The Role of Dopamine D3 Receptors in Tobacco Use Disorder: A Synthesis of the Preclinical and Clinical Literature

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Abstract Tobacco smoking is a significant cause of preventable morbidity and mortality globally. Current pharmacological approaches to treat tobacco use disorder (TUD) are only partly effective and novel approaches are needed. Dopamine has a well-established role in substance use disorders, including TUD, and there has been a long-standing interest in developing agents that target the dopaminergic system to treat substance use disorders. Dopamine has 5 receptor subtypes (DRD1 to DRD5). Given the localization and safety profile of the dopamine receptor D3 (DRD3), it is of therapeutic potential for TUD. In this chapter, the preclinical and clinical literature investigating the role of DRD3 in processes relevant to TUD will be reviewed, including in nicotine reinforcement, drug reinstatement, conditioned stimuli and cue-reactivity, executive function, and withdrawal. Similarities and differences in findings from the animal and human work will be synthesized and findings will be discussed in relation to the therapeutic potential of targeting DRD3 in TUD.

Keywords Dopamine · Dopamine receptor D3 · Nicotine dependence · Smoking cessation · Tobacco use disorder

1 Introduction

This chapter provides an overview of the role of the dopamine receptor D3 (DRD3) in processes relevant to tobacco use disorder (TUD). To begin, we define TUD and introduce the problem with the existing pharmacological treatments, we summarize the importance of the dopaminergic system in TUD, and we outline what the DRD3 is and why it may be an important target for novel pharmacological treatments for TUD. We then review existing preclinical and clinical studies relevant to the role of DRD3 in TUD. The resulting translational synthesis presented facilitates discussion of the future therapeutic potential of DRD3 as a novel target for tobacco smoking cessation as well as identifying future avenues for research in this field.

2 Tobacco Use Disorder

TUD is a Diagnostic and Statistical Manual of Mental Disorders (DSM-5) substance use disorder characterized by a problematic tobacco use pattern. TUD symptoms may include compulsive use which may manifest as use despite negative consequences, unsuccessful attempts to control use, and strong persistent craving or urge to use. Symptoms may also include the development of tolerance (i.e., requiring more tobacco to achieve the desired effect or a diminished effect with continued use of the same amount) or the development of dependence and the presence of a withdrawal syndrome (American Psychiatric Association 2013). The principal addictive component found in tobacco products is nicotine (Benowitz 2010).

Tobacco smoking is a global public health problem. There are over 1 billion smokers worldwide (World Health Organization 2019), the prevalence of daily smoking was estimated at 15% in 2015 (Peacock et al. 2018) and in 2018 nearly 75% of the 34 million smokers in the USA were estimated to be daily smokers (Creamer et al. 2019). This level of tobacco smoking is associated with high rates of morbidity and mortality. For instance, it has been estimated that tobacco use is associated with thousands of billions of dollars in health care costs and losses in productivity (Goodchild et al. 2018; Makate et al. 2019) and over eight million deaths annually (World Health Organization 2019). Health outcomes and the risk of dying from smoking-related diseases are improved by smoking cessation (Jha et al. 2013) but unfortunately TUD is a chronic relapsing condition characterized by repeated cycles of quitting and relapse (Chaiton et al. 2016; Leshner 1997).

3 Pharmacotherapy for Smoking Cessation

There are currently three established first-line medications that the U.S. Food and Drug Administration (FDA) has approved for smoking cessation: nicotine replacement therapy (NRT), bupropion (Zyban), and varenicline (Chantix). NRT acts via agonist action at nicotinic acetylcholine receptors mimicking the nicotine normally delivered via tobacco use, bupropion is a norepinephrine and dopamine reuptake inhibitor as well as having antagonist properties at nicotinic acetylcholine receptors, and varenicline binds highly selectively to $\alpha4\beta2$ containing nicotinic acetylcholine receptors where it acts as a partial agonist (for a full review of the pharmacological mechanisms of action of NRT, bupropion, and varenicline, see Aubin et al. (2014)). All three pharmacotherapies improve abstinence rates compared to placebo with meta-analytic evidence using abstinence data from more than 101,000 participants across 267 studies suggesting that the efficacy of NRT and bupropion is similar while the efficacy of varenicline is superior to both NRT and bupropion alone (Cahill et al. 2013).

Modeling of data from over 40 smoking cessation trials suggests that 12-month abstinence rates with these three evidence-based medications is 23% or less (Jackson

et al. 2019). While this does represent a significant improvement over unaided quit attempts, where as few as 3–5% of attempts may be successful (Hughes et al. 2004), there is clearly room to improve abstinence rates further. In addition, evidence suggests diminishing benefits from the use of smoking cessation pharmacotherapy over the first 12 months (Agboola et al. 2015; Rosen et al. 2018). For instance, varenicline appears to be better at assisting smokers into initial abstinence rather than maintaining abstinence over the longer term (Agboola et al. 2015). In summary, relapse remains the most likely outcome of any cessation attempt even when using an evidence-based FDA-approved medication and existing smoking cessation pharmacotherapy has focused on modulating activity at the nicotinic acetylcholine receptor. There is therefore a strong clinical and public health need to discover and implement novel smoking cessation pharmacotherapy with improved efficacy capable of supporting the maintenance of long-term abstinence.

4 Dopaminergic System and Tobacco Use Disorder

The catecholamine neurotransmitter dopamine and the dopaminergic mesocorticolimbic circuitry (specifically the mesolimbic pathway, which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the ventral striatum, and the mesocortical pathway, which projects from the VTA to the prefrontal cortex) have long been implicated in substance use disorders (Feltenstein and See 2008). For instance, nicotine induces dopamine release in non-human primates (Marenco et al. 2004) and in humans, cigarette smoking induces dopamine release in these midbrain and cortical dopaminergic regions (Brody et al. 2004; Le Foll et al. 2014a, b; Wing et al. 2015). The ability of nicotine to increase midbrain dopamine is thought to underlie its reinforcing and motivational effects with the magnitude of dopamine release following smoking challenge associated with motivation to smoke (puff rate) and a reduction in both craving and withdrawal symptoms (Le Foll et al. 2014a, b).

In addition to its critical role in heightened nicotine reinforcement, dopamine or neuroadaptation within the dopaminergic system has been studied in association with several other addiction-relevant processes. For example, the conditioned learning of drug-related cues and the attribution of incentive salience that is thought to be an important motivational driver of use (drug "wanting") as well as underlying cue-induced urge to use (drug "craving") involve dopamine and the mesolimbic dopaminergic circuitry (Berridge 2007). Dopaminergic tone in the NAc has also been found to correlate with somatic and affective symptoms of a mecamylamine precipitated withdrawal syndrome in nicotine-dependent rats (Hildebrand et al. 1998; Natividad et al. 2010; Zhang et al. 2012) suggesting midbrain dopaminergic involvement in nicotine withdrawal. In addition, dopaminergic neuroadaptation in mesocortical projection regions resulting in reduced activity in the cingulate gyrus and dorsolateral prefrontal cortex have also been reported in those with substance use disorders and are thought to account for impairments in inhibitory control and

executive function that characterize those with substance use disorders (Volkow et al. 2009). Indeed, both hypo- and hyperdopaminergic states have been postulated to account for various substance use disorder phenomena depending on the absence or presence of drug-related cues (Leyton and Vezina 2014) and the dopamine hypothesis of drug addiction (Melis et al. 2005) implicates a long-lasting hypodopaminergic state throughout the addiction cycle including persistence of this state in withdrawal. As dopamine and neuroadaptation within the dopaminergic system are involved in several processes considered to drive compulsive drug use and relapse, this neurotransmitter system represents a valid target for novel pharmacotherapies for smoking cessation.

5 Dopamine Receptor D3

Five dopamine receptors named in the order of their date of cloning and forming two major receptor sub-classes, based upon their pharmacology and sequence homology, have been identified through which the actions of dopamine are mediated. DRD1-like receptors (DRD1 and DRD5) are G-protein-coupled receptors (GCPRs) which activate adenylyl cyclase (AC) and stimulate production of cyclic adenosine monophosphate (cAMP). Conversely, DRD2-like receptors (DRD2, DRD3, and DRD4) are GCPRs that inhibit AC activity and the production of cAMP (Jaber et al. 1996). DRD3 shares approximately 50% homology with DRD2 (Sibley and Monsma 1992) and since it was first described in 1990 (Sokoloff et al. 1990) there has been much interest in characterizing functions that may distinguish DRD3 from DRD2. DRD2 has been a historical pharmacological target of interest, particularly for schizophrenia and Parkinson's disease. Modulation of DRD3 is of particular interest in substance use disorders due to its localization in addiction-relevant areas of the brain (Le Foll et al. 2000, 2005a). The greatest density of DRD3 is found in limbic regions, known to be associated with reward, motivation, and emotion (Gurevich and Joyce 1999; Murray et al. 1994), including addiction-relevant processes briefly described above. For instance, DRD3 has been found to be localized to the islands of Calleja, mammillary bodies, the NAc shell, the frontoparietal cortex, the substantia nigra/ventral tegmental area, and cerebellar lobules 9 and 10 (Diaz et al. 2000). Midbrain DRD3 is localized to tyrosine hydroxylase containing neurons suggesting a pre-synaptic, autoreceptor function at these sites (Diaz et al. 2000).

The restricted localization of DRD3 along with the increased selectivity of behavioral effects observed with DRD3 modulating agents in comparison with those believed to occur with DRD2 agents (for further discussion on this, see Le Foll et al. (2014b)) suggests that treatments targeting the DRD3 may have fewer side effects. For example, Parkinson's-like side effects that are often seen with DRD2 antagonists were not observed with the DRD3 antagonist, SB-277011-A (Reavill et al. 2000). Despite the theoretical interest in modulating the DRD3 for the treatment of TUD and for substance use disorders more generally, there have been surprisingly few studies examining the role these receptors play in processes relevant

to TUD, or the effects of DRD3 modulating pharmacological agents in nicotine-dependent animals or in humans with TUD. One reason for this has been the historical lack of selective DRD3 agents. In this chapter, we review studies conducted using animal models of nicotine dependence and the existing human studies in TUD in order to provide a translational synthesis of the role of the DRD3 in TUD and to uncover the therapeutic potential of pharmacologically modulating this receptor as a novel smoking cessation strategy.

6 *DRD3* Genetic Polymorphisms and Nicotine Dependence

Candidate gene studies focusing on the dopaminergic system have demonstrated that the *dopamine receptor D3* (*DRD3*) gene is significantly associated with nicotine dependence severity in European Americans and Han Chinese, with weaker associations found in African Americans (Huang et al. 2008; Wei et al. 2012). One study investigating 13 single nucleotide polymorphisms (SNPs) within the *DRD3* gene in 2,037 participants suggested that the rs6280 SNP, a functional polymorphism corresponding to a serine to glycine substitution at position 9 in the extracellular N-terminal domain of the DRD3 (Ser9Gly) resulting in higher dopamine affinity and amplified intracellular signaling, was likely driving the association between the *DRD3* gene and nicotine dependence (Huang et al. 2008). The glycine allele at this Ser9Gly polymorphism is associated with both frequency (time to first cigarette) and quantity (heaviness of smoking) of smoking indices and in addition to this, one study also found an interaction between polymorphisms of the gene encoding the DRD2 and the *DRD3* gene impacting nicotine withdrawal severity, specifically the "trouble concentrating" symptom (Vandenbergh et al. 2007). Other genetic studies have implicated a role for DRD3 in smokers with mental health disorders that are known to be associated with increased prevalence of TUD and difficulty quitting smoking. For instance, the rs1025398 polymorphism within the *DRD3* gene has been found to be associated with quantity of tobacco smoked in schizophrenia patients (Novak et al. 2010) and the rs2399496 polymorphism, a *DRD3*-associated polymorphism located approximately 1.5 kb downstream of the *DRD3* gene, is associated with depression and nicotine dependence comorbidity (Korhonen et al. 2014). The same study also found a rs2399496 genotype–nicotine dependence interaction whereby there was an almost sixfold increase in depression risk for individuals with nicotine dependence and two copies of the minor allele of the rs2399496 polymorphism compared to those without nicotine dependence and with two copies of the major allele (Korhonen et al. 2014). Taken together, the candidate gene evidence presented here provides correlational support for the involvement of DRD3 in TUD. However, polymorphism within the *DRD3* gene was not associated with either short- or long-term quitting (Ton et al. 2007) and genome-wide association studies have tended not to find an association between the *DRD3* gene and nicotine dependence or other smoking traits (e.g., Quach et al. (2020)), which weakens evidence supporting a role for DRD3 in TUD and as a target

for treatment. Nevertheless, given the positive findings described above in those with mental health disorders, future studies that ascertain if *DRD3* genetic variance is associated with difficulty quitting, particularly among vulnerable populations with mental health disorders, may lead to more personalized treatment approaches in these groups.

7 Dopamine Receptor D3 Density

Preclinical evidence suggests there may be upregulation of DRD3 with repeated administration of substances of abuse. This contrasts with the findings for DRD2 that typically display lower expression in response to repeated exposure to drugs of abuse (Martinez et al. 2004; Volkow et al. 1996, 2004). For instance, upregulation of DRD3 expression has been documented in response to repeated administration of cocaine and alcohol (Neisewander et al. 2004; Vengeliene et al. 2006). However, this is not without exception and repeated exposure to amphetamine has been found to be associated with downregulation of DRD3 (Chiang et al. 2003). In line with the majority of preclinical findings, studies with repeated administration of nicotine in rats have also shown upregulation of DRD3 expression (Le Foll et al. 2003a, b). However, downregulation of DRD3 has also been reported resulting from stimulation of α4β2 nicotinic acetylcholine receptors (Acharya and Kim 2019), while a further study suggests there may be sex differences in DRD3 levels following repeated nicotine administration, with female rats exhibiting decreased levels of DRD3 compared to males (Harrod et al. 2004).

In humans, positron emission tomography (PET), a molecular imaging technique that uses radioactive labeling to visualize receptor density amongst other things, can be used to assess dopamine receptor levels in the intact, living brain. Evidence from human PET studies has largely corroborated preclinical findings in that increased DRD3 levels have been reported in stimulant users (Boileau et al. 2012, 2015, 2016) and in the hypothalamus, but not the striatum, of those with alcohol use disorder (Erritzoe et al. 2014) compared to healthy controls. In addition, greater expression of DRD3 has been found in post-mortem brain studies following cocaine overdose (Mash 1997; Segal et al. 1997; Staley and Mash 1996). However, in human tobacco-related studies no difference in DRD3 levels was found in striatal autopsy samples of elderly smokers compared to former smokers and non-smokers (Court et al. 1998). In another study, the lymphocytes of smokers had 30% lower DRD3 mRNA expression compared to non-smoker controls, with no such reduction observed in former smokers. In addition, this study also showed that DRD3 mRNA expression negatively correlated with heaviness of smoking (Czermak et al. 2004).

PET studies in smokers using the radiotracers [^{11}C]-raclopride or [^{18}F]-fallypride, which bind non-selectively to DRD2 and DRD3, have tended to find lower levels of striatal DRD2/DRD3 in smokers compared to non-smokers (Albrecht et al. 2013; Fehr et al. 2008; Wiers et al. 2017) and suggest that male but not female smokers may exhibit DRD2/DRD3 downregulation (Brown et al. 2012). However, the lack of

studies with DRD3 selective radiotracers makes interpretation of these findings difficult. Development of [^{11}C]-(+)-PHNO is improving our understanding of DRD3 in TUD but there have been few studies using this radiotracer. While [^{11}C]-(+)-PHNO is also non-selective, it has been described as DRD3-preferring (Narendran et al. 2006) and methods have been developed to differentiate between DRD2 and DRD3 binding based upon local DRD2 and DRD3 densities at specific regions of interest, therefore allowing for a more sensitive and selective assessment of DRD3 binding than was previously possible (see Le Foll et al. 2014a, b). In addition, [^{11}C]-(+)-PHNO may be more sensitive to measuring smoking-induced dopamine release than [^{11}C]-raclopride (Gallezot et al. 2014). Indeed, acute smoking challenge after overnight abstinence reduces [^{11}C]-(+)-PHNO binding in both DRD2- and DRD3-rich (e.g., ventral pallidum) areas suggesting that smoking induces dopamine release in DRD3-rich regions (Le Foll et al. 2014a, b). Taken together, TUD-relevant preclinical and human studies investigating DRD3 density have provided mixed findings in terms of whether there is up- or downregulation of these receptors following repeated administration of nicotine. However, since DRD3-regions experience smoking-induced dopamine release, it is possible these receptors mediate at least some addictive behaviors that maintain smoking.

8 Reinforcement

One established means of assessing the reinforcing properties of substances of abuse is to measure the propensity with which animals will self-administer them (Weeks and Collins 1964). To achieve this, animals are surgically implanted with an intravenous catheter that extends into the jugular vein to allow for rapid bolus injections of the drug. Animals are then trained to press a lever to receive intravenous infusions of drug. The operant chamber that houses the animal generally has two levers: presses on one lead to infusions of the drug while the second lever is an inactive lever. Presses on the inactive lever have no programmed consequences but serve as a measure of changes in non-selective motor activity. In one study, it was found that the DRD3 antagonist SB-27011-A (0, 3, 10 mg/kg, i.p.) had no effect on responding on either lever under a fixed-ratio schedule of reinforcement under which every second response on the active lever produced an infusion of nicotine (Andreoli et al. 2003). Thus, it appears that DRD3 may not influence nicotine reinforcement. Similarly, the DRD3 partial agonist BP897 (0.3, 1, 3 mg/kg, i.p.) had no effect on responding on either the active or inactive lever for nicotine under a fixed-ratio 5 (every 5 lever presses was reinforced) schedule of reinforcement (Khaled et al. 2010).

A related study investigated the effects of SB-277011A (3, 10, 30, 56 mg/kg) on responding for nicotine under a progressive ratio (PR) of reinforcement. Under a PR schedule of reinforcement animals are required to make progressively more responses for every subsequent infusion of drug. At some point, the animal will no longer work for drug, and this represents the “break point.” PR schedules are thought

to provide a measure of the rewarding properties of a drug (Richardson and Roberts 1996). In one study (Ross et al. 2007), SB-277011-A decreased the number of reinforcers earned and responses for nicotine under a PR schedule, but only at the highest dose. SB-277011-A had no effect on responding for food under a PR schedule suggesting that the effects on responding for nicotine were specific to the drug and not due to other non-selective effects. However, it should be noted that 56 mg/kg of SB-277011-A is a very high dose of drug which may not be entirely selective for DRD3. Indeed, this dose also decreased locomotor activity, which is generally thought to be due to actions at the DRD2 and not the DRD3 (Reavill et al. 2000).

Indirect evidence for a role of DRD3 in reward is provided by one study of the effects of SB-277011-A (3, 6 or 12 mg/kg) on nicotine-enhanced brain stimulation reward. In the brain stimulation reward procedure, an animal is trained to respond on a lever for stimulation directly into the reward centers of the brain. Nicotine and other stimulants potentiate the responding of animals for brain stimulation reward and are thought to reflect the rewarding properties of the stimulants. Pre-treatment with SB-27011-A dose-dependently attenuated nicotine-enhanced brain stimulation reward (Pak et al. 2006). This suggests that DRD3 may participate in some capacity in the rewarding properties of nicotine, even if DRD3 antagonists do not directly impact on the ability of nicotine to support responding for nicotine on its own.

In humans, a common method for assessing the relative reinforcing effects of drugs of abuse is the forced-choice task (Jones and Comer 2013). This task operationalizes how rewarding a participant finds the drug of choice relative to other drug or non-drug options by quantifying the number of times it is selected. For example, in one study, smokers genotyped for the Ser9Gly polymorphism in the *DRD3* gene sampled nicotine-containing and denicotinized cigarettes before making a number of forced choices between the two cigarettes in a double-blind procedure. Smokers selected nicotine-containing cigarettes more than they did denicotinized versions suggesting they found the nicotine in the cigarettes reinforcing. However, the Ser9Gly polymorphism had no impact on the frequency of nicotine choices (Chukwueke et al. 2020).

Behavioral economic procedures have also been used to assess the reinforcing value of cigarettes in smokers. For example, the Cigarette Purchase Task (CPT) is a validated measure (Mackillop et al. 2016) that operationalizes the reinforcing value of cigarettes in monetary terms (or cigarette demand). One study examined the effects of pramipexole, a DRD3-preferring (but non-selective DRD2/DRD3) agonist on the CPT and a choice procedure where smokers could earn cigarettes, chocolate, or music. Dependent smokers had greater demand for cigarettes on the CPT and selected cigarettes more than an alternative reward compared with occasional smokers. However, pramipexole had no effect on demand for cigarettes or on the number of cigarette choices (Lawn et al. 2018). Taken together, while the number of human studies examining the potential role of DRD3 in nicotine reinforcement is limited, studies in smokers lend support to the preclinical self-administration findings suggesting that DRD3 are not directly implicated in nicotine reinforcement.

9 Conditioned Stimuli

Conditioned stimuli are environmental stimuli paired with substances of dependence that can induce powerful urges for the drugs by themselves. The results of preclinical studies suggest that responding for nicotine is notably influenced by the presence of conditioned stimuli (Caggiula et al. 2002a, b). In this regard, a number of studies have found that DRD3 antagonists reduce conditioned activity when rats are exposed to an environment paired with nicotine. That is, rodents are naturally inquisitive animals and changes in locomotor activity induced by substances of dependence are believed to activate a natural reward-seeking response in rats (Wise and Bozarth 1987). In one study, SB-277011-A (3, 6, or 12 mg/kg, i.p.) reduced nicotine-induced cue-induced conditioned locomotion (Pak et al. 2006). Another study found that both SB-277011-A and BP 897 reduced conditioned hyperactivity in a nicotine-paired context (Le Foll et al. 2003a, b). There was no effect of these treatments in saline control rats, suggesting that the effects were not on motor activity per se. The DRD3 partial agonist BP 897 also did not affect novelty-induced locomotion, further supporting the conclusion that these treatments do not affect non-selective motor activation.

By comparison to the effects of DRD3 antagonists and partial agonists on conditioned locomotion, SB-277011-A had no effect on responding for a conditioned stimulus. After training to respond for nicotine under a fixed-ratio schedule of reinforcement in the presence of a conditioned stimulus, the drug was withheld and responding for the stimulus on its own was measured. SB-277011-A (0, 3, 10 mg/mg, i.p.) did not affect this responding (Andreoli et al. 2003). Similarly, it had no effect on latencies to respond for the CS. Thus, there appear to be some discrepancies in the role of DRD3 ligands in stimulus-maintained behavior. One explanation for these differences may reflect the fact that conditioned locomotion is under the control of a passively presented stimuli, where responding for the stimulus is an active form of stimulus presentation. Studies have shown that dopamine is increased after presentation of passive stimuli but not actively earned stimuli (Di Ciano et al. 1998a, b; Ito et al. 2000, 2002). DRD3 may be important specifically in behaviors under the control of passively presented stimuli.

In humans, reactivity to smoking-related cues is typically indexed as change from baseline physiological arousal or urge/craving to smoke once these conditioned cues have been presented, and relative to neutral cues. In one such study, the subjective cue-induced craving from smokers genotyped for the Ser9Gly polymorphism in the *DRD3* gene was examined before, during, and after exposure to smoking and neutral cues. Smoking-related cues elicited greater craving in smokers compared to neutral cues. Further, those smokers that were glycine carriers exhibited an attenuated cue-induced craving compared to smokers that were not glycine carriers (Chukwueke et al. 2020). This study implicates DRD3 in reactivity to conditioned smoking cues. However, the direction of the findings is somewhat surprising given that the glycine allele at the Ser9Gly polymorphism has previously been associated with both frequency and heaviness of smoking (Vandenbergh et al. 2007).

Potentially, frequency and heaviness of smoking in glycine carriers may be mediated by means other than cue-induced craving but these cue-reactivity findings will need to be replicated.

Dependent smokers tend to orient their attention toward smoking-related stimuli (i.e., they exhibit an attentional bias to conditioned smoking cues). In one study, the effects of the DRD3-preffering agonist pramipexole on visual fixations toward smoking and money stimuli were examined in smokers in a double-blind placebo-controlled crossover design. Pramipexole reduced the initial attention orienting bias toward smoking-related stimuli compared to money and reduced the urge to smoke following the visual fixation task suggesting that pramipexole can reduce the salience of smoking-related cues (Freeman et al. 2015). These human studies, taken together with preclinical findings, suggest that DRD3 is likely to play an important role in the expression of conditioned cue-induced behavior in smokers.

10 Conditioned Place Preference

Another means of testing the conditioned rewarding properties of drugs is through the conditioned place preference (CPP) model (Tzschentke 1998). In this paradigm, rats learn to associate different environments with unique outcomes (drug or non-drug). One side of the box is paired with a drug of reward and the other with placebo or another control. Since the two sides of the box vary on sensory qualities, the animal learns that one side is associated with reward. On test day, the animal is placed in the middle of the two sides of the box and the time spent on either side is measured. Animals tend to spend more time in the side of the box paired with reward. In one study, the DRD3 partial agonist BP 897 (0.1, 0.3, 1 mg/kg) or the DRD3 antagonist ST198 (3, 30, 100 mg/kg) blocked the expression of CPP when rats were injected with these agents prior to the test session (Le Foll et al. 2005b). In another study (Pak et al. 2006), pre-treatment with SB-277011-A (3, 6, or 12 mg/kg) dose-dependently attenuated nicotine CPP. When tested on its own, SB-277011-A had no effects on its own and did not induce a place aversion when paired with one side of a CPP box. Thus, it appears that the effects of DRD3 antagonists on CPP are not related to any aversive properties of these ligands, but rather, they are due to an impact of these antagonists and partial agonists on CPP. These findings are supported by the results of other studies that found that a number of DRD3 antagonists (Micheli et al. 2007), as well as 1 and 3 mg/kg of GSK598809 (Mugnaini et al. 2013), dose-dependently reduced nicotine CPP. This effect was apparent when administered 0.5 h before the test, but was attenuated with a 4 h pre-treatment interval, and there was no effect with an 8 h pre-treatment interval (Mugnaini et al. 2013). It should be noted that CPP is an example of behavior controlled by the presentation of passive stimuli and these findings are therefore consistent with those reviewed above (Le Foll et al. 2003a, b; Pak et al. 2006), which found effects of DRD3 antagonists and partial agonists on conditioned locomotion.

11 Reinstatement

Substance use disorder has been characterized as a chronic relapsing disorder (Leshner 1997). Thus, potential treatments for substance use disorder have often focused on the ability of the potential intervention to prevent relapse to drug use. Relapse to drug use is known to be induced by a number of environmental factors including contexts, conditioned stimuli, stress, and exposure to the drug itself. This type of relapse is modeled by the reinstatement paradigm (Epstein and Preston 2003). In this model, animals are trained to respond for a drug to a certain criterion before access to the drug is suspended. After discontinuation of the drug, responding for the drug decreases or extinguishes. The "relapse" occurs when responding on the drug-appropriate lever in reinstated by exposure to stress, contexts, conditioned stimuli, or injections of the drug itself.

In one study, SB-277011-A (0, 3, 10 mg/kg, i.p.) decreased nicotine-induced reinstatement, suggesting that DRD3 antagonists may attenuate this type of relapse (Andreoli et al. 2003). No effects were seen on responding on the inactive lever, suggesting that the effects were selective for nicotine and did not represent changes in motor activity or other activating effects. Similarly, SB-277011-A reduced cue-induced reinstatement (Khaled et al. 2010) without effect on the inactive lever and also attenuated context-induced reinstatement (Sabioni et al. 2016). It should be noted that the DRD3 partial agonist (Pilla et al. 1999) BP 897 (0.3, 1, 3 mg/kg, i.p.) had no effect on cue-induced reinstatement (Khaled et al. 2010). Thus, DRD3 antagonists (SB-277011-A) and partial agonists may have differential efficacy in treating relapse.

Taken together with findings described in the conditioned stimuli section (above), evidence implicates DRD3 in addictive processes that involve the processing of conditioned cues (such as reinstatement of drug seeking in the presence of cues as discussed here, and cue-induced craving, and attentional orienting to drug-related stimuli discussed above).

12 Drug Discrimination

Drug discrimination is a paradigm that tests the similarity in interoceptive or subjective effects produced by exposure to different drugs (Solinas et al. 2006). In this model, the animal is trained to respond on two levers. Responding on one lever is reinforced in the presence of a drug such as nicotine, and the other in the presence of a control, such as saline. When trained, the nicotine is replaced with a test substance such as the potent and selective DRD3 antagonist SB-277011-A and responding on the two levers is measured. If the animal responds more on the drug-appropriate lever, then it can be concluded that the test agent has interoceptive/subjective properties that are similar to the original drug.

DRD3 agents do not appear to impact the drug discriminative effects of nicotine. In one study, a DRD3 partial agonist and DRD3 antagonist did not substitute for nicotine in a test of drug discrimination (Le Foll et al. 2005a, b). When given prior to responding for various doses of nicotine, neither drug produced a shift in the dose-response curve, suggesting that DRD3 agents do not impact the subjective effects of nicotine. However, further studies are required to determine if these findings are specific for these DRD3 compounds or whether they constitute a class effect.

13 Sensitization

Behavioral sensitization to nicotine appears following repeated administration. It is the process in which this repeated administration produces a progressively greater behavioral response and has been suggested to model some aspects of drug use in humans (Sax and Strakowski 2001). In the sensitization procedure, rats are injected with a rewarding drug repeatedly for several days prior to a no-drug period of a few weeks. When challenged with the drug after a period of withdrawal, the locomotor response to the drug is typically greater than that observed during the initial exposure. In one study (L. N. Smith et al. 2015), the DRD3 antagonist GR 103691 was given either daily during the initial exposure to nicotine or during the test session after 3 weeks of withdrawal. Injections during the initial phase are believed to test the effects of GR 103691 on the induction of sensitization, while pre-treatment on the test day reflects the effect of the treatment on the expression of sensitization. In this study, GR 103691 blocked the induction but not expression of sensitization. Thus, this study provides some evidence for a role of DRD3 in the acquisition of sensitized responding to reinforcing drugs. It should be noted, however, that the effects of GR 103691 on the induction of sensitization were only found in adolescent rats and not in adult rats. This might suggest that DRD3 plays a particular role in the acquisition of behavioral sensitization when nicotine use or smoking onset occurs during specific developmental periods, however, more studies are required to confirm this.

14 Executive Function

It has been proposed that cognitive enhancement, particularly enhancement of executive functions such as working memory, response inhibition, and cognitive flexibility, may be a treatment target for addictions (Sofuoglu et al. 2013). However, existing pharmacotherapy for substance use disorders has limited impact on executive function (Butler and Le Foll 2019). Executive dysfunction is a hallmark feature of addictions that is exacerbated during early abstinence and is associated with relapse. For example, nicotine withdrawal-related deficits in working memory and

response inhibition predict smoking relapse (Patterson et al. 2010; Powell et al. 2010).

Preclinical evidence suggests that DRD3 antagonists may improve cognitive performance including on tasks of executive function (Nakajima et al. 2013). For example, the DRD3 antagonist S33138 improved 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced or aged-related deficits in cognitive flexibility performance on an attentional set-shifting task and working memory performance in a delayed matching-to-sample task in rhesus monkeys (Millan et al. 2010). In concordance with these findings, DRD3 knock-out mice performed better on an attentional set-shifting task (Glickstein et al. 2005) and ameliorated age-related deficits on the Morris water maze task of spatial working memory (Xing et al. 2010) compared to wild-type mice. However in contrast, spatial working memory deficits in DRD3 knock-out mice have also been reported (Glickstein et al. 2002) and the DRD3 preferring antagonist nafadotride had no effect on a reversal learning task of cognitive flexibility in rats (Boulougouris et al. 2009). Together these studies provide tentative support for DRD3 antagonists improving aspects of executive function, particularly where baseline impairments are present. It is possible that DRD3 antagonism during early abstinence may ameliorate withdrawal-related executive dysfunction however, studies are required to confirm this speculation.

In humans, the Ser9Gly polymorphism of the *DRD3* gene was associated with perseverative errors on the Wisconsin Card Sorting Task, a measure of cognitive flexibility in a Chinese sample (Lane et al. 2008) also implicating DRD3 in executive function performance. However, the non-selective DRD2/DRD3 antagonist haloperidol reduced response inhibition (No-Go accuracy) in a Go/No-Go task (Luijten et al. 2013). However, it is important to consider here that the actions of haloperidol at DRD2 and not DRD3 may account for the deficits in response inhibition found in this study given that evidence from the schizophrenia literature suggests that DRD2 antagonism may impair cognitive performance in contrast to the potential effectiveness of DRD3 antagonists at reducing cognitive dysfunction (Millan and Brocco 2008).

Deficits in impulsivity are a core neurocognitive feature of substance use disorders including TUD (Lee et al. 2019; J. L. Smith et al. 2014). However, impulsivity is a multifaceted construct that is commonly operationalized in terms of two distinct sub-dimensions: impulsive action (response inhibition, i.e. having difficulty inhibiting a prepotent response) and impulsive choice (i.e., having difficulty delaying gratification, for further discussion of the non-unitary nature of impulsivity, see Broos et al. (2012)). The DRD3 preferring agonist pramipexole had no effect on temporal discounting of monetary reward in smokers (Freeman et al. 2013) suggesting DRD3 may not be implicated in impulsive choice. However, further research might consider if DRD3 is implicated in temporal discounting of cigarettes. Future studies should also examine the association between DRD3 density and the impact of selective DRD3 modulation on tasks of impulsive action in smokers. This is particularly important given that response inhibition predicts smoking relapse (Powell et al. 2010) and because impulsive action, but not impulsive choice, can predict drug-induced dopamine release in the NAc and the attribution of salience to

conditioned stimuli (Zeeb et al. 2016). Indeed, previous PET imaging studies have found significant positive associations between [^{11}C]-(+)-PHNO binding and impulsiveness in cocaine-dependent participants and in pathological gamblers (Boileau et al. 2013; Payer et al. 2014). These studies implicate DRD3 in impulsive action and self-report measures of impulsivity and suggest there may be a transdiagnostic association between DRD3 and impulsive action across substance and behavioral addictions.

15 Withdrawal Signs

Nicotine withdrawal symptoms including irritability, anxiety, difficulty concentrating, restlessness, increased appetite, depressed mood, and sleep problems may be experienced after quitting or when reducing tobacco use. This withdrawal syndrome often occurs 4–24 h following cessation and peaks on approximately the third day of abstinence, gradually reducing over the proceeding 3–4 weeks (McLaughlin et al. 2015). Withdrawal symptoms are associated with smoking relapse supporting a negative reinforcement interpretation (Robinson et al. 2019) whereby negative or aversive states motivate tobacco smoking resumption. Therefore, reducing severity of the withdrawal syndrome may be an important aspect of smoking cessation treatment.

As discussed above, DRD3 antagonists may be a novel target for acute abstinence-induced impairments in executive function. Similarly, DRD3 antagonists may reduce tobacco craving in early abstinence. In one study, smokers administered a single dose of GSK598809, a selective DRD3 antagonist, resulting in submaximal (72–89%) DRD3 occupancy reduced craving following overnight abstinence (Mugnaini et al. 2013). In contrast, there is also some evidence that agonist activity at DRD3 can alleviate other abstinence-induced nicotine withdrawal signs. For example, one preclinical study found that pramipexole, a DRD3-preferring (but non-selective DRD2/DRD3) agonist, reduced some of the somatic withdrawal signs (teeth chattering/chews and shakes) present during acute nicotine withdrawal in rats (Ohmura et al. 2011). In another study in smokers, the effects of pramipexole on reward responsivity were investigated. Reduced reward responsivity has been observed during acute abstinence compared to satiation and a single dose of pramipexole after 2 h of abstinence enhanced reward responsivity compared to placebo in a double-blind crossover study (Freeman et al. 2013).

Taken together, these studies suggest that DRD3 modulation can reduce acute nicotine withdrawal signs. However, there have been only a limited number of studies investigating the potential of DRD3-selective agents to attenuate withdrawal symptom severity. Future preclinical and human research should determine which withdrawal signs from the entire constellation of withdrawal syndrome symptoms DRD3 modulation can improve, whether this modulation is beneficial at alleviating withdrawal signs at longer durations of withdrawal, and whether symptom attenuation impacts relapse/quit success.

16 Summary of Translational Synthesis

Tables 1 and 2 summarize the findings of the preclinical and clinical studies reviewed here. Overall, findings of the reviewed studies provide some evidence for a treatment potential of DRD3 agents in TUD. However, there are some inconsistencies and further studies are warranted to establish further if there is benefit to this pharmacological approach. Evidence suggests that DRD3 may be particularly important for diminishing the impact of cue-controlled behavior. In preclinical studies, both DRD3 antagonists and partial agonists decreased nicotine-induced

Table 1 Summary of the preclinical/animal studies reviewed

Paradigm/index	DRD3 manipulation	Finding
Reinforcement		
Self-administration under fixed-ratio schedule	DRD3 antagonist DRD3 partial agonist	– –
Self-administration under progressive-ratio schedule	DRD3 antagonist	↓
Nicotine-enhanced brain stimulation reward	DRD3 antagonist	↓
Nicotine conditioned place preference	DRD3 antagonist DRD3 partial agonist	↓↓ ↓
Reinstatement		
Nicotine-induced reinstatement	DRD3 antagonist	↓
Cue-induced reinstatement	DRD3 antagonist DRD3 partial agonist	↓ –
Context-induced reinstatement	DRD3 antagonist	↓
Conditioned stimuli		
Conditioned locomotion	DRD3 antagonist DRD3 partial agonist	↓↓ ↓
Responding for a conditioned stimulus (conditioned reinforcement)	DRD3 antagonist	–
Other		
Drug discrimination	DRD3 antagonist DRD3 partial agonist	– –
Induction of behavioral sensitization	DRD3 antagonist	↓
Executive function		
Drug- and age-induced deficits in attentional set-shifting and working memory	DRD3 antagonist	↓
Reversal learning	DRD3 preferring antagonist	–
Attentional set-shifting	DRD3 KO mice	↑
Working memory	DRD3 KO mice	↑↓
Withdrawal signs		
Somatic signs (teeth chattering/chews/shakes)	DRD3 preferring agonist	↓

Abbreviations: – = No effect, ↓ = Limited evidence of reduction, ↓↓ = Strong evidence of reduction, ↑ = Limited evidence of increase, ↑↑ = Strong evidence of increase, ↑↓ = mixed evidence

Table 2 Summary of the clinical/human studies reviewed

Paradigm/index	Pharmacological agent/genetic polymorphism	Finding
Reinforcement		
Nicotine choice under forced choice	Ser9Gly	–
Nicotine choice vs alternative reinforcer	DRD3-preferring agonist	–
Cigarette demand on the cigarette purchase task	DRD3-preferring agonist	–
Conditioned stimuli		
Cue-induced craving	Ser9Gly (Gly carriers) DRD3-preferring agonist	↓ ↓
Attentional orienting to smoking cues	DRD3-preferring agonist	↓
Executive function/cognitive control		
Perseverative errors on the Wisconsin card sorting task	Ser9Gly (heterozygous genotype)	↑
Response inhibition in a go/no-go task	Non-selective DRD2/3 antagonist	↓
Temporal discounting	D3 preferring agonist	–
Relationship between impulsivity and DRD3 receptor density	PET radiotracer [^{11}C]-(+)-PHNO	↑*
Acute withdrawal signs		
Craving after overnight abstinence	DRD3 antagonist	↓
Acute abstinence-induced reduction in reward responsivity	DRD3-prefering agonist	↑

Abbreviations: – = No effect, ↓ = Limited evidence of reduction, ↓↓ = Strong evidence of reduction, ↑ = Limited evidence of increase (* = positive association), ↑↑ = Strong evidence of increase, ↑↓ = mixed evidence

conditioned activity and CPP. However, the effects seem selective to passively presented cues such as contexts in these experimental animals. DRD3 antagonists also blocked cue-induced and context-induced reinstatement (as well as nicotine-induced reinstatement) suggesting utility in preventing relapse that is triggered by tobacco-related cues. These preclinical findings suggest that DRD3 agents may be helpful in controlling the "craving" and urges induced by passive exposure to drugs paired with nicotine and may also help attenuate relapse to nicotine use, although further human data testing this hypothesis is needed.

While there is some degree of translational agreement that DRD3 modulation is implicated in cue-controlled behavior, there are translational inconsistencies regarding the direction of these effects when different DRD3 agents are used. For instance, antagonists and partial agonists appear to be beneficial in preclinical models while only the DRD3-preferring agonist pramipexole has been shown to both reduce initial attentional orienting to smoking cues (suggesting a role in cue salience) and reduce craving from overnight abstinence. Further, while some genetic evidence implicates the DRD3 in cue-reactivity, findings were in the opposite direction to what would be hypothesized. Further, genetic evidence has been mixed with genome-wide association studies tending not to implicate the DRD3 loci in TUD and one study explicitly finding no association between polymorphism in the *DRD3* gene and short- or

long-term quitting. Alongside the mixed findings regarding DRD3 expression, these inconsistencies attenuate our confidence in the hypothesis that DRD3 modulation is a promising pharmacological target for smoking cessation. There have however been very few pharmacological studies conducted in humans, with the majority focusing on pramipexole. Further studies with antagonists or partial agonists are now warranted given the promising preclinical findings in relation to cue-controlled behavior.

There were no effects on responding for nicotine or on the discriminative properties of nicotine, suggesting that these ligands do not impact the rewarding or subjective properties of nicotine. Here, there is translational agreement as some human genetic and pharmacological studies also suggest a lack of involvement of DRD3 in nicotine reinforcement in smokers.

DRD3 antagonists may have cognitive enhancing properties particularly where baseline impairments exist and so may offer potential to attenuate executive dysfunction that is exacerbated by withdrawal, but further studies are needed in this area. For instance, it may be particularly interesting to see if selective DRD3 antagonists impact tasks of response inhibition in withdrawn smokers. DRD3 agents also appear to reduce withdrawal signs but again studies are limited in number and have been mixed, with both DRD3 antagonists and DRD3 agonists shown to reduce different withdrawal signs.

Taken together, translational evidence suggests that further studies are warranted with the most compelling evidence suggesting that DRD3 is an important mediator of cue salience and cue-controlled behaviors. Indeed, previous work investigating the impact of a DRD3 agonist and a DRD3 antagonist on maladaptive decision making has shown that the presence or absence of salient cues within the task determines whether DRD3 agents impact choice (Barrus and Winstanley 2016). Additionally, the DRD3 antagonist GSK598809 reduces attentional bias to palatable food cues in overweight and obese participants suggesting that the proposed role of the DRD3 in mediating the effects of cues is not restricted to TUD but may apply more generally to any salient or appetitive cues (Nathan et al. 2012).

Existing pharmacotherapy appears to be better at assisting people into abstinence rather than helping them to maintain longer duration abstinence (Agboola et al. 2015). The finding that DRD3 may be especially important for cue-mediated behavior may indicate that DRD3 agents may have greater success with sustaining abstinence because cues have such a persistent and enduring effect on human craving and relapse (e.g., Bedi et al. (2011)). Further, there may also be implications for TUD treatment in those with psychiatric comorbidities, for example depression. There is increased smoking prevalence in those with depression, and depressed smokers often have greater levels of dependence and have more difficulty quitting. Positive associations have been reported between depression severity and activation of brain regions involved in attributing smoking cue salience as well as between current depression symptoms and tobacco cue-reactivity (Kushnir et al. 2013; Weinberger et al. 2012). Therefore, DRD3 agents may be particularly effective at attenuating cue salience and cue-mediated behavior, which may improve relapse rates, in this group. Further clinical studies with DRD3 modulating agents are

warranted to establish if targeting this receptor in chronic relapsing and difficult to treat groups may improve abstinence rates compared to existing pharmacotherapy.

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He has participated in a session of a National Advisory Board Meeting (Emerging Trends BUP-XR) for Indivior Canada and has been a consultant for Shinogi. He is supported by CAMH, Waypoint Centre for Mental Health Care, a clinician-scientist award from the Department of Family and Community Medicine of the University of Toronto and a Chair in Addiction Psychiatry from the Department of Psychiatry of University of Toronto.

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