Abstract

Substance addiction is a maladaptive behavior characterized by compulsive and uncontrolled self-administration of a substance (drug). Years of research indicate that addictive behavior is the result of complex interactions between the drug, the user, and the environment in which the drug is used; therefore, addiction cannot simply be attributed to the neurobiological actions of a drug. However, despite the obvious complexity of addictive behavior, animal models have both advanced understanding of addiction and contributed importantly to the development of medications to treat this disease. We briefly review recent animal models used to study drug addiction and the contribution of data generated by these animal models for the clinical treatment of addictive disorders.

Key Words: addiction; dependence; drug abuse; memory; reinforcement; reward; rodent model

Introduction

Is drug addiction a single disease or a collection of different diseases that share common features of compulsive drug use behavior? The current state of addiction research gives the impression that addiction is a collection of diseases (e.g., cocaine addiction, heroin addiction, and so forth) that share common behavioral features, although most researchers do not hold this view. The downside of this multidisease concept is that it creates challenges for the development of effective treatment strategies. For example, both cocaine and amphetamine are central nervous system stimulants, but they have completely different treatment strategies. Although it is true that these drugs exert their action through different receptors and modulate different neurotransmitter systems, the addictive nature of the drugs converges on the neurocircuitry that underlies their rewarding properties. The convergence argues for the idea that drug addiction is a single disease—a disease of the reward circuit that drives maladaptive behavioral responses to positive and/or negative reinforcement. Thus, conceptual models of drug addiction that incorporate all drug classes could significantly advance understanding of the addicted brain.

This review is organized according to addiction to specific classes of drugs because research programs tend to focus on specific drugs (e.g., cocaine, amphetamines, opioids, nicotine, or alcohol). We discuss various animal models that are used to study drug addiction and dependence, with particular emphasis on investigations of the reward system, which acts as a convergent point for drug actions. We also discuss how gene-targeting technologies have advanced understanding of addictive behaviors and how animal research has informed clinical treatments of drug addiction. We conclude with thoughts about particularly promising directions for addiction research.

Criteria for the Development of a Valid Animal Model

Drug addiction is a disease characterized by compulsive, uncontrolled drug-seeking and drug-taking behavior that is very difficult to quit despite the user’s recognition of its harmful consequences (Hasin et al. 2006). Drug dependence is characterized by withdrawal symptoms in the absence of the drug that drive individuals to resume drug taking. For example, cocaine withdrawal produces profound fatigue, alcohol withdrawal produces anxiety and sometimes seizures, and opiate withdrawal results in marked dysphoria. Addicts resume drug taking to alleviate the negative symptoms of withdrawal, a phenomenon termed negative reinforcement.

Evidence indicates that, even in the absence of withdrawal symptoms, animals, like humans, self-administer psychoactive substances to experience the pleasurable (rewarding) effects of a drug. This phenomenon is termed positive reinforcement. Thus, a valid animal model of drug addiction should exhibit both negatively reinforced drug-seeking behavior to alleviate withdrawal symptoms and positively reinforced voluntary drug-using (drug self-administration) behavior to induce pleasurable sensations.

Because it is often impractical and unethical to perform research on addictive behavior in humans, the use of animal models makes it possible to gain insights essential for developing effective treatment strategies for such behavior. Animal models have become indispensable for the development of...
of drug addiction treatments because they enable mapping of the specific regions of the brain where individual drugs exert their actions and determination of the mechanisms by which drugs produce their effects. Animal models also permit testing of the pharmacological efficacy and verification of the biosafety of medications before they are used in clinical practice (Lynch et al. 2010).

**Negative Versus Positive Reinforcement Theories of Drug Addiction**

Given the severity of withdrawal symptoms for many drugs, it is not surprising that negative reinforcement was the prevailing viewpoint during the early years of addiction research (discussed in Ahmed and Koob 1998; Ahmed et al. 2000). A major scientific advance occurred when Olds and Milner (1954) reported a “positive reinforcement brain center” and demonstrated that rats self-administer electric stimulation at selective brain regions such as the nucleus accumbens (NAc1) and ventral tegmental area (VTA1). After many more years of research, it was determined that animals also self-administer psychoactive drugs into these brain areas even in the absence of withdrawal symptoms, thereby establishing the “reward” theory of drug self-administration (reviewed in Wise 1996).

These studies determined that the positive reinforcement brain center first described by Olds and Milner consists of VTA dopaminergic cell bodies and NAc terminals (Corbett and Wise 1980; Wise 1981). In addition, investigators found that different drugs have different sites of action in the reward system. For example, the rewarding properties of morphine (opioids or opiates) are mediated by synapses at VTA dopamine cell bodies, alcohol reward is mediated by VTA neurons (Brodie et al. 1999), and NAc dopamine terminals are the site of action for amphetamine and cocaine (Broekkamp et al. 1975; Colle and Wise 1988).

Taken together, these observations indicate that the site of action that regulates the rewarding properties of drugs depends on the drug in question. Opiates and alcohol disinhibit VTA dopaminergic neuronal cell bodies, causing the release of dopamine at nerve terminals in the NAc. In contrast, cocaine and amphetamine exert their effects on dopaminergic neuronal terminals to increase dopamine concentrations at NAc synapses.

**Modeling Relapse of Drug-Taking Behaviors in Animals**

Many natural experiences important to survival are highly rewarding and cause increased dopamine release in the NAc. The reward system is closely tied to the memory system, and associative memory processes linking positive emotions with certain experiences and behaviors help individuals find the “right” kind of food, choose the “right” mate, and survive to pass on their genes (Kelley 2004). Similarly, individuals remember the positive emotions caused by a psychoactive drug and its associated environmental cues.

Models that use the conditioned place preference (CPP1) paradigm take advantage of these powerful and long-lasting memories for drug-associated environmental cues (conditioned stimuli) to evoke drug-seeking behavior (Hernandez and Kelley 2005; Robinson and Berridge 1993; Stewart et al. 1984). For example, when morphine or cocaine treatment is paired with a specific environment, rats later spend significantly more time in the environment in which they received the drug.

Intracranial infusion of morphine into the VTA produces CPP (Bozarth et al. 1980; Olmstead and Franklin 1997; Phillips and LePiane 1980), as does intracranial administration of amphetamine into the NAc (Josselyn and Beninger 1993; Schildein et al. 1998). And conversely, when a given environment is paired with an aversive stimulus such as naloxone (an opioid antagonist), rats later avoid that environment (Mucha et al. 1982), suggesting that the environment is perceived as a place of punishment. CPP is thus an extremely useful experimental tool for exploring associations between reward and memory systems and determining the reward value of different drugs.

**Modeling Drug Self-Administration in Animals**

Drug self-administration animal models developed over the past 40 years in an effort to mimic human drug addiction have helped pinpoint dopamine as a primary mediator of brain reward pathways where cocaine, amphetamines, and nicotine clearly act. In addition, the development of receptor gene research has been integral in determining that dopamine acts on D1 to D4 dopamine receptors coupled to G protein signaling systems (for review see Missale et al. 1998). Activation of these signaling pathways leads to changes in neuronal function that in turn result in the expression of addictive behavior(s) (Schultz 2010; Wise 2008). Furthermore, glutamate, γ-aminobutyric acid (GABA1), serotonin, and norepinephrine play modulatory roles in regulating dopaminergic neuronal activity, making these neurotransmitters potential targets for drug addiction treatments (Kalivas and Volkow 2011).

Several classes of psychoactive drugs—psychostimulants (e.g., cocaine, amphetamines), opioids, nicotine, and alcohol—are widely used in the population, and their chronic use causes significant health problems and is of great concern to society. In the sections below, we discuss the animal models used to study self-administration of these drugs.

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1Abbreviations that appear ≥3x throughout this article: CPP, conditioned place preference; GABA, γ-aminobutyric acid; KO, knockout; MDMA, 3,4-methylenedioxy-N-methamphetamine; NAc, nucleus accumbens; VTA, ventral tegmental area.
Psychostimulant Addiction

The most commonly abused schedule I or schedule IV\(^2\) psychostimulants include cocaine, amphetamine, and 3,4-methylenedioxy-N-methamphetamine (MDMA\(^1\) or “ecstasy”).

All three psychostimulants increase synaptic dopamine concentrations, but their mechanisms of action differ. Cocaine inhibits the dopamine transporter and thus prevents reuptake of dopamine into presynaptic elements. Amphetamines produce their effects by reversing the reuptake of dopamine, serotonin, and/or norepinephrine in the brain (Gudelsky and Yamamoto 2008; Sager and Torres 2011). MDMA also selectively targets the serotonin reuptake transporter (Seger 2010). Repeated exposure to MDMA may lead to sensitization of dopaminergic responses to the substance, thereby increasing an individual’s addiction risk (Schenk 2011; Schenk et al. 2011). MDMA has recently gained tremendous popularity due to its availability.

**Cocaine**

Cocaine has been shown to interact with the dopamine transporter (DAT), so it was anticipated that knockout (KO)\(^3\) of the DAT gene would alter behaviors related to cocaine addiction such as cocaine self-administration and reward in the CPP paradigm. Overall, studies have demonstrated that cocaine-activated locomotor activity is decreased or eliminated in DAT knockouts; for example, Giros and colleagues (1996) reported that cocaine-induced locomotion and CPP are attenuated in DAT KO mice.

In contrast, cocaine self-administration patterns in DAT KO animals are less clear. Some studies suggest that such animals display substantially decreased self-administration (Thomsen et al. 2009a), whereas others report that self-administration is unaffected (Rocha et al. 1998; Tilley et al. 2007). Thus, unknown factors likely influence cocaine addictive behaviors to cause different study outcomes.

Another problem with DAT knockout is that significant compensatory changes can occur in KO animals. To overcome potential compensation caused by gene deletion, Chen and colleagues (2006) used a knock-in (KI) mouse line carrying a functional but cocaine-insensitive DAT. In these mice, cocaine administration suppressed locomotor activity, did not increase extracellular dopamine levels in the NAc, and failed to produce cocaine reward. Furthermore, the mice did not self-administer cocaine (Thomsen et al. 2009b). Thus a functional DAT is necessary and sufficient to maintain cocaine addiction.

In addition to the DAT KO and KI animals, other transgenic mice have been developed to study the effects of cocaine: DAT-overexpressing transgenic mice (Donovan et al. 1999), vesicular monoamine transporter KO mice (VMAT2), cocaine-insensitive mice, DAT-serotonin (SER) reuptake transporter (DAT/SER) double-KO mice, and dopamine-deficient mice (Hnasko et al. 2007). Data from these transgenic lines suggest that the dopaminergic system interacts with serotonergic signaling to influence the acquisition of cocaine CPP (Hnasko et al. 2007). The involvement of serotonin and serotonin receptor subtypes in cocaine sensitization, discrimination, self-administration, reinstatement of cocaine-seeking behavior, and CPP in laboratory animals has been reviewed elsewhere (Filip et al. 2010).

Studies in rodents suggest that dopamine D\(_3\) receptor antagonists (Song et al. 2012) and monoamine transporter inhibitors (Peng et al. 2010) reduce cocaine self-administration. A primary concern about using DAT inhibitors to treat cocaine addiction is that they may behave like cocaine and support self-administration. Data from DAT KI mice suggest that selective blockade of cocaine interactions with DAT may be an alternative approach to examine the role of DAT in cocaine addiction.

Treatment of cocaine addiction is a formidable clinical challenge (Somaini et al. 2011). Therapeutic agents are not readily available, but animal and clinical research offers some promise for the development of potential treatments. For example, the dopamine agonist bromocriptine lowers the threshold for the rewarding effects of cocaine in rodents (Knapp and Kornetsky 1994; Ushijima et al. 1995; Weissenborn et al. 1996), and controlled human trials have indicated that, in addition to bromocriptine, other such agonists (amantadine, carbamazepine, and desipramine) are effective in relieving some of the symptoms of cocaine abstinence (Withers et al. 1995). However, the efficacy of these treatments in a clinical setting has been mixed (Montoya et al. 2002).

**Amphetamines**

Amphetamines (including methamphetamine and MDMA) work by different mechanisms to increase synaptic dopamine concentrations. Unlike cocaine, amphetamine blocks the vesicular transporter to reverse dopamine reuptake (release) (Seiden et al. 1993; Sulzer et al. 2005).

In a DAT KO mouse model, the rewarding effects of amphetamine remained intact in the CPP paradigm. However, amphetamine-induced CPP is abolished by pretreatment of mice with a serotonin 5-HT\(_1\)A antagonist (Budzig et al. 2004). These results are consistent with the hypothesis that amphetamines interact not only with dopamine but also with serotonin and norepinephrine systems to exert their rewarding effects (Bhatia et al. 2011).

Efficacious pharmacological treatments for psychostimulant amphetamine addiction are not available in clinical practice despite the social problems associated with this drug (Huddleston et al. 2008). But rodent models demonstrate that the memory system may be a candidate for treatment (Lee et al. 2006). For example, long-term methamphetamine exposure in the rat leads to motor sensitization, which can be prevented by combining the nonselective dopamine agonist pergolide with the 5-HT3

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\(^1\)The US Drug Enforcement Agency classifies controlled substances according to five schedules; information is available on the DEA website (www.deadiversion.usdoj.gov/schedules/index.html).

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antagonist ondansetron (Bhatia et al. 2011). Thus, drug-seeking behavior can be reversed in addicted animals by administering first a selective dopamine agonist to “reactivate” the addiction “circuit” and then a 5-HT3 antagonist to block memory reconsolidation of methamphetamine sensitization and addiction (Bhatia et al. 2011). This approach holds promise for new pharmacological treatment of stimulant addiction including cocaine and amphetamines.

Opioids

The opioid analgesics—morphine, diacetylmorphine (heroin), and other compounds that share morphine-like properties—produce rewarding effects through their actions on endogenous opioid receptors, and frequent use leads to tolerance and dependence.

Mechanisms

Opioids activate μ and δ opioid receptors in the VTA and NAc, leading to the release of dopamine (Hirose et al. 2005; Yoshida et al. 1999). In the VTA, opioid-activated μ opioid receptors result in decreased GABA inhibition (disinhibition of GABAergic neurons) (Johnson and North 1992).

Studies using animal models have shown that opioid agonists with selective affinity to μ opioid receptors possess the highest abuse potential (Devine and Wise 1994), but δ opioid receptor agonists also induce rewarding effects in animals (Hutcheson et al. 2001). Pharmacological studies have shown that δ opioid receptors are about 100 times less effective than μ opioid receptors in maintaining intracranial self-administration and striatal dopamine release (Devine et al. 1993).

The κ opioid receptors appear to play a negative regulatory role such that κ agonists increase brain reward thresholds for intracranial self-administration (Beguin et al. 2008; Carlezon et al. 2006) and cause aversive effects (Land et al. 2008). In addition, κ receptor gene knockout results in elevated dopamine levels in the NAc (Chefer et al. 2005), indicating that this knockout may directly alter the rewarding property of opioids.

Future treatment strategies will benefit from the outcome of studies using various opioid receptor transgenic animals to map the involvement of these receptor subtypes on opioid tolerance, dependence, and self-administration.

Treatment

Treatment of opioid addiction is a two-step process that involves detoxification and relapse prevention. Detoxification is designed to remove the drug from the patient, but withdrawal symptoms occur when addicts stop using opioids and often are severe enough to cause relapse into drug-taking behavior.

Because treatment of opioid addiction by detoxification alone leads to high rates of relapse (Lobmaier et al. 2010), the most effective means of relapse prevention is agonist replacement therapy (Lobmaier et al. 2010; Veilleux et al. 2010). This treatment involves use of a less efficacious and longer-acting opioid agonist to decrease the frequency of drug taking. For example, buprenorphine is a μ opioid receptor partial agonist that dissociates slowly from the receptor and thus produces smaller effects and prolonged duration of actions.

Methadone is the most common replacement medication, typically presented in a tapered procedure during 10 to 28 days of detoxification (Gossop et al. 1989; Strang and Gossop 1990). Buprenorphine, buprenorphine-naloxone, and other opioid agonists such as heroin, slow-release oral morphine, codeine, and levomethadyl acetate hydrochloride (LAAM) are also used (Veilleux et al. 2010). In addition, buprenorphine, clonidine, or lofexidine are sometimes used to decrease craving (Gossop 1988; Gowing et al. 2009).

Nicotine

Mechanisms

Nicotine is the major active component in tobacco smoke that supports smoking behavior and nicotine addiction (Polosa and Benowitz 2011). It works by activating brain nicotinic receptors (nAChRs), which are ligand-gated cation channels that conduct Na+, K+, and/or Ca2+ currents (Taly et al. 2009). nAChRs are formed from different subunits, α2–9 and β2–4, that are encoded by 17 different genes. The two main types of nAChRs that have been identified are the homo-oligomer receptors (e.g., the α7 nAChRs) and the hetero-oligomer receptors (e.g., the α4β2 nAChRs and other oligomers). The α7 receptors, present in many brain areas, are characterized by fast activation, low ligand affinity, and high Ca2+ permeability. In contrast, the α4β2 nAChRs are high-affinity and slow-desensitizing receptors. Nicotine activates nAChRs in the VTA (α4β2, α5β2, α6β2, α6β3, α3β4, and α7 isoforms) and NAc (α4β2, α4α5β2, α6β2β3, and α6α4β3 isoforms), leading to dopamine release in these brain areas that mediates reward.

Gene deletion studies have been useful in determining the involvement of specific nAChR isoforms in nicotine self-administration. For example, mice lacking β2, α4, or α6 subunits do not self-administer nicotine, but do so when these receptor subunits are reexpressed in the VTA. In contrast, α7 gene knockout did not affect nicotine self-administration (Pons et al. 2008). Moreover, deletion of α5 or overexpression of β4 increased nicotine self-administration. α5 subunit, which is highly expressed in dopaminergic neurons (Klink et al. 2001), regulates nicotine self-administration in an animal model of nicotine addiction (Changeux 2010).

Treatment

There have been significant efforts in recent years to promote smoking cessation, but cessation is different from the treatment of nicotine addiction.

The current practice for smoking cessation is to use nicotine patches to sustain nicotine addiction without smoking.
To cure the addiction, however, one must stop taking nicotine, and currently there is no effective therapy for this condition.

Clinical practice suggests that nicotine replacement therapy (bupropion, varenicline, and other nicotinic receptor partial agonists) and second-line medications such as nortriptyline and clonidine can ease craving (Fiore and Jaen 2008; Polosa and Benowitz 2011). In addition to dopamine- and serotonin-based drugs, glutamatergic medications may be useful for the treatment of nicotine addiction (Olive et al. 2012) as preclinical studies suggest that glutamatergic transmission plays a critical role in drug addiction including drug reward, reinforcement, and relapse (Bird and Lawrence 2009; Moussawi and Kalivas 2010). Various other drugs tested for their treatment potential in nicotine addiction are discussed in a review by Polosa and Benowitz (2011).

Models of Alcohol Consumption

One feature of alcoholism is the consumption of large quantities of alcohol. It is known that animals may drink alcohol for caloric purposes. However, a rat that drinks alcohol for the pharmacological effects must consume enough alcohol to have a blood ethanol concentration (BEC) of 80 to 100 mg/dL.

Among the five rat lines genetically selected for high alcohol consumption, Sinclair and colleagues (1989) developed the ALKO AA (alcohol-preferring) rats, which prefer 10% alcohol solution over water. They differ from the nonpreferring (ANA) line of rats in alcohol-related reinforcement behaviors, alcohol metabolism, alcohol tolerance, and alcohol-induced neurochemical changes (Kiianmaa et al. 1991).

The second line is the Sardinian alcohol-preferring line of rats (sP; Colombo 1997), which consume more than 4 g/kg of 10% alcohol solution during the first alcohol drinking session and can drink up to 6 g/kg of alcohol in subsequent weeks. They are reported to achieve pharmacologically relevant BEC at each drinking session and to exhibit “binge”-like drinking behavior (i.e., three drinking bouts per day; Loi et al. 2010).

The third line, Marchigian Sardinian (msP) rats, was genetically selected for the animals’ high alcohol preference from the original sP rats (Ciccocioppo et al. 1998). Although the msP rats share many of the sP rats’ phenotypic traits (e.g., alcohol preference and binge-like drinking behavior), they are also highly vulnerable to stress-induced relapse of alcohol consumption (Ciccocioppo et al. 2006). Indeed, they exhibit many of the behavioral traits of human alcoholics.

The fourth line of “alcoholic” rat was selectively bred to exhibit high alcohol consumption, resulting in the highly useful alcohol-preferring P rat line at Indiana University (Li et al. 1987). P rats exhibit voluntary alcohol consumption of 10 to 30% alcohol solution to the point of intoxication, and bar-press to self-administer alcohol resulting in pharmacologically relevant BECs (in the range of 50–200 mg%; McBride and Li 1998). P rats also show binge-like drinking patterns during the dark cycle, consuming about 6 g/kg of ethanol during a 1-hour access period (Bell et al. 2006). In addition to consuming high quantities of alcohol, P rats are less sensitive to the sedative and aversive effects of alcohol (Stewart et al. 1996), exhibit greater responses to its euphoric (stimulatory) properties (Bell et al. 2006), and show enhanced anxiety-related behaviors (Stewart et al. 1993). The P rats self-administer alcohol in a variety of experimental paradigms (e.g., intragastric, intracranial, and operant administration; Bell et al. 2006) and work very hard to obtain alcohol (Penn et al. 1978). Thus, the P rat appears to be a valid animal model for human alcoholism (Li et al. 1987).

The fifth rat line is the UCh-B line. In the 1940s, researchers at the University of Chile used genetic selection to develop a rat model for high alcohol consumption, resulting in the selection and breeding of high- and low-alcohol-consuming rats (UCh-abstainer, or UCh-A, and UCh-bibulous, or UCh-B,
respective) (Tampier et al. 1984). Although these animals were the earliest known strains of rats that differ in alcohol preference, they were not widely used in alcohol research outside South America. Thus, the validity of this rat strain as a model for alcohol addiction research remains to be determined.

Models of Binge Drinking

Binge drinking is defined as a pattern of alcohol consumption that results in a BEC of more than 80 mg% in about 2 hours (Crabbe et al. 2011). This clearly harmful drinking behavior (NIAAA Newsletter 2004) is practiced by a growing number of young drinkers: the 2010 NIDA-sponsored Monitoring the Future Survey reports that rates of binge drinking (defined as five or more drinks in a row in the previous 2-week period) were a worrisome 8%, 16%, and 25% among 8th, 10th, and 12th graders, respectively (Tampier et al. 1984). Although these animals drink to intoxication in a short period of time and consume more alcohol per drinking bout (Rhodes et al. 2005).

Recent data also demonstrate that limited access to alcohol during adolescence causes increased baseline (Metten et al. 2011; Strong et al. 2010) and dependence-related alcohol consumption in adulthood (Gilpin et al. 2012). Thus, limited-access adolescent drinking paradigms appear to be successful in modeling both the binge-like pattern of adolescent drinking behavior and the consequences of adolescent alcohol consumption on adult alcohol use and risk of dependence.

The addictive properties of alcohol may be mediated by GABA neural transmission. Alcohol has been shown to dis-inhibit VTA GABA neurons (Brodie et al. 1999), resulting in the release of dopamine in the NAc. Connexin-36 (Cx36) gap junctions regulate the functional activity of GABA neurons in the VTA. Cx36 KO mice exhibit less motor impairment by acute alcohol administration and drink significantly less alcohol than wild types in a binge DID paradigm. Decreased drinking in Cx36 KO mice may be due to a diminished hedonic valence for alcohol (Steffensen et al. 2011). GABA_A receptors are known to mediate various effects of alcohol including behavioral sensitivity and consumption (for review see Boehm et al. 2006). GABA_A receptors are composed of α1–6, β2–3, γ2, and/or δ subunits, and these receptor activities are determined by the composition of subunits. For example, δ subunit KO resulted in significantly lower alcohol consumption (Mihailek et al. 2001), but α5 subunit gene deletion had no effect on alcohol reward (Stephens et al. 2005). Moreover, mice lacking PKCε (PKCε) drink less alcohol and show greater alcohol sensitivity (Newton and Messing 2007; Wallace et al. 2007). However, systematic studies are needed to validate these models for altering alcohol consumption.

Treatment

Treatments for alcohol abuse have not advanced much since the early 1900s. Disulfiram (Antabuse), used to deter individuals from drinking alcohol, has been prescribed in clinical practice since the 1940s. This drug prevents aldehyde dehydrogenase from breaking down acetaldehyde to form acetic acid, resulting in a buildup of acetaldehyde in the body that causes aversive reactions such as flushing, increased heart rate, and nausea. Given these adverse effects, the primary barrier for employing disulfiram as a clinical treatment is patient compliance; thus a disulfiram implant is a treatment choice for some medical practitioners.

Neurobiological research using animal models indicates that opioid receptors and β-endorphin systems modulate alcohol consumption behavior, presumably via the corticomesolimbic dopamine system (Anton 2008; Haile et al. 2008; Rosner et al. 2010). For example, opioid receptor antagonists such as naltrexone and nalmefene reduce alcohol consumption (Garbutt 2010; Lobmaier et al. 2010; Rosner et al. 2010).

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Both human and animal studies suggest that binge-like alcohol exposure during adolescence is particularly harmful to brain and behavioral development. It is not known, however, how normal adolescent changes in psychosocial, endocrine, and brain function increase risky behaviors such as alcohol use, and how early alcohol use in turn alters the trajectory of adolescent development toward addiction risk. Animal models and controlled environmental conditions are necessary for disentangling these issues, especially given that alcohol use in humans is often accompanied by other potential mediating factors such as stress and drug use. Thus, it is important to include developmental aspects in animal models of alcohol abuse to improve scientific understanding of the etiology of alcoholism.

Animal studies should also model key aspects of human adolescent alcohol use such as increased alcohol intake relative to adults and binge drinking to intoxication. Rodent models are emerging that meet these criteria for adolescent drinking. For example, investigators have studied adolescent rats and mice that voluntarily drink more than adults under both continuous-access (Doremus et al. 2005; Tolliver and Samson 1991; Truxell et al. 2007; Vetter et al. 2007) and limited-access conditions (Maldonado-Devincci et al. 2010; Metten et al. 2011). In addition, some adolescent rodents actually do drink to intoxication, especially when tested in limited-access paradigms (Rhodes et al. 2005; Strong et al. 2010).

Limited-access paradigms have been particularly valuable in inducing adolescent binge-drinking behavior. “Drinking in the dark” (DID) models allow temporary access (2–4 hours) to alcohol during the dark phase of the light:dark cycle, when animals are most active. Although overall alcohol intake is lower relative to continuous-access drinking paradigms, animals drink to intoxication in a short period of time and consume more alcohol per drinking bout (Rhodes et al. 2005).

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Recent studies also suggest that gamma-hydroxybutyric acid (Addolorato et al. 2009), acamprosate (Mann et al. 2008), baclofen (Soyka and Rosner 2010), and desipramine (O’Brien et al. 2011) may have potential for the treatment of alcohol dependence, most likely through varied and unidentified mechanisms. This variability is not surprising given that alcohol addiction is a polygenic disease that involves many neurobiological pathways and numerous genes (for review see Goldman et al. 2005). As such, finding an effective treatment for alcohol addiction is a significant scientific challenge.

**Perspectives and Other Considerations**

One promising area of addiction research is the study of the interactions between memory and reward neural circuitry. It is clear from the literature that relapse into drug seeking is a key feature of addiction, and that drug-seeking behavior for all classes of drugs is driven in part by associations formed between drug-related stimuli and the rewarding effects of a drug (Miller and Marshall 2005).

Associations between drug-paired cues and the rewarding effects of a drug can be conceptualized as an “addiction memory” (Kelley 2004). In this view, addiction is composed of two primary processes—the acquisition and the extinction of the cue-paired reinforcing effects of a drug. Thus, failure to extinguish an acquired “memory of addiction” may lead to relapse.

In line with this reasoning, recent studies have emphasized the importance of drug-cue extinction in addiction treatment (Dhonnchadha and Kantak 2011; Weiss 2010). Extinction is not memory erasure per se but rather involves the formation of new memories that inhibit the existing memory. Interestingly, the process of extinction is sensitive to different memory-forming techniques as well as to medications that improve memory and enhance the efficacy of exposure therapy (Taylor et al. 2009).

In addition to extinction processes, other means of disrupting addiction memories are available; for example, interfering with drug memory reconsolidation shows some promise (Milton and Everitt 2010; Milton et al. 2012). Memory reconsolidation, considered to be a process distinct from extinction, occurs immediately after a memory is reactivated or retrieved, when the newly retrieved memory is vulnerable to modification. Thus, manipulating memory reconsolidation processes may disrupt cue-drug memories in animal models of drug relapse. For example, despite evidence that cocaine addiction is resistant to extinction (Weiss et al. 2001), recent work using a CPP model demonstrated that the N-methyl-D-aspartate (NMDA) antagonist MK-801 disrupts reconsolidation of cocaine-associated memories in rats (Brown et al. 2008) and that the addiction memory can thus be “erased” by manipulating reconsolidation processes.

A greater combined understanding of the neurobiological processes involved in memory extinction and reconsolidation will support the development of efficacious medications for the therapeutic treatment of drug addiction.

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**Disclosure**

The authors declare no conflict of interest. The opinion expressed in this article is exclusively the authors’ own and is not a reflection of the policies of the University of Colorado Denver Anschutz Medical Campus. The university is not liable for any legal problems as a direct result of this publication.

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