UNDERSTANDING COCAINE REWARD: A SHIFT IN PERSPECTIVE

Devin Walker

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ABSTRACT

Background and Rationale
Cocaine is known to prevent the uptake of monoamines (dopamine (DA), serotonin (5-HT) and norepinephrine (NE)) by transporters. However, understanding of how cocaine produces rewarding and reinforcing effects remains limited. For many years, cocaine's rewarding and reinforcing effects were explained by cocaine's action on the DA transporter (DAT), preventing reuptake of DA and increasing dopaminergic neurotransmission in the mesolimbocortical pathways. This explanation will henceforth be referred to as the 'DAT hypothesis'. However, novel, competing theories of cocaine's mechanism of action are emerging, one of which describes multi-transporter participation. In this review, the shortcomings of the DAT hypothesis, evidence supporting multi-transporter participation, and current gaps in understanding cocaine's rewarding and reinforcing effects will be explored.

Hypothesis
The mechanism of cocaine's rewarding and reinforcing effects is likely more complex than the DAT hypothesis proposes, involving actions on multiple monoamine transporters.

Aims
In this review, limitations of the DAT hypothesis, the multi-transporter explanation, and knowledge gaps in cocaine's mechanism of producing rewarding and reinforcing effects will be summarized. Next steps will be proposed.

Main Findings
The DAT hypothesis has significant limitations and refutations. For example, homozygous DAT knockout mice exhibit cocaine conditioned place preference (CPP) and self-administer cocaine, indicating DAT is not necessary for cocaine's rewarding or reinforcing effects. One novel hypothesis posits cocaine acts at multiple transporters, including DAT, the 5-HT transporter (SERT) and NE transporter (NET) to mediate such effects. Moreover, while dopamine pathways' participation in drug reinforcement mechanisms have been well established, it is also possible DA-independent mechanisms contribute to cocaine's rewarding and reinforcing effects. Additionally, SERT's ability to 'compensate' for lack of functional DAT and thereby maintain cocaine reward suggests cocaine's mechanism of generating rewarding and reinforcing effects has some intrinsic redundancy. Ultimately, the findings discussed in this review suggest cocaine reward and reinforcement are mediated by a diffuse mechanism involving DAT, SERT and NET. However, other targets of cocaine such as intracellular sigma-1 receptor and Toll-like receptor 4 may also be involved in mediating its rewarding and reinforcing effects.

Conclusions and Significance
Understanding cocaine's mechanism of producing rewarding and reinforcing effects is clinically relevant, because understanding this pharmacology may aid in the development of more effective therapies for cocaine addiction. This goal is globally relevant, because cocaine has become one of the most frequently consumed illegal drugs over the past 30 years. As such, seeking to understand cocaine's mechanism of generating reward and reinforcement is a valuable endeavor.

Introduction: Background, Rationale, Objective

Cocaine is an addictive stimulant drug produced from the leaves of the Erythroxylum coca plant and sold in two forms: cocaine powder and "crack" (Dinis-Oliveira, 2015; Ryan, 2019). Cocaine powder is commonly inhaled or dissolved in water and injected while crack is smoked. Although cocaine is used across all demographic groups, the drug is frequently abused by adolescents and young adults (Ryan, 2019). Alarmingly, cocaine dependence develops faster than marijuana or alcohol dependence (Wagner & Anthony, 2002). In fact, cocaine dependence develops within the first year of use for 5 - 6% of users. Additionally, the earlier a young adult tries cocaine, the higher the risk he or she develops issues related to cocaine (Wagner & Anthony, 2002). In terms of relative drug harmfulness, cocaine's ranking varies depending on the ranking criteria applied. While one study which considered three categories of harm - physical harm to the drug user, risk of developing drug dependence, and social harm of drug use on families, communities and societies - ranked cocaine as the 2nd most harmful drug after heroin, another study which categorized types of harm as either harming others or harming self deemed crack cocaine to be the 3rd most harmful drug after alcohol and heroin (Nutt, King, Saulsbury, & Blakemore, 2007).

Despite the prevalence of cocaine use and its consequences, how cocaine generates rewarding and reinforcing effects remains mysterious. Cocaine's effects on the mesocorticolimbic dopaminergic system – involved in reward and inhibition - have been extensively studied and have led to the "DAT hypothesis" (Ryan, 2019). While the DAT hypothesis has served as the dogma of cocaine's rewarding and reinforcing effects, the hypothesis has limitations. This review will explore the DAT hypothesis and its shortcomings, analyze the multi-transporter explanation, summarize knowledge gaps and propose next steps.

This review's objective is to further understand cocaine reward and reinforcement as this may facilitate development of more effective therapeutics for cocaine users and addicts.

The DAT-is-it Hypothesis and its Limitations

MJ Kuhar, a primary proponent of the DAT hypothesis, described in 1991, "cocaine binds at the dopamine transporter and mainly inhibits neurotransmitter re-uptake; the resulting potentiation of dopaminergic neurotransmission in mesolimbocortical pathways ultimately causes reinforcement" (Kuhar, Ritz, & Boja, 1991). In other words, this hypothesis proposes that cocaine's inhibition of DA uptake by DAT increases DA levels in synapses within the mesocorticolimbic system and thereby causes cocaine reward (Kuhar et al., 1991).

The DAT hypothesis is built upon research. Many studies have supported DA pathways' involvement in drug reinforcement. First, inhibition of the DA receptor alters self-administration of psychostimulants. For example, one study demonstrated that chlorpromazine – a DA receptor D2 antagonist – increased cocaine self-administration by Rhesus monkeys (Wilson & Schuster, 1972). This increase may be due to chlorpromazine's blocking of cocaine's rewarding effects; if chlorpromazine blocked cocaine's rewarding effects, the monkeys may have self-administered more cocaine to compensate. Note, however, that this result can also be interpreted as indicative of an increase in cocaine's reinforcing effects; perhaps chlorpromazine led the monkeys to self-administer more cocaine because cocaine acted as a stronger reinforcer after D2 receptor blockade. Additionally, studies have illustrated that cocaine reinforcement relies on DA signaling but not NA signaling. One such study showed that 6-hydroxydopamine (6-OHDA)-induced lesion of the nucleus accumbens (NAc) decreased DA in the NAc by 90% and striatal DA by 24% and decreased cocaine self-administration by rats (Roberts, Corcoran, & Fibiger, 1977). In contrast, 6-OHDA-induced lesion of the dorsal and ventral NA bundles decreased NA

in the hippocampus and cortex by 96% and NA in the hypothalamus by 72% but did not reduce cocaine self-administration. In addition, a correlation between DAT inhibition and cocaine reinforcement has been found. In one study, the relative potencies of cocaine and cocaine-like drugs in inhibiting [3H]mazindol from binding DAT in the rat striatum correlated with their relative potencies in self-administration by monkeys (Ritz, Lamb, Goldberg, & Kuhar, 1987). Notably, this supports the idea that DAT blockade is sufficient for cocaine's reinforcing effects.

More recently, researchers have tested the DAT hypothesis by generating knock-in mice possessing a mutant DAT which transports DA but has reduced sensitivity to cocaine (Chen et al., 2006). The mutant DAT's decreased sensitivity to cocaine means that doses of cocaine which inhibit WT DAT should not significantly inhibit the mutant DAT. This was confirmed in the present study, in which 20 mg/kg cocaine increased extracellular DA in the NAc of WT mice but not in mutant DAT mice. In a CPP test, doses of 5 and 20 mg/kg cocaine led to CPP in WT mice but not in mutant DAT mice. Since the researchers found that cocaine CPP persisted in DAT knockout mice, the lack of cocaine CPP observed in mutant DAT mice appeared to be due to cocaine's inability to inhibit the mutant DAT and thereby increase DA neurotransmission. This finding further supports the idea that DAT blockade is sufficient for cocaine's rewarding effects.

However, there are limitations to the DAT hypothesis. One of the most significant limitations is that while DAT blockade appears sufficient to generate cocaine's rewarding and reinforcing effects, DAT blockade is not *necessary* for these effects. This has been demonstrated by homozygous DAT knockout mice which exhibited CPP (Sora et al., 1998) and self-administered cocaine (Rocha et al., 1998). Together these results imply DAT blockade is not necessary for cocaine's rewarding or reinforcing effects, challenging the DAT hypothesis. To complicate things further, some studies suggest DAT blockade is not sufficient for cocaine's

reinforcing effects. One study demonstrated that, in contrast to cocaine, GBR-12909, a selective DAT inhibitor, was not self-administered by rats (Tella, Ladenheim, Andrews, Goldberg, & Cadet, 1996). The failure of this selective DAT inhibitor to produce reinforcing effects further challenges the DAT hypothesis. One hypothesis as to why GBR-12909 and other selective DAT inhibitors are not self-administered at rates comparable to cocaine is that cocaine functions as a DAT reverse agonist, reversing DAT function and thus promoting DA efflux (Heal, Gosden, & Smith, 2014). Notably, if true, this fundamentally sets cocaine apart from GBR-12909 and other selective DAT inhibitors which simply reduce DA uptake by DAT.

The Multi-Transporter Explanation of Cocaine Reward

Cocaine not only targets DAT, but also targets SERT and NET, blocking uptake of DA, 5-HT and NE (Rocha, 2003). However, whether cocaine blocks uptake of 5-HT and NE at concentrations encountered by human cocaine users remains unclear. Nevertheless, cocaine's multiple binding sites suggest that cocaine may alter dopaminergic neurotransmission in the mesocorticolimbic region through multiple, independent or connected pathways. Alternatively, cocaine may generate its rewarding and reinforcing effects independently of this dopaminergic system through its effects on 5-HT and NE signaling.

To understand how each monoaminergic system individually contributes to cocaine reward, the genes encoding DAT, SERT and NET have all been deleted in various studies. For example, a mouse model lacking NET has been generated, and these animals demonstrated lower NE clearance, increased extracellular NE, and increased cocaine CPP (Xu et al., 2000). This finding indicates that NET may play a role in mediating cocaine's rewarding effects. It is possible NET mediates cocaine's rewarding effects by modulating the midbrain's dopaminergic signaling. Striatal DA and DA metabolite concentrations as well as DA synthesis rates were

decreased by ~20% in the NET-/- mice compared to WT mice (Xu et al., 2000). However, NET-/- mice developed stronger cocaine CPP than WT mice. This seemingly contradictory observation led researchers to consider postsynaptic responses. Through a mixed D2/D3 receptor agonist (quinpirole) and a [35S]GTPγS binding assay, it was illustrated that striatal D2 and D3 receptors were more efficiently linked to their G proteins in NET-/- mice than WT mice. This increased efficiency in receptor-G protein coupling may facilitate increased D2/D3 sensitivity in the midbrain dopaminergic system of NET-/- mice, and this increased D2/D3 sensitivity may explain NET-/- mice's enhanced cocaine CPP. It is important to note, however, that D2 receptors are located not only postsynaptically but also presynaptically (Ford, 2014). However, the researchers do not discuss the possibility that presynaptic D2 receptors may also have altered efficiency in their linkage to G proteins in the NET-/- mice, and this lack of discussion limits this study's conclusiveness. Regardless, these results support the idea that the DAT hypothesis is oversimplified, because the knockdown of NET enhances cocaine's rewarding effects, indicating NET participates in the mechanism(s) by which cocaine generates rewarding effects.

The multi-transporter explanation of cocaine's rewarding effects has gained traction partly because many compounds which inhibit DAT with high potency fail to produce rewarding effects as strong as cocaine's (Sora et al., 1998). For example, mazindol does not carry the same abuse or addiction potential cocaine carries, but the molecule potently inhibits both DAT and NET while moderately inhibiting SERT. Comparing mazindol to cocaine, it is possible that mazindol's failure to produce strong rewarding effects derives from its lack of SERT inhibition. However, other factors including but not limited to the speed at which mazindol reaches the brain after administration and how quickly the drug is metabolized may also limit mazindol's rewarding effects. Also, as previously discussed, cocaine may act as a DAT inverse agonist,

limiting the usefulness of a comparison of mazindol and cocaine. Nevertheless, researchers have hypothesized that DAT and SERT provide redundancy, so that if DAT is knocked out, SERT can mediate cocaine's rewarding effects, and vice versa. To test this hypothesis, double knockout mice lacking either one or two copies of the genes encoding DAT and SERT were generated (Sora et al., 2001). While the pattern of results was quite complex, the most compelling finding was that DAT+/- SERT-/- mice maintained cocaine CPP while DAT-/- SERT+/- and DAT-/- SERT-/- mice failed to exhibit cocaine CPP. This finding represents the first time a small set of genes have been identified which – when knocked out – eliminate cocaine's rewarding effects. The researchers extrapolate that cocaine may act at both DAT and SERT to produce rewarding effects and/or DAT or SERT – through redundancies - may be able to compensate for the absence of the other, preserving cocaine's rewarding effects (Sora et al., 2001). Additionally, because DAT+/- SERT-/- mice maintained cocaine CPP while DAT-/- SERT+/- mice did not, dopaminergic neurotransmission likely plays a more central role than serotonergic neurotransmission in cocaine's rewarding effects.

Current Knowledge Gaps in Cocaine Reward

Currently there are several knowledge gaps in the field of cocaine reward and reinforcement. One remaining question is whether CPP accurately predicts drug self-administration. If a mouse fails to express cocaine CPP, spending equivalent amounts of time in the cocaine-paired and saline-paired compartments of its test cage, can it be assumed that this mouse will not self-administer cocaine? The answer remains uncertain. While CPP scores indicate how much time an animal spends in an environment it has associated with a rewarding stimulus (e.g. cocaine), thereby measuring the stimulus' rewarding effects, drug self-administration paradigms directly measure an animal's tendency to administer the given drug and thus measure the drug's

reinforcing effects. Another key difference is that CPP testing involves passive drug administration, while self-administration involves active drug seeking behavior. One significant concern about CPP use in experiments aiming to understand cocaine's rewarding and reinforcing effects in humans is its lack of face validity, because CPP has never been experimentally demonstrated in humans (Bardo & Bevins, 2000). Perhaps the closest phenomenon to CPP which has been illustrated in humans is the tendency to choose a pill which has been associated with a drug experience over a pill which has been associated with a placebo experience, but this does not reflect preference for an environmental context that has been associated with a drug.

Another remaining question in the field is whether cocaine's route of administration impacts the mechanism(s) by which it generates its rewarding effects. This question has arisen because cocaine CPP depends on DA neurotransmission when the cocaine is administered intravenously (IV) or intracerebrally (ICV) (Morency & Beninger, 1986; Spyraki, Nomikos, & Varonos, 1987), but not when it is given by intraperitoneal (IP) injection (Spyraki, Fibiger, & Phillips, 1982). In other words, giving a DA receptor antagonist can prevent IV or ICV cocaine CPP but not IP cocaine CPP (Nomikos & Spyraki, 1988). This discrepancy raises the question of whether cocaine CPP testing reflects a different reward-generating mechanism or process potentially involving different substrates when the route of cocaine administration varies. In an attempt to answer this question, researchers have searched for other differences in cocaine CPP between IV and IP administration routes. One such difference involves dose-response effects; while IV cocaine at doses of 0.5-2.5 mg/kg produced CPP in rats, a dose of 10 mg/kg was required for IP cocaine to produce an equivalent CPP in rats (Nomikos & Spyraki, 1988). This dose-effect difference raises another question of whether CPP testing is perhaps inadequate to assess the rewarding effects IP cocaine generates.

In addition, while the limitations of the DAT hypothesis and evidence supporting multi-transporter participation in cocaine reward discussed in this review are compelling, understanding of the relative roles of DAT, SERT and NET in mediating cocaine's rewarding and reinforcing effects remains limited. Likewise, understanding of the extent to which cocaine's rewarding and reinforcing effects depend on dopaminergic neurotransmission in mesolimbocortical pathways remains limited; it is possible that cocaine's targeting of SERT and NET contribute to cocaine's rewarding and reinforcing effects through mechanisms independent of dopaminergic neurotransmission. As such, understanding of how cocaine's rewarding and reinforcing effects develop on a molecular level remains insufficient. Of course, research in humans on cocaine use also remains limited, and understanding cocaine's rewarding and reinforcing effects in animal models may not translate to such understanding in humans.

Conclusions and Next Steps

Cocaine's mechanism of generating rewarding and reinforcing effects is complex. The DAT hypothesis is oversimplified; cocaine does not generate rewarding and reinforcing effects through blockade of DAT alone. Instead, cocaine acts in a diffuse manner with many targets including but not limited to DAT, NET and SERT. It appears that cocaine's actions at these targets ultimately increase DA neurotransmission, but this increase in DA neurotransmission cannot be assumed to be a cause of cocaine's rewarding or reinforcing effects.

Considering current knowledge gaps, one valuable next step would be conducting studies which use drug self-administration and other methodologies more directly associated with drug-taking behavior than CPP to measure cocaine's rewarding and reinforcing effects. Secondly, studies which aim to identify additional targets of cocaine implemented in its rewarding and reinforcing effects may offer greater mechanistic understanding. Recently, researchers have

suggested that cocaine exerts its reinforcing effects not through DAT blockade but instead by mediating afferent input to DA neurons in the midbrain (Oliva & Wanat, 2019). This hypothesis has arisen because DAT function was found to be only slightly limited by cocaine doses that were reinforcing in self-administration paradigms (Brodnik, Ferris, Jones, & Espana, 2017). It is important to note that the inhibition of DAT function (or inhibition of DA uptake) does not equate to DAT occupancy. In fact, while 1 mg/kg cocaine has been found to occupy 70-80% of DATs in binding and PET studies, this dose only minimally inhibited DA uptake as demonstrated by fast cyclic voltammetry (Brodnik et al., 2017). While the hypothesis that cocaine exerts its reinforcing effects by mediating afferent input to DA neurons in the midbrain has been proposed, with the VTA as a region of particular interest, which VTA afferents, which neurons in the VTA and what specific synaptic changes on DA and non-DA neurons in the VTA are involved remains unclear (Oliva & Wanat, 2016). Thus, more thorough study of the neural circuits underpinning cocaine's reinforcing effects may serve as a next step. Other potential targets of cocaine which merit further investigation include the intracellular sigma-1 receptor which may participate in a DA-independent mechanism in D1 receptor-expressing NAc neurons contributing to cocaine's reinforcing effects (Delint-Ramirez, Garcia-Oscos, Segev, & Kourrich, 2020) and Toll-like receptor 4 on microglial cells which seems to participate in cocaine signaling that induces extracellular dopamine in the NAc and maintains cocaine CPP and self-administration (Northcutt et al., 2015). Thirdly, studies which use animal models that are highly relevant to humans such as primates will continue to be valuable. Ultimately, more robust understanding of cocaine's mechanism of generating rewarding and reinforcing effects may facilitate development of more effective therapeutics for human cocaine users, aiding in the fight against addiction.

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