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Commentary

Medication discovery for addiction: Translating the dopamine D3 receptor hypothesis

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ABSTRACT

The dopamine D3 receptor (D3R) has been investigated as a potential target for medication development to treat substance use disorders (SUDs) with a particular focus on cocaine and methamphetamine. Currently, there are no approved medications to treat cocaine and methamphetamine addiction and thus developing pharmacotherapeutics to complement existing behavioral strategies is a fundamental goal. Novel compounds with high affinity and D3R selectivity have been evaluated in numerous animal models of drug abuse and favorable outcomes in nonhuman primate models of self-administration and relapse have provided compelling evidence to advance these agents into the clinic. One approach is to repurpose drugs that share the D3R mechanism and already have clinical utility, and to this end buspirone has been identified as a viable candidate for clinical trials. A second, but substantially more resource intensive and risky approach involves the development of compounds that exclusively target D3R, such as GSK598809 and PG 619. Clinical investigation of these drugs or other novel D3R-selective agents will provide a better understanding of the role D3R plays in addiction and whether or not antagonists or partial agonists that are D3R selective are effective in achieving abstinence in this patient population.

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1. Overview of the challenge in medications development for substance use disorders: focus on cocaine and methamphetamine

Major challenges exist for developing medications to treat substance use disorders (SUDs) in general, and psychostimulant addiction, in particular. Despite a considerable global burden [1], the negative health and societal consequences of cocaine and methamphetamine abuse have continued unabated. Based on decades of research, it is clear that therapeutic strategies that include medications are necessary to reduce, and ultimately, eliminate illicit drug taking. Nevertheless, translation from mechanistic target identification to preclinical testing in animal models of self-administration and relapse through clinical evaluation of novel or repurposed molecules has progressed at a snail's pace. The reasons for failure to deliver effective medications to treat psychostimulant addictions have been described and debated (e.g., [2]). The lack of consistent efforts in drug development for this patient population in the private sector has historically been a barrier to success. Further, the multi-billion dollar price tag [3] coupled with the high risk of developing psychiatric medications has contributed to the recent exodus of big pharma from development of drugs that act on the central nervous system (CNS). This disengagement from psychiatric drug development will undoubtedly further slow this process because of downstream effects on smaller pharmaceutical and biotech firms that have traditionally relied on the resources of big pharma in the latter stages of drug development [4]. Translation from animal to clinical studies, low medication compliance during the conduct of clinical trials, placebo effects, and the current FDA perspective to demonstrate complete abstinence, as opposed to reduction in drug

Abbreviations: SUD, substance use disorder; CNS, central nervous system; D2R, dopamine D2 receptor; D3R, dopamine D3 receptor; D4R, dopamine D4 receptor; ^{11}C-PHNO, [^{11}C]-(+)-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b]-[1,4]-oxazine-9-ol; ADME, absorption distribution metabolism excretion; AUC, area under the curve; ATDP, Addiction Treatment Discovery Program; CTN, Clinical Trials Network; PET, positron emission tomography.

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use [5], all provide formidable challenges to the successful development of medications to treat SUDs [2,6].

Nevertheless, scientific advances have led to the identification of "druggable" targets, and medicinal chemistry efforts have, in turn, resulted in the development of small molecules that show promise in preclinical models of addiction. In this commentary, we present the dopamine D3 receptor (D3R) as a uniquely suited target for drug development, with D3R antagonists and partial agonists showing promise in models of cocaine and methamphetamine abuse. We briefly summarize recent advances in the discovery of small molecules that bind with high affinity and selectivity to D3R and have properties in preclinical models that forecast successful translation to the clinic. We highlight selected novel agents and in addition, present promising data on a repurposed molecule, buspirone, as a candidate for clinical trials.

2. Why the dopamine D3 receptor (D3R) may be a uniquely suited target for psychostimulant abuse and addiction

Although both cocaine and methamphetamine are psychostimulants and bind to all three monoamine transporters (norepinephrine, dopamine, serotonin), their mechanisms of action differ. Cocaine blocks neurotransmitter transport into the cell, but cannot be transported itself, whereas methamphetamine serves as a substrate, competing for the neurotransmitter both at the membrane and vesicular transporters, ultimately facilitating the release of neurotransmitter into the synapse. Although all three transporters are affected by chronic use of these drugs and the neurotoxicity associated with methamphetamine is certainly one consequence of this, it is the dopamine transporter that appears to be most closely linked to the psychomotor stimulant and euphoric effects produced by these agents.

Chronic exposure to cocaine and/or methamphetamine causes long lasting molecular and cellular neuroadaptations of the mesencephalic dopaminergic system that may ultimately contribute to the addict's inability to stop taking drugs, despite serious negative consequences [7–10]. Indeed, an increased extracellular concentration of dopamine has been implicated as a critical factor in morphological changes that can lead to changes in neural plasticity and behavior. These changes may contribute to excessive activation of all dopamine receptor subtypes [11]. Specifically, increased expression and function of D3R upon exposure to psychostimulant drugs has led to further investigation into the role of D3R in cocaine and methamphetamine addiction [12–14]. In addition, the restricted high density localization of D3Rs in neurocircuits that play a critical role in emotional and cognitive functions as well as increases in D3R in the ventral striatum of human cocaine fatalities [15,16] has further heightened interest in D3R. More recently, PET studies using the D3R-preferential ligand [^{11}C]-(+)PHNO in methamphetamine polydrug abusers showed upregulation of D3R but not D2R in this subject population [17]. These studies, coupled with preclinical studies that will be briefly summarized below suggest that normalization of D3R function may reduce vulnerability to relapse in psychostimulant abuse.

3. D3R selective antagonists and partial agonists

A seminal report describing the D3R-selective partial agonist/antagonist BP 897 (Fig. 1) (hD3R and hD2R K_i = 0.92 and 61 nM, respectively) showed inhibition of conditioned cue-controlled cocaine-seeking behavior in rats without producing rewarding effects of its own [18]. Many subsequent studies [19] expanded these results in other models of cocaine and methamphetamine

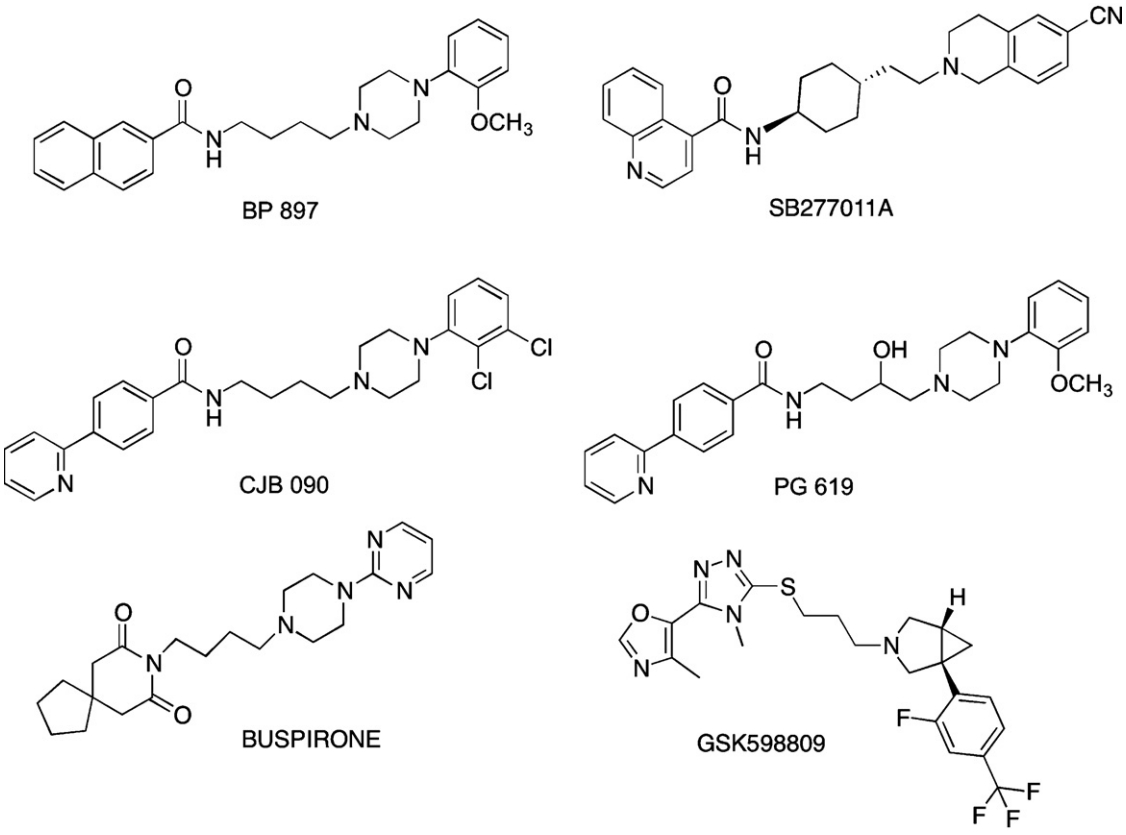

Fig. 1. Chemical structures of D3R selective ligands.