from ever being tested in animal models, or have prevented clinical assessment despite a desirable preclinical profile. This challenge has slowed advancement of our understanding of the role the DA D_3 receptor plays in addiction and how selective blockade or partial stimulation of this receptor subtype will affect behavior, *in vivo*.

Optimizing the physical and "druglike" properties of a molecule, while retaining the desired pharmacological profile obtained through SAR deductions, requires a form of "molecular tinkering." This involves identifying functional groups that are pharmacophoric elements, but have undesirable physical properties or lead to unwanted metabolism, and modifying them. In the case of D_3 receptor antagonists, the high molecular weights (>400) and cLogP values (>5) are predicted to have poor bioavailability or unacceptable metabolic profiles. As the length of the molecule and terminal aryl groups are necessary for high D_3 affinity and selectivity, incorporating heteroatoms, replacing lipophilic substituents, such as the aryl chloro groups, with small heterocycles, and incorporating heteroatoms into the linking chain are all strategies that have been undertaken. The resulting molecules target Lipinski "rule of 5" parameters [e.g., (1) <5 H-bond donors (e.g., OH or NH), (2) <10 H bond acceptors (e.g., N and O), (3) MW<500 and cLog P in the 2–5 range,[165,166] and (4) an appropriate ADMET (adsorption, distribution, metabolism, excretion and toxicity] profile.[167]

The evolution of behaviorally active new D_3 receptor antagonists/partial agonists in models of addiction

D_3 receptor antagonists from SB-277011A: Investigators at GlaxoSmithKline have published a comprehensive design strategy beginning with the now "classic" SB-277011A.[38] As discussed in Part I, second section, SB-277011A is a highly selective D_3 receptor antagonist with good oral availability and significant effects in many models of drug seeking and reinstatement. Nevertheless, this compound was not studied clinically due to *in vitro* metabolism studies in liver microsomes that demonstrated rapid metabolism by aldehyde oxidase, predicting low bioavailability in humans.[40] Hence, the design of a compound with otherwise similar pharmacological characteristics of SB-277011A, but that would not be metabolized by aldehyde oxidase was undertaken. This investigation resulted in the discovery of the 5-methyl-sulfonyloxy benzazepine SB-414796 (Fig. 6) and analogues thereof, some of which were highly D_3 selective over D_2 (250-fold).[40] SB-414796 was reported to be the overall best candidate for *in vivo* investigation, in this series, with a D_3 K_i = 4 nM and D_2 = K_i = 400 nM and with similarly selective functional potency as a D_3 receptor antagonist. In addition, this compound was >100-fold D_3 selective in a panel of >60 receptors and ion channels.[40] Despite promising *in vivo* results (see Part I, second section), further development of SB-414796 was halted due to its affinity for the human ether-a go-go K^+ channel (hERG), which is a predictor of undesirable prolongation of the cardiac QT interval.[41] Extensive SAR studies commenced to reduce the hERG channel affinity of the molecules while retaining all other desirable pharmacological properties. The problematic pharmacophoric elements of both SB-277011A and SB-414796 were identified as being the cyclohexyl ethyl linker and the amide, as well as the sulfone substitution on the benzazepine ring system of SB-414796. Systematic and molecular model-predicted structural modification and replacement of these functional groups with isosteric moieties led to a new series of molecules. Herein the sulfone was replaced with an oxazole and the amido cyclohexylethyl linker was replaced with a thio-linked triazole. Many of these resulting compounds demonstrated high affinity and selectivity for the D_3 receptor.[41] Additional fused benzazepine analogues have also been described.[168,169] The lead compound in these efforts (compound **35** in Ref. 41) was selected for *in vivo* investigation based on its overall *in vitro* profile (Fig. 6) and its appropriate selectivity for D_3 over hERG channel affinity. In addition it showed a promising metabolic P450 profile and excellent PK. *In vivo* studies

conducted on compound **35** in comparison to the other D_3 receptor antagonists from GlaxoSmithKline are described in detail in Part I, second section.

D_3 receptor antagonists based on S33084: The design and synthesis of S33084 was first described in 1999, wherein the conformationally constrained *trans* benzopyrano[3,4-c]pyrrolidines were deemed structurally constrained derivatives of the D_3-preferential agonist (+)-7-OH-DPAT.[149] Addition of a biphenylbutylamide terminus resulted in the high-affinity and D_3-selective antagonist S33084 (Fig. 7). [^{3}H]-S33084 was synthesized as a potential D_3-selective radiolabel that displayed high-affinity, saturable, reversible, and specific binding in CHO cells stably transfected hD_3 receptors.[170] Nevertheless, poor bioavailability limited preclinical development of this agent and a second compound from this series, S33138, was chosen for further pharmacological evaluation (Fig. 7).[92,171,172]

In S33138, the arylamide is reversed as compared to S33084, in that the phenyl ring is attached to an ethyl linker and the acetamide is appended in the *para*-position of this phenyl ring, resulting in a compound that does not extend into the chemical space deemed ideal for D_3 receptor selectivity. As predicted, according to the original report, the D_3 affinity for S33084 (K_i = 0.3 nM) and selectivity over D_2 (100-fold) were higher than for S33138. Nevertheless, extensive pharmacological, neurochemical and behavioral characterization of S33138 was pursued.[92,171,172] Indeed, the procognitive profile of S33138 as well as S33084 and SB-277011A has recently been described as an important attribute of D_3 receptor antagonists and contrasts to D_2 receptor antagonists, which compromise cognitive performance.[85,173] Although development of this compound was primarily directed toward an antipsychotic medication, human comorbidity of schizophrenia with drug addiction[174] suggests that it may be efficacious in models of drug addiction. A recent study has reported that S33138, at very low doses (0.156–0.625 mg/kg of body weight intraperitoneally) attenuated cocaine-enhanced BSR and dose-dependently (0.156–2.5 mg/kg, intraperitoneally) inhibited cocaine-induced reinstatement of cocaine-seeking behavior.[175] As is typical for selective D_3 receptor antagonists, the lower doses of S33138 did not affect cocaine self-administration under low FR1 schedule of reinforcement, although the higher dose of 5 mg/kg effectively reduced cocaine self-administration, probably reflecting a D_2 receptor antagonist effect at this dose. It was noted that at the higher dose of 5 mg/kg, effects on locomotion and food reward were probably mediated through D_2 blockade and could limit therapeutic usefulness of this agent.[175]

D_3 partial agonist based on BP 897: BP 897 binds with high affinity and preferentially to DA D_3 receptors over D_2 receptors.[176] It was first introduced as a D_3 partial agonist and was the first in this class of drugs to show inhibition of conditioned cue-controlled cocaine-seeking behavior, in rats, without producing rewarding effects of its own.[176] Many subsequent studies expanded these results showing that BP 897 attenuated the discriminative stimulus effects of both cocaine and methamphetamine[177] and blocked cocaine-conditioned behavior.[178,179] Further studies using this agent provided significant groundwork for the role DA D_3 receptors play in cocaine associated cues[24] and drug seeking beyond cocaine to other drugs of abuse, such as nicotine and methamphetamine.[3,27,45,59] Nevertheless, its intrinsic efficacy at D_3 receptors has been disputed, depending on what functional assay is used for assessment[154,155] and its behavioral profile is similar (see, however, significant differences in dose–response curves) to those of the prototypic D_3 receptor antagonists, such as SB-277011A and NGB 2904, suggesting that either intrinsic efficacy as measured *in vitro* is not a predictor of D_3-mediated behavior or, as BP 897 shows off target actions as a D_2 receptor antagonist and at 5-HT and α-adrenergic receptors, actions at these sites might confound interpretation of mechanisms underlying observed behavioral actions. Therefore, significant medicinal chemistry has been undertaken to synthesize more D_3-selective receptor antagonists and partial agonists, based on the BP 897 pharmacophore.

The results of these drug design efforts have produced many high-affinity DA D_3 receptor selective agents, with various efficacies in many cell-based functional assays. Unfortunately, very few of these have been tested beyond *in vitro* characterization, so that the question of intrinsic activity and optimal behavioral efficacy remains unanswered. One exception is a recently described analogue of BP 897, RGH-237 (Fig. 8). RGH-237, like BP 897, has the *n*-butylbenzamide structure appended to a substituted phenyl piperazine.[156] Side-by-side comparisons of binding were reported for rat D_2 and D_3 receptors, in which BP 897 was eightfold higher in D_3 affinity, but significantly less selective (165 versus >1800).[156] However, in this assay, SB-277011A was also shown to be highly D_3 selective (>2900-fold), which far exceeds its selectivity reported in human D_3 versus D_2 receptor binding.[38] In this report, human D_3 receptor binding was only reported for RGH 237, which had a K_i = 6.7 nM compared to the originally reported K_i = 0.9 nM for BP 897. In addition, RGH-237 showed very low D_2 affinity, and thus is highly D_3 selective. Functional activity as measured in a [^{35}S]-GTPγS binding assay, showed RGH-237 to be a partial agonist at both D_2 and D_3 receptors, in contrast to both BP 897 and SB-277011A, both of which were full antagonists. PK studies in rats showed RGH-237 to have very poor brain penetrability with a brain/plasma ration of 0.047, as compared to 4.9 for BP 897. Nevertheless, when tested in many models of cocaine-induced place preference, self administration and cue-induced reinstatement of cocaine seeking, RGH-237 showed a behavioral profile consistent with both SB-277011A and BP 897,[156] either supporting the author's view that D_3 partial agonists have efficacy in these models and may be important to target as medications or that the *in vitro* functional assays are not predictive or exhibit “functional selectivity” profiles[157] that cannot be correlated with *in vivo* behaviors, at this time.

D_3 receptor antagonists and partial agonists based on NGB 2904: Because NGB 2904 and BP 897 are structurally quite similar, analogues of one or the other can be considered to belong to a single class of agents. Although, originally the 2-OCH_3-phenylpiperazine moiety of BP 897 was associated with partial agonists, whereas the 2,3-diCl-phenylpiperazine of NGB 2904 was associated with D_3 receptor antagonists, this has not held up with hundreds of analogues having been tested in many functional assays.[151,180] Indeed, analogues that have been tested in more than one functional assay often have shown varying efficacies, as described for BP 897, which has been another challenge to interpretation of mechanisms underlying the behaviors of these compounds, *in vivo*.

As described in previous sections, NGB 2904 has served as a prototypical D_3 receptor antagonist in many behavioral studies, especially in animal models of addiction. Nevertheless, its poor water solubility and high lipophilicity precluded this compound from being a viable candidate for clinical development. Structural modification following the preceding SAR described and then molecular modification to attempt to reduce lipophilicity has led researchers to discover highly selective and potent D_3 receptor antagonists and partial agonists that may be more suitable for *in vivo* investigation and for potential clinical development than the parent drug (Fig. 9). One resulting compound from these efforts was the *trans*-olefin analogue of NGB 2904, wherein the 2-fluorenylcarboxamide group of NGB 2904 was replaced with the less lipophilic heteroaromatic 2-pyridylphenyl group, effectively reducing the cLogP by >1 log unit and improving D_3/D_2 selectivity from 60- to 130-fold.[150] This compound, PG01037, was a water-soluble and highly potent D_3 receptor antagonist and was chosen for *in vivo* investigation in behavioral models of drug addiction.

Because of the challenge of determining D_3 receptor mediated effects *in vivo*, a D_3 agonist-induced yawning model was designed. This model, wherein yawning in rats is induced with a D_3-preferential agonist, such as 7-OH-DPAT or PD128,907, showed a dose-dependent inverted U-shaped curve that reflected a D_3 agonist mediated induction of yawning, followed by a D_2 agonist mediated decrease in yawning.[159] In part, this model was validated

by D_3 receptor antagonists, such as SB-277011A, to exclusively right-shift the ascending (D_3 mediated) limb of the yawning curve without affecting the descending (D_2 mediated) limb. Through extensive pharmacological experimentation, other D_3-mediated effects on hypothermia and penile erection have been discovered, that are not related to drug addiction, but can serve as *in vivo* models to assess intrinsic activity of D_3 receptor selective agents, *in vivo*. Hence, PG01037, which was discovered to be a high-affinity and D_3 receptor selective antagonist[150,152] showed a dose-dependent rightward and downward shift of the ascending limb of the PD128,907-induced yawning curve and had no effect on the descending limb, supporting its characterization as a D_3 receptor antagonist.[159–161] Recently, phMRI studies have shown that PG01037 rapidly enters the brain and localizes in D_3 but not D_2 receptor–rich regions in rat brain at a dose of 2 mg/kg i.v.[151] Subsequent testing of PG01037 in many models of cocaine and methamphetamine abuse in rats and squirrel monkeys suggest that PG10137 behaves similarly to the prototypic D_3 receptor antagonist, NGB 2904 and SB-277011A. For example, PG01037 does not attenuate cocaine self-administration in squirrel monkeys, but is effective in attenuating cocaine-induced cocaine seeking and the discriminative stimulus effects of cocaine without altering food-maintained behavior or inducing adverse motor effects, such as catalepsy.[181] Further, whereas PG01037 had no effect on methamphetamine self-administration under an FR2 reinforcement schedule in rats, it significantly lowered the breakpoint levels for methamphetamine self-administration under a PR schedule of reinforcement, suggesting that PG01037 produces a significant reduction of methamphetamine's rewarding efficacy and/or of motivation for drug-taking and drug-seeking behavior. In addition, PG01037 significantly and dose-dependently inhibited methamphetamine-enhanced BSR. However, PG01037 itself caused a dose-dependent inhibition of BSR, an effect not observed with the selective D_3 receptor antagonists SB-277011A and NGB-2904, but similar to that seen with nonselective D_2 receptor antagonists and the partial D_3 agonist BP 897, in the BSR paradigm. This finding suggests that PG01037, at high doses, may have actions at other receptors *in vivo* that affect BSR.[182]

In another behavioral study in rhesus monkeys, NGB 2904 was compared to a partial agonist CJB 090 (Fig. 9),[152] a simple saturated butyl-linked analogue that preceded the discovery of PG01037. In this study, both compounds dose-dependently blocked quinpirole-induced yawning in the monkeys and neither compound generalized for the discriminative stimulus of cocaine.[95] Whereas CJB 090 shifted the cocaine dose–response curve to the right, NGB 2904 had no effect on cocaine's discriminative stimulus effects in these rhesus monkeys. CJB 090 also decreased both cocaine and food-maintained responding, whereas NGB 2904 had no effect, suggesting that either this disconnect in behavioral profiles is due to other pharmacological differences between NGB2904 and CJB 090 or the partial agonist profile of CJB 090 is indeed significant. Further evaluation of more D_3-selective partial agonists in these paradigms is required before any conclusions can be made regarding mechanism and the relationship between intrinsic activity, as measured *in vitro*, and behavior.

In an attempt to further improve the D_3 receptor antagonist for *in vivo* investigation, addition of an hydroxyl (OH) group onto the butylamide linking chain and further modifications to the arylamide group have been made to result in high-affinity and D_3-selective agents with antagonist or partial agonist profiles, *in vitro*.[151] Very recently, a new series of compounds have been disclosed that optimize this structural class giving compounds, such as PG723, high affinity and D_3 selectivity coupled with a cLogP of 3.3 (nearly 4-log units below the parent NGB 2904; Fig. 9).[153] In addition, separation of the enantiomers of PG648 resulted in the first report of enantioselectivity in this class of compounds with the *R*-enantiomer (Fig. 9) being 15-fold more selective than the *S*-, but only at D_3 receptors. The lack of robust enantioselectivity at the D_2 receptor subtype suggests a point of attachment that differs between the D_2 and D_3 receptor proteins. This was further characterized with chimera

studies wherein chimeras in which the second extracellular loop (E2) of the D_3 receptor was placed into the D_2 receptor (D_2/D_3E2) and conversely, the second extracellular loop of the D_2 receptor was placed into the D_3 receptors (D_3/D_2E2).[153] A comparison of the affinities of the *R*- and *S*- PG648 for the wild-type (D_2 or D_3) receptors and the two chimeric D_2-like receptors (D_2/D_3E2 and D_3/D_2E2) showed the D_2/D_3E2 receptor modestly increased the binding affinity compared to wild-type D_2 receptor. In addition, the substitution of the D_2E2 loop onto the D_3 receptor scaffold decreased the affinity of the *R*-PG648 by eightfold and *S*-PG648 by fourfold compared to the wild-type human D_3 receptor.[153]

Thus, the evolution of SAR at D_3 receptors, starting with the D_3 receptor antagonist, NGB 2904, has led to the discovery of some of the most D_3-selective compounds to date. Compounds, such as PG648, show high affinity (K_i = 1 nM) for D_3 and ~400-fold selectivity over the D_2 receptor subtype. Importantly, the first enantioselective D_3 receptor antagonists (*R*- and *S*-PG648) have been identified wherein enantioselectivity is more pronounced at D_3 than at D_2, and that a binding region on the second extracellular loop E2 may play a role in both enantioselectivity and D_3 versus D_2 binding selectivity. These lead compounds also have appropriate physical properties for *in vivo* exploration and therefore will be useful in determining how intrinsic activity at D_3 receptors tested *in vitro* is related to behavior in animals. Furthermore, these novel and selective D_3 receptor antagonists and partial agonists will undoubtedly aid in further determining the role of D_3 receptors in addiction and other neuropsychiatric disorders.

Part III: Translational research: from preclinical efficacy to clinical proof of concept

Selective DA D_3 receptor antagonists and possible clinical endpoints

The foregoing parts of this review have demonstrated that selective D_3 receptor antagonists can be successfully designed with favorable pre-clinical safety profiles and considerable efficacy in preclinical models of addiction, particularly in those paradigms thought to model relapse in the human disease. How might these selective D_3 receptor antagonists transition into the clinic?

Substance dependence disorders are the clinical expression of drug addiction in humans. The essential clinical hallmarks of substance dependence are uncontrolled, escalating use of the substance to the exclusion of other life-sustaining activities (e.g., work, relationships). Even when the user knows that continued use may harm himself/herself or others, drug use is continued, ultimately leading to significant distress.[183] Tolerance to the effects of the substance and withdrawal symptoms when the substance use is stopped are also hallmark traits that can be modeled in the preclinical laboratory.[183,184] However, there are some uniquely human elements in this clinical disorder that may not be adequately modeled in animals. These differences pose significant challenges to progress in the development of medications to treat substance dependence. First, acquisition is typically spontaneous in humans, not artificially induced, as is necessary in animals. Second, continued use is not necessarily regulated by time or place in human substance dependent individuals, as the individual is free to obtain the substance and use it wherever and whenever desired, although one could argue that distribution patterns of illicit substances provides some regulation of supply and environment. Third, only in some cases (e.g., hospitalization or source supply issues) is human substance use extinguished due to lack of supply. So, in fact, the substance dependent individual who wants to achieve abstinence must do so despite free accessibility to the substance. These differences may prove to be important and challenging in translating preclinical findings into the clinic.

In medication development, proof of concept (POC) is the clinical experiment (clinical trial) that is designed to test the hypothesis that the new medication has some efficacy in the treatment of substance dependence in humans. The POC trial is performed prior to committing the resources to the large scale trials (~3000 subjects) required for registration. A medication could have efficacy in any or all of the following: (1) in enhancing the ability to stop using the substance, (2) in the treatment of withdrawal symptoms, or (3) in preventing relapse to use after abstinence has been achieved (or relapse to heavy use after a reduction in use). Endpoints depend upon which of these efficacy criteria are chosen and can therefore be quit rates, reduction in withdrawal symptoms, or relapse (conversely abstinence) rates over time.

Could selective DA D_3 receptor antagonists be effective in enhancing the ability to stop using the substance (i.e., quitting)?—The process of not using the substance is complex, requiring first a readiness to stop (reduce use), stopping (or reducing use) itself, and then staying stopped (or at a reduced level of use). Each of these processes may have different neurochemical and psychodynamic substrates. There is no animal model for self-motivated stopping. Extinction may not model this process well. Furthermore, we know little about the neurochemical substrates of readiness for change (stopping) and in the absence of preclinical models, and we currently have no data to suggest that selective D_3 receptor antagonists would enhance a readiness to stop substance use, although we cannot exclude this possibility.

Could selective DA D_3 receptor antagonists prevent withdrawal symptoms when the substance use is stopped?—Sudden stopping of many of the substances used by dependent individuals produces withdrawal symptoms. In fact, the first medication treatments for substance dependence focused on withdrawal, making the appropriate assumption that withdrawal symptoms may contribute to continued use and early relapse.[185,186] In opiate, alcohol and nicotine dependencies, withdrawal complicates the early abstinence phase, and in some cases can be fatal.[186] Hence, the initial strategy for medication development for substance dependence was agonist replacement for these dependencies. Consequently clinical trials to demonstrate efficacy in these dependencies were designed to include both the initial withdrawal phase through later abstinence. Agonist replacement in the short- or long-term has been shown to be an efficacious strategy for maintaining abstinence in opiate and nicotine dependence, but has been less helpful in alcohol dependence.[187] There is no reason to expect selective D_3 receptor antagonists to be effective for withdrawal symptoms although to date, no published preclinical studies have specifically tested this hypothesis.

Could selective DA D_3 receptor antagonists be effective in relapse prevention?—Based upon their efficacy in animal models of reinstatement to drug-seeking behavior, selective D_3 receptor antagonists would be expected to reduce drug-, cue-, and stress-driven consumption post-abstinence. Thus, selective D_3 receptor antagonists should be efficacious in preventing relapse, which is known to be drug, cue, and/or stress induced.[188] As these effects on cue- and stress-induced reinstatement have been observed across all addicting drugs in preclinical models, selective D_3 receptor antagonists might be considered optimal medications for the prevention of relapse in the newly abstinent substance dependent individual across all substance dependencies.

Clinical trials for proof of concept for selective DA D_3 receptor antagonists

In the past, because most medications developed for the treatment of substance dependence have been agonist replacements, the typical clinical trials for POC would include acute quitting/withdrawal and abstinence phases together. Traditional endpoints have therefore

been quit rates and abstinence (or conversely relapse rates) in those who quit, either as a point prevalence, or continuous abstinence across a specified time period, usually 12 or fewer weeks.[189] Recently, however, a reduction in consumption (dose or frequency) has also been considered a reasonable endpoint in alcohol dependence.[190] Registration type clinical trials need to demonstrate efficacy (preferably abstinence) across a 6-month or 12-month span, but treatment periods can be limited to 12 weeks or less.[189]

If relapse prevention is the expected target endpoint of a novel medication, as might be the expected efficacy for selective DA D_3 receptor antagonists, then POC trial designs that are different from those developed for agonist replacement medications could be used. The first of these would be a design in which a withdrawal phase precedes randomization to either placebo or the new medication in a blinded parallel design that can last 6–12 weeks. This is the approach often used in alcohol dependence studies when the medical treatment of withdrawal is required. The approach could also be applied to nicotine dependence using nicotine replacement therapies during the acute withdrawal phase leading to a randomization phase that is a blinded, placebo controlled, parallel arm design.[191] Some of the operational problems with these designs are that individuals who successfully quit during the withdrawal phase may decline to enter the randomization phase, and/or the rate of successful quitting (achieving abstinence) may be so small that large numbers of subjects must be enrolled for a relatively few subjects in the two arms of the randomization phase. These two factors may lead to a need to enroll around 425 subjects for a study that needs 85 in each arm of the placebo controlled randomization phase (placebo versus new medication). Although costly, such POC trials mimic the type of trial needed for registration and may therefore provide a sense of reduced risk for the medication development team. These types of trials take on average, 1–3 years for completion and final analysis. In such trials, exposure to cue and stress is uncontrolled, as subjects, who are outpatient, carry on with their lives. An alternative to these types of trials is a trial setting in which cue and/or stress are relatively controlled.

Animal models of substance dependence can also be studied in man, using human laboratory techniques.[191] The human laboratory can model (1) cue-induced craving in abstinent individuals, (2) choice or reward paradigms, (3) PR paradigms, and (4) how much an individual is willing to work for a given substance in the abstinent state (nicotine, alcohol). While all of these models, which have *face validity*, have been studied in the human laboratory with various substances, none to date have been shown to have *predictive validity* in demonstrating medication efficacy, particularly with a new (unknown effect) medication. From a medication development standpoint, if these types of assessments had demonstrated predictive validity, they would be the preferred POC trial method, requiring small sample sizes (perhaps only 40 subjects) and relying *primarily* on crossover rather than parallel designs. These would also be relatively short studies, requiring perhaps 6 months to 1 year to provide complete data.

One of the most studied translational medicine aspects of substance dependence is cue-induced craving, which can be studied in the human laboratory and/or in combination with imaging assessments. Highly reproducible findings have been observed in cue-induced craving in newly abstinent alcoholics[192,193] and although not as consistent, similar findings have been observed in cue paradigms in abstinent smokers.[194,195] Cue-induced changes in fMRI in cocaine-dependent individuals are also fairly reproducible. The effect of a new medication on these reproducible cue-induced fMRI signals could be relatively easily determined in either single or repeat dose, parallel or crossover design, using a small number of subjects and completing the trial in a relatively short time period. One such trial is starting for a selective DA D_3 receptor antagonist (see http://clinicaltrials.gov/).

Other surrogate markers might include abstinence-induced cognitive changes, such as interference on the Stroop task. It is well known that the abstinent smoker, for instance, will have an altered reaction time to cigarette cues than neutral cues in the Stroop task, known as attentional bias induced by cues. Medication effects can be determined in this paradigm.[196] If a compound, such as a selective D_3 receptor antagonist, is effective in preventing cue-induced relapse it would be expected to prevent abstinence-induced cognitive changes, many of which are cue induced. This could be demonstrated in a single or repeat dose crossover study, as has been done recently for Varenicline® in smoking abstinence.[197] One such trial is ongoing with a D_3 receptor antagonist (see http://clinicaltrials.gov).

Recently, several investigators have embarked on studies using medications with known efficacy to develop predictive validity for these types of laboratory studies.[195,197,198] In one of these paradigms, a forced brief relapse (known as a lapse) can be instituted and the subjects followed afterward for regained and maintained abstinence.[197] Such a study requires perhaps 2–4 weeks per subject in a crossover design (depending upon the time to steady-state and half-life of the medication) and in a parallel design would require around 2 weeks/subject. This would result in a short, small trial that could lead to POC for a new medication in substantially less than 1 year. Depending upon the risk comfort level of the medication development group, such small studies could serve as POC trials. However, at the present time, the process of validating these surrogates as predictors of outcome in clinical trials is ongoing. Medication development teams are viewing the ongoing studies with interest, but most are not entirely ready to use such a paradigm on which to base the major expenditure of a full phase III development program.

We should also mention that because [^{11}C]-PHNO is available for positron emission tomography studies, receptor occupancy by the selective D_3 receptor antagonists can be determined with some certainty in human subjects. Hence reliable dosing in man can be based on a receptor occupancy that predicts preclinical efficacy. Such precise predictions allow the possibility of combined phase IIb/III trials allowing for more rapid progression of the medication to approval.

It is beyond the scope of this chapter to discuss the merits of a short-term (12 weeks or less) treatment for a chronic disease that relapses upon withdrawal of effective treatment at an approximate rate of 60–80% across all substances at the end of a year.[199] In other chronic disease models, treatment continues until the disease is eradicated by other means (e.g., weight reduction in the case of obesity related diabetes or hypertension) or continues for the life of the patient (e.g., hypothyroidism, heart failure). A better model for substance dependence might be the model used for major depressive disorder. That model proposes acute treatment of 4–9 months post clinical response for the first episode, but even longer treatment for two or more episodes.[200] Perhaps this would be the preferred model for first quit and any subsequent relapses for the substance dependencies as well. Such a treatment paradigm is one for which selective D_3 receptor antagonists would be uniquely suited, perhaps providing long-term relapse prevention for the highly recurrent and relapsing disorders of substance dependence.

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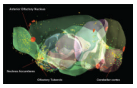

Figure 1.
Three-dimensional reconstruction of the expression of the DA D_3 receptor in the mouse brain (strain, C57BL/6J; age, 56 days; sex, male; technique: *in situ* hybridization, riboprobe RP_060412_04_A01) using the Allen Brain Atlas (Brain Explorer Version 1.4.1. Build 32, © 2006–2007 Allen Institute for Brain Science) and the Anatomic Gene Expression Atlas. Highest expression/densities were observed in the ventral striatum, olfactory tubercle, lateral septum, medulla, pallidum, and thalamus. (In color in *Annals* online.)

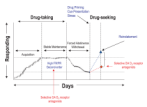

Figure 2.
Drug self-administration paradigm with its drug-taking and drug-seeking components. Selective DA D_3 receptor antagonists do not affect drug self-administration under low fixed-ratio schedules of reinforcement but rather regulate the motivation to self-administer drugs under schedules of reinforcement that require an increase in work demand. These selective antagonists also seem to be particularly effective in preventing drug-seeking behavior evoked by reexposure to either the drug itself (drug priming), environmental cues that had been previously associated with drug taking (cue presentation), or stressors (stress) after behavioral extinction. (In color in *Annals* online.)

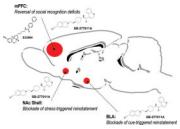

Figure 3.
Some key neurocircuits that might be modulated by selective blockade of the DA D_3 receptor. This scheme is based on recent information provided by local microinfusion of selective DA D_3 receptor antagonists into specific brain areas. NAc shell, shell subregion of the nucleus accumbens; BLA, basolateral amygdala; mPFC, medial prefrontal cortex. (In color in *Annals* online.)

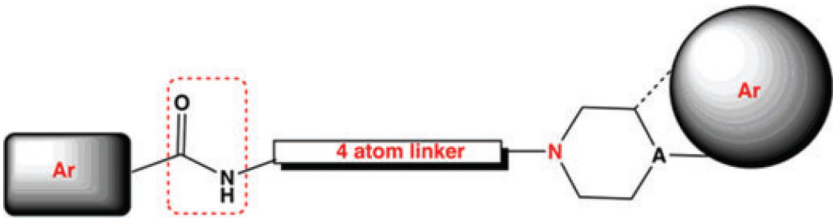

Figure 4.
Structure–activity relationship template for high-affinity and selective D_3 receptor antagonists. (In color in *Annals* online.)

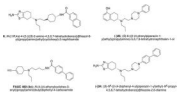

Figure 5.
Hybrid D_3 partial agonists.

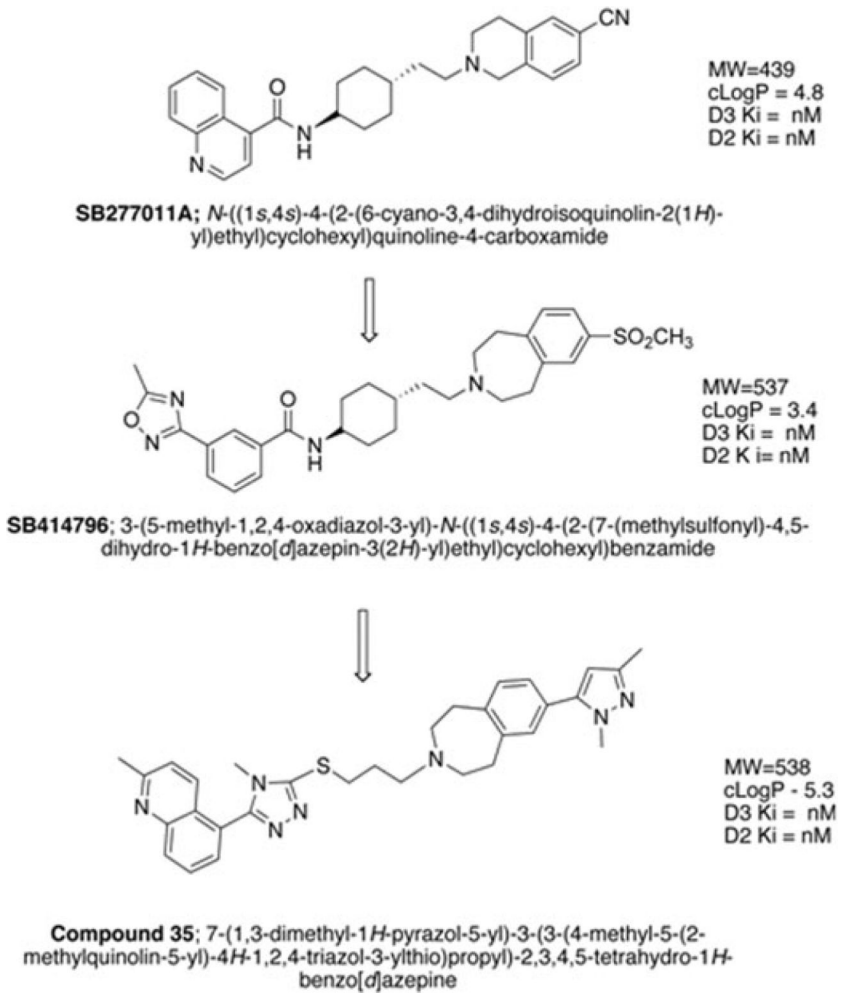

Figure 6.
Evolution of the D_3 receptor antagonists from GlaxoSmithKline.

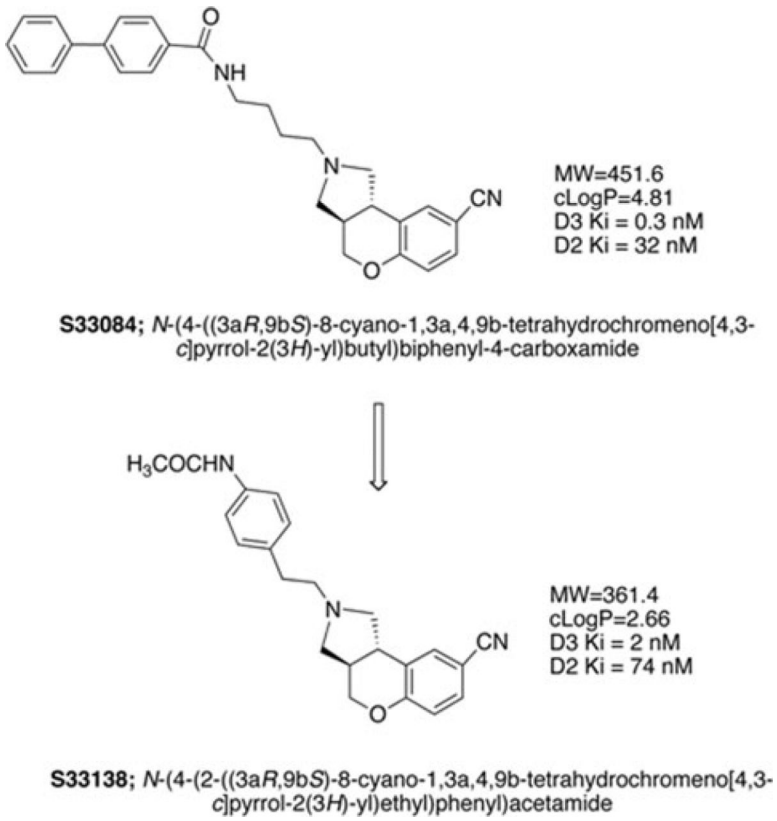

Figure 7.
Evolution of the D_3 receptor antagonists from Servier.

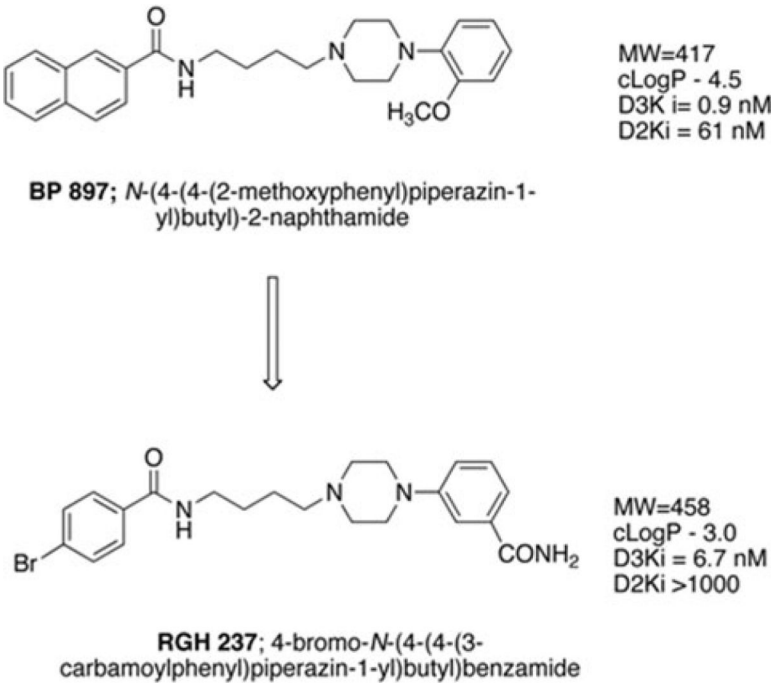

Figure 8.
Evolution of RGH-237 from BP 897.

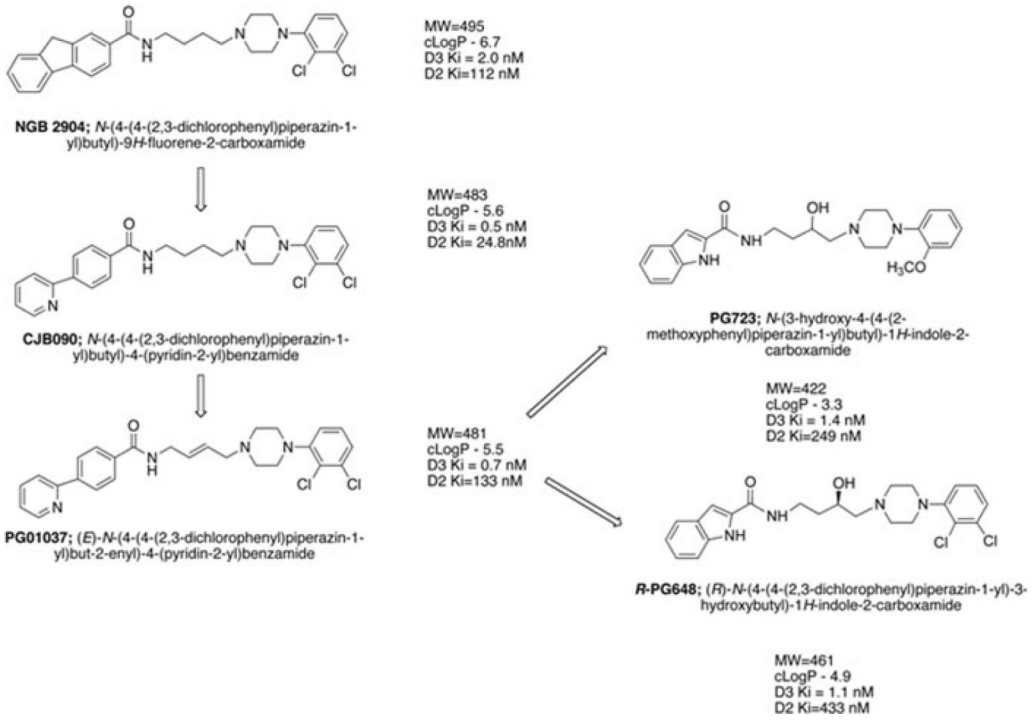

Figure 9.
Evolution of D_3 receptor antagonists from NGB 2904.