The Neurobiology of Cocaine Dependence and Its Clinical Implications

March 01, 2007
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Cocaine dependence is a devastating disorder that is associated with a host of medical and psychosocial risks. This complex disorder is made up of distinct clinical components that are interwoven into a cycle of addiction (Figure 1). Cocaine activates ancient pleasure centers that dominate our thoughts, behaviors, and priorities, producing a pleasure-reinforced compulsion to use the drug. Repeated use dysregulates brain pleasure centers and paves the way to addiction through craving and impaired hedonic function.1 Euphoria and craving drive the cycle of addiction through positive and negative reinforcement, respectively, and they provide targets for pharmacological interventions.

Cocaine may also dysregulate neurons in the prefrontal cortex (PFC), which is the part of the brain that weights the motivation to use cocaine. PFC dysfunction, in turn, may contribute to loss of control and denial. Human and animal research has identified neuronal mechanisms that underlie many of the clinical aspects of cocaine dependence, support a disease concept, and provide guidance for urgently needed pharmacological treatments.2

Cocaine-induced euphoria
Cocaine produces pleasure that far exceeds the normal range of human experience and becomes inexorably crystallized in memory. The lure of cocaine euphoria should never be underestimated in clinical practice; its sheer power is illustrated by the fact that laboratory animals with unrestricted access to cocaine will self-administer until death. Cocaine produces a brief rush of pleasure and a constellation of stimulant effects (Table)3 that notably includes sexual arousal. Indeed, several lines of evidence indicate that cocaine activates sex reward circuits in the brain.3 Within minutes, cocaine pleasure gives way to intense craving that drives characteristic cocaine binges. As cocaine addiction progresses, individuals become increasingly willing to risk family turmoil, job loss, incarceration, medical problems, and even death in pursuit of the drug.

Table
Symptoms of cocaine intoxication and withdrawal*

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<thead>
<tr>
<th>Intoxication</th>
<th>Withdrawal</th>
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<tbody>
<tr>
<td>Euphoria</td>
<td>Depression</td>
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<tr>
<td></td>
<td>(suicidality)</td>
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<tr>
<td>Wakefulness</td>
<td>Hypersomnia</td>
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<td>Anorexia</td>
<td>Increased appetite</td>
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<td>Psychomotor</td>
<td>Psychomotor</td>
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Cocaine euphoria has traditionally been ascribed to increased dopamine neurotransmission in the nucleus accumbens (NAc), a "universal addiction site" where addictive drugs and natural rewards (eg, sexual behaviors) have long been known to increase dopamine levels. Dopamine is released into the NAc by axons from the ventral tegmentum area (VTA), a reward-related midbrain region that also innervates the PFC, amygdala, and other limbic sites. Target neurons in the NAc have long axons that project to distant regions and release endogenous opioids (enkephalin or dynorphin) and γ-aminobutyric acid (GABA). These neurons have massive dendritic trees that can accommodate projections from as many as 400,000 neurons located in the PFC and other conscious structures, enabling the NAc to funnel, process, and transmit cortical information throughout reward-related circuits.

Cocaine increases synaptic dopamine levels in the NAc by blocking the dopamine transporter (DAT), a reuptake site that normally serves to clear dopamine from the synapse. Positron emission tomography (PET) demonstrates a close correlation between cocaine euphoria and the rate by which dopamine effectively binds the DAT. This explains why rapid routes of administration (eg, smoking, injecting) are associated with intense euphoria. PET studies using [11C] raclopride, a radioligand that competes with dopamine at D2 receptors, further demonstrate that stimulant euphoria is closely correlated with dopamine neurotransmission.

Although this and other evidence for dopamine involvement in cocaine euphoria is compelling, glutamate is also important. Mice bred to lack the glutamatergic mGluR5 receptor will not self-administer cocaine, despite elevated dopamine levels in the NAc. Furthermore, it has recently been demonstrated that dopamine VTA neurons also release glutamate and form glutamatergic synaptic connections in the NAc. These and other findings suggest that cocaine euphoria requires concurrent glutamate and dopamine neurotransmission.

Studies estimate that about 70% of the vulnerability for acquiring cocaine dependence is genetically determined and genetic factors that enhance cocaine euphoria are likely to increase addiction vulnerability. The availability of D2 receptors on PET is a constitutional trait that varies considerably among individuals, and stimulant-naive individuals with low D2 availability report markedly enhanced euphoria after their first stimulant dose. Since low D2 availability has been reported in patients addicted to cocaine, methamphetamine, alcohol, and opioids, it may mark an inherited vulnerability to addictive illness.

Studies also demonstrate that low D2 availability can be acquired, since cocaine administration in nonhuman primates produces low D2 availability along with an increased propensity to...
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Published on Physicians Practice (http://www.physicianspractice.com)

self-administer cocaine.\textsuperscript{15} Furthermore, low D\textsubscript{2} availability is associated with reduced metabolism in the PFC in cocaine dependence.\textsuperscript{5} This fascinating marker is among the most promising findings in addiction neurobiology.

Blocking drug euphoria is an established pharmacological strategy to weaken the cycle of addiction. Although cocaine euphoria is associated with increased dopamine and glutamate neurotransmission, neither GABA agonists (which reduce dopamine and glutamate release) nor dopamine antagonists convincingly blunt euphoria in controlled studies.\textsuperscript{3,16} A vaccine that blocks the euphoric effect of cocaine by slowing its passage across the blood-brain barrier is under investigation.\textsuperscript{17} And 2 separate research groups have reported that modafinil blocks cocaine euphoria under controlled conditions.\textsuperscript{18,19} It is not known how modafinil blocks cocaine euphoria, but its ability to bind the DAT might prevent access to cocaine. Modafinil promoted cocaine abstinence in a controlled pilot study,\textsuperscript{20} and it is currently under investigation in 3 large, government-sponsored clinical trials.

**Cocaine withdrawal and hedonic dysregulation**

Cocaine users may experience withdrawal symptoms that are opposite those seen during intoxication (Table) and probably reflect brain changes associated with severe addiction.\textsuperscript{22} Unlike withdrawal symptoms produced by alcohol, sedatives, and opioids, cocaine withdrawal has never been deemed sufficiently protracted or severe to warrant medical detoxification. It was therefore surprising to find that the presence of withdrawal symptoms at treatment onset reliably predicts poor clinical outcome.\textsuperscript{22} This finding suggests that cocaine withdrawal is just a tip of the iceberg that marks more persistent dysregulation of brain pleasure circuits by chronic exposure to cocaine;\textsuperscript{2} this dysregulation is demonstrated by neuroimaging abnormalities in addicted patients, altered neurotransmitter and receptor levels,\textsuperscript{9} changes in gene expression,\textsuperscript{23} elevated reward thresholds,\textsuperscript{24} and even distortions in neuronal morphology associated with the cocaine-addicted brain.\textsuperscript{25}

Evidence that chronic cocaine use produces dopamine hypoactivity is provided by neuroimaging studies in addicted patients\textsuperscript{26,27} and by several lines of human and animal research that have been reviewed elsewhere.\textsuperscript{9} Patients with cocaine addiction who have evidence of dopamine hypoactivity have very poor clinical outcomes,\textsuperscript{21} and dopamine depletion has long been associated with cocaine-induced hedonic dysregulation and baseline craving.\textsuperscript{28}

Chronic cocaine exposure may suppress dopamine activity through dynorphin, an aversive endogenous opioid that inhibits VTA neurons via k-opioid receptors (Figure 2). Autopsy studies show high levels of dynorphin and k-opioid receptors in cocaine abusers,\textsuperscript{30} as well as dopamine depletion,\textsuperscript{31} and hedonic dysregulation associated with elevated reward thresholds is produced by k-opioid agonists in animal models.\textsuperscript{32}

Animal studies also demonstrate that chronic exposure to cocaine depletes glutamate\textsuperscript{33} and elevates GABA\textsuperscript{34} in the NAc, which would suppress spike formation in this reward region. Dopamine (D\textsubscript{2})\textsuperscript{35} and glutamate (mGluR2/3)\textsuperscript{36} autoreceptors are also down-regulated after cocaine treatment, perhaps to compensate for dopamine and glutamate depletion. Similarly, the finding of low D\textsubscript{2} availability in patients addicted to cocaine\textsuperscript{5} may reflect autoreceptor down-regulation in response to dopamine hypoactivity.\textsuperscript{37}

Reversing cocaine-induced neuroadaptations with dopamine/glutamate agonists or GABA/dynorphin antagonists might normalize hedonic function and improve clinical outcome. Selective k-opioid antagonists are not currently available, but 2 randomized, placebo-controlled studies of dopamine-enhancing agents have recently been reported. Modafinil (400 mg/d), a weak DAT antagonist, promoted abstinence in cocaine-dependent participants (n = 62),\textsuperscript{21} as did disulfiram (250 mg/d; n = 121),\textsuperscript{38} which may increase brain dopamine levels by inhibiting dopamine b-hydroxylase. Conversely, the dopamine antagonist olanzapine (10 mg/d) actually increased cocaine use under controlled conditions (n = 30).\textsuperscript{39} Hedonic dysregulation resulting from chronic cocaine administration has not been adequately researched, and reliable measures of hedonic function are curiously absent in a scientific community that measures nearly everything else.

**Craving**

Cocaine craving takes different forms that emerge at various times during active cocaine use and recovery. Cocaine-related cues trigger intense craving, even after months or years of abstinence and represent a common avenue to relapse. Craving is also amplified by life stress and by cocaine itself, which is surely the most powerful craving trigger. These forms of precipitated craving are targeted by relapse prevention strategies that include cue avoidance, stress management, and the cornerstone principle of complete abstinence.

Baseline craving, which occurs without discernible precipitants, is the least studied yet possibly most important form of craving in persons who are actively addicted. A relationship between baseline craving and dopamine depletion is suggested by the fact that each is instantly reversed but then
quickly exacerbated by the administration of cocaine. Baseline craving gradually diminishes during abstinence to pro- vide relief and momentum during early recovery.

Animal studies demonstrate that the distinct forms of craving have different and sometimes opposite neuronal mechanisms, implying that a battery of anticraving medications might ultimately be necessary in the treatment of cocaine dependence. Most of what we know about craving neurobiology has been provided by reinstatement studies in which animals are trained to self-administer cocaine. Cocaine self-administration is extinguished by replacing cocaine with saline but can later be reinstated with small doses of cocaine, cocaine-paired cues, or stress, providing animal models of cocaine-induced, cue-induced, and stress-induced craving.

Cocaine-induced craving underscores the fact that cocaine does not produce satiety, and the tease of a single cocaine dose might be comparable to sexual arousal resulting from the activation of sex reward circuits. A glutamate mechanism for cocaine-induced craving has been identified by studies showing that N-acetylcysteine obliterates cocaine reinstatement by normalizing glutamate levels in the NAc. A recent study reported that N-acetylcysteine is well tolerated by patients who are addicted to cocaine, and it may improve cocaine withdrawal and baseline craving.

Glutamate-enhancing agents might limit drug exposure by reducing the desire to engage in protracted binges. Avoiding conditioned elements of the drug environment (people, places, and things) that trigger intense craving is an important principle of addiction treatment. Over the past decade, numerous PET and functional MRI studies in cocaine-addicted subjects have reported hypermetabolic responses in glutamate-rich limbic and frontal brain regions (eg, amygdala, orbitofrontal cortex, anterior cingulate) during cue-induced craving. This amazing neuronal response to cues correlates with the intensity of craving and substantiates the biological basis of cocaine dependence. Interestingly, the same brain regions that become hypermetabolic during cocaine cues in patients who are addicted are also activated by sexually explicit videos in persons without cocaine addiction; this reiterates cocaine's ability to hijack the sex reward circuits.

Cue-induced reinstatement studies link the phenomenon with increased dopamine and glutamate neurotransmission in the basolateral amygdala, PFC, and NAc. These structures receive dopamine projections from the VTA, which shows remarkable responses to reward-related environmental cues. Single-cell recordings of VTA neurons demonstrate burst-firing in response to environmental cues and a plunge below baseline firing if the expected reward does not materialize. Dopamine firing patterns in response to reward-related cues are mirrored by neuronal activity in the glutamate-rich orbitofrontal cortex, which receives sensory information from the thalamus and drives phasic VTA activity (Figure 2). These findings provide additional evidence of concurrent dopamine and glutamate signaling during activities involving hedonic function.

Cue-induced reinstatement can be blocked by reducing dopamine or glutamate release, and by antagonists at dopamine D1, glutamate amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors. Topiramate is an AMPA antagonist that also elevates levels of GABA, which would reduce dopamine and glutamate activity. Topiramate (200 mg/d) improved cocaine abstinence after several weeks of treatment in a recent controlled trial (n = 40), although its effect on cue-induced craving was not measured. Baclofen, a GABA agonist that reduces dopamine and glutamate neurotransmission, reduced cue-induced limbic activation in a small pilot study, and a controlled study reported that baclofen (60 mg/d) promoted abstinence in a subgroup of patients who were cocaine-dependent (n = 70).

Limbic activation on neuroimaging provides a fortuitous biological marker of cue-induced craving that could be used to develop medications to reduce cue salience. It is remarkable that the same frontal regions that become hypermetabolic during cue-induced craving are hypometabolic at baseline in patients who use cocaine, and it is tempting to speculate that the result- ing signal change (peak minus base-line) contributes to the salience of cocaine cues. Cue-induced craving is a persistent phenomenon that is directly linked to relapse. Its effective treatment would represent a major therapeutic breakthrough.

Stress-induced craving has traditionally been viewed as a psychological desire to escape stress by using cocaine. However, animal studies also suggest a biological basis, because stress-induced reinstatement is dependent on the release of corticotropin-releasing factor (CRF), a stress hormone. CRF activates reward-related circuitry in animals pretreated with cocaine. Stress releases CRF in all rats, but only releases dopamine after cocaine treatment, which is a critical finding because stress-induced reinstatement depends on dopamine neurotransmission. CRF releases dopamine in cocaine-pretreated rats by elevating VTA glutamate levels; CRF does not elevate dopamine in cocaine-naive animals, suggesting that glutamate and dopamine antagonists...
might ameliorate stress-induced reinstatement. CRF antagonists, once available, should also be tested as treatments for stress-induced craving. Noradrenergic hyperactivity is also associated with stress-induced reinstatement, perhaps explaining why the β-adrenergic antagonist propranolol (100 mg/d) promoted abstinence in a subgroup of patients with cocaine dependence (n = 108).54

**Loss of control**

PFC dysfunction is increasingly viewed as a core component of cocaine dependence that may contribute to loss of control and even denial, which was once viewed as purely psychological.51 Neuroimaging studies demonstrate that patients with cocaine addiction have reduced frontal metabolism2 and diminished frontal gray matter density,55 and perform poorly on neuropsychological tests that assess PFC function.3 Abnormalities of the PFC may predate or result from the use of cocaine, although the latter is suggested by animal studies reporting reduced cell counts, distorted morphology, and altered electrophysiological properties of PFC neurons after cocaine exposure.51 The PFC is the seat of executive function in the brain and its dysfunction could contribute to impaired decision making, inappropriate risk tolerance, poor impulse control, and even denial in patients with cocaine addiction. Agents that activate the PFC might improve clinical outcome in cocaine dependence.

**Conclusion**

Cocaine acutely activates but chronically dysregulates brain pleasure centers that have evolved to ensure survival. Although there are currently no approved drugs for the treatment of cocaine dependence, medications that address the effects of cocaine on these powerful circuits are under investigation as a means of improving clinical outcome. The pharmacological reversal of cocaine-induced neuroadaptations is perhaps the most attractive strategy because it is aimed at brain normalization. Pharmacological treatments are also being developed to block cocaine euphoria and dampen craving that is precipitated by stress, cocaine-related cues, and the use of cocaine. Advances in cocaine neurobiology provide insight into many of the baffling clinical features of cocaine dependence. For instance, cocaine's actions on sexual pleasure circuits provide insight into the compelling nature of this addiction. Despite compelling scientific evidence that cocaine dependence is a brain disease, it is still viewed more as a choice by the general public and neither treated nor covered by medical insurance on parity with traditional medical illnesses.43 However, further advances in the neurobiology of cocaine dependence promise to reduce its stigma and improve its clinical outcome by guiding the development of effective medication.

**References:**


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