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Review article

Dopamine D3 receptor-based medication development for the treatment of opioid use disorder: Rationale, progress, and challenges

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ABSTRACT

Opioid abuse and related overdose deaths continue to rise in the United States, contributing to the current national opioid crisis. Although several opioid-based pharmacotherapies are available (e.g., methadone, buprenorphine, naloxone), they show limited effectiveness in long-term relapse prevention. In response to the opioid crisis, the National Institute on Drug Abuse proposed a list of pharmacological targets of highest priority for medication development for the treatment of opioid use disorders (OUD). Among these are antagonists of dopamine D3 receptors (D3R). In this review, we first review recent progress in research of the dopamine hypothesis of opioid reward and abuse and then describe the rationale and recent development of D3R ligands for the treatment of OUD. Herein, an emphasis is placed on the effectiveness of newly developed D3R antagonists in the animal models of OUD. These new drug candidates may also potentiate the analgesic effects of clinically used opioids, making them attractive as adjunctive medications for pain management and treatment of OUD.

Drug overdose is the leading cause of accidental deaths in the United States, with opioids being the most commonly abused drug class. In 2017, more than 70,000 Americans died from drug overdose, mainly from opioids (Centers for Disease Control and Prevention, 2019; Colon-Berezin et al., 2019). While abuse of prescription opioids (e.g., oxycodone) has played a significant role in the opioid crisis, advancing to heroin, that can be laced with the synthetic opioid, fentanyl or its analogs, is another devastating factor ravaging communities across North America (Drug Enforcement Administration, 2007; Somerville et al., 2017). Indeed, the recent increase in drug overdose deaths is so steep (Colon-Berezin et al., 2019; Jannetto et al., 2019; Rudd et al., 2016) that it has contributed to the reduction in the country's life expectancy over the last three years (Centers for Disease Control and Prevention, 2019) and to the declaration of a national opioid crisis (White House, 2017). This crisis will undoubtedly be exacerbated by the current COVID-19 pandemic (Volkow, 2020).

While opioid addiction is taking a toll on American society (NIDA, 2016), available treatments for long term abstinence provide limited effectiveness (Kleber, 2007; Nielsen et al., 2016; Stotts et al., 2009). The currently available opioid agonist medication methadone or the partial agonist buprenorphine have shown some effectiveness in reducing drug craving and withdrawal, and naloxone can rapidly reverse the effects of opioid overdose (Jordan et al., 2019a; Koehl et al., 2019; Mattick et al., 2014; Volkow et al., 2019). However, chronic opioid treatment carries the risk of abuse liability and side effects such as constipation, nausea, vomiting and/or respiratory depression that can be lethal (Benyamin et al., 2008; Kheradmand et al., 2010). In addition, among those who receive such treatment, discontinuation rates over 30 days after treatment initiation are high (up to 70 %) (Morgan et al., 2018).

The biggest challenge in the treatment of opioid use disorder (OUD) continues to be relapse prevention for which pharmacotherapies have had limited success. It is estimated that up to 90 % of individuals will return to drug use within a year after termination of treatment (Darke et al., 2007; Grella and Lovinger, 2011; Hser et al., 2015; Nosyk et al., 2013; Vaillant, 1973). Overall, the prevalence of abstinence from opioid use is low (less than 30 % after 10–30 years of observation), and many individuals tend to use other drugs and alcohol even during opioid abstinence (Grella and Lovinger, 2011). Therefore, immediate solutions for the opioid crisis and developing more effective treatments for OUD are desperately needed. The ideal therapeutic for the treatment of OUD would be a medication that reduces opioid abuse and prevents relapse without producing deleterious side effects on it own.

As part of the National Institutes of Health, the National Institute on Drug Abuse (NIDA) is devoted to addressing the opioid crisis and has proposed a list of the 10 highest priority pharmacological targets for medication discovery research (Rasmussen et al., 2019). One of the highlighted targets on this list is the dopamine D3 receptor (D3R). These receptors are highly expressed in the mesolimbic system,

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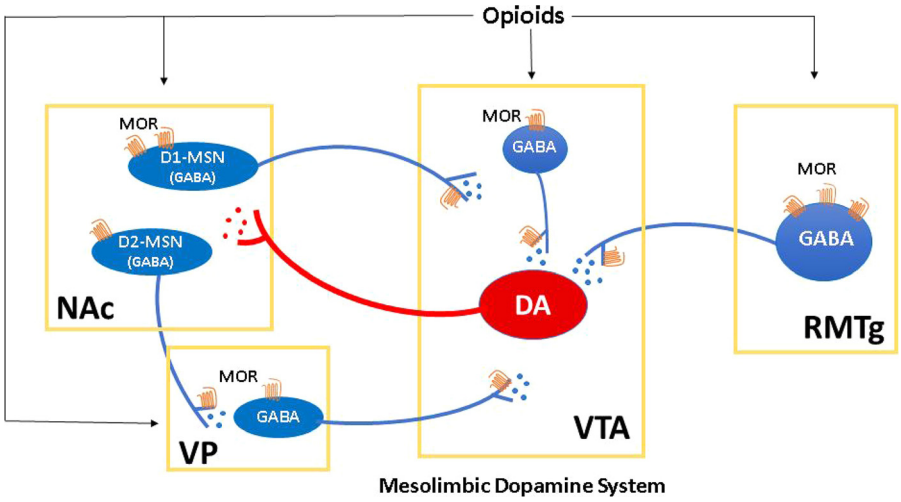

Fig. 1. Dopamine (DA) hypothesis of opioid reward. The mesolimbic DA system originates with DA neurons in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc) and prefrontal cortex. VTA DA neurons receive GABAergic inputs from multiple brain regions including the VTA, NAc, ventral pallidum (VP), and rostromedial tegmental nucleus (RMTg). Mu opioid receptors (MOR) are highly expressed in GABAergic neurons, particularly in the RMTg . Opioids bind to MORs, producing an inhibitory effect on GABA neuron activity and GABA release from the terminals in the VTA that subsequently disinhibits VTA DA neurons. Recent studies suggest that opioid-induced DA neuron disinhibition is caused by inhibition of GABA release onto DA neurons mainly from the RMTg, modestly from the NAc and VP, and minimally from the VTA GABA interneurons.

including regions such as the nucleus accumbens (NAc), amygdala, olfactory tubercle, and insular cortex; brain regions that play a pivotal role in reward and motivation (Bouthenet et al., 1991; Diaz et al., 1994; Gurevich and Joyce, 1999; Levant, 1997). This restricted localization of D3Rs predicts a lack of extrapyramidal side-effects associated with D2-like receptor antagonists (Galaj et al., 2014; Ross et al., 2007; You et al., 2018) in treatment approaches and has led to the discovery of a number of highly selective D3R antagonists or partial agonists. Several D3R ligands have been tested extensively in animal models of psychostimulant (cocaine, methamphetamine) use disorders and produced promising results, which have been reviewed comprehensively elsewhere (Heidbreder, 2005; Keck et al., 2014; Le Foll et al., 2014; Le Foll and Di Ciano, 2015; Newman et al., 2012; Sokoloff and Le Foll, 2017; Xi and Gardner, 2008, 2007). Perhaps, as opioids produce their euphoric and antinociceptive effects through opioid receptors, less attention has been directed toward the potential utility of D3R ligands for the treatment of OUD. In this review, we will first describe the neural mechanisms underlying opioid reward, focusing on the dopamine (DA) hypothesis, followed by the rationale for developing D3R-based pharmacotherapies for OUD. We then will review recent progress in preclinical and clinical studies supporting the utility of novel D3R antagonists in the treatment of OUD. Emphasis is placed on the efficacy of D3R ligands in attenuation of opioid reward and propensity to relapse, core features of opioid addiction. Among animal models, intravenous drug self-administration, conditioned place preference (CPP) and intracranial self-stimulation (ICSS) are commonly used procedures to evaluate drug rewarding effects, whereas reinstatement of drug-seeking behavior triggered by drugs, cues or stress is often used to model relapse in humans.

1. Rationale for developing D3 receptor-based medication strategy

1.1. Dopamine hypothesis of opioid reward

The rewarding effects of opioids are mediated by stimulation of opioid receptors, of which there are four primary subtypes: mu, kappa, delta, and opioid-receptor like-1 (also known as the nociception receptor). Although all opioid receptor subtypes are involved in the pharmacology of opioid actions, mu opioid receptors (MORs) have been recognized as the primary mediators of the opioid rewarding effects that can lead to abuse and/or dependence (Darcq and Kieffer, 2018; Wang, 2019). Thus, a major focus in medication discovery research has been on developing various MOR agonist (e.g., methadone), partial agonist (e.g., buprenorphine), or antagonist (e.g., naloxone) therapies for OUD (Jordan et al., 2019a). Although methadone or buprenorphine maintenance therapy is frequently used as the first-in-line treatment for controlling withdrawal symptoms and illicit opioid intake, these opioids are less effective in relapse prevention (Jordan et al., 2019a). In addition, methadone has significant abuse potential, as demonstrated in a number of clinical and preclinical studies (Jordan et al., 2019a), making it a Schedule II drug. Thus, in search for alternative therapeutic strategies for OUD it is imperative to focus on ligands such as D3R antagonists that lack abuse liability (Beardsley et al., 2001; Jordan et al., 2019b; Song et al., 2014; Spiller et al., 2008; Xi et al., 2006). Also, it is important to expand our understanding of the neural mechanisms underlying opioid reward to develop better pharmacotherapies for OUD. To date, the neural mechanisms underlying opioid reward have not been fully elucidated. A well accepted view is that both DA-dependent and DA-independent mechanisms might be involved in opioid reward (Fields and Margolis, 2015; Steidl et al., 2017).

1.1.1. VTA GABA disinhibition hypothesis

Receptor ligand autoradiography and genetic knock-in tagging of opioid receptors with fluorescent markers have been used to detect mu and delta opioid receptor expression in the brain (Erbs et al., 2015; Kitchen et al., 1997; Mansour et al., 1987). In the midbrain, MORs are found mainly in the substantia nigra, a structure adjacent to the ventral tegmental area (VTA) (Méndez et al., 2003; Tempel and Zukin, 1987), while in the VTA MOR-immunostaining is found mainly on non-dopamine neurons (Garzón and Pickel, 2001). Opioids, that bind to MORs, Gi-protein coupled receptors (Kosterlitz and Paterson, 1980; Pasternak and Wood, 1986), appear to directly inhibit VTA GABAergic neurons that provide tonic inhibition to neighboring VTA DA neurons (Gysling and Wang, 1983; Johnson and North, 1992; Margolis et al., 2014). Based on these findings, it was proposed that opioid-induced reward might require disinhibition of adjacent DA neurons through inhibitory GABAergic interneurons (Gysling and Wang, 1983; Johnson and North, 1992) (Fig. 1). This VTA GABA-DA disinhibition hypothesis continues to be influential as it provides a neurophysiologically tested model linking opioid reward with the well-defined mesolimbic DA reward system. This hypothesis was later supported by a series of behavioral studies demonstrating that morphine can be self-administered directly into the VTA (Bozarth and Wise, 1981; David and Cazala, 1994; Devine and Wise, 1994; Welzl et al., 1989) and intra-VTA infusions of morphine, DAMGO (a MOR agonist), or endomorphin-1 (an endogenous MOR ligand) can lead to the acquisition of CPP (Bals-Kubik et al., 1993; Phillips and LePiane, 1980) or support self-administration (Zangen et al., 2002). In contrast, MOR antagonists, such as naloxone, when infused to the VTA can effectively block morphine CPP (Olmstead and Franklin, 1997).

1.1.2. NAc GABA disinhibition hypothesis

The striatum, composed of the dorsal and ventral part with NAc, receives DA inputs from the VTA and substantia nigra pars compacta (SNc) and is a key substrate for natural and drug rewards (Merrer et al., 2009). Striatal medium-spiny neurons (MSNs) fall into two classes, D1- or D2-receptor-expressing MSNs. D1-MSNs with high expression of MORs send GABAergic projections to the substantia nigra and VTA while D2-MSNs to the globus pallidus/ventral pallidum (Cui et al., 2014). Earlier studies showed that rats learn to self-administer opioids directly into the NAc (Olds, 1982), suggesting an important role of the NAc in opioid reward. A recent study using conditional MOR-KO mice (Dlx5/6-Cre × *Oprm1*-flox) demonstrated that selective deletion of MORs from both D1- and D2-MSNs significantly increased heroin self-administration and decreased locomotor response to heroin (Charbogne et al., 2017). In addition, the conditional MOR-KO mice in striatal GABA neurons displayed higher break-point for heroin-taking and higher cue-induced reinstatement responding, but failed to show changes in heroin-induced CPP and heroin-induced striatal DA release (Charbogne et al., 2017). These findings suggest that deletion of the MORs in both D1- and D2-MSNs significantly alters motivation for heroin-taking rather than heroin reward. In contrast, another report from the same group showed that genetic deletion of MORs abolished the analgesic effect of morphine, as well as CPP and physical dependence, while ectopic rescue of MOR expression in striatal prodynorphin-positive neurons (i.e., D1-MSNs) restored opioid-induced CPP, locomotor sensitization, to some extent, opioid self-administration, in MOR-KO mice (Cui et al., 2014), suggesting an important role of D1-MSNs in opioid reward (Cui et al., 2014). Although the neural circuits underlying these findings remain to be determined, it was proposed that D1-MSNs with rescued MORs may form monosynaptic GABAergic inputs onto the DA neurons in the VTA and SNc (Cui et al., 2014). This hypothesis is supported by neuroanatomical evidence that D1-MSNs in the direct pathway preferentially form monosynaptic connections with DA neurons in the VTA and SNc (Fujiyama et al., 2011; Watabe-Uchida et al., 2012), but not supported by functional evidence that NAc MSNs preferentially synapse on non-DA neurons in the VTA (Xia et al., 2011). Thus, it is conceivable that a NAc GABA disinhibition mechanism may contribute to opioid reward (Fig. 1).

1.1.3. VP GABA disinhibition hypothesis

As stated above, striatal D2-MSNs mainly project to the globus pallidus (GP) and ventral pallidum (VP). VP GABA neurons receive direct input from NAc D2-MSNs and project to a number of brain regions including the VTA (Floresco et al., 2003). Early studies indicated that approximately half of VP neurons are inhibited by local application of DAMGO (Mitrovic and Napier, 1995). Intra-VP morphine was sufficient to induce motor sensitization, while blockade of VP MORs attenuated morphine-induced motor sensitization (Mickiewicz et al., 2009). A recent electrophysiological study indicated that optogenetic activation of VP GABA terminals in the VTA elicited inhibitory postsynaptic currents (IPSCs) in both DA and non-DA neurons, and these IPSCs were inhibited by the MOR agonist DAMGO (Hjelmstad et al., 2013), suggesting that opioid inhibition of VP GABA neurons may also contribute to disinhibition of VTA DA neurons (Fig. 1).

1.1.4. RMTg GABA disinhibition hypothesis

In addition, recent studies indicate that GABA neurons in the rostromedial tegmental nucleus (RMTg), known as the tail of the VTA (Barrot et al., 2012), send inhibitory projections to VTA DA neurons (Jhou et al., 2009a; Lecca et al., 2012) (Fig. 1). The RMTg is both anatomically and functionally distinct from the VTA as the majority of RMTg neurons are GAD67-positive GABAergic cells (Jhou et al., 2009a; Olson and Nestler, 2007). Functional assays suggest the presence of MOR expression in the cell bodies of RMTg GABA neurons (Jhou et al., 2009a; Wasserman et al., 2016) and their projection terminals in the VTA (Jalabert et al., 2011). A lack of DA neurons in the RMTg is a key feature that distinguishes this region from the VTA and SNc (Jhou et al., 2009a, 2009b; Olson and Nestler, 2007). Electrophysiological recordings show that systemic or local administration of opioids strongly inhibits RMTg GABA neurons that leads to disinhibition of DA neurons in the VTA and SNc (Jalabert et al., 2011; Lecca et al., 2012; Matsui and Williams, 2011). In support of this premise are the studies showing that rats can learn to self-administer opioids into the RMTg more vigorously than into the VTA and intra-RMTg infusions of opioids can lead to the acquisition of CPP (Jhou et al., 2012). Intra-RMTg infusions of morphine can also increase open-field locomotion (Steidl et al., 2017) but reduce intravenous heroin self-administration (Steidl et al., 2015). These findings have been corroborated by a subsequent study showing that chemogenetic excitation of RMTg GABA neurons using the hM3Dq DREADD inhibits systemic morphine-induced locomotion, while chemogenetic inhibition of RMTg GABA neurons via hM4Di DREADD facilitates systemic morphine-induced locomotion (Wasserman et al., 2016). Matsui and colleagues who examined GABAergic inhibitory postsynaptic currents (IPSCs) evoked by selective optical stimulation of afferents originated from the VTA, NAc or RMTg found that the inhibition induced by MOR agonists was pathway dependent (Matsui et al., 2014). Morphine induced ~50 % inhibition of IPSCs evoked by optical stimulation of GABA neurons from the RMTg, ~20 % inhibition from the NAc, and minimal (~10 %) inhibition from the VTA interneurons (Matsui et al., 2014). These findings suggest that opioid-induced disinhibition of DA neurons might be mediated mainly by inhibition of GABA afferents from the RMTg, rather than from NAc or VTA GABA interneurons (Matsui et al., 2014) (Fig. 1). This hypothesis has been further supported by an *in vivo* experiment showing that morphine, when infused locally into the RMTg, increases the firing rate of DA neurons but when infused into the VTA, it fails to alter the firing of DA neurons (Jalabert et al., 2011).

1.1.5. DA-independent mechanism of opioid reward

However, not all evidence supports the DA disinhibition hypothesis. For example, DA-deficient mice (i.e. mice with genetic deletion of tyrosine hydroxylase, the DA synthesis enzyme) can express morphine CPP (Hnasko et al., 2005). Chemical lesions of DA terminals in the NAc with 6-OHDA were shown to produce no effect on heroin self-administration (Dworkin et al., 1988; Gerrits et al., 1994; Pettit et al., 1984). In addition, the non-selective DA antagonists alpha-flupenthixol and haloperidol significantly decrease cocaine, but not heroin, self-administration (Ettenberg et al., 1982; van Ree and Ramsey, 1987), suggesting that cocaine and heroin rewards are mediated by different mechanisms. In addition, morphine can be self-administered directly into the NAc by rats and mice (Amalric and Koob, 1985; David and Cazala, 2000; Olds, 1982) and intra-NAc microinjections of the peripherally limited opioid antagonist methylnaloxonium can block heroin-induced hyperlocomotion in rats (Amalric and Koob, 1985). In contrast, pharmacological blockade or downregulation of NAc dopamine D1 receptors (D1Rs) attenuates cocaine but not heroin self-administration (Gerrits et al., 1994; Pisanu et al., 2015). Thus, the question whether dopaminergic mechanisms alone are responsible for opioid reward is still passionately debated (Badiani et al., 2011; Blum et al., 2015; Nutt et al., 2015).

1.1.6. Opioids activate a subpopulation of VTA DA neurons

To further address this controversy, a more recent study examined VTA DA neuron responses to heroin using c-Fos immunohistochemistry and *in vivo* Ca^{++} imaging (GCaMP6) techniques. Heroin injection activated DA neurons in freely moving, drug naive rats mainly in the medial part of the VTA and increased DA release primarily in the medial shell of the NAc, as assessed by a genetically encoded DA reporter (Corre et al., 2018). Optogenetic activation of VTA DA neurons has been shown to be rewarding, while optogenetic activation of VTA GABA neurons is aversive (Corre et al., 2018; Tan et al., 2012; van Zessen et al., 2012). Chemogenetic inhibition of DA neurons in the

medial part of the VTA blocked intravenous heroin self-administration and systemic administration of heroin also inhibited the rewarding effects produced by optogenetic inhibition of VTA GABA neurons (Corre et al., 2018). These findings suggest that opioids may selectively activate a subpopulation of VTA DA neurons, producing rewarding effects (Corre et al., 2018), which may partially explain the conflicting findings described above. In other words, there is a portion of DA neurons in the VTA that are highly sensitive to heroin, while DA neurons in other parts of the VTA are not. Nevertheless, these new findings provide convincing evidence that DA is at least partially involved in the rewarding effects of opioids and other non-DA mechanisms remain to be determined.

1.2. D3Rs as promising therapeutic targets for OUD

Identification of the role of DA in opioid reward processes clearly points towards DA receptors as potential targets for the treatment of OUD. DA receptors belong to the G protein-coupled receptor (GPCR) superfamily and are divided into D1-like (D1 and D5) and D2-like (D2R, D3R, D4R) receptors. Since D4 and D5 receptor densities are very low in the mesolimbic DA system (Meador-Woodruff et al., 1992; O'Malley et al., 1992), current attention in drug development toward substance use disorders has largely been focused on the D1R, D2R, and D3Rs (Cho et al., 2010; Galaj et al., 2018; Heidbreder, 2005). Among the three DA receptors, of particular interest are D3Rs.

First, D3Rs have a unique anatomic distribution as they are preferentially localized in the mesolimbic DA system, including the NAc, islands of Calleja, and olfactory tubercle (Bouthenet et al., 1991; Diaz et al., 1994; Levesque et al., 1992). In addition, a modest density of D3Rs is also expressed in the basolateral nucleus of the amygdala and hippocampus, the regions that regulate motivational behaviors and relapse to drug seeking (Basile et al., 2006; Di Ciano, 2008). In contrast, D1Rs and D2Rs feature a broader distribution and higher concentrations in the brain (Dearry et al., 1990; Weiner et al., 1991) and alteration of these receptors is often associated with unwanted side-effects such as extrapyramidal movement disorders, cognition dysfunction, dysphoria, prolactin secretion, and catalepsy (Cho et al., 2010; Millan et al., 1995). Thus, the relatively focal expression of D3Rs in the mesolimbic system makes the D3Rs a promising therapeutic target for substance use disorders.

Second, D3Rs have the highest affinity for endogenous DA of all known receptors (Levant, 1997; Levesque et al., 1992; Sokoloff et al., 2001), suggesting their prominent role in the normal functioning of the mesolimbic DA system. Third, it is well documented that drugs of abuse may up-regulate D3Rs in the mesolimbic DA system. A series of studies have shown that chronic exposure to cocaine and cocaine overdoses are associated with increased D3R expression in the striatum of human victims and experimental animals (Boileau et al., 2012; Le Foll et al., 2002; Mash and Staley, 1999; Neisewander et al., 2004; Segal et al., 1997; Staley and Mash, 1996). In addition, other psychostimulants, like nicotine, can induce behavioral sensitization and significantly increase D3R binding and mRNA levels in the NAc shell (Le Foll et al., 2003). Furthermore, repeated administration of morphine was shown to produce significant increases in D3R mRNA in the caudate–putamen and ventral midbrain, including the SNc and VTA with a significant decrease in D2R mRNA in the caudate–putamen (Spangler et al., 2003). This selective upregulation of D3R expression following repeated drug exposures suggests an important role for D3Rs in the development of addiction.

The role of D3Rs in opioid related-behaviors has also been extensively studied with transgenic D3-KO mice. Genetic deletion of D3Rs in D3-KO mice attenuates opioid action, including opioid reward. We have recently reported that D3-KO mice, in contrast to wild type mice, display a higher rate of heroin (and cocaine) self-administration, greater motivation for drug, and a higher level of drug-seeking during extinction and a reinstatement test (Boateng et al., 2015; Song et al., 2012; Zhan et al., 2018). We also demonstrated that the elevated drug intake by D3-KO mice was accompanied by decreased DA response to heroin or cocaine in the NAc, suggesting that the observed increase in drug self-administration might indicate compensatory responses due to reduced opioid or cocaine reward (Song et al., 2012; Zhan et al., 2018). This is consistent with the findings that D3-KO mice also displayed attenuated locomotor response to acute cocaine or heroin (Song et al., 2012; Zhan et al., 2018) and blockade of the development of locomotor sensitization to intermittent morphine administration (Li et al., 2010; Lv et al., 2019; Narita et al., 2003). Deletion of D3Rs also attenuated morphine-induced tolerance in analgesia and withdrawal symptoms (Li et al., 2012). In contrast to the above, it was also reported that genetic deletion of D3Rs enhances opioid-induced CPP and locomotor activity (Frances et al., 2004a; Narita et al., 2003). These data suggest that D3Rs play an important role in opioid reward, analgesia and opioid withdrawal.

Finally, inspired by the essential role of DA in psychostimulant reward, D3Rs have been extensively studied as potential therapeutic targets for psychostimulant abuse and addiction. In support of this notion are the findings that D3R antagonists or partial agonists can reduce motivation to psychostimulant seeking in multiple animal models of relapse (Chen et al., 2014; Galaj et al., 2014; Gilbert et al., 2005, 2005; Higley et al., 2011, 2011; Peng et al., 2009, 2009; Song et al., 2014; Xi et al., 2006, 2004). In addition, under a progressive ratio (PR) schedule of reinforcement, during which work demands for drug self-administration are progressively increased, treatment with D3R antagonists reduce break points (BPs) for cocaine self-administration (Heidbreder, 2005; Keck et al., 2015, 2014; Le Foll et al., 2014; Newman et al., 2012; Sokoloff and Le Foll, 2017), suggesting a reduction in motivation for drug or drug reward. These findings have been corroborated by reports that D3R antagonists can reduce cocaine- or methamphetamine-enhanced brain stimulation reward (Pak et al., 2006; Song et al., 2014; Vorel et al., 2002; Xi et al., 2006, 2005) and block cocaine- or methamphetamine-induced CPP (Aujla and Beninger, 2005; Galaj et al., 2014; Hachimine et al., 2014; Song et al., 2013; Vorel et al., 2002). Indisputably, D3R antagonists are highly promising candidates in translational medication development for the treatment of psychostimulant use disorders [for reviews see (Heidbreder, 2005; Heidbreder and Newman, 2010; Keck et al., 2015, 2014; Le Foll et al., 2014; Le Foll and Di Ciano, 2015; Newman et al., 2012; Sokoloff and Le Foll, 2017)] and may be therapeutically beneficial for preventing and/or treating OUD.

2. Progress in preclinical research

Despite a plethora of evidence supporting an important role of D3Rs in drug reward and addiction, the therapeutic potential of D3R-based compounds *in the treatment of OUD* has been largely ignored until recently. Based on the above rationale for developing D3R-based pharmacotherapies for treatment of substance use disorders, D3R antagonists or partial agonists might be equally or possibly more effective in reducing opioid reward and relapse.

2.1. Older generation D3R antagonists and partial agonists

2.1.1. BP897

BP897 is a potent D3R partial agonist with ~70-fold selectivity for D3R (K_i = 0.92 nM) over D2Rs (K_i = 61 nM) and other receptors such as 5-HT1A receptors (K_i = 84 nM), adrenergic alpha1 (K_i = 60 nM), and alpha2 adrenoreceptors (K_i = 83 nM) (Pilla et al., 1999) (Fig. 2; Table 1). The pharmacological action of BP897 on cocaine reward and relapse has been studied exclusively in experimental animals (see reviews by (Heidbreder, 2005; Heidbreder and Newman, 2010; Keck et al., 2014; Xi and Gardner, 2008). A few studies also evaluated the potential utility of BP897 on OUD. When administered prior to morphine CPP conditioning sessions, BP897 enhanced the acquisition, but when administered prior to the CPP expression test, it reduced

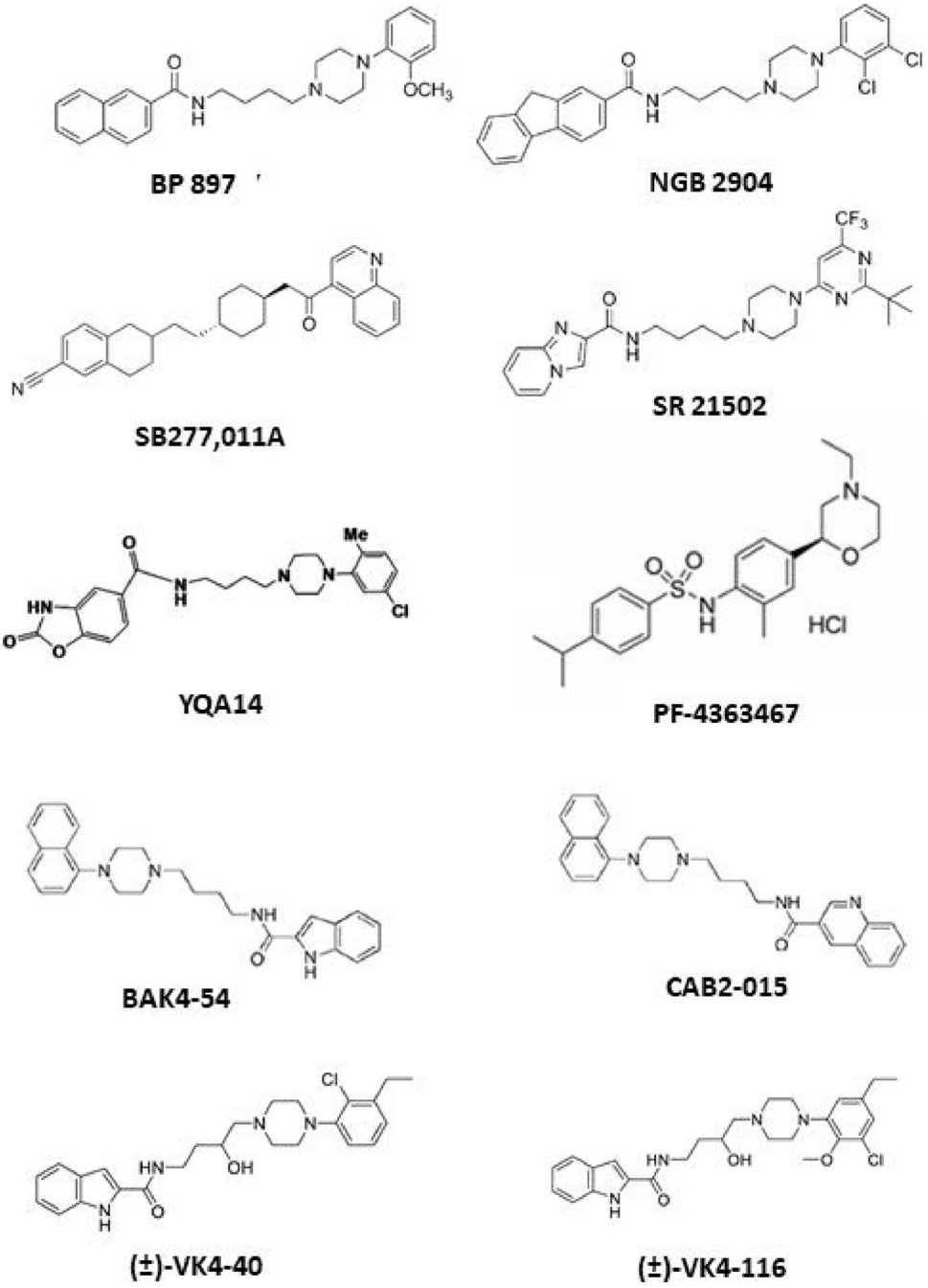

Fig. 2. Chemical structures of D3R antagonists or partial agonists tested in animal models of opioid abuse and addiction.

morphine CPP in WT mice, but not in D3-KO mice (Frances et al., 2004a, 2004b), suggesting D3R-mediated effects. In addition, BP897 reduced morphine cue-induced c-fos activation in the somatosensory cortex of WT, but not D3-KO mice (Frances et al., 2004a). In contrast, BP897 did not alter morphine-induced analgesia (Frances et al., 2004b), something that the next generation of D3R ligands would soon be capable of doing.

Initial enthusiasm for BP897 soon diminished as additional findings that BP897 also behaves as a potent antagonist at D2Rs (pK_b = 8.05) (Wicke and Garcia-Ladona, 2001; Wood et al., 2000). Indeed, BP897 was reported to produce aversive side-effects, as assessed in brain-stimulation reward and conditioned place aversion (CPA) paradigms (Duarte et al., 2003; Gyertyan and Gal, 2003) that may be directly related to D2R blockade. Further, at high doses, BP897 induced catalepsy in rats, ptosis and lethargy in monkeys and potentiated the hypothermic effect of R(+)7-OH-DPAT (D2/3R agonist), also most likely through its action at D2R (Beardsley et al., 2001; Garcia-Ladona and Cox, 2003; Pilla et al., 1999).

2.1.2. NGB 2904

As more challenges with BP897 transpired, scientific interest shifted to another D3R antagonist, NGB 2904 (Fig. 2). NGB 2904 was first reported in 1998 and described as a selective D3R antagonist (K_i = 0.90 nM), displaying 150-fold selectivity for primate D3Rs (K_i = 1.4 nM) over D2Rs (K_i = 217 nM) (Yuan et al., 1998) and 800-fold selectivity for rat D3Rs (K_i = 1.1 nM) over D2Rs (K_i = 911 nM) (Table 1) (Newman et al., 2003). In regard to its pharmacokinetics, NGB 2904 showed a moderate distribution and high blood clearance (74 % of rat liver blood flow) after a single intravenous injection at a dose of 0.5 mg/kg. NGB 2904 was able to penetrate the rat blood brain barrier with

Table 1
In vitro receptor binding affinities and selectivity of D3R ligands on D3Rs over D2Rs.

Compound	hD2R (Ki, nM)	hD3R (Ki, nM)	D2/D3 Ratio	Reference
BP897	61	0.92	70	Pilla et al. (1999)
NGB 2904	217	1.4	150	Yuan et al. (1998)
SB-277011A	2820	10.7	263	Newman et al. (2005)
SR 21502	511	4.2	120	Ananthan et al. (2014)
YQA14	335.3	2.11	159	Song et al. (2011)
PF-4363467	3.1	692	223	Wager et al. (2017)
BAK4-54	12.9	0.12	109	Boateng et al. (2015)
CAB2-015	15.8	0.35	45	Boateng et al. (2015)
(±)-VK4-116	11,400	6.8	1700	Kumar et al. (2016)
R-VK4-116	10,800	7.4	1735	Shaik et al. (2019)
(±)-VK4-40	151	0.36	417	Kumar et al. (2016)
R-VK4-40	219	0.89	247	Shaik et al. (2019)

a steady state brain/ plasma ratio of 1:1.7, reaching the absolute level of 62 ng/g (Xi and Gardner, 2007). In animal models of addiction, NGB 2904 was shown to reduce the rewarding effects of psychostimulants and to inhibit cue-induced drug seeking (Gilbert et al., 2005; Spiller et al., 2008; Xi et al., 2006). Also, NGB 2904 itself demonstrated low abuse liability as when substituted for cocaine, it was not able to maintain self-administration in rats nor did it alter electrical brain-stimulation reward (BSR) on its own (Xi et al., 2006).

Interestingly, pretreatment with NGB 2904 produced a modest, but not significant, reduction in heroin-enhanced BSR (Xi and Gardner, 2007). NGB 2904 was also tested in a heroin relapse paradigm (Table 2). In rats with a history of heroin self-administration that underwent 48-h food deprivation prior to a reinstatement test, NGB 2904 caused a significant reduction in heroin seeking (Tobin et al., 2009). However, NGB 2904 had no effect on cue-induced reinstatement of heroin seeking (Tobin et al., 2009), suggesting a limited therapeutic potential for OUD. To our knowledge, NGB 2904 has not been tested in opioid self-administration or CPP paradigms that would allow further evaluation of its potential utility in the treatment of OUD.

Further, newer generation analogues of NGB2904, including PG01037 (Newman et al., 2005) have provided important tools toward D3R-based medication development and have shown promising results in animal models of psychostimulant abuse and addiction (Heidbreder and Newman, 2010). However, to date, their efficacy against opioid-related behaviors was unknown until recently (see Sections 2.2.2 and 2.2.3).

2.1.3. SB277,011A

Among the originally reported D3R antagonists, SB277,011A has been the most extensively studied. SB277,011A is a highly selective and potent D3R antagonist with 120- and 80-fold selectivity for D3Rs over D2Rs in human (K_i = 10.7 nM for D3R; K_i = 2820 for D2R) and rat (K_i = 11.2 nM for D3R; K_i = 1050 for D2R), respectively (Reavill et al., 2000) (Fig. 2, Table 1). In regards to its pharmacokinetics, central nervous system (CNS) penetration studies showed that SB277,011A readily entered the brain, with a steady-state brain/plasma ratio of 3.6:1 (as compared to 1:1.7 for NGB 2904) reaching an absolute brain level of 147.3 ng/g (in contrast to 62 ng/g for NGB 2904) (Reavill et al., 2000). The literature provides compelling evidence that SB277,011A can attenuate the rewarding effects of cocaine, nicotine and methamphetamine, reduce break-points in responding for psychostimulants and

Table 2
In vivo behavioral effects of several D3R antagonists or partial agonists in animal models of opioid abuse and addiction.

D3R Ligand	Major behavioral findings	References
BP 897	↓ Morphine-induced CPP (acquisition, expression) No effect on opioid analgesia	Frances et al. (2004a)
NGB 2904	No effect on heroin-enhanced eICSS ↓ Stress-induced reinstatement of heroin-seeking No effect on heroin-primed reinstatement	Xi and Gardner (2007); Tobin et al. (2009)
SB277,011A	↓ Heroin-induced CPP (acquisition, expression) ↓ Heroin self-administration	Boateng et al. (2015); Ashby et al. (2003)
YQA14	↓ Morphine-induced CPP (expression, reinstatement) No effect on the acquisition of morphine CPP ↓ Morphine-induced sensitization	Lv et al. (2019); Hu et al. (2013)
SR 21502	↓ Heroin-induced CPP (expression) ↓ Cue-induced reinstatement ↓ Opioid tolerance and withdrawal	Galaj et al. (2015) Eon et al. (2015)
PF-4363467	↓ fentanyl self-administration ↓ cue/drug-induced reinstatement ↑ Oxycodone analgesia	Wager et al. (2017)
BAK4-54	↓ Oxycodone-induced hyperactivity ↓ Heroin or oxycodone self-administration ↓ Extinction response ↓ Oxycodone-primed reinstatement	You et al. (2017); Boateng et al. (2015)
CAB2-015	↓ Oxycodone-induced hyperactivity ↓ Heroin or oxycodone self-administration ↓ Extinction response ↓ Oxycodone-primed reinstatement	You et al. (2017)
(±)-VK4-116	↓ Oxycodone-induced hyperactivity ↓ Oxycodone-induced CPP ↓ Heroin or oxycodone self-administration (FR2, PR) ↓ Extinction response ↓ Oxycodone-primed reinstatement ↓ Oxycodone withdrawal-induced CPA ↑ Oxycodone analgesia ↓ Withdrawal-induced hyperalgesia and irritability	You et al. (2018); Kumar et al. (2016); de Guglielmo et al. (2020)
R-VK4-40	↓ Brain-stimulation reward by stimulation of VTA DA neurons ↓ Oxycodone self-administration (FR2, PR) ↑ Oxycodone analgesia	Jordan et al. (2019b)

reinstatement of drug-seeking [see reviews by (Heidbreder, 2005; Heidbreder and Newman, 2010; Keck et al., 2014; Xi and Gardner, 2008)].

Notably, SB277,011A has also been evaluated in animal models of opioid addiction (Table 2). Four days of heroin *vs*. saline conditioning produced significant heroin CPP in rats while pretreatment with SB277,011A prior to each heroin injection reduced the acquisition of CPP (Ashby et al., 2003). When administered prior to a CPP test, SB277,011A reduced the expression of heroin CPP (Ashby et al., 2003), suggesting that it can reduce the rewarding effects of heroin and heroin cues. These findings are in line with reports that SB277,011A can reduce responding for heroin self-administration in WT mice, but not in D3-KO mice (Boateng et al., 2015) (referred as Compound 2 in this report), further suggesting its effects are mediated by D3Rs.

However, the initial enthusiasm for this D3R antagonist quickly diminished due to its high clearance in primate and human liver homogenates (CLi = 7.4 and 27 ml/min/g liver tissue, respectively), poor oral bioavailability (about 35 % in rats and 2 % in primates), and very short half-life (half-life of 2 h in rats and < 20 min in primates) (Austin et al., 2001; Reavill et al., 2000; Stemp et al., 2000). In addition, SB277,011A and a newer generation D3R antagonist (GSK598,809) were reported to increase blood pressure, particularly when combined with cocaine (Appel et al., 2015; Jordan et al., 2019c), making them less desirable candidates for the treatment of cocaine and opioid use disorders.

2.1.4. YQA14

YQA14 is a highly selective D3R antagonist that was reported to bind to two binding sites on the D3R, $K_{i\text{-}High}$ (0.68×10^{-4} nM) and $K_{i\text{-}Low}$ (2.11 nM), and at the respective binding sites it shows approximately 5,000,000-fold and 150-fold selectivity for D3R over D2R (Song et al., 2011). Moreover, *in vivo* pharmacokinetic assays suggest that YQA14 has improved oral bioavailability (> 40 %) and a longer half-life (> 2 h in humans) as compared to SB277,011A (approximately 20 min) (Hu et al., 2013). When tested in behavioral paradigms, YQA14 has been shown to inhibit morphine-induced behavioral sensitization in WT mice but not D3 KO mice (Lv et al., 2019). In addition, YQA14 was effective in blocking the expression and drug-primed reinstatement of morphine CPP but not the acquisition of CPP (Hu et al., 2013). YQA14 has not been tested in intravenous opioid self-administration paradigms.

2.1.5. SR 21502

From efforts focusing on the acylaminobutylarylpiperazine class of D3R ligands, SR 21502 (Fig. 1) was identified as a ligand with high affinity for D3Rs (K_i = 4.2 ± 0.6 nM) and > 120-fold binding selectivity over D2Rs (K_i = 511 ± 66 nM) (Fig. 2, Table 1). In functional activity assays using forskolin-stimulated cAMP accumulation and agonist-stimulated mitogenesis assays, this compound was characterized as an antagonist/weak partial agonist at the D3R and an antagonist at the D2R (Ananthan et al., 2014). In animal models, SR 21502 was shown to be effective in reducing the rewarding effects of cocaine, motivation for cocaine seeking and cue-induced relapse in rodents [see review by (Galaj et al., 2018)].

The therapeutic potential of SR 21502 seemingly expands to opioid-related behaviors (Table 2). Ranaldi and colleagues demonstrated that SR 21502 also dose-dependently reduced the expression of heroin CPP and attenuated cue-induced reinstatement of opioid-seeking behavior in animals with a history of heroin self-administration (Galaj et al., 2015). When co-administered with morphine, SR 21502 reduced morphine-induced analgesia tolerance as evidenced by a reduction in the rightward shift of the dose-response function (Eon et al., 2015). In an assessment of opioid dependence using naloxone-induced withdrawal, mice with a history of SR 21502 and morphine co-treatment exhibited less withdrawal symptoms than mice given a standard morphine treatment, suggesting that SR 21502 might diminish opioid tolerance and physical dependence (Eon et al., 2015).

It is noteworthy that none of the older generation compounds were tested for their effects on opioid induced anti-nociception. A key characteristic that the newer generation D3R ligands display is to either have no effect on analgesia or enhance the analgesic effects of sub-optimal doses of oxycodone (see Section 2.2.4 and 2.2.5)

2.2. Newer generation D3R antagonists and partial agonists

An enormous challenge is to develop D3R antagonists or partial agonists with a high degree of selectivity for D3Rs over D2Rs and improved bioavailability and pharmacokinetics profiles (Heidbreder, 2008; Heidbreder and Newman, 2010; Keck et al., 2014; Newman et al., 2012). High selectivity would make it possible to minimize D2R-mediated extrapyramidal symptoms and more precisely target D3Rs within the mesolimbic system that is largely implicated in addiction. Improved bioavailability and pharmacokinetics profiles would open the door to translational studies for their potential utility in the treatment substance abuse in humans.

2.2.1. PF-4363467

PF-4363467 developed by Pfizer, Inc. was characterized as a dual D3/D2R antagonist with high affinity for the D3R (D3R K_i = 3.1 nM) and good selectivity over D2R (D2R K_i = 692 nM) (Fig. 2) (Wager et al., 2017). It exhibits excellent brain penetration in rats, with equivalent free drug levels in plasma and brain compartments (Wager et al., 2017). In animal models of drug addiction, PF-4363467 reduced fentanyl self-administration and robustly attenuated drug/cue-induced reinstatement of fentanyl seeking in rats without producing extrapyramidal symptoms, despite high D2R occupancy (85.9 % at 32 mg/kg dose) (Wager et al., 2017), suggesting that it deserves further studies as a potential pharmacotherapy for the treatment of OUD.

2.2.2. BAK4-54

BAK4-54 [(described as Compound 16 in.(Boateng et al., 2015) (Fig. 2) is a newer generation D3R ligand with a dual functional profile. At low doses it was identified as a D3R antagonist (IC_{50} = 8.0 nM) and at higher doses a partial D3R agonist (25 % stimulation, EC_{50} = 140 nM; Table 1) (Boateng et al., 2015). In a radioligand binding assay, BAK4−54 showed high affinity for D3Rs (K_i = 0.12 nM) with 100-fold selectivity for D3Rs over D2Rs (K_i = 12.9 nM). In a metabolic stability assay with mouse liver microsomes fortified with nicotinamide adenine dinucleotide phosphate (NADPH), BAK4-54 showed improved metabolic stability, as compared to earlier generation D3R antagonists, remaining at 37 % level in the plasma 1 h after incubation and with half-life time $t_{½}$ = 67.5 min (Boateng et al., 2015).

Given its improved pharmacokinetic profile, the therapeutic utility of BAK4-54 has been explored in animal models of OUD (Table 2). BAK4-54 has been shown to be effective in reducing heroin and oxycodone self-administration under a FR1 schedule of reinforcement (Boateng et al., 2015; You et al., 2017). BAK4-54 attenuated heroin self-administration in WT mice, but not in D3R KO mice, suggesting D3R-mediated effects (Boateng et al., 2015). In addition, repeated administration of BAK4-54 facilitated extinction of oxycodone seeking and its acute administration reduced drug-primed reinstatement of oxycodone seeking in rats (You et al., 2017). BAK4-54, at higher doses, also reduced oxycodone-induced increases in locomotion without affecting spontaneous locomotor activity or sucrose self-administration, suggesting that its attenuating effects are opioid-specific (You et al., 2017). These findings are in line with previous reports that other D3R antagonists can reduce opioid-related behaviors (Ashby et al., 2003; Frances et al., 2004a; Galaj et al., 2015; Tobin et al., 2009).

2.2.3. CAB2-015

Concurrent with the development of BAK4-54 (Fig.1; Table 1), CAB2-015 [described as Compound 32 in(Boateng et al., 2015)] was

reported to behave as a D3R antagonist (IC_{50} = 7.4 nM) and a partial D3R agonist at higher doses (31 % stimulation, EC_{50} = 20 nM). In a radioligand binding assay, CAB2-015 showed high affinity for D3Rs (K_i = 0.35 nM) and D2Rs (K_i = 15.8 nM) but lower selectivity (45-fold) for D3Rs over D2Rs (Boateng et al., 2015). CAB2-015 also displayed high affinity for the 5-HT receptor subtypes (K_i = 2.46 nM for 5-HT_{1A}, 0.33 nM for 5-HT_{2A}, 3.80 nM for 5-HT_{2C}) and behaved as a potent 5-HT_{1A} agonist (Boateng et al., 2015). When tested for phase 1 metabolic stability after oral administration, in mouse liver microsomes fortified with NADPH, CAB2-015 showed better metabolic stability than older generation D3R antagonists or its analogue, BAK4-54, remaining at 54 % level in the plasma over 1 h with half-life time $t_{½}$=41.8 min (Boateng et al., 2015).

CAB2-015 was also effective in reducing drug self-administration maintained by multiple doses of oxycodone in rats, shifting the dose-response curve downward (Table 2) (You et al., 2017). In a mouse drug self-administration paradigm, CAB2-015 reduced heroin intake in WT mice and at high doses also in D3-KO mice, suggesting its attenuating effects on heroin self-administration are mediated by both D3Rs and non-D3Rs, presumably D2Rs and 5-HT receptors to which CAB2-015 show high binding affinities (Boateng et al., 2015). In addition, CAB2-015 displayed the ability to facilitate abstinence from oxycodone, as assessed by reductions in lever pressing during extinction (You et al., 2017). In an animal model of relapse, CAB2-015 attenuated reinstatement of oxycodone seeking induced by drug priming, suggesting its therapeutic utility in relapse prevention (You et al., 2017). In addition, CAB2-015 also reduced sucrose self-administration, demonstrating a propensity to decrease other rewarding substances, in contrast to BAK4-54.

2.2.4. (±)VK4-116 and its R-enantiomer

More recent efforts have used the D3R crystal structure in drug design (Chien et al., 2010; Keck et al., 2014). Improvement in D3R selectivity and drug-like properties came to fruition with the development of (±)VK4-116 (Fig. 2). Described as Compound 19 in.(Kumar et al., 2016), (±)VK4-116 is characterized as a highly selective D3R antagonist with 1700-fold binding selectivity for D3Rs (K_i = 6.84 nM) over D2Rs (K_i = 11400) (Table 1), showing moderate affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors (Kumar et al., 2016). Of note, (±) VK4-116 does not bind to mu, kappa or delta opioid receptors at a concentration of 10 μM (Kumar et al., 2016). In the quinpirole-stimulated mitogenesis assay with CHO cells transfected with human D3Rs, (±)VK4-116 behaved as an antagonist with an IC_{50} = 360 nM (Kumar et al., 2016). When tested for phase 1 metabolism in a mouse liver microsomes assay fortified with NADPH, (±)VK4-116 showed very high metabolic stability after oral administration with > 80 % remaining in the plasma over 1 h (Kumar et al., 2016). These findings have been corroborated by further metabolic analyses using rat, rhesus monkey and human liver microsomes (You et al., 2018). In all three species, (±)VK4-116 showed high stability, with the highest metabolic stability in rat (> 85 % remaining at 1 h) and long half-life ($t_{1/2}$ =250, 116 and 102 min in rat, human and monkey, respectively), suggesting that (±)VK4-116 is a novel D3R antagonist with excellent brain penetration and a stable metabolic profile. These findings are especially exciting given that D3R antagonists have been notorious for their metabolic instability and poor pharmacokinetics hence, hindering their efficacy and translational potential (Keck et al., 2015).

Emerging evidence suggests that (±)VK4-116 can attenuate opioid-induced behavioral effects (Table 2). Mice repeatedly treated with oxycodone showed increased locomotor activity over time, suggesting oxycodone behavioral sensitization. Pretreatment with (±) VK4-116 reduced the acute effects of oxycodone and blocked the development of oxycodone sensitization in mice (Kumar et al., 2016). In addition, when co-administered with oxycodone prior to each oxycodone conditioning session, (±)VK4-116 dose-dependently reduced the acquisition of oxycodone-induced CPP in rats, suggesting potential preventive utility for OUD (Kumar et al., 2016). (±)VK4-116 has been also tested in intravenous opioid self-administration paradigms where pretreatment with (±)VK4-116 during the first 5 days of oxycodone self-administration attenuated the acquisition of self-administration in rats (You et al., 2018). In rats well-trained to self-administer oxycodone under a FR2 schedule of reinforcement, (±)VK4-116 reduced drug self-administration maintained by different doses of oxycodone, also suggesting therapeutic utility for OUD (You et al., 2018). In addition, treatment with (±)VK4-116 decreased the escalation of oxycodone self-administration in male and female rats with extended access to drug (de Guglielmo et al., 2020). Further evaluation of (±)VK4-116 indicated that it can reduce break-points for oxycodone under a PR schedule of reinforcement, facilitate extinction of drug seeking and reduce drug-primed reinstatement of oxycodone seeking in rats, suggesting its ability to diminish motivation for oxycodone, cravings and relapse (You et al., 2018). Given that (±)VK4-116 produces no effects on inactive lever pressing or sucrose self-administration, it was suggested that is safe, does not alter non-drug reinforcement, nor does it produce motoric impairment (You et al., 2018). Further, in an assessment of opioid dependence using naloxone-induced withdrawal, pretreatment with (±)VK4-116 dose-dependently reduced naloxone-precipitated conditioned place aversion in rats (You et al., 2018) and withdrawal-induced hyperalgesia and irritability-like behaviors (de Guglielmo et al., 2020), suggesting that (±)VK4-116 has the ability to attenuate opioid withdrawal symptoms.

Opioids are often prescribed as the first line of analgesics for the treatment of severe or chronic pain, but their long-term effectiveness is limited due to the development of tolerance, opioid-induced hyperalgesia and abuse liability (DuPen et al., 2007; Joseph et al., 2010). Therefore, alternative anti-nociceptive treatments are of particular interest. Interestingly, (±)VK4-116 has been recently shown to potentiate the analgesic effects of oxycodone, as assessed in a hot plate assay (You et al., 2018). Rats pretreated with (±)VK4-116 prior to oxycodone treatment displayed longer latencies in response to thermal pain compared to oxycodone alone treatment. This unique characteristic of (±)VK4-116 may be advantageous in pain management therapy as it suggests that lower doses of prescription opioids could be used to mitigate pain when combined with (±)VK4-116, and thus reduce the risk of abuse and the development of dependence.

As (±)VK4-116 has a chiral center in its linking chain, it was important for us to separate the enantiomers and further assess their pharmacological properties since R- and S-enantiomers may have different receptor binding properties and pharmacokinetic profiles. The synthesis of enantiomers was recently achieved and both R- and S-VK4-116 were evaluated for their *in vitro* profiles (Shaik et al., 2019). Additional development of of the eutomer, R-VK4-116 is underway.

It is well known that D3Rs are also expressed in renal arteries in the kidney, which regulates blood pressure. Blockade of peripheral D3Rs may cause sodium retention and, consequently, hypertension by antagonizing the inhibitory effects of DA on sodium transport (Zeng et al., 2008, 2004). Such effects are observed in mice with genetic deletion of D3R alleles that developed elevated systolic blood pressure and diastolic hypertension (Jose et al., 1997). These adverse effects of D3R antagonists would be problematic in people who suffer from substance use disorders given the cardiovascular consequences of cocaine abuse (Goldstein et al., 2009; Zimmerman, 2012) and renal injury observed in some alcohol and drug users (Bundy et al., 2018; Crowe et al., 2000). In addition, people who abuse opioids often use cocaine and other drugs of abuse. Therefore, the combination of heroin, cocaine and some D3R antagonists might be of particular concern. As described above, the D3R antagonists SB277011A and GSK598,809 were reported to increase blood pressure in dogs and rats, especially in the presence of cocaine (Appel et al., 2015; Jordan et al., 2019c). In contrast to these findings, we have recently reported that the both enantiomers of VK4-116 and a close analogue, VK4-40 (Shaik et al., 2019) do not exhibit adverse cardiovascular effects (Jordan et al., 2019c). In particular, rats

implanted with telemetric devices and treated with cocaine or oxycodone showed increases in blood pressure, heart rate, body temperature and locomotor activity (Jordan et al., 2019c). R-VK4-116 reduced body temperature when administered alone. Pretreatment with R-VK4-116 also reduced oxycodone-induced increases in body temperature and blood pressure. Similarly, cocaine-induced increases in blood pressure and heart rate were attenuated by R-VK4-116 (Jordan et al., 2019c). The reasons for why R-VK4-116 does not share the cardiovascular effects of previously evaluated D3R antagonists are unknown at present, but it has been suggested that differences in cardiovascular parameters might be related to differences in greater selectivity for D3Rs over other receptors (e.g. D1, D2 or 5-HT receptors) that also play a role in cardiovascular tone (Alves et al., 2019; Cuevas et al., 2013; Goldberg, 1984; Thomas et al., 2013; Zeng et al., 2004). Nevertheless, these unique characteristics make R-VK4-116 an attractive lead candidate in translational medicine for opioid, and perhaps psychostimulant, use disorders. In fact, based on compelling preclinical findings suggesting the therapeutic utility of R-VK4-116, the National Center for Advancing Translational Sciences (NCATS) has begun Investigational New Drug (IND) development of this compound for the prevention and treatment of OUD under the NIH Helping to End Addiction Long-term Initiative (HEAL).

2.2.5. (±)VK4-40 and its R-enantiomer

(±)VK4-40 [described as compound 23 in.(Kumar et al., 2016) (Table 1)] is a close analogue of (±)VK4-116 that was identified as a D3R partial agonist with high affinity for D3Rs (K_i = 0.36 nM) over D2Rs (K_i = 151 nM) but lower selectivity (417-fold) for D3Rs over D2Rs relative to (±)VK4-116 (Kumar et al., 2016). As with (±)VK4-116, (±)VK4-40 has a chiral center in its linking chain, which has been resolved (Shaik et al., 2019). R-VK4-40 was determined to be a D3R antagonist, whereas the S-enantiomer was a partial agonist with high affinity for D3Rs (K_i = 0.89 nM) vs. D2Rs (K_i = 219 nM) and 247-fold D3R selectivity (Shaik et al., 2019). Indeed, different efficacies between enantiomers have been reported before for PG648, another high affinity D3R antagonist that was developed for psychostimulant use disorders (Keck et al., 2015; Newman et al., 2009) but has not been evaluated in animal models of OUD.

Based on a Phase 1 metabolic assay with rat liver microsomes, R-VK4-40 was determined to be metabolically stable in the presence of NADPH with 86 % remaining level in the plasma over 1 h (Jordan et al., 2019b). R-VK4-40 also showed excellent brain penetration. After oral administration at the dose of 10 mg/kg, R-VK4-40 achieved a maximum concentration in brain 2 h post-administration (Jordan et al., 2019b).

When evaluated in animal models of OUD (Table 2), R-VK4-40 dose-dependently inhibited oxycodone self-administration maintained under FR1 and PR schedules of reinforcement in rats (Jordan et al., 2019b). Jordan and colleagues also evaluated the effects of R-VK4-40 on optogenetic intracranial self-stimulation (aka oICSS) maintained by optical activation of VTA DA neurons in the presence or absence of oxycodone. Transgenic DAT-cre mice were injected with Cre-dependent light-sensitive channelrhodopsin (ChR2) virus that was expressed into VTA DA neurons under the DA transporter promoter. DAT-cre mice were then trained to press the lever for oICSS. Optogenetic activation of VTA DA neurons produced robust oICSS responding that was attenuated by R-VK4-40 treatment in a dose-dependent manner, suggesting that the rewarding effects of oICSS are mediated at least in part by D3Rs. While low doses of oxycodone enhanced and high doses of oxycodone reduced oICSS, pretreatment with R-VK4-40 blocked oxycodone-enhanced oICSS (Jordan et al., 2019b), suggesting that R-VK4-40 can reduce the rewarding effects of oxycodone.

Notably, during a hot plate assay, R-VK4-40 did not compromise the analgesic effects of oxycodone and in fact, it increased latencies to emission of thermal nociceptive response, shifting the oxycodone-dose response curve upward (Jordan et al., 2019b), suggesting an additive analgesic effect to oxycodone. Interestingly, R-VK4-40 alone produced similar analgesic effects as those produced by oxycodone without affecting locomotor activity or performance on the rotarod test (Jordan et al., 2019b). These findings suggest that R-VK4-40 exhibits similar anti-nociceptive characteristics to those of R-VK4-116. Although specific mechanisms underlying R-VK4-40-induced analgesic effects are yet to be determined, it is noteworthy that D3-KO mice also show abnormal responses to thermal pain stimulation (hyperalgesia or hypoalgesia), as assessed in hot plate and tail flick assays (Brewer et al., 2014; Li et al., 2012; Zhu et al., 2010).

The spinal cord, specifically the dorsal horn, is the first CNS site processing nociceptive information where D3Rs and MORs are expressed (Abbadie et al., 2002; Levant and McCarson, 2001; Ray and Wadhwa, 2004). While MORs modulate pain-related information (Goff et al., 1998; Millan et al., 1988), DA seems to mediate pain-associated responses (Clemens and Hochman, 2004; Garraway and Hochman, 2001; Keeler et al., 2012) and D3Rs in the dorsal horn seem to modulate the MOR system (Brewer et al., 2014). It is conceivable that the MOR-D3R interaction takes place in the dorsal horn during pain processing and D3R antagonists likely potentiate the analgesic effect of MOR-based opioids through this mechanism. Clearly, more research is needed to further address mechanistic underpinnings of D3R effects on analgesia. Nevertheless, given that R-VK4-40 may augment the analgesic effects of the commonly prescribed analgesic oxycodone, these exciting findings unlock clinical possibilities in the realm of pain management, offering the options of prescribing opioids at lower doses and potentially mitigating the risks of opioid-induced tolerance, respiratory depression and addiction.

Importantly, similarly to R-VK4-116, R-VK4-40 has been reported to lack the adverse cardiovascular effects that are common among other D3R antagonists (Jordan et al., 2019c). A recent telemetry study reported that R-VK4-40 alone reduced blood pressure and heart rate in rats. Pretreatment with R-VK4-40 attenuated oxycodone-induced increases in blood pressure and oxycodone or cocaine-induced increases in heart rate and body temperature (Jordan et al., 2019c). It is unclear how R-VK4-40 and R-VK4-116 reduce cardiovascular parameters in oxycodone or cocaine-exposed rats. However, it is conceivable that these effects are mediated by D3Rs or 5-HT receptors rather than D2R antagonism given the fact that these ligands show moderate binding affinities for 5-HT receptors, high selectivity for D3R over D2R and that the D2R antagonism in fact increases blood pressure and heart rate (Jordan et al., 2019c).

3. Challenges in translational research

Although D3Rs have long been a focus of medication development for addiction, translational potential of D3R-targeted ligands to clinical settings has, to date, been limited. Two approaches in D3R-based medication development research have been used: repurposing medications already approved by the FDA for other disorders and developing novel D3R antagonists.

3.1. Buspirone

Buspirone is a FDA-approved medication used for the treatment of anxiety. Its therapeutic effects are believed to be mediated by its partial agonist action at 5-HT_{1A} receptors $K_{i\text{-High}}$ (19.2 nM) and $K_{i\text{-Low}}$ (111 nM) (Noël et al., 2014). However, buspirone has moderately high affinity to D3Rs (Ki = 98 nM) (Bergman et al., 2013; Kula et al., 1994), suggesting a potential involvement of D3Rs in its anxiolytic effects or anti-addictive effects. Preclinical studies showed that buspirone can reduce opioid-induced CPP, morphine sensitization, withdrawal-related hyperalgesia (Haleem et al., 2014; Haleem and Nawaz, 2017) as well as attenuate tolerance to analgesic effect of morphine (Nayebi et al., 2010). However, in rats trained to discriminate morphine from saline, buspirone failed to block the discriminative stimulus effect of morphine and was partially substituted for U50,488, a kappa opioid agonist

(Powell et al., 1994).

As preclinical studies suggest buspirone may act at the D3R and mitigates some behavioral effects of abused drugs, it has been proposed that buspirone might be effective for a clinical population struggling with addiction (Bergman et al., 2013; Newman et al., 2012). However, clinical studies found little or no significant benefits of buspirone in relapse prevention for smoking (Schneider et al., 1996) and in reductions of drug (cocaine, cannabis) and alcohol consumption (Malec et al., 1996a, 1996b; McRae-Clark et al., 2015, 2009; Winhusen et al., 2014). Although the mechanisms underlying these negative findings are unclear, they might partially be explained by its non-selectivity and low occupancy at the D3Rs in human brain. At a relatively high dose (120 mg), buspirone has been reported to produce only a modest (< 25%) displacement of [^{11}C-(+)-PHNO] binding in brain regions with high density of D3Rs (Le Foll et al., 2016). To date, there has been no clinical trial to evaluate the effectiveness of buspirone in controlling opioid intake and relapse. However, buspirone has been shown to reduce withdrawal symptoms in heroin addicted individuals (Buydens-Branchey et al., 2005; Rose et al., 2003), suggesting that it may be effective, perhaps adjunctively with other medication and psycho-social options, in the treatment of OUD. Overall these findings suggest that more selective D3R antagonists with higher D3R affinity, and thus the potential of greater brain D3R occupancy, might be more suitable for clinical investigation.

3.2. GSK598,809

To our knowledge, there have been only a few D3R antagonists (GSK598,809, ABT-925, and S33138) that progressed to clinical trials (Le Foll et al., 2014; Wager et al., 2017). GSK598,809, with higher affinity to D3Rs than buspirone, showed effectiveness in reducing craving for cigarettes (Mugnaini et al., 2013). Using ^{125}I-7OH-PIPAT autoradiography and ^{11}C-PHNO positron emission tomography, Mugnaini and colleagues showed a direct relationship between the occupancy of the D3Rs by GSK598809 in rat, baboon, and human brains and its effectiveness in reducing nicotine-seeking/rewarding behaviors. In rats, GSK598809 dose-dependently reduced nicotine CPP whereas in human smokers it alleviated craving for nicotine (Mugnaini et al., 2013). In addition, GSK598,809 has been shown to be effective in reducing appetitive responses and attentional bias to food cues in overweight and obese individuals (Mogg et al., 2012; Nathan et al., 2012). Although GlaxoSmithKline opted to not pursue GSK598,809, cardiovascular effects recently reported may have precluded further development for SUD (Appel et al., 2015; Jordan et al., 2019c). (Begining a new paragraph) Compared to both GSK598809 and buspirone, newer generation D3R antagonists such as VK4-116 and VK4-40 display several unique advantages – higher D3R selectivity, improved pharmacokinetic profiles, enhanced opioid analgesia and minimal side effects. More importantly, these novel D3R antagonists, in addition to their low abuse liability have been shown to be highly effective in reducing opioid self-administration, motivation for drug and opioid seeking, making them promising candidates for clinical trials.

4. Future directions

Given the staggering numbers of opioid-related casualties and the lack of effective therapies in relapse prevention, the development of novel pharmacotherapies for OUD is of ultimate importance. As the opioid epidemic derived from the rampant misuse of prescribed and illegal opioids is taking its toll on our communities, non-opioid therapeutic approaches are desperately needed. An ideal pharmacotherapeutic would be the one that can control compulsive opioid taking, attenuate the rewarding effects of opioids, diminish craving and, perhaps most importantly, prevent relapse. In addition, a desirable therapeutic would also be able to ameliorate opioid withdrawal symptoms and either have no effect on or preferably potentiate opioid analgesic effects, while itself lacking abuse potential. Thus far, several newly developed D3R antagonists, as described above, meet these criteria.

We note that most of the recent studies were performed in males, and potential sex differences in efficacy of D3R antagonists are unknown, although in one study (de Guglielmo et al., 2020) no sex differences were found. Importantly, the chronic use of D3R ligands has not been extensively studied and more studies are needed to determine whether newly developed D3R antagonists are effective against other commonly abused opioids such as fentanyl and its analogs or can alleviate physical withdrawal. Comparative studies between D3R antagonists and partial agonists may also be required to determine optimal efficacy and compliance in the treatment of OUDs.

In conclusion, based on the empirical evidence stemming from animal research, further investigation of novel D3R ligands as potential therapeutics for the prevention and treatment of OUD is critical. Notably, such efforts have been recently recognized by NIDA (Rasmussen et al., 2019), which proposed D3Rs as high priority pharmacological targets for rapid medication development aimed at combatting the current opioid crisis. Investment in compounds such as R-VK4-116 and R-VK4-40 by the NIH with funding from HEAL is the first step.

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