Dopamine dysfunction in stimulant-use disorders: Mechanistic comparisons and implications for treatment

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Abstract

Dopamine system deficiencies and associated behavioral phenotypes may be a critical barrier to success in treating stimulant use disorders. Similarities in dopamine dysfunction between cocaine and methamphetamine use disorder but also key differences may impact treatment efficacy and outcome. This review will first compare the epidemiology of cocaine and methamphetamine use disorder. A detailed account of the pharmacokinetic and pharmacodynamic properties associated with each drug will then be discussed, with an emphasis on effects on the dopamine system and associated signaling pathways. Lastly, treatment results from pharmacological clinical trials will be summarized along with a more comprehensive review of the involvement of the trace-amine associated receptor on dopamine signaling dysfunction among stimulants and its potential as a therapeutic target.

Introduction

Stimulants continue to rank as the most commonly abused agents worldwide, second only to cannabis. The most frequently abused psychostimulants include cocaine, amphetamine and methamphetamine. Here, amphetamine and methamphetamine will be referred to by the class name, amphetamines, unless the discussion is specific to either amphetamine or...
methamphetamine. Decades of addiction research using both animal models of addiction and advanced neuroimaging techniques, provide evidence of long-lasting changes in neurochemical networks, particularly the dopaminergic system. These neurochemical abnormalities are a potential substrate for the affective and behavioral sequelae of cycles of addiction, including craving, uncontrolled drug intake and withdrawal. Cocaine shares dopamine-enhancing properties with S-methamphetamine and S-amphetamine, but the drug classes differ in their effects on components of the dopamine system. For example, dopamine transporter (DAT) numbers are decreased in chronic methamphetamine users but are either increased or unchanged in chronic cocaine users. Pharmacokinetic differences between cocaine and amphetamines may contribute to divergent actions on the dopamine system, including differential agonism of amphetamine-type stimulants and cocaine at the trace amine associated receptor 1 (TAAR1) to modulate dopamine signaling.

This paper will review the current understanding of the effects of cocaine and amphetamines on dopamine receptors and transporters and offer hypotheses to explain the similarities and differences between the drug classes, as well as examine the literature on pharmacological approaches to treatment. Lastly, a review of clinical investigations in combination with preclinical evidence may present new and promising therapeutic avenues.

Epidemiology and morbidity

Methamphetamine is the preferred amphetamine in the US and, as the price per gram of methamphetamine continues to decrease and potency and availability increase, so does the number of methamphetamine-related deaths. In Oregon, for example, methamphetamine-related deaths increased over 400% from 2009 to 2018 and outnumbered heroin-related deaths by the end of the decade. Over the same time period, methamphetamine accounted for 89% of drug-related violent crimes and 69% of drug-related property crimes. Like methamphetamine, cocaine-related overdose deaths have doubled between 2007-2017 with a 34.4% increase between 2016-2017 in the US.

The risks of medical morbidity differ between amphetamines and cocaine. A five-fold risk for hemorrhagic stroke is associated with amphetamine use, twice that of cocaine use, while a 5.7-fold increased risk for ischemic stroke was associated with cocaine use but not with amphetamine use. Furthermore, methamphetamine users were 19% more likely than cocaine users to develop an acute myocardial infarction. Although cocaine and amphetamines are both sympathomimetic drugs, differences in rates of cardiovascular and cerebrovascular complications may be attributed to the longer half-life of amphetamines during which cardiac demand is elevated.

Stimulant use is often associated with irritability, interpersonal sensitivity, physical aggression, psychomotor agitation and uncontrolled anger. Early abstinence is accompanied with mood disturbances, along with elevated levels of depression, anxiety, restlessness and intense drug craving. Individuals who abuse amphetamines or cocaine can also develop paranoia, hallucinations, and psychotic behavior. Stimulant-induced psychosis, however, is more common with the use of amphetamines than with cocaine, possibly due to the longer persistence of amphetamines in the brain.
causing prolonged activation of mesolimbic dopamine pathways, which may also lead to more violent behaviors 12, 18.

Although both cocaine and amphetamine use have been associated with perpetration of crime and violence, chronic use of methamphetamine has been more closely related to violent behavior than that of cocaine 12, 19. For example, higher psychopathy ratings and number of total criminal convictions were related to lower levels of corticostriatal resting-state functional connectivity in methamphetamine users 20. Thus, reduced cortical regulation of reward networks in methamphetamine users may predispose them to antisocial behavior and criminality. It is unknown, however, whether resting-state functional connectivity is associated with psychopathy or criminal behavior in cocaine users.

**Pharmacokinetics**

Although amphetamine and methamphetamine have similar subjective effects, methamphetamine is thought to be more addictive 21. The N-methyl group on the molecule renders methamphetamine more lipid-soluble than amphetamine, facilitates the transport of the substance across the blood–brain barrier and inhibits enzymatic degradation by monoamine oxidase (MAO) 22. Methamphetamine also inhibits DAT-mediated dopamine reuptake more efficiently than amphetamine 23.

Both human and animal studies demonstrate differences between cocaine and methamphetamine on dopamine kinetics. Higher levels of intrasynaptic dopamine and slower clearance of methamphetamine compared to cocaine contributes to longer behavioral effects, oxidative stress and damage to the dopaminergic system 24, 25. The duration of action for cocaine is approximately 1-3 hours while that for amphetamines are approximately 8-13 hours 26, 27. In non-human primates, [11C]cocaine and [11C]S-methamphetamine showed differences in brain distribution, kinetics and clearance rates. Although [11C]S-methamphetamine peaked more slowly than [11C]cocaine, it also cleared more slowly and its distribution extended beyond the striatum to cortical brain regions 28. Similarly, in humans, cocaine was concentrated in only the striatum and its uptake and clearance was faster than that of methamphetamine 29.

**Pharmacodynamics of the monoamine system**

Amphetamines and cocaine inhibit the reuptake of monoamine neurotransmitters, such as norepinephrine, dopamine, and serotonin and thereby enhance the intrasynaptic levels of these molecules. Multiple effects in the central nervous system result from increased cytoplasmic and extracellular concentrations of these neurotransmitters 22. Although both classes have broadly similar neurochemical and behavioral effects, there are important differences, such as the chronic effects of amphetamines on the dopaminergic system due to the intracellular effects at the vesicular monoamine transporter 2 (VMAT2) and TAAR1 receptor, neither of which is affected by cocaine.

Amphetamines are substrates of synaptic monoamine transporters, and can thus affect cytoplasmic concentrations of monoamines by interactions with intracellular targets such as VMAT2 30, 31, MAO 32, tyrosine hydroxylase 32 and the intracellular TAAR1 receptor.

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5. Amphetamines substantially elevate intracellular dopamine levels by altering dopamine synthesis, packaging and release in the dopaminergic terminal. Amphetamines compete with other substrates of VMAT2, a transporter that translocates monoamines from cytosol into synaptic vesicles. Amphetamines inhibit the ability of MAO to degrade excess intracellular dopamine and increase the expression of tyrosine hydroxylase, the rate limiting step for dopamine biosynthesis, resulting in further increase in intracellular dopamine. Amphetamines reduce cytoplasmic dopamine by facilitating dopamine release by reversing the direction of the DAT.

Cocaine, on the other hand, binds to monoamine transporters and blocks clearance of the transmitters from the synapse, but, because it is not a substrate of the DAT, does not interact with intracellular targets. Although significant attention has been focused on the role of dopamine neurotransmission in psychostimulant addictions, it is noteworthy that, among monoamine transporters, cocaine has the highest affinity for the serotonin transporter, whereas amphetamines have the strongest affinity for the norepinephrine transporter. The reinforcing properties of cocaine and amphetamines, however, are correlated with DAT affinity and not with affinity for the serotonin or norepinephrine transporters, consistent with the central role of dopamine as a mediator of reward.

**Stimulants and synaptic levels of dopamine**

Cocaine and amphetamines both increase intrasynaptic dopamine levels, which significantly contribute to the reinforcing effects of psychostimulants. Cocaine- and methamphetamine-induced increases in intrasynaptic dopamine positively correlates with self-reports of euphoria in humans. In rodent models, acute self-administration of cocaine and amphetamines increase extracellular dopamine levels in the nucleus accumbens. Chronic exposure to stimulants in rodents, however, leads to striatal dopamine depletion. For example, rats receiving a neurotoxic regimen of methamphetamine exhibited a reduction in dopamine concentration of 56% in the caudate nucleus and 30% in the nucleus accumbens. Similarly, a recent meta-analysis of seven clinical studies of dopamine release in chronic stimulant users (2 studies of amphetamine, 5 of cocaine) found a robust decrease in dopamine release in patients relative to controls. Postmortem studies in humans also show lower striatal dopamine levels in both cocaine and methamphetamine users compared to controls.

**Stimulant effects on dopamine transporter availability**

Neurochemical and biochemical studies of addiction show decreases in brain markers of the degeneration of pre-synaptic dopamine nerve terminals with methamphetamine exposure. Non-human primates exposed to escalating doses of methamphetamine show a reduction in DAT availability, and in mice, autoradiographic experiments show DAT depletion as soon as 24 hours after methamphetamine exposure and a 60% depletion 2 days following methamphetamine exposure. In addition, in vivo amphetamine and methamphetamine exposure in rats caused a reduction in DAT availability. Interestingly, animal
studies have found increases, decreases or no change in DAT levels following cocaine administration. These discrepant results are partly explained by the length of cocaine administration and number of days of withdrawal before DAT assessment. In non-human primates, decreases in DAT density occur with short cocaine self-administration periods (<3 months), while longer administration periods (1.5 years) lead to increases in striatal DAT densities.

Postmortem studies also found decreased striatal levels of DAT in methamphetamine users, while DAT binding was markedly increased in cocaine users. In line with these studies, two recent meta-analyses of human neuroimaging investigations systematically examined the effects of stimulant use on D2/3 and DAT availability. Random effects analyses showed that methamphetamine users had a robust decrease in striatal DAT availability, whereas cocaine users had increased numbers of DAT in the striatum. The significant differences between these drugs in the pharmacokinetic clearance rates and pharmacodynamics on DAT levels most likely contribute to differences in DAT availability.

**Stimulant effects on dopamine receptor availability**

Dopamine D2-type receptor availability has been used as a biomarker for the investigation of postsynaptic dopamine function in both human stimulant users and animals. Similar to human studies showing reduced striatal D2/3 availability in users of both classes of stimulants, non-human primates consistently show decreases in striatal D2-type binding following administration of cocaine or methamphetamine. Dopamine D3 receptors also have a role in mediating behavioral responses to psychostimulant drugs. A number of studies using D3-knockout mice suggest that one function of the D3 receptor is to modulate behaviors by inhibiting activation of dopamine D1 and D2 receptors. D3-knockout mice exhibit heightened locomotor responses to cocaine, amphetamine and morphine and produce greater conditioned place preference than wild types following low doses of amphetamine. However, one study shows that increased D3 receptor binding is associated with an escalation of cocaine intake. Pharmacological studies using D3 receptor agonists and antagonists also suggest that D3 receptors play a critical role in the motivation for drugs. Selective D3 receptor antagonists show reduced responding for cocaine and methamphetamine in rats during high demand reinforcement schedules. Although the exact involvement of D3 receptors in addiction is unclear, the above studies in combination with results showing greater D3 than D2 receptor saturation following stimulant exposure indicate a role for D3 receptors in the biobehavioral response to stimulants.

In vivo neuroimaging studies of human methamphetamine and cocaine dependence have examined D3 receptor density using the radioligand \[^{11}C\]-(+)-propyl-hexahydro-naphtho-oxazin (\[^{11}C\]-(+)-PHNO). Although \[^{11}C\]-(+)-PHNO lacks absolute specificity for D3 receptors, it does have higher differential binding at this receptor subtype. Methamphetamine users compared to healthy controls exhibit greater relative binding (ratio of D3 to D2 receptors) in the substantia nigra, a region with high expression of D3 receptors, and show a decrease in amphetamine-induced D3 binding, suggesting greater...
amphetamine-induced dopamine release in the substantia nigra 68. Methamphetamine users, however, exhibit less binding in D2-rich striatal regions compared to controls, which may be attributed to low striatal D2-type receptor availability associated with methamphetamine use 67. Cocaine users also exhibit greater D3-type binding in the substantia nigra 69. Furthermore, a postmortem study of cocaine users found an increase in $[^3\text{H}]-(+)-7$-OH-DPAT binding in the lateral and medial divisions of the substantia nigra as well as higher D3 receptor binding in the caudate, putamen and nucleus accumbens 70. Although previous human neuroimaging studies with $[^{11}\text{C}]-(+)$-PHNO did not show a reduction in D2/3 receptor availability in cocaine users 69, 71, a more recent study extends these results to show that individuals with cocaine use disorder demonstrate lower binding potential ($BP_{ND}$) in the striatum and greater $BP_{ND}$ in the midbrain as well as lower regional striatopallidal D2 binding and greater regional pallidonigral D3 binding in relation to years of cocaine use 72.

The evidence suggests that dopamine D3 compounds are promising candidates for addiction therapies. However, both D3 agonists and antagonists have shown to attenuate some components of the addiction cycle, such as drug seeking, self-administration, and cue- and stress-induced reinstatement 65. While D3 receptor agonists such as 7-OH-DPAT reduce cocaine-seeking behavior, D3 receptor antagonists attenuate cue-reinstatement of drug responding 65. The efficacy of treatments targeting D3 receptors could therefore vary with length of abstinence or functional selectivity.

Pharmacological studies also indicate a role for D1-type dopamine receptors in psychostimulant reinforcement 73, 74. Self-administration studies show that rats and non-human primates self-administer full D1-type agonists and that systemically administered D1-type antagonists decrease the reinforcing efficacy of cocaine 75-79. Cocaine self-administration paradigms in rats and in non-human primates show a down-regulation of striatal D1 receptors after a withdrawal period of 18-24 hours 80, 81. The effects of methamphetamine on D1 receptors after a withdrawal period of less than 24 hours are inconclusive 82-84; however, persistent D1 receptor upregulation (21 days) is reported in the substantia nigra 83, but not in the striatum 82, 83.

While cocaine exposure causes reduced dopamine D1 receptor levels in animals, human in vivo and ex vivo studies show no differences in D1 receptor binding in cocaine users. A PET study using the ligand $[^{11}\text{C}]$NNC112 (8-chloro-7-hydroxy-3-methyl-5-(7-benzofuranyl)-2,3,4,5-tetrahydro-IH-3-benzazepine) showed no differences between cocaine-dependent and control subjects in D1 receptor availability 85. However, despite no differences in D1 receptor binding, D1 receptor availability was negatively associated with the choice to self-administer cocaine. Similar results were obtained in methamphetamine use disorder, with no significant differences in D1 binding compared to controls 86. In a postmortem study, cocaine users show no difference in D1 receptor protein immunoreactivity while methamphetamine users show an increase in the nucleus accumbens compared to controls 87. Together, the results suggest that D1 receptors are somewhat protected from the stimulant-induced increases in synaptic dopamine, perhaps because of relatively low D1 receptor affinity for dopamine compared to D2 receptors.
Summary of MA and Cocaine effects on dopamine targets

Overall, chronic stimulant use is associated with decreased dopamine release and D2 receptor availability compared to controls but amphetamines cause substantial decreases in DAT binding and potentially a bigger effect on D1 receptor availability than for cocaine (Figure 1). The magnitude of deficiencies in dopamine release and D2 receptor availability between cocaine and amphetamines has not been well studied nor have the interactions between these markers of dopamine signaling been evaluated within or across cocaine- and methamphetamine-use disorder. Studies that directly compare abnormalities in dopamine function between stimulant classes and the interaction with dopaminergic markers has the potential to critically inform medication development and may improve the efficacy of current treatment avenues as summarized below.

Treatment

Despite high rates of attrition and relapse, cognitive behavioral therapy, contingency management, and motivational interviewing are the current options for treating stimulant dependence. Although there are no approved pharmacological treatments for stimulant dependence, many clinical trials are testing potential pharmacotherapies, many of which target the dopamine system.

Several recent systematic reviews and meta-analyses have investigated pharmacological treatments for amphetamine and cocaine use disorders. Meta-analyses specifically investigating the use of prescription psychostimulants for amphetamine and cocaine use disorders, showed no effect on sustained abstinence from amphetamines; however, there was an effect for sustained abstinence from cocaine with higher doses of psychostimulants, particularly prescription amphetamines. Meta-analyses investigating multiple drug classes showed that bupropion, psychostimulants, and topiramate may improve abstinence in cocaine use disorder. For methamphetamine use disorder, anticonvulsants, antipsychotics, opioid receptor antagonists, varenicline, and atomoxetine were ineffective; however, methylphenidate did show some promise in reducing methamphetamine use. Taken together, these somewhat unremarkable pharmacotherapy results for both cocaine and amphetamine treatment indicate that other options should also be evaluated as potential targets for treatment.

Trace amine associated receptor 1 (TAAR1) and new treatment approaches.

A recently recognized critical difference between amphetamines and cocaine is the agonism of the former, but not the latter, at the intracellular TAAR1 receptor. TAAR1, a G-protein receptor, is expressed in dopaminergic brain regions, including ventral tegmental area (VTA), substantia nigra pars compacta and ventral (including nucleus accumbens) and dorsal striatum. A mutation in mouse Taar1 that produces a non-functional receptor accounts for 60% of the variance in methamphetamine intake in lines of mice selected to either drink or avoid a methamphetamine solution. The methamphetamine high drinking line was homozygous for the non-functional Taar1 allele, while methamphetamine low drinking mice had at least one allele that produced a functional receptor. As amphetamine-
induced dopamine release is increased in Taar1 knockout mice, the blunted effect of methamphetamine in mice with functional TAAR1 receptors is likely due to the reduction in TAAR1 mediated dopamine signaling. This observation is consistent with human studies showing that striatal dopamine signaling is related to addiction severity and treatment response.

Humans, who almost all have functional TAAR1 receptors, readily self-administer methamphetamine, as do rats and non-human primates. Therefore, TAAR1 influences in humans may be more complicated than in mice. Polymorphisms in the TAAR1 gene produce functional, sub-functional and non-functional variants, although the sub-functional or non-functional variants are rare. Recently, Loftis et al. found that a synonymous single nucleotide polymorphism (SNP) in the human TAAR1 gene was associated with increased craving in methamphetamine users. Roles for non-functional TAAR1 genotypes have been proposed in obesity, schizophrenia and ‘mental illness’.

TAAR1 influence is implicated in cell bodies (VTA) and terminal field levels (nucleus accumbens and striatum) of dopamine neurons. The potential sites of TAAR1 action are determined by the requirement that amphetamines be transported into neurons via the DAT in order to interact with the intracellular TAAR1 receptor. In midbrain dopamine neurons (likely a major site for TAAR1 effects), amphetamine stimulation of TAAR1 initiates a complex cascade of effects that includes internalization of the DAT and the excitatory amino acid transporter 3 (EAAT3); the latter clears glutamate from the peri-neuronal space. As single dose stimulation of TAAR1 by amphetamine results in initial internalization of the DAT but subsequent termination of internalization, it is possible that chronic methamphetamine use results in persistent DAT trafficking. As cocaine is not transported by the DAT and is not a TAAR1 ligand, this effect would not be expected with cocaine. This is consistent with the robust reductions in DAT numbers in methamphetamine users but increases in cocaine users.

In addition to dopaminergic effects, a role for glutamate in TAAR1-mediated effects of methamphetamine is also strongly supported. For example, there are TAAR1-mediated effects of methamphetamine on glutamate regulation of VTA dopamine neurons. Furthermore, incubation of methamphetamine craving depends on methamphetamine-induced plasticity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) transmission in the nucleus accumbens. Finally, activation of downstream targets of striatal projections is dependent in large part upon striatal and VTA excitation by glutamatergic inputs. Changes in the strength of these inputs (synaptic plasticity) will no doubt modulate the response of downstream regions to dopamine.

As noted above, chronic use of amphetamines and cocaine have differential effects on dopamine targets. Decreased DAT in (meth)amphetamine users is possibly due to amphetamine agonism at the TAAR1 receptor as well as kinetic mechanisms. As cocaine is not transported, the increase in DAT number in chronic cocaine users likely results from compensatory upregulation of the DAT in response to continued blockade.
TAAR1 and Implications for treatment

Several full and partial agonists at the TAAR1 receptor have been developed recently 116-118. As TAAR1 stimulation decreases dopamine release in the striatum, animal studies have examined the effect of TAAR1 agonists on addictive behaviors [See 119 for review]. Interestingly, despite the disjunct actions of methamphetamine and cocaine at TAAR1 at the synaptic level, the partial TAAR1 agonist, RO5263397, reduces development of sensitization and cue-induced reinstatement for both substances 110 and the compound presents as a possible model agent for methamphetamine replacement therapy 120. TAAR1 receptor activation decreases dopamine signaling in mesocorticolimbic and corticostriatal networks 109, 110, while treatment with a TAAR1 antagonist 116 or knocking out the Taar1 rodent gene 101 is associated with increased striatal dopamine signaling. Therefore, the effects of TAAR1 agonists on addictive behavior associated with both stimulant classes is hypothesized to derive from reduced striatal dopamine release. Emphasizing the importance of TAAR1 in methamphetamine addiction, a recent paper found increased craving for methamphetamine in a subset of humans with a common TAAR1 genotype 105.

There are no differentiating effects of TAAR1 on amphetamine or cocaine self-administration in animal models and cocaine is not an agonist for TAAR1. The use of TAAR1 agonists and the associated effect on dopamine signaling, however, may still be beneficial for cocaine-use disorder, a population where DAT expression is intact. The influence of time course may be critical in testing and evaluating TAAR1 agents. The acute effects of methamphetamine agonism at TAAR1 is DAT sequestration, followed by inhibition of sequestration via two different G protein signaling pathways. TAAR1 agonists, secondary to blunting dopamine release, may have similar effects on initial drug use or maintenance in animal models. As methamphetamine agonism of TAAR1 likely contributes, in part, to the consistent reports of decreased DAT, and methylphenidate has shown some promise in methamphetamine addiction, perhaps the use of TAAR1-targeted pharmacotherapies in conjunction with methylphenidate may increase therapeutic effectiveness of these medications. There are, however, currently no clinical trials to test TAAR1 agonists in human addictive disorders, although two TAAR1 agonists are in phase II trials for the treatment of schizophrenia. Differences in the efficacies of TAAR1 agents in amphetamine vs. cocaine use disorders may become apparent when testing the effect of TAAR1 agents in chronically using populations.

Conclusion

Together, the results support targeting the neurobiological pathology of the dopamine system as a promising avenue for the treatment of stimulant use disorders. This is in line with studies showing that, in both cocaine and methamphetamine use disorders, higher levels of D2-type receptor availability and dopamine release is associated with better response to contingency management 102, 121. In addition to protecting against relapse and contributing to the success of treatment, improvements in dopamine signaling may also ameliorate the behavioral and cognitive phenotypes that accompany addiction 122. Cocaine and methamphetamine show similarities in dopamine dysfunctions; however, the magnitude of severity of dopamine deficiencies between stimulants play key roles in medication
effectiveness along with some key differences, such as DAT or TAAR1 expression. In addition to the differences between cocaine and amphetamines on dopamine function as factors in the efficacy of treatment options, the lack of compliance and differences in the frequency and duration of treatments may also have impact on the lack of definitive results in clinical trials. In addition, psychiatric comorbidity, baseline drug use, levels of education and neurocognitive impairments also complicate treatment outcomes 123. While these variables need to be considered when examining the success or failure of pharmacotherapies, they are insufficient if individual variability in neurobiological factors that determine the response to medications exists between treatment-seeking participants. Future studies investigating new pharmacotherapies while considering the interactions between psychosocial variables, psychiatric comorbidities, demographic variables and neurobiological variability would greatly advance the development of tailored treatment approaches for stimulant use disorders.

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Figure 1. Mechanistic comparisons of methamphetamine and cocaine and the implications for treatment.

Similarities and differences between methamphetamine and cocaine on dopamine signaling may confer differences in treatment approaches.