Background

Cocaine and other amphetamine-like psychostimulants have been a significant part of the human pharmacopoeia for thousands of years. However, the appearance of these substances in Western societies has been relatively recent, cocaine having debuted as both a local anesthetic and a psychostimulant in the 19th century. Over the course of the next century, it became increasingly clear that the amphetamine-like psychostimulants carried serious abuse liability, as well as producing a prominent paranoia-like syndrome among many individuals who chronically used this class of drugs. The abuse liability of these drugs has resulted in sociological use patterns that have been described as epidemics, such as the methamphetamine epidemic in Japan in the 1950s, the cocaine epidemic in the United States in the 1980s, and the crack cocaine epidemic of the 1990s. The high abuse liability of this class of drugs relies on both pharmacological properties and the sociological characteristics of how the drugs are introduced into various societies around the world. This article will not significantly address the sociology of psychostimulant abuse, which involves diverse events ranging from the use of amphetamines by Japanese soldiers in World War II, to the formulation of crack as a less expensive version of cocaine in the United States, to the introduction of prescription formulations to regulate eating habits or to treat attention deficit-hyperactivity disorder. Rather, we will review the basic pharmacology of amphetamine-like...
drugs, integrate these molecular mechanisms into the brain circuitry of reward, and describe how these drugs are thought to create pathological changes in reward and learning circuitry. Finally, this knowledge will be amalgamated into a vision of future pharmacotherapies for treating psychostimulant addiction.

**Basic pharmacology of amphetamine-like psychostimulants**

The defining mechanism of action of amphetamine-like psychostimulants as a class of drugs with high abuse liability is the ability to bind to dopamine transporters (DAT).9,10 Dopamine transporters are a member of a class of proteins that eliminate monoamines, including dopamine, from the synaptic cleft after neuronal release.11 This protein has a high affinity for dopamine relative to other monoamines, such as norepinephrine or serotonin, and while all the readily abused psychostimulants bind to DAT, they may also bind to the other monoamine transporters with greater or lesser affinity.9,12 To some extent, the relative profile of binding by individual drugs to the different transporter proteins explains different characteristics of the drugs. Most striking, for example, is 3,4-methylenedioxymethamphetamine (MDMA) which has a relatively higher affinity for serotonin transporters, and is thereby a mild hallucinogen and neurotoxic to serotonin axon terminals,13,14 while methamphetamine binds more avidly to DAT, which explains its greater toxicity at dopamine terminals, as well as its propensity to induce paranoid psychosis-like symptoms.15 While the binding to other monoamine transporters contributes to the antidepressant and hallucinogenic characteristics of some psychostimulants, it is the binding to DAT that provides the major influence on abuse liability, which is the focus of this review.

There are two major categories of interaction by amphetamine-like psychostimulants with DAT, but in all cases the end result is to inhibit the elimination of dopamine from the synapse and thereby increase the quantity and half-life of synaptic and extrasynaptic dopamine levels.16,17 The first mechanism is typified by cocaine and methylphenidate that bind to DAT, but are not transported into the presynaptic terminal as surrogate dopamine. Therefore, when these drugs bind to DAT the increase in extracellular dopamine relies primarily on normal synaptic release, which is more amenable to physiological feedback regulation.18 The second mechanism is typified by amphetamines, and involves not only binding to DAT, but also translocation into the cell in place of dopamine.1 In addition, these drugs enter dopamine synaptic vesicles, where the fact that these compounds are basically charged degrades the pH gradient necessary to sequester dopamine into the vesicle.19 This in turn results in a large buildup of dopamine in the cytosol, thereby reversing the direction of DAT to release dopamine into the extracellular space rather than facilitating its removal. Regardless of the precise interaction with DAT by individual amphetamine-like psychostimulants, this class of drugs dramatically elevates extracellular dopamine, and this action is thought to be the initiating molecular event that reinforces drug-seeking behaviors, ultimately culminating in addiction.20,21

**How release of dopamine by psychostimulants initiates addiction**

Dopamine release is physiologically employed to signal novel, motivationally relevant environmental events. Thus, when an organism encounters a novel stimulus, whether a positive stimulus such as a food reward or a negative stimulus such as a stressor, the activity of dopamine cells in the ventral tegmental area, and dopamine release in axon terminal fields in the prefrontal cortex, nucleus accumbens, and/or amygdale, are altered.22,23 An important characteristic of this brain-environment interaction is that the ability of a given stimulus to increase dopamine cell firing and release decreases with repeated presentation of the stimulus. However, it can be shown that if a motivationally neutral stimulus (such as a light or tone) is associated with the motivational event in such a manner that the neutral stimulus predicts arrival of the motivational event, the ability of the motivational stimulus to release dopamine is transferred to the neutral stimulus.24 Thus, the neutral stimulus now causes dopamine release in a manner predicting arrival of a motivationally relevant event. Based upon these data, the role for dopamine release in the mesocorticolimbic brain regions is twofold: (i) to cue the organism that a novel motivationally relevant event is
occurring and that adaptive behavioral responses need to be engaged (eg, approach a reward or avoid a stress); (ii) once the behavioral response is established, dopamine release is antecedent to the appearance of the motivationally relevant event and is triggered by environmental associations that the organism has made with the event as part of learning the adaptive behavioral response. In this way, dopamine serves to alert and thereby prepare the organism for an impending important event.

The primary differences between psychostimulant-induced dopamine release and release associated with normal learning about important environmental events such as rewards and stressors is: (i) since psychostimulants block the elimination of dopamine through DAT, the level of dopamine achieved far exceeds what is possible from a biological stimulus; (ii) in contrast to biological stimuli that cease to release dopamine once an approach or avoidance response to that stimulus has been learned, psychostimulants continue to release large amounts of dopamine upon every administration (with the possible exception of extended binging that can temporarily deplete dopamine stores). Thus, with psychostimulants, each administration releases dopamine into mesocorticolimbic regions, causing further associations to be made between the drug experience and the environment. In this way, it is thought that the more a psychostimulant is administered, the more learned associations are made with the environment and the more effective the environment becomes at triggering craving and drug-seeking. It is this “overlearning” of drug-seeking behaviors by progressive associations formed between repeated drug-induced dopamine release and the environment that is thought to lead to increased vulnerability to relapse.

How psychostimulant-induced dopamine release creates pathological neuroplasticity in cortical regulation of behavior

As outlined above, psychostimulant-induced dopamine release is responsible for reinforcing behaviors designed to seek and administer the drugs. The dopamine projections involved in this process are outlined in Figure 1A, and as indicated, the most critical projection in this regard is the projection from the ventral tegmental area dopamine cells to the nucleus accumbens. For example, if psychostimulant-induced release of dopamine in the nucleus accumbens is impaired, this affects the acquisition of drug-seeking behaviors, and can markedly influence the amount of drug taken in a well-trained subject. Thus, the learning of a task to obtain the drug and the amount of drug taken in a given session is strongly regulated by dopamine release in the accumbens. However, when an animal has been withdrawn from repeated psychostimulant use, and drug-seeking is initiated by an environmental stimulus such as a cue previously paired with drug delivery, or a novel stressor, it is dopamine release in the prefrontal cortex and amygdala, respectively, that mediates the reinstatement of drug-seeking. Thus, relapse can be induced by dopamine release in prefrontal and allocortical brain regions, and reflects the aforementioned physiological role of dopamine release as a predictive antecedent to stimulus (drug) delivery. What this implies is that chronic release of dopamine by repeated psychostimulant administration may be modifying cortical and allocortical regulation of behavior. Figure 1B shows that the cortical and allocortical regulation of behavior is primarily mediated by glutamatergic...
The neuroimaging literature clearly shows metabolic activation of regions of the prefrontal cortex, including portions of the anterior cingulate and ventral orbital cortices, and the amygdala during cue-induced craving for amphetamine-like psychostimulants.34 A variety of studies have linked this activation of corticofugal glutamate transmission with craving in psychostimulant addicts or drug-seeking in animal models of addiction. The neuroimaging literature clearly shows metabolic activation of regions of the prefrontal cortex, including portions of the anterior cingulate and ventral orbital cortices, and the amygdala during cue-induced craving for amphetamine-like psychostimulants.34 Interestingly, while a cue or low dose of psychostimulant markedly increases metabolic activity in the prefrontal cortex and amygdala, in the absence of a learned drug association the prefrontal cortex is hypoactive.40 The reduction in basal metabolic activity is taken to indicate a potential deficit in cognitive ability to regulate relapse, and recent cognitive testing in psychostimulant addicts confirms the presence of certain cognitive dysfunctions related to impulse control and switching behaviors in an adaptive manner to changing environmental circumstances.31-45 A strong role for activation of both the prefrontal cortex and amygdala has been confirmed in animal studies. Thus, pharmacological inhibition of either of these regions prevents the reinstatement of drug-seeking in animals withdrawn from drugs that have undergone extinction training.36-44 Moreover, a marked release of glutamate is measured in the nucleus accumbens of animals initiating drug-seeking in response to a stressor, and this glutamate is derived from increased activity in the projection from the prefrontal cortex to the nucleus accumbens.49,50 Accordingly, drug-seeking is abolished by inhibiting glutamate receptors in the accumbens.51-53 One final set of studies to be considered regarding cortical glutamate is the recent evidence that as drug-seeking becomes more compulsive there is a gradual shift to greater reliance on corticostriatal habit circuitry, and less involvement of prefrontal to accumbens circuitry.54 This possibility is supported by animal models in two ways: (i) if animals that have been trained to self-administer cocaine are left in abstinence for an extended period, drug-seeking is augmented,55 and in this case inhibition of the prefrontal cortex or amygdala no longer inhibits drug-seeking induced by drug-associated stimuli. However, inhibition of the dorsolateral striatum is still effective at blocking drug-seeking56; (ii) as training of an animal in drug-seeking paradigms progresses it is possible to show a gradual increase in dopamine released into the caudate in favor of release into the nucleus accumbens.57 This is illustrated in Figure 1A, showing that dopamine release into the caudate can regulate habitual behaviors. On one hand, these data point to the possibility that in treating compulsive relapse we should be focusing on regulation of corticostriatal habit circuitry, including glutamate input to the caudate from sensory-motor cortex and dopamine input from the substantia nigra. However, these studies have been conducted in rats in whom the frontal cortex is poorly evolved, and given the marked activation produced in the prefrontal cortex and amygdala by drug-associated stimuli in psychostimulant addicts, the conclusion that compulsive relapse is entirely derived from corticostriatal habit circuitry may be an oversimplification. Indeed, it has been argued that a primary role for therapy in treating addiction is to strengthen prefrontal regulation of drug-seeking behaviors, whether through psychosocial interventions or pharmacotherapy.37,58,59

**Enduring psychostimulant-induced neuroplasticity in the prefrontal to accumbens glutamate projection**

Given the apparent critical role played by glutamatergic afferents to the nucleus accumbens in initiating drug-seeking or craving, recent studies have identified a number of enduring cellular changes in glutamate transmission that may be critical pathological neuroadaptations to psychostimulant use, and may serve as targets for pharmotherapeutic intervention. In general the neuroplasticity can be categorized as postsynaptic, presynaptic and nonsynaptic (ie, residing predominantly in glia). However, since these processes are intimately related to each other, it is perhaps best to consider all the adaptations as changes in glutamate homeostasis, the end result of which is a psychostimulant-induced enduring change in the fidelity of communication between the prefrontal cortex and the nucleus accumbens, and the regulation by this projection of corticostriatal habit circuitry. It has been proposed that this loss of fidelity results in a weakening or loss in the capacity of psychostimulant addicts
to cognitively intervene in habitual behaviors, thereby making drug-seeking more difficult to control and increasing the vulnerability to relapse.\textsuperscript{27} As mentioned above, drug-seeking is associated with a large release of prefrontal glutamate into the nucleus accumbens. The large release of glutamate during drug-seeking is all the more remarkable because it was discovered using microdialysis, which is not a very sensitive measure of glutamate transmission.\textsuperscript{60} Indeed, when animals are trained to seek a biological reward, such as food, microdialysis cannot measure glutamate release.\textsuperscript{70} Thus, the large psychostimulant-induced release of glutamate has been hypothesized to be a pathological and perhaps critical mediator of relapse. This hypothesis is supported by the fact that treatments interrupting synaptic glutamate release also inhibit drug-seeking. This includes a variety of pharmacological treatments that have the potential to be developed into pharmacotherapeutic agents, as outlined below. Perhaps in part a consequence of the massive synaptic glutamate release occurring during psychostimulant-seeking behavior, a number of marked changes in postsynaptic glutamate transmission have been measured in animals withdrawn from chronic cocaine or amphetamine administration. Perhaps among the most dramatic is an increase in the density of dendritic spines in the nucleus accumbens.\textsuperscript{61} Importantly, this appears to be accompanied by an increase in the insertion of $\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors into the membrane of spiny neurons in the accumbens.\textsuperscript{62} and is associated with an increase in electrophysiological sensitivity to AMPA receptor stimulation (as measured by the AMPA:N-methyl D-aspartate [NMDA] ratio).\textsuperscript{63} Moreover, a number of other proteins regulating the fidelity of postsynaptic glutamate transmission are altered after chronic cocaine use, including proteins that regulate the structure and function of the protein scaffolding in which the glutamate receptors are embedded, including postsynaptic density (PSD)-95 and Homer proteins, among others.\textsuperscript{64,65} Also, in addition to AMPA ionotropic glutamate receptors, signaling through metabotropic glutamate receptors is downregulated.\textsuperscript{66,67} Finally, this psychostimulant-induced postsynaptic neuroplasticity is associated with changes in the biochemical machinery regulating spine formation, notably an increase in actin cycling and formation of F-actin (a primary structural protein regulating spine morphology and the insertion of proteins into and out of the membrane).\textsuperscript{68} Taken together, these findings indicate that significant changes have been produced by psychostimulants in the way that synaptically released glutamate will be interpreted by postsynaptic cells. However, it is important to note that this knowledge is nascent and emerging. Thus, there remain many apparent contradictions in the literature regarding changes in specific proteins, and in the overall direction of synaptic grading (ie, is postsynaptic glutamate transmission augmented or inhibited by chronic psychostimulant administration).\textsuperscript{69} Therefore, for now it is probably not prudent to speculate on the type of drug development that may arise from this particular direction of research into psychostimulant-induced changes in glutamate signaling.

### Ideas for pharmacotherapies based upon psychostimulant-induced plasticity in glutamate transmission

As outlined above, given our current state of knowledge it is more likely that pharmacotherapeutic restoration of normal glutamate release may be a more successful approach than manipulating postsynaptic proteins responsible for and/or associated with changes in the fidelity of postsynaptic glutamate transmission. In part, this is due to the relatively contradictory status of the emerging literature on postsynaptic plasticity. Moreover, it has been hypothesized that the adaptations in presynaptic glutamate release may be at least partly causal in the postsynaptic adaptations, posing the possibility that if the pathological release of glutamate can be successfully ameliorated, postsynaptic normalization may follow.\textsuperscript{27} Pharmacotherapeutic targets for regulating the pathological synaptic glutamate release seen in the accumbens of psychostimulant-seeking animals can be placed into two categories: (i) targets based upon psychostimulant induced changes in proteins regulating synaptic glutamate release; (ii) proteins that produce a general decrease in excitatory transmission. Compounds in the first category are likely to be the most specific for psychostimulant addiction, and perhaps carry the least number of unwanted side effects, while the latter category may be less selective not only regarding effects on other addictive drugs, but also in terms of unwanted side effects. \textit{Table I} lists some potential pharmacotherapeutic targets according to these two categories. Neuroplasticity produced by chronic cocaine administration that could potentially contribute to pathological

| Pharmacotherapeutic Targets | Remarks |
|-----------------------------|---------|
| PSF-95                      | Downregulated by chronic cocaine |
| Homer proteins              | Downregulated by chronic cocaine |
| AMPA receptors              | Increased in density |
| Metabotropic glutamate receptors | Downregulated |

\textit{Table I} lists some potential pharmacotherapeutic targets according to these two categories.
glutamate release includes downregulation of cystine-glutamate exchange, downregulation of glial glutamate transporters, and downregulation of release-regulating presynaptic metabotropic glutamate receptors (mGluR2/3). Importantly, these three changes are interrelated due to the cystine-glutamate exchanger and glutamate transporter regulating extrasynaptic glutamate tone on release regulating mGluR2/3.70,71 Drugs have been examined in animal models of psychostimulant addiction, and to a lesser extent in clinical trials with cocaine addicts that regulate one or more of these processes. For example, N-acetylcysteine upregulates cystine glutamate exchange, and has been shown in animal models to prevent synaptic glutamate release associated with drug-seeking, restore inhibitory tone on synaptic release through activation of mGluR2/3, and to inhibit the desire for cocaine in a double-blind cue-reactivity trial in non-treatment-seeking cocaine addicts.71 Also, mGluR2/3 agonists have proven effective at inhibiting cocaine seeking in animal models; however, unlike N-acetylcysteine, food-seeking was inhibited at only a 3- to 10-fold increase in dose relative to inhibiting cocaine-seeking.74,75 Although no studies have yet evaluated regulating glutamate transport in drug-seeking models of psychostimulant addiction, recent reports of the use of β-lactam antibiotics to increase glutamate transporter membrane insertion poses an interesting possibility for pharmacologically overcoming the cocaine-induced downregulation of glutamate transporters. Finally, while the mechanism is not clear, modafinil has been reported to increase extracellular glutamate levels, which would restore tone on release inhibiting mGluR2/3.76 Notably, modafinil has been found to successfully decrease cocaine relapse in a number of clinical trials.77-78

The primary drugs in the category of nonspecific inhibitors of synaptic glutamate release include a variety of γ-aminobutyric acid (GABA)-mimetic compounds. These range from relatively specific agonists at GABA receptors, such as baclofen, which inhibit synaptic glutamate release to a host of less selective compounds known to increase GABA transmission via interactions with synthetic or elimination mechanisms, such as topiramate or vigabatrin. For all of these compounds there is preclinical and clinical data to support some potential efficacy.79-85 However, as predicted, especially for the nonselective GABAmimetics untoward side effects, such as sedation, are reported.

Conclusions

This review has endeavored to transport the reader from the initiating molecular actions of amphetamine-like psychostimulants on dopamine systems in the brain to enduring neuroplasticity produced in glutamate transmission responsible for communicating from prefrontal and allocortical brain regions through the nucleus accumbens to motor regulatory systems. Moreover, by examining molecular neuroplasticity produced in excitatory synapses by chronic psychostimulant administration, it is possible to make some deductions about potential pharmacotherapeutic interventions. Indeed, there already exists an emerging literature supporting this approach in developing potential pharmacotherapies for treating psychostimulant addiction. Importantly, this is a nascent and emerging science, and while much has been discovered, the cutting edge of discovery into the neuroplasticity produced by psychostimulants is understandably contradictory. As further discoveries are made that allow us to understand the nature of these contradictions, it should follow that additional targets will emerge to provide potential novel pharmacotherapies for treating psychostimulant addiction.

Table I. List of compounds that affect glutamate neurotransmission with potential pharmacotherapeutic value in treating addiction to amphetamine-like psychostimulants. mGluR2/3, metabotropic glutamate receptors; GABA, γ-aminobutyric acid; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid

| Directly reducing glutamate transmission | Indirectly inhibiting glutamate transmission |
|----------------------------------------|------------------------------------------|
| **Compound**                           | **Target**                               | **Compound** | **Target** |
| N-acetylcysteine                       | Cystine/glutamate exchanger              | Baclofen     | GABA-b receptor |
| β-lactam                               | Glutamate transporter                    | Topiramate   | GABA-a and AMPA |
| mGluR2/3 agonist                       | mGluR2/3                                 | Vigabatrin   | GABA transaminase |
| Modafinil                              | mGluR2/3                                 |              |              |

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Cocaina y psicoestimulantes tipo anfetamina: circuitos neuronales y neuroplasticidad glutamatérica

Aunque es bien conocida la farmacología de los psicoestimulantes tipo anfetamina a nivel de los transportadores de dopamina, ha sido difícil abordar la adicción a esta clase de drogas. La razón de esta discordancia se explica porque si bien el mecanismo molecular de la acción de la anfetamina es crítico para reforzar el uso de la droga, éste representa sólo el primer paso en una secuencia de numerosos acontecimientos neurológicos en los circuitos cerebrales. Esta revisión resume el efecto de los psicoestimulantes en las proyecciones mesocorticolímbicas de dopamina que median el efecto de refuerzo, y cómo esta acción en último término conduce a una neuroplasticidad patológica permanente en las proyecciones glutamatéricas desde la corteza prefrontal hasta el núcleo acumbens. Se describen las neuroadaptaciones moleculares inducidas por el abuso de psicoestimulantes en la neurotransmisión glutamatérica, y a partir de esta información se identifican potenciales blancos farmacoterapéuticos, en base a las modificaciones en la neuroplasticidad inducida por psicoestimulantes.

Cocaina et psychostimulants amphéthaminoides : circuits neuronaux et neuroplasticité du glutamate

En dépit d’une bonne compréhension de la pharmacologie des psychostimulants amphéthaminoides au niveau des transporteurs de la dopamine, il semble difficile de faire face à l’addiction à cette classe de médicaments. Cette discordance s’explique ainsi : si le mécanisme moléculaire de l’action amphéthaminique est essentiel pour renforcer l’action du médicament, il ne représente qu’une première étape dans une succession de nombreux événements neuroplastiques dans le circuit cérébral. Cette revue souligne l’effet des psychostimulants sur les projections méso-cortico-limbiques dopaminergiques qui médient l’effet de consolidation et explique comment cette action mène finalement à une neuroplasticité pathologique persistante dans les projections glutamatergiques, du cortex préfrontal au noyau acumbens. Les neuroadaptations moléculaires induites par l’abus des psychostimulants sont décrites en ce qui concerne la neurotransmission du glutamate, et des cibles pharmacothérapeutiques potentielles sont identifiées à partir de ces informations, basées sur la neuroplasticité réversible ou annulable induite par les psychostimulants.

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