

Adaptations of Presynaptic Dopamine Terminals Induced by Psychostimulant Self-Administration

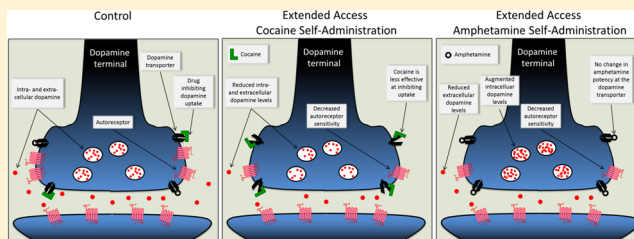
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ABSTRACT: A great deal of research has focused on investigating neurobiological alterations induced by chronic psychostimulant use in an effort to describe, understand, and treat the pathology of psychostimulant addiction. It has been known for several decades that dopamine neurotransmission in the nucleus accumbens is integrally involved in the selection and execution of motivated and goal-directed behaviors, and that psychostimulants act on this system to exert many of their effects. As such, a large body of work has focused on defining the consequences of psychostimulant use on dopamine signaling in the striatum as it relates to addictive behaviors. Here, we review presynaptic dopamine terminal alterations observed following self-administration of cocaine and amphetamine, as well as possible mechanisms by which these alterations occur and their impact on the progression of addiction.

KEYWORDS: Drug abuse, self-administration, cocaine, amphetamine, addiction, dopamine



Investigations of the neurochemical mechanisms underlying psychostimulant addiction have largely focused on the dopamine system. Dopaminergic neurons that project from the ventral midbrain and synapse on medium spiny neurons in the striatum mediate the reinforcing properties of psychostimulants and also encode the relationships between drug effects and environmental stimuli that predict the availability and delivery of drug.^{1,2} Indeed, pharmacological and genetic manipulations have demonstrated that dopamine signaling in the nucleus accumbens (NAc) is necessary for self-administration of psychostimulants in rodents.^{3–6} In addition to mediating the acute rewarding effects of abused drugs, this circuit is markedly dysregulated following chronic psychostimulant administration, and it is thought that alterations in dopamine neurotransmission underlie the increased motivation to obtain psychostimulants observed in psychostimulant abusers.⁷ Here we will review the consequences of psychostimulant self-administration on presynaptic dopamine terminal function in an effort to understand the dopaminergic adaptations that are involved in the process of addiction (Table 1).

Psychostimulants are most often classified under two broad categories, depending on their mechanism of action at the dopamine transporter (DAT) (Figure 1). “Blockers”, such as cocaine, elevate dopamine levels through inhibition of the DAT, preventing reuptake from the extracellular space and thereby increasing the concentration and time that dopamine spends interacting with its receptors.¹ “Releasers”, such as amphetamine (AMPH), also slow dopamine uptake through competitive DAT inhibition, but unlike blockers, releasers act as substrates for the DAT and are transported across the plasma

Table 1. Summary of the Effects of Cocaine and Amphetamine Self-Administration on Presynaptic Dopamine Terminal Function^a

	cocaine	amphetamine
tonic signaling	↓	↓
electrically evoked release	↓	↑
phasic (cue-evoked) signaling	↓	unknown
autoreceptors	↓	↓
uptake	variable	no change
potency	↓ ^b	no change

^aFor discussion of findings see: Tonic signaling and electrically evoked release (subsection 1.1), phasic (cue-evoked) signaling (subsection 1.2), autoreceptors (section 2), uptake (section 3), potency (subsection 3.1). ^bPotency changes are dependent on pattern of intake, with continuous intake producing decreased potency (tolerance) and intermittent intake producing increased potency (sensitization).

membrane. Once inside the cell, releasers collapse vesicular pH gradients, allowing dopamine to flow out of the vesicle and into the cytoplasm.^{1,8,9} AMPH “reverses” the DAT such that dopamine is moved from the cytoplasm to the extracellular space, in the opposite direction to normal dopamine transport, thus elevating synaptic dopamine levels.^{1,9} Although the discriminative stimulus properties (i.e., the internal subjective

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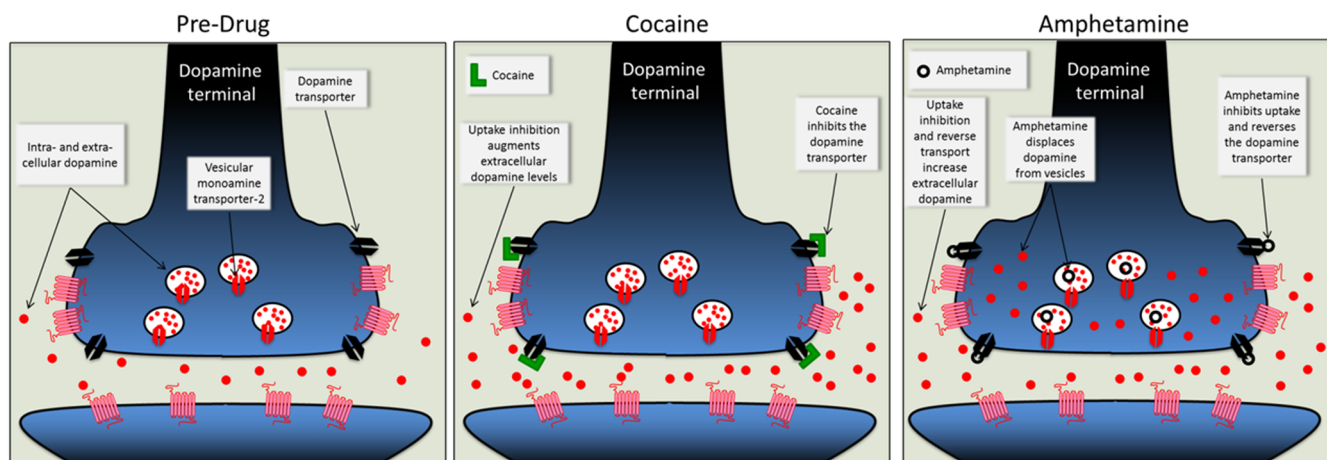


Figure 1. Depiction of the dopamine terminal (left) and the acute effects of cocaine (middle) or amphetamine (right) on dopamine neurotransmission.

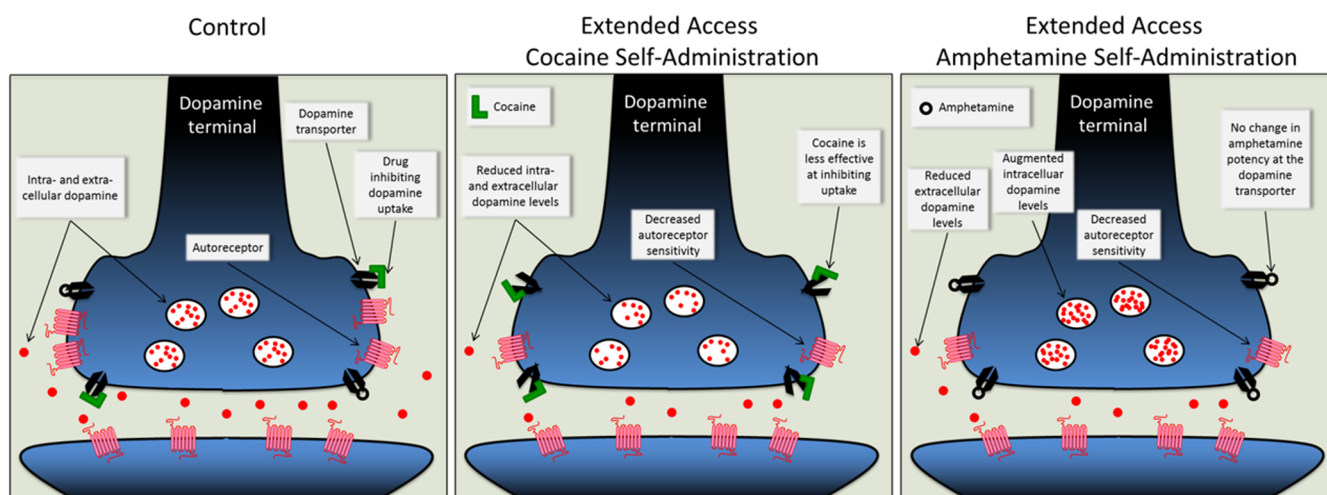


Figure 2. Depiction of the dopamine terminal (left) and the effects of extended access self-administration of cocaine (middle) or amphetamine (right) on presynaptic regulators of dopamine neurotransmission.

qualities, or how it “feels”) of these two drug classes are indistinguishable¹⁰ and their reinforcing properties are comparable,¹¹ the neurochemical alterations that result from chronic administration of blockers or releasers are often divergent.^{12,13} Because a focus of much of the preclinical addiction literature has been finding a treatment that reduces addictive-like behaviors, it is particularly important to describe the neurobiological impact of these two types of drugs following repeated use, in order to determine whether differential pharmacological interventions based on abused drug class may be advantageous. Thus, we will focus on the similarities and disparities between the consequences of cocaine and AMPH self-administration on dopamine presynaptic terminals in the NAc (Figure 2).

While many psychostimulants inhibit the dopamine, norepinephrine, and serotonin transporters, only the DAT has been shown to be responsible for the rewarding and reinforcing properties of these compounds, as well as their locomotor stimulating effects. First, DAT knockout animals are unresponsive to the locomotor stimulating effects of both cocaine and AMPH¹⁴ and, in fact, exhibit reductions in locomotor activity when administered stimulants, through elevations in serotonin levels.¹⁵ In addition, transgenic animals

that express mutated transporters that have intact dopamine uptake function but decreased cocaine binding, coined “cocaine-insensitive transporters”, are insensitive to the rewarding effects of cocaine.¹⁶ In regard to the subjective effects of psychostimulants, drugs that bind only to the DAT have similar rewarding and reinforcing effects as those that bind to all three monoamine transporters, such as cocaine and AMPH, confirming that DAT inhibition mediates their discriminative stimulus effects.^{17,18} Finally, in human studies, drug binding at the DAT in the NAc has been shown to be correlated with the self-reported “high” experienced by the user following administration of both cocaine¹⁹ and AMPH.²⁰ Taken together, these results highlight the fact that the DAT is essential for the reinforcing and rewarding effects of psychostimulants.

1. PRESYNAPTIC DOPAMINE RELEASE

Dopamine cell firing is considered to be either “tonic” (pacemaker-like slow (2–10 Hz) which determine basal extracellular dopamine levels) or “phasic” (rapid (≥ 20 Hz) discrete bursts of firing (4 or more action potentials)) which produce transient, large-amplitude increases in dopamine levels.^{21,22} Tonic dopamine levels preferentially activate high

affinity D2-type dopamine receptors, while phasic dopamine release saturates D2-type receptors and activates low affinity D1-type dopamine receptors.²³ Tonic and phasic signaling are both required for the execution of motivated behaviors and work together to reinforce advantageous outcomes while reducing disadvantageous behaviors. Recent work from Hernandez et al.²⁴ demonstrated that increased dopamine tone (tonic levels) enhanced reward seeking and hypothesized that this could be due increased reward elicited by subsequent environmental events. In other words, increases in dopamine tone prime the system to be more responsive to phasic signaling events, making rewarding stimuli more salient.

1.1. Extracellular Dopamine Tone. Basal dopamine levels, or dopamine tone, are continuously present at a steady-state in the extracellular space and exert inhibitory feedback onto dopamine neurons through activation of presynaptic D2-type autoreceptors to regulate tonic levels as well as the frequency and amplitude of phasic release events.^{23,25} Drug-induced decreases in basal dopamine levels, or hypodopaminergic states, have long been hypothesized to mediate anhedonia during psychostimulant withdrawal and thereby contribute to the difficulty in achieving sustained abstinence.^{26,27} Indeed, reductions in tonic dopamine levels have been linked to increases in intracranial self-stimulation thresholds (i.e., animals need a greater stimulation to produce reinforcement), indicating that animals are less sensitive to rewarding stimuli.²⁸ Thus, drug induced reductions in tonic dopamine neurotransmission may drive reductions in reward and reinforcement elicited by nondrug stimuli, such as food or social interactions, a phenomenon which is commonly observed in psychostimulant addicts during abstinence.^{29,30}

Both cocaine and AMPH acutely elevate tonic dopamine levels,¹ but result in reduced basal extracellular dopamine levels as measured by microdialysis 18 h following extended access self-administration, possibly as a compensatory response to chronic drug-induced dopamine elevations.^{12,31} One possible mechanism for reductions in basal dopamine levels following cocaine or AMPH self-administration is that increased synaptic dopamine levels, due to drug-induced inhibition of uptake, are subject to enzymatic degradation rather than repacking into vesicles; thus release may be reduced, and more dependent on dopamine synthesis. In support of this hypothesis, we have observed reductions in electrically evoked dopamine release following extended access cocaine self-administration (refs 12, 13, and 32–34 but see ref 35), suggesting that intracellular dopamine levels are reduced. In contrast, following extended access AMPH self-administration, intracellular and extracellular levels appear to be differently affected, whereby extracellular levels are decreased¹² and electrically evoked dopamine release is increased³⁶ (Figure 2).

1.2. Phasic Dopamine Signaling. Phasic dopamine cell firing, typically defined as a burst of 4 or more action potentials at a rate of ≥ 20 Hz, produces large transient increases in striatal dopamine release, resulting in dopamine concentrations estimated to be in the hundred micromolar range within the synapse.^{23,37} Elevated dopamine concentrations produced by phasic burst firing saturate D2-type receptors and activate D1-type dopamine receptors.²³ The signal is quickly terminated via reuptake through the DAT as the neurotransmitter diffuses out of the synapse and into the extrasynaptic space. Phasic dopamine signaling often occurs in response to cues predicting drug availability and is directly linked to the selection and execution of goal-directed movement.^{2,38–41}

Conditioning experiments have shown that both reinforcers and their antecedent cues can elicit a phasic dopamine response, depending on training session.^{42–44} Indeed, with the initial or unexpected presentation of a reward, a phasic dopamine response occurs immediately following reward presentation. With repeated cue-reward pairings the dopamine response is shifted so that it occurs in response to the cue predicting reward availability, which then promotes seeking behavior for the anticipated reward.^{2,45–47} The strong cue-reward associations formed during drug use are postulated to play an integral role in driving the inelastic drug seeking behaviors that are characteristic of addicted individuals.

Both cocaine and AMPH acutely augment the amplitude and frequency of phasic dopamine signals^{48,49} which likely results in enhanced phasic dopamine responses to environmental stimuli when cocaine or AMPH are “on board”. Changes in dopaminergic responses to drug-paired stimuli are particularly important, as it is hypothesized that cue-induced drug seeking is responsible for craving and relapse, which can occur even after years of abstinence.^{50,51} Indeed, the magnitude of dopamine signaling during the presentation of cocaine-associated stimuli is predictive of craving.⁵² However, while one may postulate that repeated cocaine self-administration would increase the phasic dopamine response to cocaine-associated cues, recently it was shown that during extended access cocaine self-administration, the amplitude of cue-induced phasic dopamine release progressively decreased over sessions.⁵³ The decrease in phasic signaling amplitude was highly correlated with escalation of cocaine intake over sessions, suggesting that decreased cocaine-paired stimuli-induced phasic dopamine release may drive the transition from recreational to excessive cocaine use.⁵³ Further, it is possible that these changes, characterized by the inability of the dopamine system to mount an appropriate phasic dopamine response to cue/reward presentation, may prevent the formation of new, nondrug, cue-reward associations, thus increasing the difficulty of replacing drug taking and seeking with more adaptive behaviors.^{38,39}

2. D2-TYPE AUTORECEPTORS

D2-type autoreceptors are located on dopamine terminals throughout the brain and dopamine cell bodies in the ventral midbrain; activation of these receptors decreases terminal excitability, dopamine release and synthesis.^{54,55} Thus, these receptors provide a means of inhibitory feedback on dopamine neurotransmission and have been shown to be important in regulating both tonic and phasic dopamine signaling.²⁵ As such, the function of this receptor is an important determinant in reward and reinforcement. Indeed, genetic deletion of presynaptic D2 receptors greatly augments the locomotor stimulating and rewarding effects of cocaine in a place preference paradigm.⁵⁶ Additionally, mice with a genetic deletion of presynaptic D2 autoreceptors show increased reinforcing efficacy of food, suggesting that decreased autoreceptor regulation augments reward and reinforcement for both natural and drug rewards.⁵⁶

2.1. Autoreceptor Changes Following Cocaine Administration. Given the integral involvement of autoreceptor regulation in modulating dopamine neurotransmission and motivated behaviors, much work has focused on the effects of psychostimulant administration on D2-like autoreceptors. Work from our lab has shown that, following 24 h access cocaine self-administration, the ability of quinpirole, a D2-receptor agonist, to decrease dopamine release is markedly

decreased and this effect remains for 7 days of abstinence.³³ Similarly, cocaine self-administration has been shown to produce desensitization of autoreceptors on dopamine cell bodies in the midbrain.⁵⁷ These findings are consistent with other investigations showing decreased autoreceptor sensitivity following experimenter delivered cocaine measured *in vivo*^{58,59} and *ex vivo*.^{60,61} Further, cocaine-induced reductions in autoreceptor regulation have been linked to increases in the locomotor stimulating effects of cocaine⁶² and increased cocaine-induced dopamine overflow.⁵⁸ Together, these findings indicate that cocaine use “takes the brakes off” of the dopamine system via disruptions in autoregulation which may contribute to a loss of control over drug-seeking behaviors.

2.2. Autoreceptor Changes Following AMPH Administration. Similar to findings with cocaine, D2-type receptor autoregulation of presynaptic dopamine release was markedly attenuated in the NAc following 5 days of extended-access AMPH administration.³⁶ In addition, D2 receptors located on VTA dopamine cell bodies also had reduced function. Interestingly, the reductions in cell body and terminal autoreceptors occur via different mechanisms. In the midbrain, D2 autoreceptors are primarily coupled to *Gai2* for signaling; following AMPH self-administration the relationship between *Gai2* and D2 receptors is abolished.³⁶ Conversely, in striatal regions, D2 receptor coupling to either *Gai2* or *Gao* is unchanged.³⁶ The disruption of coupling in the midbrain was shown to be through enhanced RGS2 (regulator of G-protein signaling 2) activity resulting from increased RGS2 trafficking to the membrane.³⁶ RGS proteins act to terminate G-protein signaling by enhancing GTP hydrolysis by the alpha subunit of G proteins, thereby inactivating the protein and reducing signaling via concomitant signal transduction cascades.⁶³ Thus, increases in expression levels and trafficking to the membrane act to terminate signaling via D2 receptors in the midbrain, rendering them less effective at regulating cell firing and likely promoting aberrant activity. These findings provide a mechanism for previous results showing AMPH-induced reductions in autoreceptor sensitivity in the ventral midbrain,^{64,65} although this does not explain the decreased D2 regulation of presynaptic dopamine release on terminals as receptor coupling to *Gai2* or *Gao* was unchanged in the striatum.³⁶

2.3. Effect of Decreased Autoreceptor Function on Dopamine Tone. Psychostimulant self-administration-induced decreases in autoreceptor sensitivity are somewhat paradoxical, as tonic dopamine levels are also reduced following self-administration of both cocaine and AMPH (see subsection 1.1). Because autoreceptors decrease dopamine release, and negatively regulate tonic levels, it would be expected that decreased sensitivity of the receptor would produce increases in tonic dopamine levels. However, both autoreceptor sensitivity and basal dopamine levels are decreased following cocaine self-administration, suggesting that these adaptations are mediated through different mechanisms and changes in tonic dopamine levels may be due to alterations in release machinery, such as decreased readily releasable dopamine stores. The concomitant decreases in basal dopamine levels and autoreceptor sensitivity may converge to drive an overall reduction in activity of striatal regions, especially during acute withdrawal from chronic self-administration.

3. THE DOPAMINE TRANSPORTER

Dopamine uptake through the DAT is responsible for terminating phasic signaling events and has also been shown to regulate tonic extracellular dopamine levels.^{66–68} DAT expression/function can have profound effects on dopamine-mediated behaviors and is often altered by drug administration. In animal models of cocaine abuse, alterations in DAT function/expression have been variable. In our lab, we have observed increases,³³ decreases,^{12,13,32,34} and no change^{12,35,36} in dopamine uptake rates following cocaine or AMPH self-administration. Similarly, in human cocaine addicts, increased, decreased,⁶⁹ and no change in⁷⁰ DAT levels have been observed, with a preponderance of studies showing increased DAT levels in human addicts.^{71–73} However, it is possible that DAT function and affinity (for stimulants) could be changed independently of alterations in absolute levels of transporters which could have profound effects on stimulant self-administration.

3.1. Sensitization and Tolerance of Psychostimulant Effects at the DAT. Early investigations of the consequences of repeated psychostimulant administration revealed that prior drug administration can alter the ability of psychostimulants to elicit behavioral responses.^{74–76} These changes fall under two major categories: sensitization and tolerance. Sensitization is characterized by an enhancement of a particular drug effect at a given dose after repeated exposure, and is most often seen following intermittent psychostimulant administration. Conversely, tolerance occurs when more drug is needed to cause the same magnitude of a specific effect that occurred with acute administration, and is most often associated with continuous treatments. Many theories of addiction have proposed that sensitization and tolerance to drug effects are important processes that may both play a critical role the development of addiction and, as such, much work has focused on elucidating the mechanisms underlying these phenomena.^{77–80}

3.2. DAT Changes Following Cocaine Administration. With regard to cocaine, extended access self-administration has been shown to produce tolerance to the locomotor-stimulating effects of cocaine, cocaine-induced dopamine overflow measured by microdialysis, and the ability of cocaine to inhibit the DAT measured by voltammetry.^{12,13,32–35,81} We have shown that as little as 1 day of cocaine self-administration produces putative allosteric modifications to the DAT that result in decreased cocaine-induced uptake inhibition, independent of baseline dopamine uptake rate, and that the decrease in cocaine potency is present for approximately 2 weeks following cessation of cocaine intake, depending on the length of cocaine exposure.^{12,33} Additionally, we have found that, following extended access cocaine self-administration, the ability of cocaine to augment exocytotic dopamine release is blunted (ref 32 but see ref 35). Notably, the cocaine self-administration paradigms used in these studies all produce escalation of responding for cocaine, which has led to the hypothesis that tolerance to cocaine effects is a critical determinant in the development of excessive cocaine intake.^{12,13,32,34,35}

In contrast to the tolerance to cocaine effects that have been observed following self-administration, studies on the effects of experimenter-delivered cocaine have typically revealed sensitization of cocaine effects on both locomotor activity and cocaine-induced dopamine overflow as measured by microdialysis.^{76,82} Experimenter-delivered sensitization paradigms

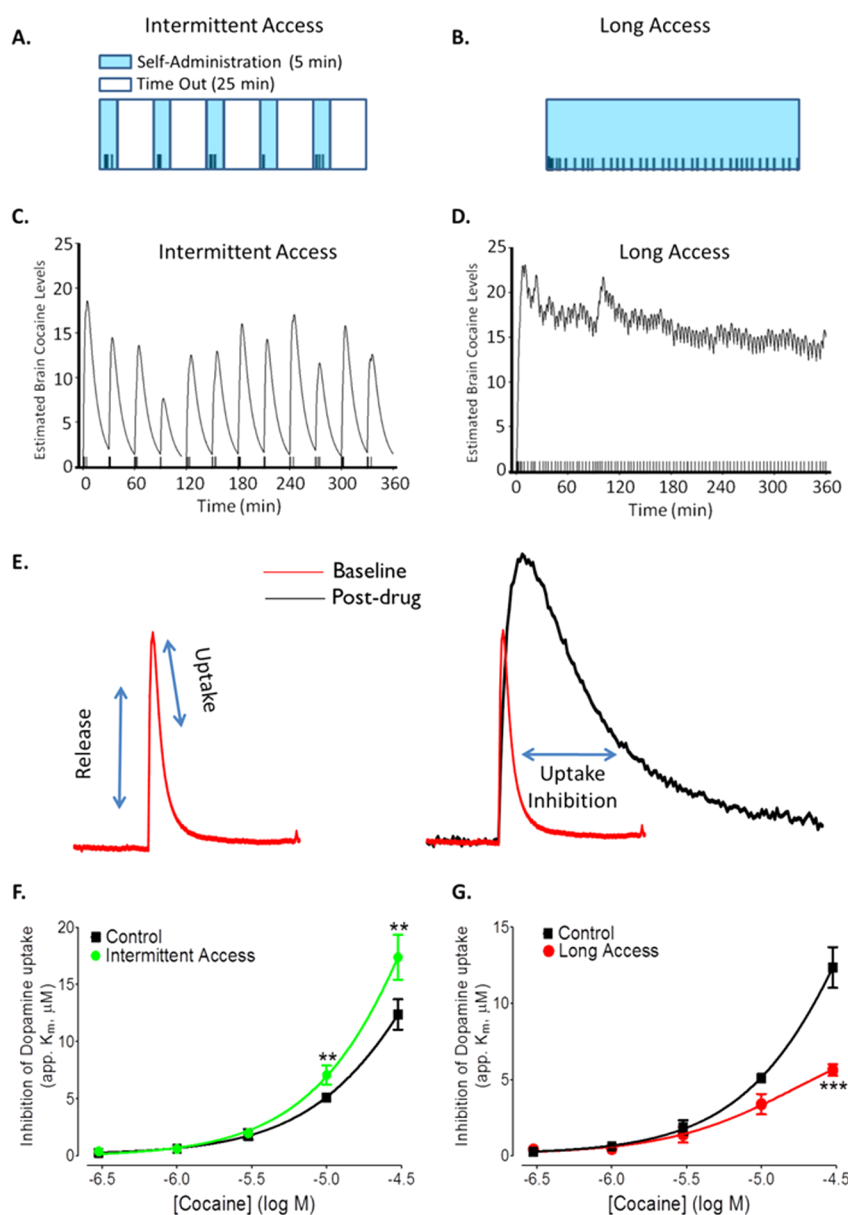


Figure 3. Tolerance and sensitization of cocaine effects at the dopamine transporter are dependent on temporal pattern of administration. (A) Representation of self-administration access periods for intermittent access and (B) long access paradigms. Intermittent access gives 5 min access bins separated by 25 min forced timeout periods, while long access allows for continuous access throughout the session. (C) Intermittent access results in spiking cocaine brain concentration. (D) Long access results in constant brain cocaine concentrations across the session. (E) Representative data depicting voltammetric measurement of release and uptake at baseline (left) and uptake inhibition following bath application of cocaine (right). (F) Intermittent access results in sensitization of cocaine potency at the dopamine transporter. (G) Long access results in tolerance to cocaine inhibition of the dopamine transporter.

often employ single daily or every-other-day injections, resulting in transient levels of drug present in the brain, followed by an abstinence period, while self-administration studies typically engender consistent, regularly spaced patterns of infusions over the course of a session, maintaining continuous concentrations of drug in the brain. A recent study revealed that changes in the ability of cocaine to inhibit the DAT following cocaine exposure are dependent on the temporal profile of administration. Thus, when cocaine is self-administered in an intermittent pattern (25 min forced timeout periods), sensitization of cocaine-induced DAT inhibition occurs; in contrast, continuous exposure, such as in traditional long-access paradigms which allow for 6 h of uninterrupted self-administration, result in tolerance to cocaine's effects at the

DAT³⁵ (Figure 3). Notably, 1 h of continuous self-administration did not alter the ability of cocaine to inhibit the DAT, suggesting that even under continuous administration conditions the development of tolerance requires greater cocaine intake than can be obtained in a 1 h session.³⁵

Alterations in the ability of cocaine to inhibit the DAT translate to behavioral shifts in cocaine effects, because intermittent cocaine administration has been shown to produce sensitization of cocaine-induced locomotion^{76,82} while continuous administration produces tolerance to cocaine-induced locomotion.^{34,83} While the effects of sensitization on cocaine self-administration behaviors have been consistent, with large increases in reinforcing efficacy following paradigms that produce sensitization,^{84,85} changes in reinforcing efficacy

following paradigms that produce tolerance have been variable. For example, both increases^{85,86} and decreases^{87,88} in the reinforcing efficacy of cocaine have been observed following paradigms that produce tolerance to cocaine effects at the DAT.

While it is clear that the pattern in which cocaine is administered is of critical importance in determining the resulting neurochemical consequences, the temporal profile of cocaine use in human abusers remains to be determined, although there is some evidence that it may be intermittent.⁸⁹ Notably, tolerance to the ability of cocaine to increase striatal dopamine levels, as well as tolerance to self-reported euphoria induced by cocaine, have been repeatedly demonstrated in cocaine-dependent individuals and because of this it has been suggested that sensitization models are not relevant to the human population.^{70,90,91} However, emerging evidence suggests that sensitization of psychostimulant effects can be observed in humans. Indeed, Boileau et al.⁹² demonstrated that in nondrug abusing subjects, short-term exposure to AMPH produced sensitization of AMPH-induced increases in dopamine levels in the ventral striatum, and that this effect was still present one year after initial exposure. Additionally, it has been suggested that the lack of sensitization of psychostimulant-induced increases in striatal dopamine in laboratory tests of human cocaine addicts may be a function of the contextual cues present during testing whereby drug-paired cues at the time of drug delivery are required for the expression of sensitization.⁹³ In support of this hypothesis, when subjects were allowed to prepare the cocaine in a familiar manner before ingesting (i.e., using a mirror and razor blade), cocaine-induced increases in dopamine signaling in the ventral striatum were positively correlated with the lifetime stimulant use of the subject.⁹⁴ In regard to the respective contributions of sensitization and tolerance to cocaine addiction, one possibility is that sensitization occurs during early recreational use, which may be more intermittent, to produce increased drug seeking and as use persists tolerance develops, leading to escalation of intake in order to compensate for decreased effects.

3.3. DAT Changes Following AMPH Administration.

While the determining factors in development of tolerance and sensitization of cocaine effects have been well-defined, less is known in regard to AMPH. Experimenter-delivered sensitization paradigms produce robust sensitization of AMPH-induced locomotion,^{95–97} similar to cocaine; however, extended access AMPH self-administration does not change the potency of AMPH at the DAT, or the ability of AMPH to increase extracellular dopamine levels as measured by microdialysis.¹² Although in this study these measures were not changed 24 h following 5 days of extended access AMPH self-administration session, it is possible that changes are apparent at different time points, or under different schedules of reinforcement. Cell culture work has shown that acute AMPH application results in rapid trafficking of DATs to the membrane (in less than 1 min),^{98,99} while continuous exposure results in a subsequent reduction in DAT surface expression that falls below predrug levels.⁹⁹ The biphasic time-dependent trafficking effect of AMPH suggests that a time-course of AMPH self-administration effects should be assessed to determine if similar effects are occurring in vivo. Regardless, these data suggest a mechanistic difference between cocaine and AMPH self-administration in the development of neurochemical adaptations to repeated use. The differences that result in the development of tolerance to cocaine effects, but not AMPH,

following extended access self-administration are unknown; however, we are currently investigating these factors.

3.4. The Effects of Altered DAT Expression on Cocaine and AMPH Potency. While repeated psychostimulant administration can alter drug–DAT interactions to cause tolerance and sensitization to the effects of the drug at the DAT, DAT expression can also be changed by drug exposure (see section 3). While there are conflicting reports in preclinical studies, it appears that increased DAT levels are a direct consequence of psychostimulant use in humans.^{71–73} Given that the DAT is the primary site of action of psychostimulant blockers and releasers, it is possible that drug-induced elevations in DAT levels observed in psychostimulant addicts may contribute to continued use of the compounds. In addition, several other neuropsychiatric disorders, including attention deficit hyperactivity disorder and post-traumatic stress disorder, engender increased DAT levels^{100,101} and are associated with increased rates of drug abuse and addiction.¹⁰² Thus, determining the role of increased DAT levels in addictive behaviors may allow for personalized therapies when treating these “at risk” populations.

To examine the relationship between psychostimulant potency and DAT levels, Salahpour et al.¹⁰³ created DAT transgenic overexpressing mice (DAT-tg) that have 4 additional copies of the DAT gene. DAT-tg mice exhibited increased locomotor response to AMPH as well as increased AMPH-induced dopamine overflow as measured by microdialysis. Conversely, DAT blockers, including cocaine, were unaffected by increasing DAT levels. These findings were confirmed and extended by data showing that potency at the DAT, as measured by fast scan cyclic voltammetry in brain slices, was increased in DAT-tg mice for AMPH and unchanged for cocaine.¹⁰⁴ Additionally, these alterations are recapitulated by pharmacologically inducing increases in DAT levels.¹⁰⁴ Further, measures of drug-seeking and reinforcement in animals with elevated DAT levels corresponded to the neurochemical potency of these compounds, where increased DAT levels produced augmented reinforcing efficacy of AMPH while cocaine was unchanged.¹⁰⁴ Together, these data suggest a causal link between DAT levels and vulnerability to AMPH abuse.

The strong relationship between DAT expression and AMPH potency may be due to several factors. First, higher DAT levels likely result in increased AMPH transport and thus augmented intracellular AMPH concentrations. In addition to increased cytoplasmic AMPH levels, higher DAT levels may also allow for augmented DAT coupling to VMAT-2 on synaptic vesicles, which together produces greatly augmented intravesicular AMPH concentrations and thereby greater vesicular depletion via AMPH-induced disruption of vesicular pH gradients.⁸ Increased vesicular depletion results in augmented cytoplasmic dopamine levels, which can then be moved into the extracellular space via DAT-mediated reverse transport more readily due to augmented DAT levels (Figure 1).

The relationship between DAT levels and AMPH potency may have profound implications for AMPH effects on striatal dopamine neurotransmission, because striatal subregions have been shown to have marked differences in DAT expression.^{105–107} Indeed, Siciliano et al.¹⁰⁷ showed that AMPH potency was greatest in dorsal regions of the striatum, where DAT levels are high, and decreased in a graded manner from dorsal to ventral, with the lowest potency in the NAc shell,

where DAT levels are lowest. This finding is particularly important as striatal subregions are involved in distinct aspects of addictive behaviors. Indeed, the ventral striatum, which receives input from limbic regions and is instrumental in assigning motivational value and encoding for discrepancies between expected and actual outcomes (see subsection 1.2), mediates the acute reinforcing effects of drugs and guides goal-directed behaviors to obtain drugs. The dorsal striatum, which is part of the sensorimotor domain, is thought to be involved in habitual behaviors and stimulus-response actions that occur in response to cue presentations.^{108–110} Thus, the variable potency of AMPH across regions may have important implications for the development of addictive behaviors. Indeed, self-administration studies have shown that AMPH engenders greater responding than cocaine on higher order schedules of reinforcement,^{11,111} which require strong cue-reward associations, while cocaine engenders greater consummatory behaviors than AMPH.¹¹² The greater propensity of AMPH to produce habitual type behaviors than cocaine may be explained by the augmented potency of AMPH in dorsal regions of the striatum.

4. PRESYNAPTIC REGULATORS OF DOPAMINE NEUROTRANSMISSION COME TOGETHER TO INFLUENCE COMPLEX MOTIVATED BEHAVIORS

It is apparent that the dopamine system is complex and many factors converge to behavioral outputs. Most investigations of the neurochemical consequences of psychostimulant administration suggest that multiple drug-induced alterations converge to cause reductions in dopamine system function. Indeed, as we have reviewed here, both basal levels, phasic signaling and autoreceptor sensitivity are attenuated by self-administration. It is likely that changes produce widespread deficits in dopamine signaling in the NAc as well as other regions. For example, functional activity is reduced in reward related brain regions following withdrawal from cocaine self-administration suggesting that there are reductions in the baseline functioning of the system.¹¹³ Additionally, there are deficits in the ability of the system to respond to stimuli. Indeed, Macey et al.¹¹⁴ show that, following both 5 and 30 days of self-administration of cocaine, functional activity in the dorsal and ventral striatum was significantly reduced. The testing was done at the end of the last session when cocaine was still on board, indicating that cocaine was less effective at stimulating glucose utilization in these areas in well trained rats than in controls. Together, these data further support the hypothesis that psychostimulants produce hypofunction of striatal regions.

5. CONCLUSIONS

In summary, while both cocaine and AMPH robustly dysregulate dopamine system function to produce addictive behaviors, the neurochemical adaptations observed following administration of the two compounds are often divergent. Additionally, the effects of both drugs can be disparate, and even opposite, depending on contingent versus noncontingent administration, temporal pattern of administration, abstinence, route of administration and intake. Together, these findings highlight the importance of selecting translational models of psychostimulant administration to accurately reproduce psychostimulant-induced neurochemical alterations in human addicts and suggest that personalized medicine, depending on

psychostimulant and profile of abuse, may be a promising avenue for pharmacotherapeutic interventions for psychostimulant addiction.

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Notes

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