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Review Article

Pharmacotherapeutic targets for regulating cocaine-induced plasticity

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Abstract

Several decades of drug addiction research have failed to yield an effective pharmacotherapy for the treatment of cocaine addiction. However, significant progress has been made in elucidating cocaine-induced long-term changes in brain function that may underlie the vulnerability to relapse. The present review discusses potential neural targets and associated pharmacotherapies for the reversal of cocaine-induced neuroadaptations. While alterations in many neurotransmitter systems are associated with cocaine addiction, the current manuscript focuses on changes in the glutamatergic and GABAergic systems, while also discussing the neurotrophic factors BDNF and GDNF. A variety of pharmaceuticals have been identified which effectively decrease drug-seeking behavior in both animal models of addiction and human clinical trials. However, the effects seen in clinical trials are modest and we propose that focus should be placed on the development of drugs which affect more than one addiction-associated neurotransmitter system.

Introduction

Psychoactive drug use has been embedded in human culture for thousands of years. Historically, members of societies all over the world have taken drugs to produce alterations in mood, energy and behavior, but only a small percentage of these users develop problems in controlling drug intake. It was not until the early twentieth century that behavioral pharmacologists began to scientifically investigate the core processes involved in the motivation to take drugs. At this time, focus was placed on the addicted individual in order to understand why humans take drugs. Opioid drugs were viewed as prototypically addictive due to the fact that they produce tolerance, dependence and a clearly visible physical withdrawal syndrome. The withdrawal from opioid drugs is extremely uncomfortable and it was hypothesized that users repeatedly consumed the drug in order to alleviate these withdrawal symptoms (1). At that time, drugs such as nicotine and cocaine, which do not produce a readily quantified physical withdrawal syndrome, were not believed to be addictive (2). A PubMed search of the literature prior to 1980 using the terms “opiate + addiction” yields 898 citations, while the search “cocaine + addiction” yields only 48 citations. However, the American cocaine epidemic of the 1980s coincided with an increase in public awareness of the inability of smokers to discontinue nicotine use even after serious adverse health consequences. These two societal issues motivated researchers to re-evaluate their views of the abuse liability of cocaine.

In the U.S.A. today, 16% of those who try cocaine become addicted (3) and cocaine use in the E.U. has reached historically high levels. A bigger problem than cocaine use may be the rates of recidivism, even for addicts who become abstinent and have strong intentions to remain that way. The high rates of relapse for cocaine are attributed to cravings for the drug, which are intense and persist for years after abstinence is attained, as well as to poor impulse control (4). Both of these phenomena are now attributed to cocaine-induced neuroplasticities and not to the moral strength of the addict (4-6).

While numerous neural adaptations in response to chronic cocaine use have been identified, two decades of research have yet to produce a treatment that can reliably and significantly decrease rates of relapse to cocaine. To “cure” addiction, we must develop pharmacotherapies that can reverse or countermand the neuroadaptations that occur upon repeated cocaine administration. As the adaptations are many and varied, a viable pharmacotherapy for cocaine addiction may need to attack more than one type of adaptation. For example, we know that there are significant adaptations within the prefrontal cortex (PFC) to nucleus accumbens (NAc) glutamate projection

after chronic cocaine administration (7), but it may not be sufficient for a successful pharmacotherapy to normalize PFC-NAc glutamate transmission since other brain systems are also altered by chronic cocaine use.

A variety of technical advances in the neurosciences over the last decade have provided the means to evaluate the development of cocaine-induced neuroplasticity and pathology. Imaging techniques such as PET and fMRI can be used to evaluate the brains of human cocaine addicts for evidence of altered metabolic and/or neuronal activity. In experimental animals, microdialysis techniques provide a means to measure the release of neurotransmitters into the extracellular space at the same time that a particular behavior is being assessed. Additionally, molecular biological techniques are available to measure mRNA and protein expression following repeated cocaine administration. Behavioral paradigms such as operant self-administration and the reinstatement of drug-seeking behavior in extinguished animals provide valuable animal models of drug addiction that are essential for testing the efficacy of potential therapies. Together, these techniques have provided much needed information about cocaine-induced neuroadaptations, which may hopefully lead to a treatment for cocaine addiction at some time in the near future. While we will refer to much of the addiction biology literature here, it is beyond the scope of this article to discuss these data in great experimental detail, and the reader is referred to several reviews written for this purpose (see 8-10).

Potential targets for reversing cocaine-induced neuroplasticities

Neurotrophic factors and addiction

1. BDNF

Brain-derived neurotrophic factor (BDNF) is the most abundant member of the family of brain neurotrophic factors which help regulate the development, maintenance and function of vertebrate nervous systems. While neurotrophic factors play essential roles in the developing nervous system, they are also important to the mature nervous system, where they modulate synaptic function and plasticity and also continue to modulate neuronal survival (11). BDNF has been shown to directly regulate the survival and differentiation of midbrain dopamine (DA) neurons both *in vitro* (12) and *in vivo* (13). As these neurons undergo modification after cocaine administration, it follows that BDNF could be involved in the long-lasting neuroadaptations that accompany cocaine addiction. Accordingly, both animal and human studies provide evidence that support this hypothesis (for review, see 14).

BDNF levels were shown to progressively increase in the rodent mesolimbic DA system during withdrawal from repeated cocaine, an effect that was accompanied by concomitant increases in responsiveness to cocaine-related cues (15). Additionally, in the reinstatement model of relapse, a single injection of BDNF into the ventral tegmental area (VTA) enhanced cocaine-seeking behavior for up to 30 days after cocaine self-administration (16). Horger *et al.* (17) showed that infusions of BDNF into the NAc increased the response to cocaine by 4-fold in a conditioned reward model. The same study revealed that infusions of BDNF into the NAc and VTA increased the initial locomotor response to cocaine injections and facilitated the development of locomotor sensitization to cocaine relative to untreated control animals. Similarly, heterozygous BDNF knockout mice developed locomotor sensitization to cocaine more slowly than wild-type mice (17).

Blood levels of BDNF have been shown to correlate with brain levels in the rat (18), and as BDNF is present in human blood (19), it is possible to compare BDNF levels of drug users with naïve patients. Kim *et al.* (20) have shown that plasma BDNF concentrations are significantly higher in methamphetamine users who had been abstinent for 30 days than in controls. Jockers-Scherubl *et al*. (21) reported that schizophrenic patients who were either cannabis users or multiple substance abusers had significantly higher serum BDNF levels than nonaddicted schizophrenics and normal controls.

Pharmaceuticals that decrease BNDF levels can potentially be effective at counteracting this cocaine-induced adaptation and their effectiveness can be monitored via blood tests. As BDNF deficiency and impaired signaling through its receptor, TrkB, have been associated with major depressive disorder, caution must be exerted in designing such pharmacotherapies. A partial TrkB agonist that would reduce the binding of endogenous BDNF may be the ideal drug. The antidepressant bupropion has been shown to decrease BDNF in the rat hippocampus, possibly through its actions as a DA reuptake blocker (22). This drug also reduces cocaine use in methadone-maintained addicts (23), as well as in cocaine addicts with attention deficit hyperactivity disorder (ADHD) (24, see also 25).

2. GDNF

Glial cell-line derived neurotrophic factor (GDNF) is a member of the transforming growth factor-β (TGF-β) family. Like BDNF, GDNF has been shown to be involved in the survival of mesolimbic DA neurons (26). GDNF activity is mediated by Ret and glial cell line-derived neurotrophic factor α1 (GFRα1) receptors. Chronic cocaine treatment decreases phosphorylation levels of the Ret receptor in the VTA (27), while 12 days of cocaine self-administration has been shown to reduce GDNF mRNA in the dorsal striatum (28). In agreement with these findings, intra-VTA infusion of GDNF blocks many cocaine-induced neuroadaptations, such as increases in the NR1 subunit of the NMDA receptor, increases in NAc ΔFosβ and protein kinase A (PKA), and increases in VTA tyrosine hydroxylase (29).

Thus, it is logical that increasing GDNF levels within the mesolimbic DA system may reverse many cocaine-related neuroadaptations and subsequently block cocaine-seeking behavior. Indeed, in rats, the acquisition of cocaine self-administration can be impaired by delivery

of GDNF into the dorsal or ventral striatum via both the implantation of a human astrocyte-like cell line that makes and secretes GDNF (28), as well as via GDNF-conjugated nanoparticles (30). Additionally, the alkaloid ibogaine has been shown to increase the expression and secretion of GDNF and also activate the Ret receptor (31). Ibogaine is a component of the root bark of the African shrub *Tabernanthe iboga,* and has been used by the Bwiti and Mbiri tribes of Africa as a stimulant drug. In rodent models of cocaine addiction, ibogaine has been shown to decrease cocaine self-administration (32) and block the sensitized DA response to a challenge injection of cocaine (33). Unfortunately, this compound is potentially neurotoxic and hallucinogenic (for review, see 34).

Glutamatergic targets

Repeated administration of cocaine significantly decreases basal levels of extracellular glutamate in the NAc of experimental animals, a phenomenon that has been found to be fundamental to the expression of locomotor sensitization that occurs in response to repeated cocaine (35) and in the reinstatement of cocaine-seeking behavior in experimental animals (7). Both the expression of sensitization (35) and the reinstatement of drug-seeking behavior (7) are accompanied by an enhanced release of glutamate into the NAc. Thus, it follows that a pharmacotherapy capable of regulating glutamate release, uptake or binding may have the potential to be highly effective in treating cocaine addiction. However, caution must be exerted because of untoward effects of activating or blocking ionotropic glutamate transmission, such as neurotoxicity and seizures or sedation, respectively. Fortunately, pharmacological mechanisms permitting more subtle modulation of glutamate transmission utilizing metabotropic glutamate receptors or metabolic glutamate pools are being developed.

1. Regulators of cystine-glutamate exchange

Basal levels of extracellular glutamate are primarily regulated by the cystine-glutamate antiporter (system xc-), which exchanges cystine found in the extracellular space for intracellular glutamate (36). System xc- is significantly downregulated after repeated cocaine administration, accounting for the low basal levels of glutamate observed in the NAc of cocaine-withdrawn animals (36, 37). Manipulating the antiporter via both intracranial perfusion of cystine and systemic administration of the cysteine prodrug *N*-acetylcysteine restores glutamate levels to pre-cocaine levels (37). Normalizing the basal levels of glutamate with *N*-acetylcysteine also prevents the increase in extracellular glutamate that occurs during the reinstatement of cocaine-seeking behavior in response to a priming injection of cocaine (38). Importantly, the effect of increasing cystine-glutamate exchange on drug-seeking behavior was shown to result from antiporter-derived glutamate stimulating $mGluR_{2/3}$ inhibitory presynaptic autoreceptors and decreasing synaptic glutamate release (39). Because *N*-acetylcysteine reduces reinstatement behavior in the rodent model of relapse, it is thought that normalizing glutamate in the NAc can reduce cocaine craving.

A double-blind, crossover clinical trial examined the ability of *N*-acetylcysteine to decrease cocaine craving in cocaine-dependent humans (40). Compared with placebo treatment, subjects treated with *N*-acetylcysteine for 3 days reported less desire to use cocaine, exhibited less reactivity to cocaine cues and showed less activity in the anterior cingulate cortex after viewing cocaine cues. This small trial included only 15 patients and these promising results are being followed up with a larger, double-blind, placebo-controlled study.

2. Ionotropic and metabotropic glutamate receptor agonists/antagonists

Synaptically released glutamate can bind to both ionotropic and metabotropic (mGluR) glutamate receptors. Glutamate binding to ionotropic receptors produces rapid increases in cell excitability, while mGluR stimulation results in more modulatory, delayed changes in cell excitability. Rodent studies using the cocaine self-administration and drug- and cue-induced reinstatement models of relapse have been useful at testing many glutamate receptor agonists and antagonists, and this work has led to human clinical trials. Extensive work has been done with NMDA receptor antagonists and partial agonists. The partial NMDA agonists acamprosate and *d*-cycloserine have been found to attenuate the reinstatement of cocaine-induced conditioned place preference (41) and facilitate the extinction of the place preferences (42), respectively. The NMDA/glycine-site antagonist L-701324 decreases cue-induced cocaine reinstatement, while the competitive NMDA antagonist CGP-39551 has no effect (43). The noncompetitive NMDA antagonist memantine has been shown to be effective at decreasing cocaine-induced place preference (44) and self-administration (45) in rodents. However, there is evidence that memantine can increase cocaine self-administration in rhesus monkeys (46) and enhance cocaine euphoria in humans (47). Another NMDA receptor antagonist, amantadine, does not alter the subjective effects of cocaine in humans (48), nor did it affect cocaine abstinence in a double-blind, placebo-controlled trial (49). At this time, it seems that NMDA antagonists are not effective in treating cocaine reward or relapse, while partial NMDA agonists may be useful.

Among the most promising compounds examined thus far is the AMPA/kainate receptor antagonist topiramate, which also acts to facilitate GABA transmission. Topiramate is an anticonvulsant medication that has been tested in a pilot clinical trial for the treatment of cocaine dependence. This placebo-controlled, double-blind study revealed that topiramate significantly increased abstinence rates and extended the length of abstinence (50). However, animal studies have shown that another AMPA antagonist, CNQX, has no effect on cocaine self-administration (51) but, along with the AMPA antagonist NBQX, can attenuate cue-induced reinstatement (43).

Because of the importance of the glutamate $mGluR_{2/3}$ autoreceptors in regulating glutamate release (52), it follows that drugs that target these receptors could be valuable tools for treating cocaine dependence. Indeed, the aforementioned positive effects of *N*-acetylcysteine in animal models and cocaine addicts are thought to be mediated by stimulation of $mGluR_{2/3}$ (39). Baptista *et al*. (53) reported that the $mGluR_{2/3}$ agonist LY-379268 decreased the reinstatement of cocaine-seeking behavior in rodents in a conditioned-reward paradigm, without affecting responding for a conditioned natural reward. However, Peters and Kalivas (54) found that LY-379268 decreased the reinstatement of both food and cocaine seeking. There are a number of $mGluR_{2/3}$ agonists that have yet to be tested in animal models of cocaine addiction or human clinical trials, including LY-404039, LY-418426, MGS-0008 and MGS-0028. The postsynaptic $mGluR_5$ receptors have also been targets for drugs to treat cocaine addiction. MPEP, a selective $mGluR_5$ antagonist, decreases the breakpoint for cocaine self-administration in a progressive-ratio design (55), decreases cocaine self-administration (56) and attenuates cue-induced reinstatement of cocaineseeking (43). Similarly, another $mGluR_5$ antagonist, MTEP, blocks cue-induced reinstatement of cocaine seeking (57).

3. Modulators of glutamate release

An indirect modulator of glutamate release may be the cannabinoid CB_1 receptor antagonist AM-251, which has been found to decrease cocaine-primed reinstatement while also inhibiting the increase in extracellular glutamate, but not DA, that accompanies reinstatement of cocaine seeking (58). AM-251 alone significantly increased extracellular glutamate in the NAc of rats that had self-administered cocaine; blocking $mGluR_{2/3}$ receptors prevented the AM-251-induced attenuation of cocaine seeking. Thus, akin to *N*-acetylcysteine (see above), AM-251 may be acting to elevate nonsynaptic extracellular glutamate, which then stimulates presynaptic inhibitory $mGluR_{2/3}$ receptors and reduces synaptic glutamate release. The drugs lamotrigine and riluzole are also inhibitors of glutamate release and have been tested in human clinical trials. While lamotrigine decreased the number of cocaine-positive urines in HIV patients in one study (59), it had no effect on cocaine-induced euphoria (60) or abstinence (61) in follow-up studies. Riluzole also had no effect on cocaine abstinence (62).

GABA

GABAergic medium spiny neurons of the accumbens send axons to the ventral pallidum. Cocaine-induced reinstatement is associated with reduced extracellular GABA release along this pathway, indicating a role for low GABA function in relapse to drug-seeking behavior (63). Thus, pharmaceuticals that have the ability to augment GABA transmission could potentially restore the GABAergic tone of the mesolimbic DA system and ameliorate this cocaine-induced neuroplasticity. Various GABA agonists have been shown to be effective at reducing cocaine self-administration and relapse in animal models, with mixed results in human clinical trials. For example, baclofen, a $GABA_B$ receptor agonist, decreases cocaine self-administration under FR-1 (64) and progressive-ratio schedules (65, 66). In a trial in human subjects, baclofen did not affect the subjective effects of cocaine or its reinforcing value (67). However, a pilot clinical trial indicated that baclofen treatment significantly increased abstinence rates in comparison with placebo (68). Additionally, Childress *et al.* (69) reported that pretreatment with baclofen for 7-10 days eliminated the activation of the anterior cingulate and amygdala that is normally seen in human cocaine addicts upon viewing drug-associated visual cues (70). Thus, it seems that baclofen is effective in treating cocaine craving but not necessarily the euphoria associated with self-administration.

Other GABA agonists that have been examined include vigabatrin, topiramate, gabapentin and tiagabine. In human subjects, the GABA reuptake inhibitor tiagabine has been found to attenuate the subjective effects of i.v. cocaine (71), and also produced a modest but reliable increase in cocaine-free urine samples in a pilot study of methadone-maintained cocaine addicts (72). Vigabatrin, an irreversible inhibitor of $GABA_A$ transaminase, decreases cocaine self-administration (73) and attenuates cocaine-induced elevations in NAc DA levels (74) in animals. However, while 75% of subjects remained abstinent in a clinical trial testing vigabatrin efficacy in treating cocaine dependency, 24 of the 40 subjects who were initially enrolled dropped out of the trial (75).

Gabapentin facilitates GABAergic transmission through an unknown mechanism and, similar to topiramate (see above), may also work on the glutamate system (76, 77). Human subjects have reported that gabapentin decreases the subjective effects of smoked cocaine (78), and two open-label trials found that daily gabapentin treatment reduced self-reported cocaine cravings and increased cocaine-free urine (79, 80). However, a double-blind trial with a placebo lead-in period to eliminate subjects who either become abstinent early or who were noncompliant found that gabapentin was not effective at maintaining cocaine abstinence when compared with placebo (81). While moderate success has been attained with a variety of GABA agonists that have different mechanisms of action, none of these drugs has yet been shown to produce a dramatic reduction in cocaine-seeking behavior in human addicts.

Intracellular signaling molecules

Chronic cocaine administration produces long-lasting changes in many intracellular signaling molecules of glutamate and DA receptors; these changes underlie the dysregulated glutamate release along the PFC-NAc pathway. Dopamine transmission in the PFC is essential for the reinstatement of cocaine-seeking behavior (82). The pyramidal cells of the PFC adapt to chronic cocaine by increasing levels of the activator of G-protein signaling

(AGS3) protein (83), which limits signaling through Giα-coupled receptors such as the D2 recepor (84). When AGS3 levels were reduced (via microinfusion of antisense oligonucleotides) in rats that had previously self-administered cocaine, reinstatement to drug seeking was diminished in these animals (83). Additionally, artificially increasing AGS3 levels in cocaine-naïve animals results in the increased release of glutamate in the accumbens that is seen in animals chronically treated with cocaine (83).

Also associated with chronic cocaine administration are several proteins that are found in the postsynaptic density of glutamate receptors. The Homer family proteins are downregulated after chronic cocaine and Homer knockout mice have phenotypes that are nearly identical to those of cocaine-treated animals, including a sensitized release of glutamate in the accumbens and upregulated AGS3 in the PFC (85). The protein PSD95 is also reduced after chronic cocaine (86), while F-actin is elevated (87). Thus, pharmaceuticals that could modulate these proteins may potentially reverse the cocaine-induced neuroadaptations in the glutamate system. For example, a drug that can increase levels of the Homer proteins or decrease AGS3 levels in the PFC would be a potentially useful pharmacotherapy for cocaine addiction.

Modafinil and cognitive enhancers

Modafinil is a stimulant drug that has been approved for the treatment of narcolepsy and hypersomnia in numerous countries, including France, Canada, Italy, Switzerland and the United States. Modafinil has a mechanism of action that is unique from other drugs with stimulant effects, such as cocaine and the classic amphetamine drugs (88, 89), leading many to believe that it lacks abuse potential. While it has been found to occupy the transporters for both DA and norepinephrine (NE) (90), pretreatment with an inhibitor of catecholamine synthesis does not interfere with the ability of modafinil to promote wakefulness (91), indicating that its primary mechanism of action does not depend on these neurotransmitters. Additionally, it increases locomotor activity in rodents and cats without inducing stereotypical behavior, providing further evidence for a DA-independent mechanism of action.

Clinical studies have indicated that modafinil is effective in improving cocaine abstinence rates and treatment retention in addicts scoring high on the Cocaine Selective Severity Assessment (92, 93). A double-blind, placebo-controlled trial found that modafinil (400 mg/day) significantly increased cocaine abstinence rates relative to placebo treatment over the course of 8 weeks. Additionally, the modafinil-treated subjects reported decreased cocaine craving in response to drug cues. These results confirmed those of a similar trial which used a lower dose and smaller subject pool (92), indicating that modafinil treatment could be effective in maintaining long-term cocaine abstinence.

The ability of modafinil to reduce craving and drug-seeking behavior in human cocaine addicts may arise from its ability to enhance glutamate transmission. Modafinil has been shown to increase extracellular glutamate levels (94, 95). It is thought that low basal levels of extracellular glutamate in the NAc contribute significantly to the development of cocaine craving (7). While the ability of modafinil to elevate glutamate specifically in the NAc has yet to be investigated, Ferraro *et al.* (96) have shown that modafinil inhibits GABA release in the NAc. Because glutamate release has been shown to be controlled by inhibitory GABAergic tone and the blockade of $GABA_A$ receptors in this brain area increases levels of extracellular glutamate (95), it is possible that modafinil increases glutamate levels in the NAc as well.

Additionally, an fMRI study in human subjects revealed that modafinil increases cortical activation in normal subjects and reverses low cortical activation in narcoleptic subjects (97). Modafinil also improves performance on PFC-dependent tasks in normal subjects (98), indicating that it could also reduce cocaine-seeking behavior in addicts by reversing the hypofrontal symptoms associated with cocaine addiction. The efficacy of modafinil may lie in its ability to affect multiple neurotransmitter systems, thereby affecting multiple cocaine-induced neuroplasticities.

Conclusions

The past few decades of addiction research have provided us with much information regarding the chronic neuoradaptations produced by cocaine administration. Many compounds have been found which can reverse some of these adaptations and thus block drug-seeking behavior in laboratory animals. Some of these pharmaceuticals have proceeded into human clinical trials, with poor to moderate success. At this time, no single drug has been shown to be able to consistently impact cocaine-craving and/or -seeking behavior in human addicts. We propose that an effective pharmacotherapy for cocaine addiction must reverse not just one but many of the neuroadaptations produced by cocaine administration. This might be accomplished by a single drug with multiple effects on brain chemistry and circuitry, or by administering multiple drugs with distinct mechanisms of action.

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