Cocaine Addiction: Mechanisms of Action

Despite advances in our understanding of drug addiction, millions of Americans remain addicted to drugs of abuse, and new addicts join their ranks daily. Biomedical understanding of drug addiction has been advanced through a multi-pronged approach to ascertain how drugs of abuse are rewarding to users, how repeated drug use leads to addiction, and why drug addicts face such high rates of relapse. In particular, knowledge of the neurobiology underlying these issues has been deepened through the use of animal models. The current review will present some of the recent developments in the neurobiology of drug use and addiction, revealed in part through animal models.

1. Define the mechanism of action of cocaine and how it produces its rewarding effects.
2. Describe the neurocircuitry underlying the reinstatement models of relapse and the role of the glutamatergic system in relapse.
3. List the models used in the study of the neurobiology of drug addiction and how such models may be informative for the treatment of addiction.

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Dr. LaLumiere and Dr. Kalivas have disclosed no relevant financial relationships.
DRUG ADDICTION AS LEARNING AND MEMORY

Over the past decade, it has become increasingly clear that addiction should be considered a form of dysfunctional learning and memory.1,2 Drugs of abuse, such as cocaine, have rewarding effects that reinforce the user’s behavior. As the user continues to consume the drug, various stimuli and the environment in which the drug is consumed become associated with the drug and its effects. The basic circuitry of drug addiction, therefore, maps onto the circuitry underlying learning and memory for motivated behaviors. However, chronic drug use, unlike natural motivators, produces maladaptive behavioral patterns characterized as “addiction.” Specifically, with drug addiction, individuals experience a strong drive to seek and consume the drugs of abuse to the exclusion of other activities and behaviors. Moreover, such individuals, even following extended periods of abstinence since their last drug use, face high rates of relapse to drug-seeking behaviors. Thus, despite the apparent similarities between drugs of abuse and natural motivators in terms of reinforcing behavioral patterns, qualitative and quantitative differences between the two must exist in order to explain how repeated drug use produces addiction and relapse vulnerability while natural motivators simply produce a learned set of behaviors that may be employed depending on the circumstances and needs of the individual.

DRUGS OF ABUSE: BASIC MECHANISM OF ACTION

One critical difference between the neurobiology of drug use and that of natural reward lies in the mesolimbic dopamine system. Two dopaminergic systems exist in the mammalian forebrain (see Figure 1). The substantia nigra provides dopamine to the dorsal striatum (or caudate-putamen) as part of the extrapyramidal motor system. The remainder of the forebrain receives dopaminergic projections from the ventral tegmental area (VTA). The dopamine projections from the VTA target structures known to regulate learning and memory for reinforcing behaviors, such as the nucleus accumbens, amygdala, and prefrontal cortex.

Under normal conditions, motivating stimuli, be they novel natural rewards or aversive stimuli, increase neuron firing in the VTA, as well as dopamine release in regions of the brain targeted by VTA axons.3,4 External neutral cues that are predictive of the stimulus will, over repeated pairings, also begin to elicit a similar response. However, when the reward becomes predictable, the increase in VTA neuronal firing and dopamine release ceases in response to the rewarding stimulus itself and is only evoked by the conditioned cue. Moreover, when an expected reward does not arrive, there is a decrease in dopamine neuron firing. This suggests that dopamine serves as an error prediction signal and reinforces the animal’s behavior only so long as the animal is still learning how to predict the reward and developing the corresponding behavior to obtain the reward. Dopamine does so by modulating and driving neuroplasticity mechanisms in VTA target structures. When the reinforced behavior has been well learned, the need for dopamine ends.

Like natural motivating stimuli, drugs of abuse increase dopamine, although each drug of abuse does so through different mechanisms depending on the class of drug. When dopamine is released from an axon terminal, it is normally cleared quickly from the synapse, primarily via reuptake through the dopamine transporter. Cocaine blocks the dopamine transporter, leading to a large increase in synaptic dopamine. Amphetamines act by reversing the dopamine transporter, whereas opiates, such as heroin and morphine, and alcohol are believed to act in the VTA and remove the inhibition that normally reduces the activity of VTA neurons. Unlike natural stimuli whose ability to influence dopamine release diminishes with repeated exposure, repeated use of these drugs produces a consistently large increase in dopamine with each administration. Moreover, due to the pharmacological

![Figure 1. Neural circuitry involved in drug addiction. Although not exhaustive, the structures in this figure are important for drug reward, addiction, and relapse, and include the ventral tegmental area (VTA), dorsal prefrontal cortex (PFC), basolateral amygdala (BLA), dorsal striatum (Str), nucleus accumbens (NA), and substantia nigra (SN). The VTA provides the dopamine for most forebrain structures, whereas the SN provides the dopamine for the dorsal Str (caudate-putamen). The PFC and BLA provide a glutamatergic projection to the NA.](image-url)
actions of these drugs and the lack of a natural system to regulate the drugs’ actions, the release of dopamine can far exceed what occurs naturally, particularly after administration of psychostimulants, such as cocaine. Thus, repeated drug use is believed to produce an “over-learning” of the motivated behaviors to acquire the drug as well as of the cues and environmental stimuli and circumstances associated with the drug use. This over-learning explains how drugs of abuse overpower the ability of other motivators in the person’s environment to engage the person.

Evidence for dopamine’s role in the reinforcing effects of cocaine has come from studies in which rats self-administer cocaine. In the self-administration model (see Figure 2), dopamine receptor antagonists reduce the rewarding effects of the cocaine, and moreover, when rats are trained to self-administer cocaine, they can then be switched to self-administer dopamine agonists, suggesting that activation of dopamine receptors is sufficient to maintain the rewarding effects.

Figure 1 (see page 253) shows the neurocircuitry known to be involved in drug reward and relapse. Although drugs of abuse increase dopamine levels in most forebrain structures, the critical reinforcing effects of the drugs appear to be mediated through a part of the ventral striatum called the nucleus accumbens (NA). The NA is the primary interface between limbic/memory circuitry (e.g., the amygdala and hippocampus), decision-making circuitry (e.g., the prefrontal cortex), and motor output (via the ventral pallidum, thalamus, and, eventually, the extrapyramidal motor system). Like the rest of the forebrain except for the dorsal striatum, the NA receives its dopaminergic input from the midbrain dopamine neurons in the VTA. The NA itself is subdivided into two regions: the

Figure 2. The self-administration model of drug addiction and relapse. The self-administration model has served as the gold standard of addiction research in animals because, as with humans, animals engage in specific behaviors (e.g., lever pressing) in order to receive the drug, rather than simply being given a non-contingent administration of the drug by the experimenter. In this case, the animal mimics the kinds of learning that occur with human drug abusers, as the model includes the instrumental learning involved in acquiring the drug: the environment in which self-administration occurs (usually a specific chamber), and the cues (e.g., light and tone) that can be specifically paired with drug delivery. This model lends itself to examining relapse to drug-seeking. After self-administering the drug consistently over the course of a few weeks, the animal can be switched into extinction, in which lever presses no longer produce drug delivery. Over the course of repeated sessions, the lever pressing decreases to minimal levels. The animal’s lever pressing can, however, be reinstated by presenting the cues (cue prime) or environment (context prime) formerly associated with the drug taking, by giving a noncontingent injection of the drug itself (drug prime), or by administering a major stressor immediately prior to the reinstatement session (stress prime). Each type of reinstatement models ways in which humans relapse to drug abuse. Alternatively, rather than entering extinction, animals can be left in their home cages for a period termed “abstinence.” When the animals are returned to the self-administration chamber, the animals engage in lever pressing levels that actually exceed what would normally be expected for the first day of extinction, a phenomenon known as the “incubation of craving.”

Figure 3. Generic data showing the increase in glutamate in the NA core following a reinstatement trigger. This increase is prevented by inactivating the dorsal PFC with a mixture of GABA receptor agonists (Baclofen/Muscimol), suggesting that the dorsal PFC is the source of this glutamate.
Over the past decade, it has become increasingly clear that addiction should be considered a form of dysfunctional learning and memory.

As behaviors become well learned and eventually habit-like, the memory for the behaviors shifts, in part, from the ventral to dorsal striatum.

The critical nature of the role of the NA in cocaine reward and reinforcement has been shown through a variety of studies. Self-administration of cocaine is blocked by administering dopamine receptor antagonists directly into the NA but not into the dorsal striatum. Lesions of the dopaminergic projections to the NA eliminate cocaine self-administration. However, it appears that the NA shell, rather than the core, is more important for the rewarding effects of cocaine, as rats will self-administer cocaine into the shell but not the core.

The evidence suggests that, as drug use becomes increasingly chronic and habitual, there may be a shift in the critical mediating structures from the NA shell to the NA core and, eventually, to the dorsal striatum.

NEUROBIOLOGY OF RELAPSE

As noted, the self-administration model of drug use enables the study of relapse and its underlying neurobiology in animals through the reinstatement of drug-seeking behavior. Using the extinction-reinstatement and abstinence-reinstatement models, researchers have identified critical neural substrates for the drug-seeking in each model (see Figure 1, page 253). In the extinction-reinstatement model, the prefrontal cortex-NA core pathway appears to be critical, as inactivation of either structure prevents cocaine-, cue-, context-, and stress-induced reinstatement.

Not surprisingly, the modality and nature of the reinstatement trigger is reflected in the additional structures involved in each particular reinstatement: cue triggers require the basolateral amygdala (BLA, involved in Pavlovian associations); context-triggers require the BLA and the hippocampus (involved in contextual learning); stress triggers require a variety of structures involved in mediating stress responses, including the central nucleus of the amygdala and bed nucleus of the stria terminalis.

Each of these kinds of reinstatement also depends on the VTA, the source of dopamine to much of the forebrain. However, the dopamine synapse in the NA core, known to be involved in earlier aspects of drug use, is not important for reinstatement, as blockade of dopamine receptors in the NA core does not prevent reinstatement. Rather, it appears that dopamine release in the prefrontal cortex and/or BLA provides the key dopamine signal to drive the reinstatement of cocaine-seeking behavior. These structures, in turn, provide a glutamatergic projection to the NA core, and the release of glutamate in the NA core is necessary for reinstatement.

Intriguingly, evidence with the abstinence-reinstatement model indicates that neither the prefrontal cortex nor the NA core is involved in this model of relapse. Rather, inactivation of the dorsolateral striatum (caudate-putamen) prevents reinstatement following home-cage abstinence. This finding suggests that the active learning processes involved in repeated extinction sessions induce a change in the circuitry mediating relapse and that, therefore, extinction-reinstatement and abstinence-reinstatement may model different aspects or kinds of relapse in humans. As the dorsolateral striatum mediates habit learning and the prefrontal cortex is involved in decision making, the role of the dorsolateral striatum and lack of a role for the prefrontal cortex suggests that, in this model, the rats are engaging in a form of habit behavior with little prefrontal control over their behavior. Other evidence shows that, over repeated training in a drug-seeking model, there is a gradual shift to increased dopamine release in the dorsolateral striatum over dopamine release in the NA. Together, these findings indicate that, in the addicted animal, the drug-seeking behavior is more habit-like and, thus, more dependent on habit circuitry.

The studies presented in this section raise the issue of which animal model(s) of relapse most closely reflect the human condition. It is unlikely that any specific model captures the totality of human drug addiction. Rarely are humans forc-
GLUTAMATE AND RELAPSE

As Figure 1 indicates (see page 253), the projection from the dorsal prefrontal cortex to the NA core, which is critical in all extinction-reinstatement models examined, is a glutamatergic projection. Cocaine- or stress-induced reinstatement produces a large increase in NA core glutamate levels, which is blocked by simultaneously inactivating the dorsal prefrontal cortex. However, a similar treatment to naïve animals has no effect on glutamate levels in the NA core (see Figure 3, page 254). Thus, it appears that long-term cocaine self-administration alters the glutamatergic pathway from the dorsal prefrontal cortex to the NA core such that activation of the dorsal prefrontal cortex drives the NA core and subsequent drug-seeking behavior through activation of glutamate receptors in the NA core. The BLA may play a similar role in cue- and context-induced reinstatement.

How does a non-contingent administration of cocaine or administration of a stressor increase glutamate in animals with a cocaine history but not in naïve animals? Based on a series of studies, it appears that long-term cocaine self-administration alters extracellular glutamate homeostasis in the NA core, permanently reducing basal glutamate levels relative to those found in naïve animals. The reduced basal levels, in turn, provide less activation of glutamate receptors that reside on presynaptic glutamate terminals and inhibit synaptic glutamate release, including dorsal prefrontal cortex glutamatergic inputs to the NA core. It is proposed that due to this reduced inhibitory feedback, activation of prefrontal glutamate inputs leads to a larger and prolonged release of glutamate into the NA core.

Evidence suggests that the reduced basal levels are due to dysfunction in the glutamate-cystine exchanger located in glial cells in the NA core, although the precise mechanism underlying the development of this dysfunction remains unclear. The exchanger is responsible for scavenging the extracellular space for cystine used in glutathione synthesis, and, by exchanging extracellular cystine for intracellular glutamate, maintains extracellular glutamate at a consistent level. Consistent with this hypothesis, activation of cystine-glutamate exchange by systemic administration of the cystine prodrug N-acetylcysteine, increases extracellular glutamate levels and reduces cocaine-induced reinstatement in animals and the desire for cocaine in human addicts.

TRANSLATING INTO THE CLINIC

The animal studies presented here, particularly those employing reinstatement models, suggest that drug taking and relapse occurring in humans fall along a spectrum (see Figure 4). At one end of the spectrum is the social drug user who consumes the drug only under limited, cognitively regulated circumstances and thus may not be addicted. This person’s drug use does not significantly affect non-drug related behaviors and due to the lack of consistent chronic drug use, less enduring dysfunctional change would be predicted to have been inflicted on neural circuitry. In this con-
dition, drug use would depend primarily upon the natural rewarding and reinforcing effects of the drug and the drug’s actions on the dopamine systems, particularly dopamine projections to the NA. The findings with the abstinence-reinstatement model suggest that at the other end of the spectrum is the person who engages in drug use as a habit in which decision-making occurs at a level incapable of guiding behavior in direc-
garding their drug use and are presumably utilizing their prefrontal cortex.

The hypothesized spectrum may be relevant to the Transtheoretical Model of Change that is currently popular in health psychology.30 The “compulsive relapse” user would be comparable to people in the pre-contemplation stage, who are uninterested in changing their behavior and even unaware of the negative consequences of their behavior. The “regulated relapse” part of the spectrum would encompass the four middle stages of change: contemplation, preparation, action, and maintenance. The “no relapse” end would map onto the termination stage. This comparison of models is particularly enlightening because the four middle stages of change require active thinking and cognition on the drug user’s part, as a “regulated relapse” drug user does. In fact, as with regulated relapse, someone in the contemplation and preparation stages may even still consume the drugs but is now aware of the consequences of the drug use. Moreover, as the individual moves through the stages from contemplation to maintenance, it is conceivable that the prefrontal cortex acquires greater and greater behavioral control until the individual is able to decide consistently against drug use.

CONCLUSIONS

The current spectrum model of relapse-drug use suggests that treatment should aim to move people from compulsive to regulated relapse and from regulated relapse to social drug use (or no drug use, depending on the drug of abuse and circumstances). However, the differences among the neurobiologies underlying each part of the spectrum suggest that the type of treatment may be different depending on the person’s place in the spectrum. In particular, anticraving pharmacotherapies may be particularly effective in moving people from more compulsive use to a more prefrontal cortex-dependent regulated use. In contrast, substitution therapies, such as nicotine patches or methadone, may not be effective in the compulsive users who engage in drug use as part of a non-thinking habit. Rather, such therapies may be more effective in treatment-seeking individuals, who are trying to move from regulated relapse to social/no drug use.

SUMMARY

In recent years, drug addiction has been viewed as a form of learning and memory in which the drugs influence neuroplasticity mechanisms, creating the dysfunctional motivated behavior inherent in addiction. Although natural rewards and drugs of abuse increase dopamine levels throughout the forebrain, a critical difference between the two types of stimuli lies in the fact that the dopamine response habituates to natural rewards but does not do so for drugs of abuse. The massive and repeated dopamine release in critical memory-related regions of the brain reinforces the drug-
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seeking behavior to such an extent that it produces “over-learning” for the drug-
seeking behavior and for drug-associated cues. However, this enhancement is beyond what occurs naturally and produces dysfunctional neuroplasticity that is thought to underlie addictive behaviors, particularly the high rate of relapse among drug users. Studies using animal models of relapse have elucidated some of the mechanisms involved in relapse. In particular, evidence from reinstatement animal models of cocaine seeking suggests that the prefrontal cortex projection to the nucleus accumbens becomes altered after long-term cocaine self-administration and that this neuroplasticity reduces the capacity for frontal cortex to regulate drug seeking. Thus, neuroplasticity in this prefrontal projection causes drug seeking to be more habitual and less amenable to regulation by executive thought processing. Together, these findings suggest that drug use and relapse fall along a spectrum with compulsive relapse dependent on habit-learning structures at one end and social drug use on the other, which involves substantial regulation by frontal cortex. This model of relapse behavior may provide a framework for investigating new treatments for addiction, as well as determining which treatments are most effective for particular individuals.

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