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Dopamine D4 Receptors in Psychostimulant Addiction

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Abstract

Since the cloning of the D4 receptor in the 1990s, interest has been building in the role of this receptor in drug addiction, given the importance of dopamine in addiction. Like the D3 receptor, the D4 receptor has limited distribution within the brain suggesting it may have a unique role in drug abuse. However, compared to the D3 receptor, few studies have evaluated the importance of the D4 receptor. This may be due, in part, to the relative lack of compounds selective for the D4 receptor; the early studies were mainly conducted in mice lacking the D4 receptor. In this review, we summarize the literature on the structure and localization of the D4 receptor before reviewing the data from D4 knockout mice that used behavioral models relevant to the understanding of stimulant use. Next, we present evidence from more recent pharmacological studies using selective D4 agonists and antagonists and animal models of drug seeking and taking. The data summarized here suggest a role for D4 receptors in relapse to stimulant use. Therefore, treatments based on antagonism of the D4 receptor may be useful treatments for relapse to nicotine, cocaine and amphetamine use.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Keywords

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Introduction

Dopamine (DA) is an important neurotransmitter in the brain. For more than 25 years, it has been suggested that DA systems in the brain are involved in critical functions such as the primary motivation for natural stimuli such as food, water and sex (Koob, 1992; Wise & Bozarth, 1987). DA primarily exerts its influence by interacting with, and activating, a family of G protein-coupled DA receptors. Between 1988 and 1991, five genes were identified that code for multiple DA receptor subtypes. The DA D₂ receptor gene (DRD2) was the first to be cloned (Bunzow et al., 1988; Giros et al., 1989; D.K. Grandy et al., 1989), followed by the DA D₁ receptor gene (DRD1) (Dearry et al., 1990; Monsma, Mahan, McVittie, Gerfen, & Sibley, 1991; Sunahara et al., 1990; Zhou et al., 1990), the DA D₃ (DRD3) gene (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990), the DA D₄ (DRD4) gene (H. H. Van Tol et al., 1991) and finally the DA D₅ (DRD5) gene (D. K. Grandy et al., 1991; Sunahara et al., 1991). Not only did it represent a new member of a growing family of unanticipated DA receptors, the high affinity of the antipsychotic clozapine for the DRD4 was intriguing from the standpoint of understanding this important drug's mechanism of action. Clozapine, being an antipsychotic, led to a flurry of interest in developing DRD4 agents for the treatment of schizophrenia. However, it is the highly polymorphic nature of DRD4, the large number of receptor protein variants predicted - each potentially with its own unique pharmacological and second messenger/signaling profiles (Seeman & Van Tol, 1994) – that put it among the most favorite neuropsychiatric candidate genes; a position strengthened by the repeated finding of associations between particular DRD4 VNTRs and a diagnosis of attention deficit hyperactivity disorder (reviewed in Kuntsi, McLoughlin, & Asherson, 2006)

The focus of this review will be on the putative role of the DRD4 in stimulant abuse, with a focus on the aspects of this receptor that make it a suitable target for treatment approaches for addiction to stimulants, in particular cocaine, amphetamine and nicotine. The stimulants have in common the fact that they all produce behavioral arousal, with the ability to improve cognition, a property that may confer action on the DRD4, as discussed below. The properties of the DRD4 that make it unique will be summarized, followed by a description of the localization of the DRD4. Studies linking the DRD4 to addictions, in particular smoking, will be reviewed. Finally, the studies with knock out mice and pre-clinical pharmacological studies will be reviewed with an aim to determining the role of the DRD4 in stimulant abuse.

The DRD4

Interest in DRD4 was heightened with the 1992 report (H. H. M. Van Tol et al., 1992) of considerable variation in the human gene, DRD4, and subsequent studies documenting its being among the most highly polymorphic genes in the human genome (Chang, Kidd, Livak, Pakstis, & Kidd, 1996; Lichter et al., 1993). Arguably the single most compelling

feature of DRD4 that distinguishes it from almost every other gene in the human genome is its unusual polymorphism in exon 3. This polymorphism consists of an imperfect 48-bp open reading frame that is tandemly repeated 2 to 10 times per allele (Lichter et al., 1993; H. H. M. Van Tol et al., 1992). The most prevalent DRD4 variable number of tandem repeats (VNTR) alleles are those consisting of 4-, 7- and 2-repeat alleles, with global mean allele frequencies of 64.3%, 20.6% and 8.2% respectively (Chang et al., 1996). Alleles with less than 7 repeats are generally referred to as “short alleles” (S) while those having more than 7 repeats are referred to as “long alleles” (L). When these polymorphisms are translated the resulting receptor protein domains responsible for G protein-coupling are predicted to differ by as much as 128 amino acids. Naturally this observation resulted in several early studies designed to understand what functional consequences, if any, are associated with each VNTR – a question still to be definitively answered. It should also be noted there is good evidence to support the interpretation that this intracellular domain of the receptor protein not only interacts with G proteins but also binds nuclear factors with potential consequences for gene expression (Schoots & Van Tol, 2003).

Of course two important aspects of deorphanizing a putative G protein-coupled receptor, which the DRD4 was initially, are characterizing its pharmacological profile and defining its second messenger coupling. Although initially the *in vitro* heterologous expression of DRD4 was difficult, enough protein was made so that its pharmacological profile and Gi coupling could be demonstrated. However, the tendency for heterologous D4 receptor expression to be low hampered *in vitro* efforts to broaden our understanding of the cellular processes influenced by activated D4 receptors. Once this impediment was overcome it was reported that activation of the DRD4 receptor not only inhibits cAMP production but also opens the kir3 potassium channel, activates extracellular signal-regulated kinases (ERK1 and 2), and decreases functional GABA_A receptor levels (reviewed by Rondou, Haegeman, & Van Craenenbroeck, 2010); responses that may involve receptor oligomerization (Van Craenenbroeck et al., 2011). What remains considerably more elusive is convincingly demonstrating the contribution(s) that DRD4-mediated signaling makes to human health. Over the years several approaches have been taken to this end with one of the most promising being the anatomical mapping of the receptor's mRNA and protein distribution in healthy and pathological human tissues with an emphasis on the brain because of its affinity for the atypical antipsychotic clozapine.

DRD4 Distribution

DRD4 mRNA is found in various brain regions at low density compared with DRD1 or DRD2. It is most abundant in retina (Cohen, Todd, Harmon, & O' Malley, 1992), cerebral cortex, amygdala, hypothalamus and pituitary, but sparsely in the basal ganglia, as assessed by RT-PCR and Northern blot (Valerio et al., 1994), *in situ* hybridization (Meador-Woodruff et al., 1994; Meador-Woodruff et al., 1997; O'Malley, Harmon, Tang, & Todd, 1992) and immunohistochemistry (Mrzljak et al., 1996). These studies also found DRD4 in both pyramidal and non-pyramidal cells of the cerebral cortex, particularly layer V, and in the hippocampus. Localization of DRD4 to mainly the cerebral cortex, amygdala and hippocampus has functional implications for the role of DRD4. The amygdala and hippocampus are areas that have been implicated in learning and memory (Ito, Robbins,

McNaughton, & Everitt, 2006), and in particular the amygdala is thought to be important in the learning of associations with emotional stimuli (Schultz, 2006). In this regard, the L alleles have been associated with attention for emotional stimuli (Wells, Beevers, Knopik, & McGeary, 2013) and DRD4 agonists have been shown to improve performance in cognitive tasks that are memory dependent (Bernaerts & Tirelli, 2003; Powell, Paulus, Hartman, Godel, & Geyer, 2003; Woolley et al., 2008). These are important considerations for the study of addiction, as 'craving' and drug-seeking can be powerfully elicited by environmental stimuli that have been previously paired with drug use, and thus the DRD4 may be important in this regard.

Beyond Imaging – Genetic Association Studies

The anatomical mapping approach has resulted in important fundamental knowledge, however, considerable advances were obtained from genetic association studies, in particular the initial findings that a subset of DRD4 VNTRs were found associated with personality traits including excessive impulsivity, novelty seeking and risk taking behavior (Benjamin et al., 1996; Ebstein et al., 1996; Frank & Fossella, 2011; Malhotra et al., 1996; Ptacek, Kuzelova, & Stefano, 2011). Given that associations were found between DRD4 VNTRs, impulsivity, novelty seeking and risk taking behavior it comes as no surprise there has been considerable interest in the receptor's potential role in drug taking behavior and as a target for novel abstinence medications. However, both positive and negative associations have been reported between various DRD4 alleles and methamphetamine (METH) abuse. METH abusers had a significantly higher prevalence of the seven-repeat alleles than controls, while there were no significant differences in the DRD2 or DRD3 alleles between the METH abusers and controls (Chen et al., 2004), highlighting the importance specifically of the DRD4 receptor for drug abuse. In another study, however, no differences were found for DRD4 gene exon III polymorphisms (Tsai et al., 2002). In an attempt to reconcile these disparate findings an intriguing new approach to assessing the contribution of the VNTR to drug-taking behaviors has been proposed (McGeary, 2009).

Although the studies of the relationship between alleles and DRD4 are somewhat compelling, the possible involvement of DRD4 variants in nicotine use provides the most **comprehensive information**. One study reports an association between DRD4 genotype and smoking in African-Americans but not Caucasians (Shields et al., 1998). **Comparison of male carriers of an L-allele to those with the S-allele** revealed that those with the L-allele started smoking earlier, had a higher rate of lifetime smoking, and smoked more cigarettes per day (Laucht, Becker, El-Faddagh, Hohm, & Schmidt, 2005). Interestingly, significantly less binding potential was detected using PET imaging of DRD2 receptors in carriers of DRD4 alleles with more than 7 repeats (Brody et al., 2006); decreased binding potential of (¹¹C)-raclopride is an indirect measure of DA release and implies that DA release was increased. By categorizing participants as either DRD4 S or DRD4 L, other studies have found differences between those carrying the L and S alleles on smoking cue reactivity (Hutchison, LaChance, Niaura, Bryan, & Smolen, 2002; McClernon, Hutchison, Rose, & Kozink, 2007; Munafo & Johnstone, 2008) and some suggest the L-alleles are a risk factor for heavy smoking and may influence smoking cessation outcome (David et al., 2007; Ton

et al., 2007; Vandenbergh et al., 2007); however, the authors indicate their findings are preliminary and need to be replicated in a controlled study with a larger sample size.

Even though the findings of genetic association studies are provocative and in some cases compelling, additional complementary approaches – including the development and use of animal models – will be required to provide a molecular explanation that connects a particular personality trait or mental health condition with one or more DRD4 VNTRs. Next, we will provide a short summary of the information that has been collected using knock-out and pharmacological approaches to determine the role(s) its variants play in psychostimulant drug abuse (i.e. cocaine, methamphetamine and nicotine).

DRD4 and Psychostimulant Addiction

Although genetic association studies have provided compelling results, advances in the understanding of the role of DRD4 came about from studies with genetically modified mice (Rubinstein et al., 1997; Waddington et al., 2005), and, more recently, pharmacological studies with selective DRD4 agents. At the time that the use of genetically modified mice was first proposed (1995-96), there were no selective antagonists available, and early studies into the role of the DRD4 were provided by findings with these mutants. In addition, the KO background would provide the perfect means of evaluating *in vivo* the selectivity of any emerging DRD4-selective compounds as well as any immunological reagents. In genetically modified mice, one strategy is to “knock-out” (KO) all expression of a functional DRD4 by completely eliminating the receptor protein. The strategy for targeting the *drd4* gene was accomplished relatively quickly and has been described in detailed (Rubinstein et al., 1997).

Early findings with knockout mice have confirmed the pharmacological and electrophysiological consequences of altering the number of functional DRD4 alleles, but not all of the behavioural findings have. For example, whereas the findings of Ralph et al. (1999) indicated a role for the DRD4 gene product in mediating amphetamine's disruption of prepulse inhibition of the startle response (Ralph et al., 1999), a finding that is widely accepted, the findings reported by Dulawa et al. (1999) claiming a role for DRD4 in novelty seeking behavior (Dulawa, Grandy, Low, Paulus, & Geyer, 1999) has been challenged by the results of at least two independent studies (Keck, Suchland, Jimenez, & Grandy, 2013; Powell et al., 2003). Of relevance to the focus of this review is the observation that mice completely lacking functional DRD4 are dose-dependently hypersensitive to the locomotor stimulating effect of METH (Katz et al., 2003; Rubinstein et al., 1997) and methylphenidate (Keck et al., 2013). Locomotor activity is believed to be related to addictive potential (Wise & Bozarth, 1987), and thus the findings that D4 knockout mice are hypersensitive to locomotion suggests that DRD4 may mediate propensity to addiction. However, it has been found that DRD4 knockout mice show a decreased DA response to an amphetamine challenge (Thomas et al., 2007), a finding that is not in keeping with the locomotor hypersensitivity observed, given that increased locomotion is associated with increased DA release (Kuczenski & Segal, 1989). Thus, the findings with the DRD4 knockout mice are inconclusive and it may be best to look at behavioural measures more directly related to drug addiction and to consider the findings with knockout mice together with the more recent antagonist studies. These findings are provided below and organised by animal

model. Each section begins with a description of the animal model to frame the results with knockout mice and antagonists.

Drug Self-Administration—In pre-clinical studies of drug addiction, drug self-administration has become the ‘gold standard’ for studying drugs of abuse. Once acquired, self-administration behavior remains stable over days; animals ‘titrate’ their intake of drug to maintain constant blood levels of the drug (Yokel & Pickens, 1974) and brain levels of DA (Di Ciano et al., 1995; Pettit & Justice, 1991). In one study by Thanos et al. (2010), it was found that mice lacking the DRD4 were similar to controls in responding for cocaine (P. K. Thanos et al., 2010). Consistent with the findings from knockout mice, it has been found that administration of L-745,870 has no effect on self-administration of nicotine (Yan, Pushparaj, Le Strat, et al., 2012). L-745,870 is a DRD4 antagonist with a K_i of 0.43, 960 and 2300 for DRD4, DRD2 and DRD3, respectively. It also has no appreciable binding to DRD1 or DRD5 ($K_i > 10,000$) (Kulagowski et al., 1996). Although this finding may suggest that DRD4 are not involved in drug addiction, it is important to consider these findings within a larger context. That is, it is known that when the dose of drug available is decreased, rats may increase their rate of responding to compensate for the decreased dose received (Pickens & Thompson, 1968). This is a problem with antagonists at the DRD2 (Woolverton, 1986; Yokel & Wise, 1975), but not those that target the DRD3 (Andreoli et al., 2003; Di Ciano, Underwood, Hagan, & Everitt, 2003; Gal & Gyertyan, 2003; Le Foll & Goldberg, 2006; Xi et al., 2005), **as revealed in studies with rats**. This suggests that DA DRD2 antagonists would not be ideal treatments for substance abuse, as they may increase drug intake. Thus, what the findings with the D4 knockout mice reveal is that DRD4 antagonists do not increase drug self-administration, a finding which is promising for the development of D4 antagonists as treatment for drug addiction, provided that D4 antagonists influence other models of drug addiction.

Reinstatement—Drug abuse is a chronic relapsing disorder and an understanding of the role of DRD4 in stimulant addiction can be obtained from a focus on the effects of interventions on relapse to drug seeking. The main animal models of relapse are the reinstatement models that have evolved from studies with drugs that modeled the ability of environmental stimuli (de Wit & Stewart, 1981) and drugs (Gerber & Stretch, 1975; Stretch & Gerber, 1973) to induce relapse to drug-seeking. Reinstatement is an animal model with high predictive validity (Epstein & Preston, 2003) that has been studied in rats (Chiamulera, Borgo, Falchetto, Valerio, & Tessari, 1996; Forget, Coen, & Le Foll, 2009; Khaled et al., 2010; Pushparaj et al., 2013; Shaham, Adamson, Grocki, & Corrigall, 1997), mice (Yan, Pushparaj, Gamaledin, et al., 2012), non human primates (Mascia et al.) and humans (McKee, 2009). In this model, the animal is first trained to self-administer drug and then the response is extinguished by removing the associated drug that was self-administered; responses have no consequences during extinction. Following extinction of the response, a condition, such as stress, cues or drug is introduced that reinstates extinguished responding. It has been shown that a DA D4 antagonist, L-745,870, can block the reinstatement of nicotine-seeking induced by either cues paired with the drug or re-exposure to nicotine itself (Yan, Pushparaj, Le Strat, et al., 2012). As seen in Figure 1, administration of nicotine reinstated responding to above extinguished levels, and several doses of L-745,870 reduced

this reinstatement. Similarly, cues previously paired with each self-administered nicotine infusion also reinstated extinguished responding, and L-745,870 also attenuated this. An effect on both types of reinstatement suggests that the effects of D4 antagonists may be related to an effect on relapse *per se* and not the ability of, for example, cues to maintain behavior or of nicotine to influence behavior. In sum, these findings suggest that DA DRD4 are involved in the relapse to drug-seeking. Although promising, the findings with nicotine should be generalized to other drugs of abuse to reveal the generality of the effect.

Together, the findings thus far suggest that DRD4 antagonists would be viable targets for treatments for stimulant abuse as they prolong abstinence while not increasing drug self-administration. This position is highlighted by the further findings that L-745,870 did not affect reinstatement of food seeking induced by either presentation of food or the presentation of food associated cues (Yan, Pushparaj, Le Strat, et al., 2012). Thus, the effects of DA D4 antagonists seem selective to stimulants, and do not generalize to natural rewards, meaning that their use as treatments may not impact on general motivation, a problem with DA antagonists that are used in the clinic. This is encouraging as administration of the DRD4 agonist A-412997 increased locomotor activity (Woolley et al., 2008), implicating DRD4 in general activity levels, but the lack of effect of food is informative in that the role of DRD4 in general activity levels may not play a role in behaviors motivated for drug. This hypothesis warrants further testing by examining whether DRD4 antagonists have similar effects on other types of stimulants, such as cocaine or amphetamine, or whether their effects are only on nicotine.

Drug discrimination—All drugs of abuse have interoceptive properties and in the drug discrimination procedure, the ability of rats to distinguish different interoceptive properties is tested. In the drug discrimination procedure, rats are trained, for example, to respond on a lever located on the left side of a test chamber when given a certain drug of abuse, and to respond on the right-side lever when they are given saline. Over time, animals will learn to make differential responses on the two levers. The effects of drug challenges on drug-appropriate versus saline-appropriate responding can then be determined. As illustrated in Figure 2, the amount of nicotine-appropriate responding increases with dose of a challenge dose of nicotine; nicotine feels ‘more like’ nicotine as the dose is increased. Once discriminative responding has been established, a test compound can then be administered and if the animal responds on the nicotine-appropriate lever, then this suggests that the test compound has similar interoceptive properties to the drug of abuse. Alternatively, a test compound can be administered with the drug of abuse and the effects on discrimination of responding for the drug of abuse as compared to that for saline can be determined. If the test compound decreases drug-appropriate responding then the discriminative properties of the drug of abuse have been disrupted. This is important because the discriminative properties of drugs may maintain responding for drug, and thus compounds that disrupt the discriminative properties of drugs of abuse may serve as potential treatments, especially if the animal has learned to discriminate drug from saline. As can be seen in Figure 2, the D4 antagonist L-745, 870 had no effect on discriminative responding for nicotine. At both doses of L-745,870, the dose-response function for nicotine-appropriate responding after various doses of nicotine was similar to that observed after co administration of nicotine with

vehicle (Yan, Pushparaj, Le Strat, et al., 2012). Similarly, L-745,870 also did not affect cocaine-appropriate responding when co-administered with cocaine (Costanza & Terry, 1998); in this study, L-745,870 also did not produce cocaine-appropriate responding when administered on its own. In contrast, blockade of DRD4 did block the discriminative stimulus properties of METH in mice (Yan et al., 2006). In sum, DRD4 does not appear to be involved in discriminative properties of nicotine and cocaine, but may participate to those of METH. Taken together, it appears that D4 antagonists do not have interoceptive properties that are similar to those of stimulants and they disrupt drug-seeking through mechanisms that are not related to the discriminative properties of the drug. Similarly, a D4 agonist, ABT-724 was self-administered in only one of 5 monkeys tested, and at levels lower than that for cocaine (Koffarnus et al., 2012), consistent with the lack of discriminative properties with cocaine.

Consistent with their lack of discriminative properties similar to stimulants, a number of findings suggest that DA DRD4 may not have rewarding properties on their own. For example, as mentioned above, monkeys did not self-administer the D4 agonist ABT-724 (Koffarnus et al., 2012), and thus, DA D4 agonists may not have reinforcing effects on their own. Similarly, administration of A-412997, a D4 agonist, did not induce a conditioned place preference (Woolley et al., 2008). Thus, based on the findings of Woolley et al., (2008), that a D4 agonist did not induce place preference on its own, it is possible to conclude that stimulation of DRD4 is not rewarding on its own.

Conditioned Place Preference—Another frequently used model of drug addiction is the conditioned place preference model (Liu, Le Foll, Wang, & Lu, 2008). Place preference is a well-established animal model of addiction in which two sides of a test chamber are uniquely identifiable to an animal and one side is paired with a rewarding substance while the other with vehicle. At test, the animal is placed in between the two sides and allowed to explore free of drugs. It has been reported many times, that, after administration of stimulants, the time spent on the drug-paired side is increased relative that paired with vehicle (Carr, Fibiger, & Phillips, 1989). Place preference is believed to be a measure of the rewarding aspects of drugs, especially those maintained by conditioned aspects of stimuli previously paired with drugs. In a report by Thanos et al. (2010), it was found that DRD4 knockout mice were not impaired in conditioned place preference to **methylphenidate, amphetamine and cocaine** relative to controls (P. Thanos et al., 2009). Thus, DRD4 are not involved in this measure of drug addiction. Further insights may be gained from pharmacological interventions conducted in animal studies.

Sensitization—Sensitization is a model of drug addiction based on observations that a behavioral response to drugs of abuse can increase over time with repeated exposure to the drug. In the most frequently used model of sensitization, locomotor activity counts to a stimulant challenge are obtained at baseline and again after a course of treatment with the drug. When administered intermittently (as opposed to continually) (T.E. Robinson & Becker, 1986), repeated administration of a drug can potentiate the locomotor activating effects of the drug. When administered the D4 antagonist PNU-101387G prior to the pre-treatments with amphetamine, behavioral sensitization to a subsequent amphetamine

challenge was blocked (Feldpausch et al., 1998). PNU-101387G has high selectivity for the DRD4 ($K_i=3.6$) as opposed to other DA receptor subtypes (DRD1 $K_i > 8,000$; DRD2 $K_i = 5,147$; DRD3 $K_i > 2,778$) (Merchant et al., 1996). It has been posited that the role of sensitization in addiction is to increase drug wanting over time, thus rendering the user addicted to a drug (T. E. Robinson & Berridge, 1993). Thus, DA DRD4 may be important in the development of sensitization to drugs of abuse and thereby be important in the establishment of an addiction. Again, these findings need to be replicated with other stimulants such as cocaine or nicotine to determine whether the stimulatory role of DRD4 is simply on the effects of amphetamine or whether they mediate some common aspect that underlies the sensitization process.

Conclusions

Since the cloning of the DRD4 in the 1990s, this receptor has received growing attention. Although genetic association studies have been compelling in implicating a role of the DRD4 in stimulant use, the real advances in understanding of this receptor emerged with the advent of knockout mice, and, more recently, selective pharmacological agents. When interpreting the role of DRD4 in stimulant use, the findings from the knockout mice and pharmacological interventions tell a coherent story. From the literature it is clear that DRD4 affect the reinstatement of nicotine-seeking and thus may be potential treatments for relapse, especially since DRD4 antagonists were without non-specific effects on responding for food and DRD4 agonists were not self-administered themselves (therefore they have no addictive potential). This is further supported by findings that DRD4 antagonists blocked the development of sensitization to stimulants. This finding must be taken into context with those that found no effect of D4 knockout or D4 antagonists on a place preference; perhaps DRD4 is not involved in the conditioned rewarding properties of drugs, but may, instead, mediate the relapse or other aspects of seeking. Issues that remain to be resolved are the findings of a blockade of discriminative properties of cocaine but not METH by DRD4 antagonists; further studies will need to determine whether DRD4 is involved in this function. Also, it remains to be determined whether the promising findings on reinstatement will generalize to other stimulant drugs, as the findings so far are only with nicotine. In sum, D4 antagonists may provide a means by which novel treatments for stimulant-seeking may be targeted. The fact that ligands that are available in clinic such as buspirone, are also effective DRD4 antagonists (Bergman et al., 2013) could represent a translational opportunity for future work (Le Foll & Boileau, 2013). Indeed, recent findings implicate DRD4 in gambling, which is an addictive behavior (Cocker, Le Foll, Rogers, & Winstanley, 2013).

Acknowledgment

Some descriptions of the distribution of the dopamine receptors have been reproduced with permission from Behavioral Pharmacology (Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009).

List of Abbreviations

DA dopamine DRD1 dopamine type 1 receptor

DRD2	dopamine type 2 receptor
DRD3	dopamine type 3 receptor
DRD4	dopamine type 4 receptor
DRD5	dopamine type 5 receptor
VNTR	variable number of tandem repeats
S	short alleles
L	long alleles
GABA	γ -aminobutyric acid
ADHD	Attention deficit hyperactivity disorder
METH	Methamphetamine

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Figure 1.

Effect of DRD4 antagonist L-745,870 on the mean + reinstatement of nicotine-seeking behavior in rats. A) Pretreatment of L-745,870 significantly reduced the number of active (upper) but not inactive (lower) lever presses triggered by nicotine-associated cues (n=13). B) Pretreatment of L-745,870 significantly attenuated the number of active (upper) but not inactive (lower) lever presses induced by priming injection of nicotine (0.15 mg/kg s.c.; n=23). *p<0.05; **p<0.01, ***p<0.001 vs the baseline (BL). Student's paired t-test ##p<0.01; ###p<0.001 vs the vehicle pretreatment. Taken from Yan et al. (2012), with permission.

Figure 2.

A) Dose effect functions for the discriminative stimulus effects of nicotine in rats trained to discriminate 0.4 mg/kg nicotine from saline. The percentage of responses on the lever associated with nicotine administration is shown as a function of dose (mg/kg) during tests with various doses of nicotine. The DRD4 antagonist L-745,870 administered acutely 30min before the sessions did not modify discriminative-stimulus effects of nicotine (no curve shift). B) L-745,870 also did not significantly affect rates of lever-press responding when administered together with different doses of nicotine or with vehicle. C) Effects of different doses of L-745,870 on discriminative-stimulus effects of the training dose of nicotine when L-745,870 was administered with vehicle. D) Effects of different doses of L-745,870 on rates of lever-press responding when administered together with the training dose of nicotine or with vehicle (n=9-12). Data are expressed as means ($\pm$ SEM) of the percentage of responses on the nicotine lever.