The development of pharmacotherapies for cocaine addiction has been disappointingly slow. However, new neurobiological knowledge of how the brain is changed by chronic pharmacological insult with cocaine is revealing novel targets for drug development. Certain drugs currently being tested in clinical trials tap into the underlying cocaine-induced neuroplasticity, including drugs promoting GABA or inhibiting glutamate transmission. Armed with rationales derived from a neurobiological perspective that cocaine addiction is a pharmacologically induced disease of neuroplasticity in brain circuits mediating normal reward learning, one can expect novel pharmacotherapies to emerge that directly target the biological pathology of addiction.

The exploration of the neurobiological underpinnings of cocaine addiction has evolved in two primary directions. The first has been to identify the brain site and the molecular target that cocaine binds to elicit its acute rewarding effects. The second major venue of investigation has been to understand how repeated cocaine administration changes cell signaling and brain circuitry to make the addict vulnerable to uncontrollable drug-seeking. Understanding the effects of acute cocaine has proven to be a relatively simple task. By contrast, an understanding of how the brain adapts to repeated drug exposure has coalesced more slowly. Unfortunately, as addicts typically seek treatment only after substantial changes in the brain have been wrought by years of repeated cocaine use, it is the more problematic understanding of the neurobiology of the enduring brain adaptations that has greatest therapeutic potential. Thus, successful pharmacological treatments for cocaine addiction rely on understanding the neurobiology of how the brain adapts to repeated cocaine, not on the acute drug effects. As such, discussing the enduring adaptations in brain and how those changes can be targeted with novel pharmacotherapeutic agents for treating cocaine addiction is the primary subject of this article.

Although the therapeutic focus in addiction is moving toward understanding enduring cocaine-induced changes in brain function, it is nevertheless important to understand how acute cocaine use reinforces drug-seeking behavior. It is the reinforcing value of cocaine that impels repeated drug use, and it is this repeated pharmacological insult that ultimately produces the enduring changes in brain function that underlie the behavioral pathology of addiction. In its experimentally reduced form, addiction is a pathological outcome of reward learning (ie, learning to approach an object or situation of adaptive value to the organism). Thus, cocaine provides a reward that the organism learns to obtain in the most efficient manner possible. However, unlike learning to obtain natural rewards, such as food, sex, or social cooperation, cocaine results in a pathological form of reward-seeking that is intrusive on adaptive social and personal behaviors and ultimately takes precedence over these behaviors. Therefore, while the enduring molecular changes in the brain produced by repeated cocaine use constitute the most likely therapeutic targets for treating cocaine addiction, appreciating the biology of reward learning and how cocaine usurps this brain machinery is a necessary antecedent to understanding the final molecular adaptations that underlie addiction.

HOW COCAINE USURPS PHYSIOLOGICAL REWARD LEARNING MECHANISMS

Reward learning relies heavily on the dopaminergic projections from the ventral midbrain (including the ventral tegmental area, VTA) to the nucleus accumbens, amygdala, and prefrontal cortex (see Figure 1). Like all drugs of abuse, cocaine promotes dopamine transmission in these pathways; it does so by binding to a protein...
called the dopamine transporter (DAT).\textsuperscript{3} DAT is responsible for terminating dopamine synaptic transmission by binding to dopamine and transporting it out of the synaptic cleft and back into the presynaptic terminal. By binding to DAT, cocaine prevents the removal of dopamine. This increases the effect of released dopamine by both prolonging its lifetime in the synaptic cleft and permitting dopamine to diffuse more effectively between synapses (see Figure 2).\textsuperscript{4}

During physiological reward learning, such as learning the location of a food source or where sex is available, dopamine is released.\textsuperscript{1} In simple terms, the release of dopamine elicited by encountering a novel, biologically relevant stimulus signals the brain that something important has happened and the organism needs to learn to make an adaptive behavioral response.\textsuperscript{5,6} While the precise changes produced in the neurons receiving the dopamine signal are a matter of ongoing study, it is clear that dopamine serves to change the state of the neurons such that they can more easily undergo the cellular changes (neuroplasticity) necessary to learn behaviors relevant to the biologically important stimulus (eg, we remember stimuli that are associated with reward more effectively than if associated with neutral stimuli that do not promote dopamine release). This cellular learning can take many forms, such as increasing or decreasing cell signals in response to the next related stimulus, and the breaking or forming of new synaptic connections. In either case, if a relationship between the stimulus and the behavior to approach it is learned, enduring changes in these cells are produced. Importantly, once the behavior is learned (eg, where in the cage a rat will find food), experience with the rewarding stimulus no longer activates dopamine neurons.\textsuperscript{6} Thus, further learning about this stimulus requires something new to happen in relation to the stimulus, which will promote dopamine release and result in learning about the changed stimulus.

If dopamine release is so critical for establishing adaptive behaviors after a physiological encounter with a reward, what occurs when dopamine is pharmacologically released by cocaine? First, cocaine administration results in an increase in dopamine that is markedly greater in terms of both amplitude and duration than what is physiologically induced by a novel, rewarding stimulus.\textsuperscript{7} Perhaps more important, because its molecular site of action is DAT, cocaine continues to release dopamine after each administration, even after the subject has a great deal of drug experience. As mentioned above, this is in contrast to natural rewarding stimuli, where dopamine release ceases once the organism has learned the appropriate behavioral response to the stimulus. Thus, each cocaine administration will amplify the neurological changes produced by dopamine release, while this process is self-limiting in response to natural rewards. In this way, cocaine addicts “over-learn” behaviors associated with the approach and acquisition of cocaine. This over-learned behavior, both drug-seeking itself and the intrusive thinking associated with drug-seeking (eg, craving), is not easily disrupted by other stimuli and ultimately successfully competes with biological rewards.

Given the pivotal role of dopamine in establishing addictive behaviors (ie, over-learned, compulsive behaviors related to obtaining cocaine), it is not surprising that many dopaminergic drugs have been evaluated both preclinically and clinically in an effort to ameliorate
addiction. This approach has ranged from long-acting, high-affinity cocaine-like drugs (substitution therapy modeled on the relative success of methadone in heroin addiction) to agonists or antagonists at specific dopamine receptors. One primary difficulty with this pharmacological approach is the relative importance of dopamine in the physiology of reward learning and reinforcing behavior. Impairing the dopamine system inhibits the experience of reward, seen clearly by the anhedonia elicited after treatment with dopamine antagonist antipsychotic medications. Thus, the most fruitful avenues of research into dopamine-related drugs for cocaine addiction rely on one of three strategies.

1. Drugs that are partial antagonists, thereby limiting dopamine transmission but producing neither full blockade nor full activation.
2. Dopaminergic drugs that target receptors present in high concentrations only in brain areas specific to reward, thereby limiting side effects. This is, in part, the rationale for D3 receptor agonists that exert effects on D3 dopamine receptors relatively localized to limbic brain areas thought critical for cocaine reinforcement and reward learning.
3. Indirectly modulate dopamine transmission using drugs regulating other transmitter systems, such as the use of serotonin antagonists like ondansetron.

While some preclinical data and/or pilot clinical trials support this approach in treating recidivism in cocaine addiction, there is as yet no strong clinical evidence supporting strategies targeting dopamine transmission.

SUMMARY OF HOW COCAINE USURPS REWARD LEARNING

Based upon the previous discussion, it is likely that dopamine is critical for learning behaviors to acquire most if not all rewards. However, addictive drugs produce a more profound and enduring increase in dopamine transmission than natural rewards, and importantly, while tolerance develops to the dopamine-releasing ability of natural rewards, the pharmacological increase in dopamine transmission by addictive drugs continues unabated with each exposure. Thus, continued cocaine use causes over-learning of the behaviors that lead to getting and using the drug. According to this view, the more addicted the individual, the more over-learning takes place and the more effectively drug-seeking behaviors compete with behavior to obtain natural rewards.

BRAIN CHANGES PRODUCED BY COCAINE LEARNING

As indicated above, the ability of cocaine to release dopamine to supra-physiological levels produces a pathological form of reward learning that we know as addiction. This pathology is enduring and has been studied extensively in animal models of addiction and in human addicts using neuroimaging techniques. From these studies, we know that in addition to usurping dopamine-based reward learning, cocaine has usurped much of the circuitry in which the dopamine system is embedded. Thus, exposure of cocaine addicts to cues that they have previously learned to associate with cocaine use (ie, cocaine reward learning) activates a circuit consisting of cortico-limbic brain regions illustrated in Figure 1, notably the areas of the PFC (anterior cingulate and ventral orbital cortices), amygdale, and ventral striatum (nucleus accumbens). In general, this is the same circuit that is activated by cues to motivate behaviors that enable an organism to efficiently obtain physiologically rewarding stimuli, such as food and sex. However, while the cocaine cues can uncontrollably motivate drug-seeking and -taking behaviors regardless of the negative consequences, cues associated with physiological reward initiate behaviors that are more readily modulated by external stimuli and more accessible by cognitive regulation. This distinction between behaviors to seek drug versus natural rewards to some extent defines the behavioral pathology of addiction, and should be the prime target for both pharmacological and behavioral therapies.

Although more control over experimental variables and advances in neuroimaging may yield neurobiological differences in the circuitry activated by cues associated with cocaine versus physiological reward, it is more likely that the distinctions are reflected at a biochemical level. Thus, while the corticolimbic circuitry shown in Figure 1 is shared when engaging in behaviors to obtain a drug or natural reward, there is less flexibility in the circuit when cocaine addicts are responding to an environmental situation that initiates drug-seeking than when they are behaviorally responding to a biological reward. Indeed, in the addict, the behavioral response to biological reward is often relatively weakened. Understanding the neurological basis for reduced flexibility and the resulting narrowing of behavioral options is key to understanding the pathology of addiction. Thus, the remainder of this review will be organized around a perspective that understanding the biological basis of the loss of control is the most rational strategy for identifying new pharmacotherapeutic targets to treat cocaine addiction.

Clues on Molecular Targets from Brain Circuitry

The circuit outlined in Figure 1 points to two potentially critical brain pathways and neurotransmitter systems that may be manipulated to restore normal responding in drug-associated environmental situations and thereby enhance an addict’s control over relapse to drug taking. Notably, the output from the prefrontal cortex to the nucleus accumbens is glutamatergic, and the output from the accumbens to the ventral pallidum is GABAergic and
peptidergic. There is now a great deal of cellular information on how glutamate transmission is altered by withdrawal from chronic cocaine, and while our understanding of GABA and peptide transmission is less evolved, strides are being made. Importantly, as discussed in more detail below, recent clinical trials with agents affecting glutamate and GABA transmission are showing potential utility in decreasing relapse rates and/or response to drug-associated cues among cocaine addicts.

Regulating either glutamate or GABA transmission by systemically administering drugs is potentially problematic because these transmitters are the backbone of neuronal communication in the brain, with glutamate being excitatory and GABA inhibitory. Accordingly, the end result of over- or under-stimulation of these systems ranges from death by depressing brain activity to inducing life-threatening seizures by brain over-activity. Therefore, manipulating these systems must be done carefully and through strategies that will only alter transmission within parameters that are tolerable.

**Glutamate Transmission**

Attempts to develop and test compounds that will alter glutamate transmission within tolerable boundaries has been accomplished by examining two primary mechanisms: using drugs that regulate either nonsynaptic glutamate (ie, cellular pools of glutamate not directly involved in neurotransmission) or modulatory glutamate receptors, termed *metabotropic glutamate receptors* (mGluR; this is in contrast to ionotropic glutamate receptors, which directly excite neurons). Importantly, chronic cocaine administration produces enduring changes in proteins regulating both nonsynaptic glutamate and mGluRs in precisely the brain regions thought most critical to relapse (ie, the prefrontal cortex and nucleus accumbens; see Figure 1). These glutamatergic avenues for novel drug development have focused on inhibiting the massive release of glutamate in the prefrontal cortex projection to the accumbens that is produced during cocaine-seeking in animal models of relapse, or on manipulating the proteins that allow ionotropic glutamate receptors to signal excitation to neurons. (Figure 3 outlines potential sites of action for glutamatergic drugs in the glutamate synapse.) In the former category are compounds that stimulate presynaptic inhibitory mGluRs (mechanism #1 in Figure 3) in order to decrease synaptic release of glutamate. This class of drugs has proven to be successful at suppressing drug-seeking animal models of relapse. However, no clinical trials have yet been conducted with this type of mGluR agonist in cocaine addiction. One compound that indirectly stimulates presynaptic mGluRs, N-acetylcysteine, has been investigated both preclinically and in a small clinical trial (mechanism #2 in Figure 3). N-acetylcysteine is used to restore glutathione levels in situations such as an acetaminophen overdose, by stimulating cystine-glutamate exchange. Importantly, cystine-glutamate exchange is down-regulated in the nucleus accumbens of rats withdrawn from chronic cocaine treatment and provides glutamate to presynaptic mGluRs that inhibit synaptic glutamate release. When administered to non-treatment-seeking cocaine addicts in a double-blind cross-over study, N-acetylcysteine was found to decrease the desire to use cocaine in response to presentation of a cocaine cue. Even more striking was that N-acetylcysteine treatment prevented the activation of the anterior cingulate cortex by cocaine cues. The importance of this as a mechanism of action is revealed in many neuroimaging studies showing that the activation of the anterior cingulate is an antecedent to cue-induced craving. Another compound that may act, at least partly, by inhibiting synaptic glutamate release is modafinil. Modafinil appears to increase extracellular glutamate levels in a manner similar to N-acetylcysteine by increasing metabolic pools of glutamate in the extracellular space, thereby potentially activating mGluR inhibitory
presynaptic receptors. Regardless of the precise mechanisms, recent placebo controlled, double-blind clinical trials indicate that modafinil reduces cocaine craving and rates of cocaine use.32,33

Based on animal studies, developing glutamatergic drugs that treat cocaine addiction by attenuating glutamate signaling in neurons is a viable approach. As indicated above, in general, a direct blockade of ionotropic glutamate receptors is not a viable option due to the dangers posed by completely preventing glutamate transmission. A more rational approach is to use compounds of which the maximum effect is only the partial inhibition of glutamate signaling. Included in this class of drug are the allosteric regulators of the ionotropic receptors (mechanism #3 in Figure 3A), such as D-cycloserine regulation of NMDA glutamate receptors or ampakines to regulate AMPA receptors.34,35 In addition, the activity of ionotrophic receptors can be indirectly regulating using mGluR antagonists to alter the insertion of AMPA glutamate receptors to the membrane (thereby decreasing glutamate signaling; mechanism #4 in Figure 3A). Preclinical behavioral and biochemical studies support the use of either of these approaches in treating cocaine relapse.35–38 but no clinical studies have been conducted with either the allosteric modulators or indirect regulators of ionotropic glutamate receptors.

GABA Transmission

GABA transmission serves to inhibit neuronal activity in most brain regions. Preclinical models of cocaine relapse reveal that decreased GABA release in the ventral pallidum is associated with cocaine-seeking,19,39 thereby posing the possibility that drugs capable of supporting GABA transmission may be useful therapeutic agents. Accordingly, a number of drugs that increase GABA transmission have been examined, and the general mechanisms of action by these GABAergic drugs are illustrated in Figure 3B. Importantly, because the GABAergic projection to the ventral pallidum also contains a number of neuropeptides that regulate GABA release,40 drugs that affect peptide transmission also present potential pharmacotherapeutic targets for regulating GABA transmission.

The regulation of GABA transmission within therapeutically acceptable limits has been accomplished primarily by three mechanisms (see Figure 3B):

1. The regulation of GABA release by stimulating postsynaptic metabotropic GABA receptors, GABAB receptor subtype.
2. Drugs that regulate the synthesis or degradation of GABA.
3. Peptidergic drugs regulating synaptic GABA release.

The prototype drug used to stimulate GABAB receptors is baclofen, which has been shown to inhibit circuitry associated with cocaine relapse in animal models and with craving in human addicts.41–44 Thus, akin to what has been reported for N-acetylcysteine (see above), baclofen treatment inhibits the craving-induced activation of the anterior cingulate and other limbic brain regions important in reward behavior.45 Importantly, in at least one pilot clinical trial, baclofen increased abstinence rates in cocaine addicts.43

Perhaps the most promising mechanism to date for treating cocaine relapse is related to drugs that indirectly promote GABA transmission by increasing synthesis, decreasing degradation or unknown mechanisms. Within this class are compounds used to treat epilepsy, including vigabatrin, tiagabine, valproic acid, topiramate, and gabapentin. The mechanisms of action by which vigabatrin and tiagabine increase GABA transmission are well characterized as inhibiting GABA breakdown and preventing GABA re-uptake, respectively. Valproic acid also has known actions that both potentiate synthesis and inhibit breakdown of GABA. In contrast, the mechanisms by which topiramate and gabapentin potentiate GABA transmission are not clear. Indeed, it is not clear that an effect on GABA transmission is the primary site of action, as these latter two drugs also inhibit ionotropic glutamate transmission. Importantly, the end result of the cellular actions by topiramate or gabapentin is an overall stabilization of synaptic transmission in the brain and inhibition of excessive excitation. All of these drugs have been examined in pilot clinical trials with cocaine addicts. In all cases, there is some positive evidence that this class of drugs is useful in inhibiting relapse, although a general conclusion is that the drugs need further evaluation in larger, well-controlled clinical trials. The reader is directed to recent reviews that nicely provide an overview of the evidence from clinical trials for these drugs.8,10,46

The final potentially useful mechanism for therapeutically regulating cocaine relapse via increasing GABA transmission is to take advantage of the fact that the GABAergic projection into the ventral pallidum is co-localized with neuropeptide transmitters that can regulate GABA transmission.40 This is an arena just beginning to be explored mechanistically and potentially involves the neuropeptides neurotensin, substance P, dynorphin, and enkephalin. Notably, enkephalin transmission in the ventral pallidum has recently been shown to underlie the reduction in GABA release in the ventral pallidum that occurs during cocaine-seeking in animal models.19 Moreover, blocking the mu subclass of the enkephalin opioid receptor in the ventral pallidum prevented cocaine-seeking. This finding may reveal a mechanism underlying the modest efficacy of the opioid receptor antagonist, naltrexone, in treating cocaine addiction, perhaps most successfully in patients that abuse alcohol and cocaine.46–51 It is also worthwhile to note that another neuropeptide, cocaine- and amphetamine-regulated transcript (CART), is also colocalized with GABA in neurons projecting from the nucleus accumbens to the ventral pallidum and VTA, and a variety of data
support the involvement of CART in the behavioral effects of cocaine. While CART effects on cocaine-induced behaviors vary depending on where in the brain it is injected (e.g., accumbens versus VTA), the deletion of the gene encoding CART in mice reduces the behavioral effects of cocaine, but see (Steiner et al.) indicating that pharmacologically promoting CART transmission may be useful in reducing cocaine-induced relapse.

WHY DON'T WE YET HAVE A GOOD PHARMACOTHERAPY FOR COCAINE ADDICTION?

The simplest answer to this question is that we are only on the threshold of understanding the mechanisms whereby the brain is changed by chronic cocaine and how this leads to uncontrollable drug use. Ten years ago, the focus for pharmacotherapy was based almost entirely on understanding the acute effects of cocaine to increase dopamine transmission. Over the last decade, we have learned that this is only the beginning of a neuroplastic process in the brain that involves the brain circuits responsible for learning about biological rewards and developing adaptive behaviors to obtain those rewards. Obviously, this becomes a much more complicated problem that places understanding the biology of cocaine addiction at the very core of a more general understanding of brain function. In other words, we need to understand how the brain learns and regulates behaviors before we can rationally design pharmacotherapies for treating cocaine addiction. Fortunately, in part because of the great societal need to treat addiction, large advances are being made in understanding the cellular mechanisms of learning and how learning is translated into adaptive behavior. Equally fortunate, a current understanding of these mechanisms brings us to transmitter systems where pharmacotherapeutics are actively being developed, namely, drugs to regulate glutamate and GABA transmission.

Although glutamate and GABA transmission are rational targets, a critical question in pharmacologically manipulating these systems is how to affect the uncontrollable drive to obtain cocaine without affecting the biological motivation to seek natural rewards. Fortunately, recent research has identified enduring changes produced by chronic cocaine use in specific proteins in selective brain areas that regulate glutamate and/or GABA transmission. Thus, targeting these specific changes may normalize a cocaine-induced pathology without affecting behavioral responding for biological rewards. The restoration of cystine-glutamate exchange by N-acetylcysteine is a prime example of such an approach.

Another important reason for the difficulty in finding effective drugs for treating addiction is that even if the cocaine-induced pathological plasticity is pharmacologically reversed at a cellular level, the addict will still need to extinguish responding to cocaine-associated environmental stimuli. In other words, the addict needs to learn not to respond to cues in their environment that induce taking cocaine. Reversing the molecular pathology may facilitate this extinction learning, but it cannot create the behavioral change, which can only result from behavioral therapy being provided concurrently with the pharmaco-therapeutic normalization of cocaine-induced neuroplasticity.

SUMMARY

Now that we understand cocaine addiction to be a pathological form of learning causing an unmanageable motivation to obtain a drug, it is clear that the most effective therapy for addicts will involve a multi-pronged approach. As outlined in this review, we are on the threshold of new, potentially beneficial pharmacotherapies that may normalize the biological consequences of chronic cocaine use. However, given that addiction results from pathological alterations in a large brain circuit, individual genetic and environmental factors will influence the neuroplasticity produced by chronic cocaine use, and consequently, which pharmacotherapy will be most effective. Thus, the most effective use of pharmacotherapies will likely involve drug treatments that are tailored based upon specific genetic vulnerabilities, co-morbid neuropsychiatric disorders, and the patterns of cocaine abuse. Finally, because learning is necessary for cocaine to usurp the circuitry regulating normal motivational behavior, even when the underlying molecular pathology is reversed, it will be necessary for the addict to learn to suppress the drive for cocaine and choose biological over drug reward. Thus, while our advancing understanding of the neurobiology of addiction will produce pharmacotherapies that can be powerful aids in treating cocaine addiction, for the foreseeable future, pharmacotherapy will surely need to be combined with behavioral therapy. With few exceptions, behavioral therapy will be necessary to train the addict to take advantage of the pharmacological repair and to personally and sociologically reorient their behavior toward biologically important events rather than cocaine reward.

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