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New Drugs, Old Targets: Tweaking the Dopamine System to Treat Psychostimulant Use Disorders

Amy Hauck Newman, Therese Ku, Chloe J. Jordan, Alessandro Bonifazi, and Zheng-Xiong Xi

Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health, Baltimore, Maryland 21224, USA; email: anewman@intra.nida.nih.gov

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Abstract

The abuse of illicit psychostimulants such as cocaine and methamphetamine continues to pose significant health and societal challenges. Despite considerable efforts to develop medications to treat psychostimulant use disorders, none have proven effective, leaving an underserved patient population and unanswered questions about what mechanism(s) of action should be targeted for developing pharmacotherapies. As both cocaine and methamphetamine rapidly increase dopamine (DA) levels in mesolimbic brain regions, leading to euphoria that in some can lead to addiction, targets in which this increased dopaminergic tone may be mitigated have been explored. Further, understanding and targeting mechanisms underlying relapse are fundamental to the success of discovering medications that reduce the reinforcing effects of the drug of abuse, decrease the negative reinforcement or withdrawal/negative affect that occurs during abstinence, or both. Atypical inhibitors of the DA transporter and partial agonists/antagonists at DA D_3 receptors are described as two promising targets for future drug development.

1. INTRODUCTION TO PSYCHOSTIMULANT USE DISORDERS: COCAINE AND METHAMPHETAMINE

1.1. The Problem

While the national focus has been centered on the opioid epidemic, deaths related to psychostimulants such as cocaine and especially methamphetamine have surged dramatically. According to the Centers for Disease Control and Prevention, the National Institute on Drug Abuse, and various news sources, overdose fatalities caused by psychostimulants have more than doubled over the last five years (1–5). One of the likely culprits of this increase is coadministration of the opioid fentanyl. The *Journal of the American Medical Association* reported a near-eightfold increase of unprescribed fentanyl detected in urine samples positive for methamphetamine and an 18-fold increase for urine samples positive for cocaine in 2019 (4, 6). The contamination of deadly fentanyl in nonregulated psychostimulants has thus contributed to the increase in numbers of overdose-related deaths of these drugs (7–9). Another cause of this health and societal tragedy is, ironically, the increased public awareness of the dangers of using and abusing opioids, which has led chronic opioid users to shift to psychostimulants that are viewed as less harmful (10, 11). Alarmingly, the grim picture painted by the official statistics does not account for the total number of drug-related deaths. While the number of deaths due to overdose does serve as a good metric for the lethality of these addictive substances, there are many other means by which they can inflict long-term health damage that can shorten the users' life spans (12). For example, cocaine causes severe cardio- and lung toxicity over time, and chronic users of methamphetamine not only show dramatic change in mood and behavior but also exhibit psychotic symptoms (12–16). Taking into consideration all the factors such as these, the number of deaths related to drug use could easily be double of what has been reported (12). These alarming trends resulting from increased illicit psychostimulant abuse and subsequent mortality emphasize the need for effective treatment strategies, including US Food and Drug Administration (FDA)-approved pharmacotherapies, of which none currently exist.

1.2. Potential Pharmacotherapies Under Development

Clinically, a combination of an FDA-approved medication and psychosocial treatment, termed medication-assisted treatment, more effectively treats substance use disorders than does the use of monotherapies exclusively (17–20). However, unlike opioid use disorders for which options such as buprenorphine, methadone, and naloxone exist, psychostimulant use disorders (PSUDs) lack FDA-approved pharmacotherapies (20, 21). Efforts to overcome this setback have yielded a variety of potential options. For example, an anticocaine vaccine is currently being evaluated in a phase I clinical trial. The dAd5GNE vaccine is composed of a disrupted serotype adenovirus with a GNE hapten, a cocaine analog, coupled to its capsid protein (22). The administered vaccine induces the immune system to generate anticocaine antibodies that sequester cocaine molecules in the blood and subsequently prevent cocaine from reaching the brain as the antibodies cannot cross the blood-brain barrier (BBB), thereby eliminating cocaine's stimulant effects (22). The cocaine–antibody complex also protects other organs sensitive to cocaine from damage, hence lowering the toxic effects of cocaine in the periphery as well (23). Through this strategy, cocaine self-administration behaviors and cocaine-induced hyperactivity in mouse, rat, and nonhuman primate preclinical models were effectively blocked (22–24). Although this vaccine appears to provide an effective solution to cocaine use disorder, a drawback is the necessity of a monthly vaccine regimen, with no end point provided, thus a potentially lifelong treatment (25).

In terms of pharmacotherapeutics, disulfiram is a medication that shows promise in treating cocaine use disorder, although it is FDA approved only to treat alcoholism. For its label purpose, disulfiram inhibits aldehyde dehydrogenase, which induces an aversive reaction to alcohol and

deters further intake (26). Clinically, disulfiram effectively decreases cocaine consumption for dependent individuals, likely through inhibition of dopamine (DA) β-hydroxylase, when combined with psychotherapy, although outcomes are superior in males (26–29). A report published in 2019 indicated that patients with genetically high dopamine transporter (DAT) expression levels due to the presence of two rs28363170 10-repeat allele polymorphisms in SLC6A3 (DAT1) may benefit even more from treatment with disulfiram (30).

Topiramate, a glutamate antagonist and GABA agonist, prevented cocaine self-administration and reinstatement in rodents; however, clinical trials showed insignificant improvement in patients who were administered either topiramate or placebo (31). Bupropion, a DAT inhibitor, was not significantly efficacious in treating either cocaine or methamphetamine use disorder (32, 33). Mirtazapine, which affects monoamine transporters, effectively decreased methamphetamine use (34, 35). In 2019, cholinergic medications such as galantamine, an acetylcholinesterase antagonist, were reported to successfully treat cocaine use disorder in small (7 patients) and larger (120 patients) clinical trials; further investigation is needed (31).

Perhaps more controversially, the use of DA agonists, or substitution therapy, has emerged as a highly promising pharmacological strategy for treating cocaine use disorder (31, 36, 37). Opioid agonists such as methadone and buprenorphine have successfully treated opioid use disorders; however, using the same strategy for PSUDs has thus far been rejected. Long-acting amphetamines have been efficacious in treating cocaine use disorder in clinical trials, but the retention rate of participants was poor due to stringent criteria (31, 37). Thus, studies with a larger population are needed. Atypical DAT inhibitors and DA D_3 receptor (D_3R) antagonist/partial agonists have also emerged as promising solutions to PSUDs and are discussed in detail in this review.

2. EMERGENCE OF ATYPICAL DOPAMINE TRANSPORTER INHIBITORS AS PHARMACOTHERAPIES FOR PSYCHOSTIMULANT USE DISORDERS

Cocaine and methamphetamine occupy a similar binding pocket in the DAT protein that corresponds to the substrate (DA) binding site. Cocaine and its analogs are DAT inhibitors that typically stabilize an open outward-facing conformation of the DAT and prevent DA from being recycled (38–41). Hence, the rewarding effects imparted by cocaine stem primarily from the elevated levels of DA resulting from DAT blockade. In contrast, although methamphetamine also serves as a DAT inhibitor, it is also a DAT substrate. As such, it is taken up into the cell, where it blocks the vesicular monoamine transporter, releasing DA and reversing DAT from inside the DA cell body, resulting in increased levels of mesolimbic DA that produce stimulation and euphoria that can lead to abuse (42–48).

In the mid-1990s, the Newman laboratory (49, 50) reported a series of benztropine analogs that, like the parent drug, had binding affinities at DAT that were comparable to or higher than those for cocaine, but these compounds did not have a cocaine-like behavioral profile in rodents. The term atypical DAT inhibitors was defined as compounds that do not display a cocaine-like behavioral profile despite sharing the common mechanism of action as a DAT inhibitor. Benztropine was chosen as a lead molecule due to structural features shared with cocaine (tropane ring) and another DAT inhibitor, GBR12909 (later named vanoxerine when it was advanced to clinical trials) (**Figure 1**). Benztropine is also clinically used to treat symptoms associated with Parkinson's disease, and there have been no reports of its abuse, suggesting it may be atypical.

2.1. Benztropine and Rimcazole Analogs

Modifications of the benztropine structure at the tropane *N*-, 2-, 3-, and 6,7-bridgehead were made during the 2000s to advance structure–activity relationships (SARs) across the monoamine

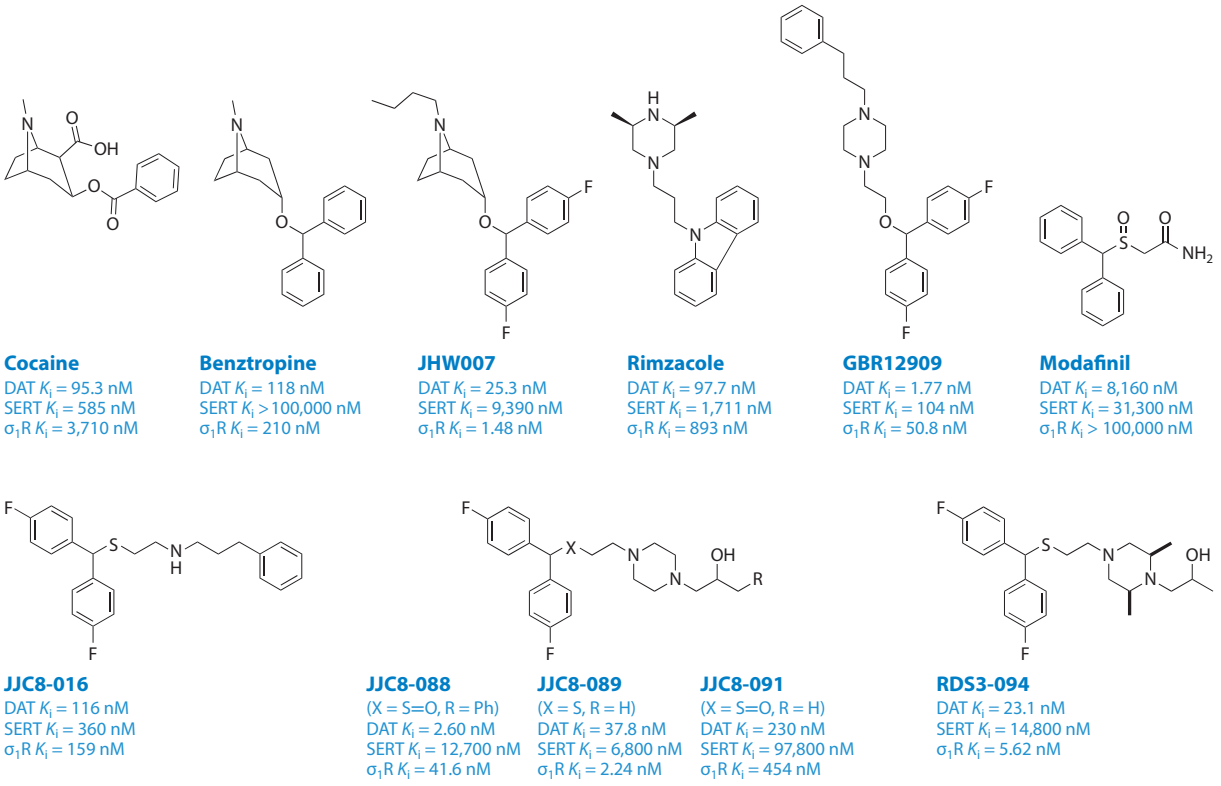

Figure 1

Chemical structures of cocaine, benztropine, JHW007, rimcazole, GBR12909, modafinil, JJC8-016, JJC8-088, JJC8-089, JJC8-091, and RDS3-094. Binding data from the Newman laboratory; data for benztropine σ_1R K_i from Reference 78. Abbreviations: σ_1R, sigma$_1$ receptor; DAT, dopamine transporter; K_i, inhibition constant; SERT, serotonin transporter.

transporters as well as σ_1 receptors (51–62). In addition, decreasing binding affinities at off-target sites such as muscarinic M_1 and histamine H_1 receptors was an important and achieved objective to ascertain that these actions were not playing a role or masking the psychostimulant behavioral effects of these novel analogs. Of note, the affinity of benztropine for muscarinic M_1 receptors is approximately 100-fold higher than its affinity for DAT, which may be related to its lack of abuse (63). Importantly, several interesting lead molecules were discovered, with the most studied, JHW007 (**Figure 1**), showing no detectable psychostimulant-like behaviors and demonstrating antagonism of behaviors produced by cocaine or methamphetamine across numerous animal models and species (64–69).

At the same time, the Newman laboratory discovered a series of rimcazole analogs (63, 70–73) that, in addition to binding with moderately high affinity to DAT, interacted with σ_1 receptors. These compounds also exhibited an atypical DAT inhibitor behavioral profile (74–76), suggesting that a dual DAT/σ_1 binding profile might be beneficial for a pharmacotherapeutic to treat PSUDs. This concept was further expanded with selected benztropine analogs (77). Of note, GBR12909 was reported to bind to σ_1 receptors (78); thus, it was posited that this dual mechanism may be shared by other compounds that had been or might be developed to treat PSUDs.

In addition to the benztropine and rimcazole analogs, other tropane-based atypical DAT inhibitors as well as numerous series of GBR12909 analogs emerged during this time (79, 80),

although extensive behavioral evaluation of these latter compounds was not reported. Moreover, both benztropine and GBR12909 were evaluated clinically as potential treatments for cocaine abuse. Benztropine failed to significantly affect responses to acute cocaine administration (81) and further evaluation was not reported. GBR12909 (vanoxerine) was advanced to phase I clinical trials before failing due to rate-dependent corrected QT (QTc) elongation in healthy subjects (82–86). However, a slow release formulation was reported in 2019 to have beneficial effects in a cocaine-abusing patient population (87).

From the outset, we noted significantly different SARs at DAT with the benztropine analogs compared with cocaine and the many analogs that were synthesized by other laboratories during that time period (63, 88). We hypothesized that although these two classes of DAT inhibitors share the same tropane ring structure, they were likely binding to the DAT differently. Furthermore, that difference in binding might, at least in part, result in a behavioral profile that was not cocaine-like but, indeed, could block cocaine from the DAT and hence mitigate cocaine's psychostimulant actions. Through extensive molecular pharmacology with DAT mutants that either had no effect on cocaine's binding affinity (e.g., Y156F) or preferred an inward-facing conformation (e.g., Y335A) that significantly reduced cocaine's binding affinity, we discovered that, in fact, the benztropine analogs appeared to prefer a more occluded, inward-facing conformation of the DAT, compared with cocaine, and these data were supported with computational studies (89). Moreover, a crystal structure confirmed in 2015 that cocaine binds to an outward-facing conformation of *Drosophila melanogaster* DAT (39), as predicted empirically and through computational models. No crystal structure of DAT with a benztropine analog has been reported.

In addition, ex vivo autoradiography studies showed that although these benztropine analogs penetrate the BBB, they are slow to occupy DAT (e.g., JHW007 requires >4 h to fully occupy the DAT), compared with cocaine, which fully occupies DAT in <30 min (64, 90). These differences in binding kinetics could also play a critical role in their behavioral profiles; extensive positron emission tomography (PET) imaging has shown that cocaine's rapid BBB penetration and occupancy of DAT are related to feeling "high" by human subjects (91). Unfortunately, none of the benztropine analogs were advanced to clinical trials.

Subsequently, inspired by its pharmacological profile and early promise in clinical studies of patients with cocaine or methamphetamine use disorders (92–95), the Newman laboratory has focused on (±)-modafinil and its (*R*)-enantiomer (96), and analogs thereof. We originally noted that although not entirely atypical, as we have defined it (i.e., a DAT inhibitor without a cocaine-like behavioral profile), *R*-modafinil had some striking pharmacological features that made it an interesting template on which to undertake SAR studies. Importantly, although it is a DA uptake inhibitor, it does not appear to have significant addictive liability in humans. Nevertheless, some people use ±-modafinil for cognitive enhancement rather than for its FDA-approved use for narcolepsy and other sleep disorders (97, 98). It is a mild stimulant in both rodents and humans, but it is not self-administered in rodents and can block some cocaine-induced behaviors (97, 98).

2.2. Modafinil Analogs

Armed with (*a*) SARs in the benztropine class of molecules and (*b*) a hypothesis that DA uptake inhibitors that prefer a more occluded inward-facing conformation may have an atypical behavioral profile, we began a synthetic campaign to identify modafinil analogs that had higher affinities for DAT compared with the parent molecule, and improved solubility and lower potential for abuse. Our goal was to discover an atypical DAT inhibitor that had the appropriate drug-like properties as well as a behavioral profile that might be developed as a therapeutic to treat PSUDs.

In our first series of modafinil analogs, we discovered that reducing the terminal amide to an amine improved DAT binding affinity (99, 100) and that the salt form of these analogs would impart improved solubility compared with that of the parent drug. The first lead in this series, JJC8-016 (**Figure 1**), demonstrated a promising behavioral profile in numerous rodent models of cocaine abuse. For example, pretreatment with JJC8-016 dose dependently inhibited cocaine-enhanced locomotion, cocaine self-administration, and cocaine-induced reinstatement of drug-seeking behavior (101). However, subsequent analysis of JJC8-016 suggested that it may bind to the human ether-a-go-go-related gene (hERG) potassium channel (102), which might predict cardiotoxicity, as had already been reported for its analog, GBR12909. hERG is involved in the repolarization of the cardiac action potential (83, 86, 103–106). Inhibition of this channel with small-molecule drugs can lead to delays in repolarization, which can lead to QT prolongation and the lethal cardiac arrhythmia torsade de pointes. The hERG channel is highly promiscuous and has a high affinity for molecules with aromatic (e.g., phenyl rings) and positively charged (e.g., protonatable amines) groups. Many FDA-approved drugs have been withdrawn from the market due to cardiotoxicity related to hERG inhibition; thus, a high affinity for hERG is a red flag for medication development (107). This also poses a significant challenge for designing drugs that are BBB penetrant and that bind with high affinity to G protein–coupled receptors or monoamine transporters. Hence, additional chemical modification of this template was undertaken to further improve the drug-like properties of this molecule, resulting in several new leads (108).

In the next series of modafinil analogs, a piperazine linker was incorporated and several interesting analogs emerged, including JJC8-088, JJC8-089, and JJC8-091 (**Figure 1**). Although initial behavioral testing in a murine locomotor assay suggested that the analog with the highest affinity for DAT, JJC8-088, might be a lead candidate for development, subsequent evaluation showed that it was not as effective as JJC8-091 in rats exposed to long-access (6 h) methamphetamine (102). Further exploration revealed that JJC8-088 was more cocaine-like than originally predicted and appeared to prefer a more open conformation of the DAT than did JJC8-091. Subsequently, JJC8-091 became the new lead molecule in this series (21) and continues to undergo development (**http://encepheal.com/**). In rodent studies, JJC8-091 reduced cocaine self-administration and cocaine-primed reinstatement of cocaine seeking (21) (**Figure 2*a*,*c***).

In 2020, Slack et al. (109) reported a new series of 2,6-dimethylpiperazine analogs to further explore SARs and improve pharmacokinetics and metabolic stability. When the 2,6-dimethyl substitution was introduced on the piperazine ring, some improvement in drug-like properties was realized. Nevertheless, the piperazine ring remains a metabolically labile functional group in this series of molecules; hence, a new series of analogs in which the piperazine ring has been replaced with a piperidine-amine or amino-piperidine function (110) is currently being evaluated in rodent models of PSUDs as well as for pharmacokinetics, metabolic stability, and off-target actions. In addition, Lubec and colleagues (111, 112) have recently reported novel heterocycle-based modafinil analogs that may be promising new leads for PSUD therapeutics.

3. INTRODUCTION TO DOPAMINE D_3 RECEPTOR PARTIAL AGONISTS/ANTAGONISTS AS POTENTIAL MEDICATIONS TO TREAT PSYCHOSTIMULANT USE DISORDERS

3.1. A Brief History of D_3 Receptor Partial Agonists/Antagonists

By blocking DA reuptake at DAT, psychostimulants such as cocaine and methamphetamine effectively prolong dopaminergic activity in the synapse at both pre- and postsynaptic DA receptors. There are five major DA receptor subtypes, classified as excitatory D_1-like receptors (including

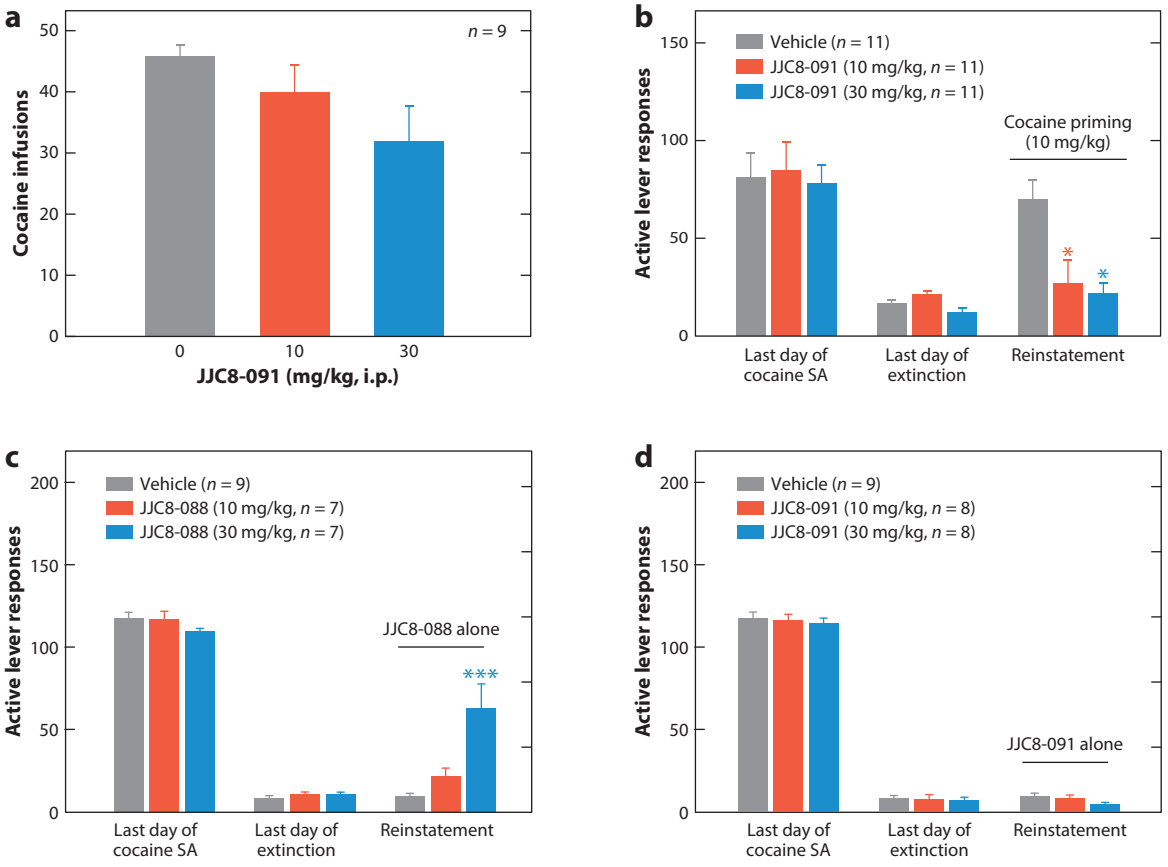

Figure 2

Effects of the novel atypical DAT inhibitors JJC8-091 and JJC8-088 on cocaine self-administration and cocaine-primed reinstatement of drug-seeking behavior in rats. JJC8-091 (*a*) did not significantly alter cocaine self-administration (0.5 mg/kg per infusion under a FR2 reinforcement schedule) but (*b*) dose dependently reduced cocaine-primed reinstatement of drug-seeking behavior. (*c*) JJC8-088 itself produced cocaine-like reinstatement of drug-seeking behavior, (*d*) whereas JJC8-091 did not (21). $^{*}p < 0.05$ and $^{***}p < 0.001$ compared with the values for the vehicle control group. Figure adapted from Reference 21. Abbreviations: DAT, dopamine transporter; FR2, fixed ratio 2; i.p., intraperitoneal; SA, self-administration.

D_1R and D_5R) or inhibitory D_2-like receptors (D_2R, D_3R, and D_4R). Relative to other DA receptor subtypes, the D_3R is of particular interest as a medicinal target due to its restricted distribution in the mesolimbic reward system, including the nucleus accumbens (e.g., ventral striatum), which plays an integral role in psychostimulant reward and abuse (113–116). Shortly after the D_3R was cloned in 1990 (116), preclinical studies revealed that D_3R-preferring ligands, such as 7-hydroxy-*N*,*N*-di-n-propyl-2-aminotetralin (7-OH-DPAT), reduce intravenous cocaine self-administration in rats (117). The D_3R received increasing interest as a medicinal target for PSUDs following reports of upregulated D_3R levels in key reward-related regions of the brain such as the nucleus accumbens, caudate/putamen, and basolateral amygdala in patients who overdosed on cocaine (118–120). PET studies using a D_3R-preferring radioligand, [^{11}C](+)PHNO, later confirmed that cocaine users exhibit upregulated D_3R binding in the substantia nigra, hypothalamus, and amygdala (121, 122).

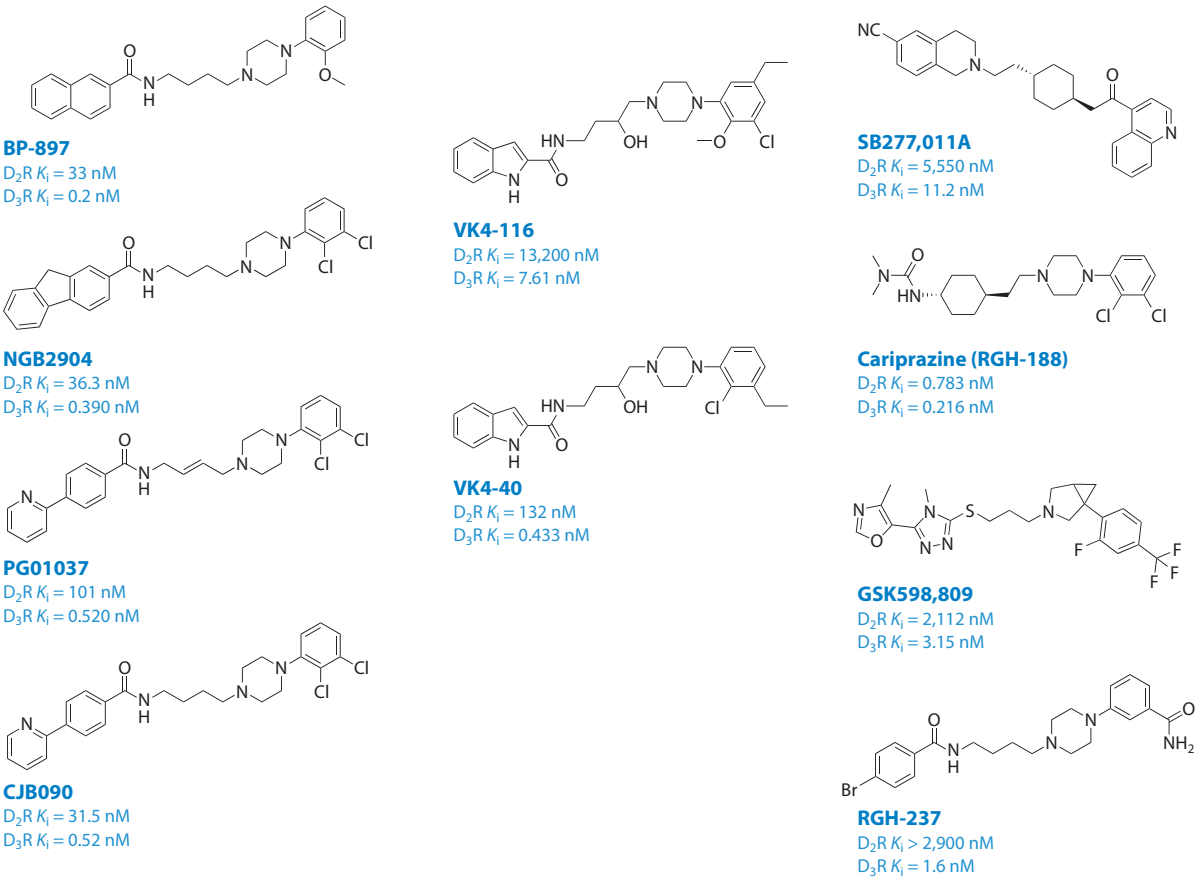

Figure 3

Chemical structures of D_3R antagonists and partial agonists studied as potential medications for PSUDs, including highly selective bitopic D_3R antagonists and partial agonists (CJB090, PG01037, VK4-116, and VK4-40) developed in the Newman laboratory (141, 142, 156). Binding data from the Newman laboratory; data for BP-897 and RGH-237 from Reference 152. Abbreviations: D_2R, D_2 receptor; D_3R, D_3 receptor; K_i, inhibition constant; PSUD, psychostimulant use disorder.

Early studies of putative D_3R medications for PSUDs were limited by poor selectivity and specificity for the D_3R over the D_2R. Advances in medicinal chemistry over the last two decades have led to significant improvements in selectivity and specificity for the D_3R (**Figure 3**). For example, the D_3R partial agonist BP-897 is ~70-fold-more selective for the D_3R over the D_2R. BP-897 reduced conditioned locomotor activity to both amphetamine and cocaine and modestly decreased lever responding to cocaine-paired cues in rats (123–126), but it was ineffective when coadministered with amphetamine or when cocaine was available for self-administration (123, 127). Similarly, SB277,011A, a D_3R antagonist with approximately 100-fold selectivity for the D_3R over the D_2R (128), dose dependently reduced cocaine-enhanced brain-stimulation reward, suppressed cocaine-conditioned place preference, and attenuated cocaine-primed reinstatement behaviors in rats (129–131). However, like BP-897, SB277,011A could not reduce cocaine intake under an easy fixed ratio 1 (FR1) reinforcement schedule (131).

In addition to limited efficacy, SB277,011A had poor translational utility due to low bioavailability (<2%) and a short half-life (<20 min) in nonhuman primates (132, 133). Subsequently,

PG01037 and its parent molecule, NGB2904 (**Figure 3**), were studied as potentially more viable D_3R antagonists, with >100-fold selectivity for the D_3R over the D_2R. In rats, NGB2904 reduced progressive ratio breakpoints for cocaine, inhibited both cocaine- and cue-primed reinstatement of cocaine seeking, and reduced cocaine-enhanced brain-stimulation reward (134). However, the reward-attenuating effects of NGB2904 could be overcome by higher doses of cocaine, and NGB2904 enhanced amphetamine-induced locomotor activity in wild-type (but not D_3R knockout) mice, suggesting possible abuse liability (134, 135). Similar to SB277,011A, PG01037 reduced progressive ratio breakpoints for methamphetamine, suppressed cue-primed reinstatement of methamphetamine seeking, and attenuated methamphetamine-enhanced brain-stimulation reward in rats, but it failed to alter methamphetamine self-administration under an FR2 reinforcement schedule in rats (136). In nonhuman primates, PG01037 reduced cocaine choice over food choice, but tolerance for these effects developed after 5 days of administration (137). Moreover, PG01037 did not effectively reduce methamphetamine choice or intake in the same self-administering rhesus monkeys (137, 138).

3.2. Cardiovascular Implications: Not a D_3 Receptor Class Effect

Despite limited efficacy for reducing psychostimulant intake when drugs are available under low-cost (FR1, FR2) reinforcement conditions, the D_3R antagonists described above significantly attenuated psychostimulant seeking under high motivation (progressive ratio) or reinstatement conditions, suggesting that D_3R antagonists may have value in attenuating relapse behaviors. However, translational efforts toward moving D_3R antagonists to the clinic were essentially halted following reports of cardiovascular side effects by GSK598,809 (139), a D_3R antagonist previously evaluated in clinical trials for smoking cessation (**https://clinicaltrials.gov/ct2/show/NCT01188967**). Briefly, GSK598,809, particularly when combined with cocaine, increased blood pressure in dogs fitted with telemetry transmitters. Because the D_3R is expressed in the kidney, the effects of GSK598,809 on blood pressure were predicted to apply to all D_3R antagonists.

Subsequent investigations following the GSK598,809 telemetry study confirmed that SB277,011A similarly increased blood pressure and heart rate in rats (140). However, two structurally unique D_3R antagonists, *R*-VK4-116 and *R*-VK4-40, which exhibit higher affinity and selectivity for D_3R than did previous D_3R ligands (1,735-fold and 305-fold more selective for D_3R over D_2R, respectively), did not potentiate the adverse cardiovascular effects caused by oxycodone or cocaine (140, 141). Instead, *R*-VK4-116 reduced cocaine-enhanced heart rate and blood pressure. *R*-VK4-40 similarly attenuated cocaine-induced increases in heart rate and further reduced blood pressure and heart rate when administered alone. The reasons for which *R*-VK4-116 and *R*-VK4-40 do not exert the same adverse cardiovascular effects as previous generations of D_3R antagonists are unclear. Differences in ligand affinity, selectivity, or unknown off-target effects or biased activation of different intracellular D_3R signaling pathways in the kidney may all play a role (140). Regardless of the reasons why, the results from using *R*-VK4-116 and *R*-VK4-40 renewed interest in the D_3R as a medication target for PSUDs and provided fresh impetus for the continued development of D_3R ligands in the treatment of PSUDs and other substance use disorders, including opioid use disorder (141–143).

3.3. Emerging Evidence Supporting D_3 Receptor Partial Agonist/Antagonist Treatments for Psychostimulant Use Disorders

Although D_3R antagonists effectively attenuate the motivation to earn psychostimulants and relapse-related behaviors in rodent models, these compounds have been relatively ineffective for

reducing cocaine intake when response requirements are low, the reinforcing value of cocaine is high, such as under low FR schedules, or both. As a result, additional efforts have focused instead on partial D_3R agonists as treatments for PSUDs. Partial agonists can functionally block the effects of drugs of abuse (due to occupation of their receptor target) but elicit partial activation of their receptor targets under abstinence conditions, thereby potentially mitigating withdrawal effects. As such, partial agonists have historically been more effective at maintaining abstinence and reducing relapse rates than antagonist therapies, particularly for opioid and nicotine use disorders (144, 145).

Prior generations of partial D_3R agonists have shown promise in attenuating psychostimulant seeking in rodent models. The D_3R-preferring partial agonist RGH-188 (cariprazine, Vraylar®) reduced cocaine intake under an FR1 schedule and suppressed cue-induced reinstatement of cocaine seeking in rats (146). However, while the D_3R partial agonists BP-897 and RGH-237 also suppress cue-driven cocaine seeking, these compounds were not effective when cocaine or methamphetamine was available for self-administration under FR schedules (123, 127). CJB090, another partial D_3R agonist from the Newman laboratory, decreased methamphetamine intake under both FR and progressive ratio schedules and more effectively attenuated psychostimulant reward than the D_3R antagonist PG01037 in rats (147) but showed mixed efficacy in nonhuman primates (148).

As with D_3R antagonists, prior generations of partial D_3R agonists have suffered from poor selectivity [BP-897 and CJB090 are ~60–70-fold-more selective for D_3R over D_2R (149–151)] or poor pharmacokinetic profiles [RGH-237 does not readily penetrate the BBB and is eliminated within ~5 hours of administration (152)]. However, a series of new D_3R ligands developed within the past five years may circumvent these limitations (141, 142). As described above, *R*-VK4-40, which attenuated the effects of cocaine on blood pressure (140), functions as a D_3R antagonist. Both the racemic (±)-VK4-40 compound and its *S*-VK4-40 enantiomer function as D_3R partial agonists. (±)-VK4-40 is ~300-fold-more selective for the D_3R than for D_2R and remains at significant levels in the brain up to 8 hours following oral administration in rats (153). Preliminary results indicate that (±)-VK4-40 attenuates cocaine self-administration and cocaine-primed reinstatement. In an optical brain-stimulation reward model, in which adenosine-associated virus-mediated channelrhodopsin 2 fused to enhanced green fluorescent protein (AAV-ChR2-eGFP) expression is driven by the DAT gene promotor selectively in ventral tegmental area (VTA) DA neurons of the midbrain (**Figure 4*a*,*b***), *R*-VK4-40 or *S*-VK4-40 alone significantly inhibits optical brain-stimulation reward maintained by selective stimulation of VTA DA neurons in transgenic DAT-Cre mice (**Figure 4*c*,*d***), and pretreatment with these enantiomers significantly blocks cocaine-induced increases in brain-stimulation reward (**Figure 4*e*,*f***). These early findings suggest that both the partial D_3R agonist (*S*-VK4-40) and the antagonist (*R*-VK4-40) have potential as putative treatments for PSUDs and critically extend the translational utility of this medication class. As such, the VK compounds are currently undergoing further development as new investigational drugs for the treatment of substance use disorders.

4. SUMMARY

There has never been a time when the development of novel strategies and pharmacotherapeutics to treat substance use disorders was more urgent. The loss of lives and livelihoods due to health challenges associated with addiction, incarceration, and stigma is unprecedented, and the resurgence of cocaine and methamphetamine use and abuse is staggering. There is no doubt that targeting multiple mechanisms for medication development is required (34, 154, 155) and that a single medication will never be a cure-all for everyone who suffers from PSUDs. Targeted

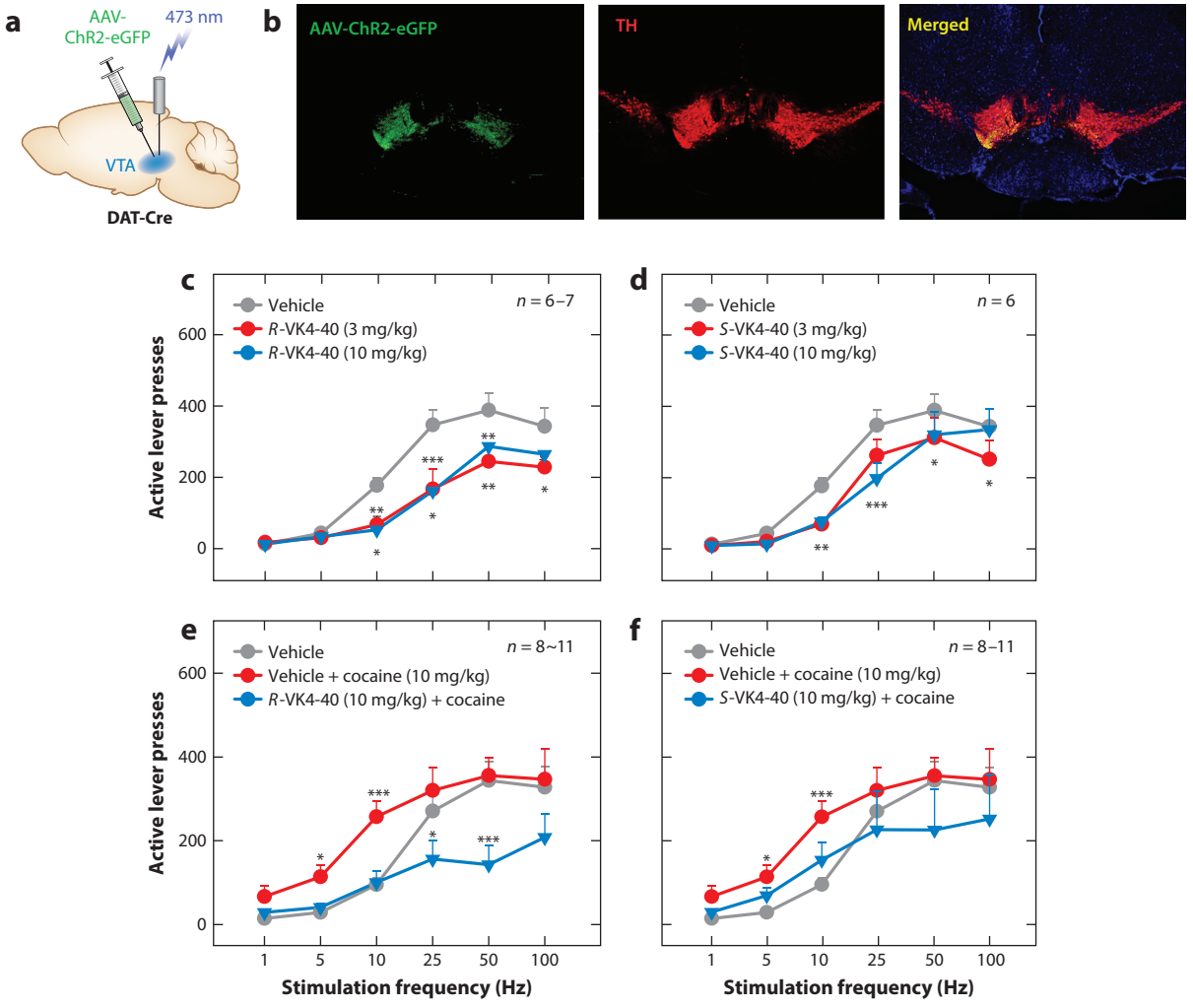

Figure 4

Effects of the enantiomers *R*-VK4-40 (a D_3R antagonist) and *S*-VK4-40 (a D_3R partial agonist) on lever responding for brain-stimulation reward maintained by optogenetic stimulation of VTA DA neurons in DAT-Cre mice. (*a*) Schematic of the experimental model illustrating AAV-ChR2-eGFP was microinjected into the VTA and an optical fiber was implanted into the VTA to stimulate DA neurons in DAT-Cre mice. (*b*) Representative images showing that AAV-ChR2-eGFP is selectively expressed in VTA TH-positive DA neurons. Systemic administration of (*c*) *R*-VK4-40 or (*d*) *S*-VK4-40 alone inhibits optical brain-stimulation reward and dose dependently shifts downward the stimulation frequency–active lever press response curve. Pretreatment with (*e*) *R*-VK4-40 or (*f*) *S*-VK4-40 dose dependently attenuates cocaine-enhanced brain-stimulation reward as assessed by the upward or leftward shift of the stimulation frequency response curve after cocaine administration. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with the values for the vehicle control group. Abbreviations: AAV-ChR2-eGFP, adenosine-associated virus-mediated channelrhodopsin 2 fused to enhanced green fluorescent protein; D_3R, D_3 receptor; DA, dopamine; DAT, DA transporter; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

medications, focused clinical trials, recognition of other mental health comorbidities, and a plethora of other challenges have made it extremely difficult to identify and ultimately provide medications for a successful treatment strategy for those who suffer from PSUDs. It is critical to identify subpopulations that are positively affected by experimental treatments, instead of only

determining that a large clinical trial failed. Undoubtedly, there are at least subpopulations of people who would benefit from the medications that have failed to receive FDA approval for PSUDs (e.g., modafinil), but we cannot stop there.

Accelerating research and engaging the pharmaceutical industry in this challenging area are critical to our success. Academic laboratories can do formidable basic and preclinical research, identify new leads, and move them forward through animal models of PSUDs. But that is not enough. There is an enormous chasm between preclinical research and actually getting a drug into phase I clinical trials, much less beyond, and this is going to require more than research funded by the National Institutes of Health (NIH). Partnerships and ongoing communication that build bridges between academia, government, and private industry are required. We have made slow but steady strides toward identifying the two sets of lead molecules described in this review: atypical DAT inhibitors and DA D_3R partial agonists/antagonists. However, reducing psychostimulant-seeking behavior in rats is not the point. Until we can get our lead molecules into the clinic and until we can determine which animal models are translational to humans, we are spinning our wheels. Our data support moving forward with either or both of these mechanistic targets and doing further medicinal chemistry to find drug candidates that have not only the desired pharmacological profile but also the appropriate pharmacokinetics, metabolic stability, and lack of off-target actions that may preclude further development due to toxicity (e.g., hERG activity). These tasks are challenging but not impossible. Indeed, the NIH Helping to End Addiction Long-term (HEAL) Initiative has been developed and funded to address the opioid crisis, and this is enormously important to ultimately curtail the unprecedented morbidity related to prescription opioid abuse that has led to increased heroin and fentanyl addiction and overdose. Lessons learned and critical research in this area will undoubtedly influence work on other substance use disorders. And although one medication or a single targeted mechanism of action is not going to mitigate all substance use disorders, there will be overlap. Indeed, the D_3R partial agonists/antagonists are excellent examples and are currently being developed toward the prevention and treatment of opioid use disorder. However, as we have discussed herein, preclinical data support their efficacy for the treatment of PSUDs. More work and resources are required. Certainly, people who suffer from PSUDs and indeed all substance use disorders are depending on us.

DISCLOSURE STATEMENT

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