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Escalation of drug self-administration as a hallmark of persistent addiction liability

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Abstract

Drug addiction is a progressive, relapsing disease comprised of interlocking stages of disordered motivation. Numerous animal models describing various stages of the addiction process have been developed over the past few decades, providing considerable advantages for the modeling of drug addiction compared with other complex psychiatric disease states. Escalation of drug self-administration has emerged as a widely accepted operant conditioning model of excessive drug intake. We further argue here that drug-escalated animals represent a comprehensive model of addiction according to the manifestations of behavioral neuroadaptations resulting directly or indirectly from excessive drug consumption. In particular, drug-escalated animals exhibit a host of symptoms in line with multiple *Diagnostic and Statistical Manual of Mental Disorders* criteria for substance dependence, which can be summarized as an emergence of uncontrollable drug-taking and drug-seeking behaviors as a consequence of within-circuit and between-circuit neuroadaptations. Such a transition from impulsive drug sampling to compulsive intake represents a highly valid conceptualization of the addiction timeline in humans, and further investigation of persistent or near-permanent (e.g. epigenetic) neuroadaptations generated by operant drug intake escalation models will continue to provide mechanisms and therapeutic interventions for reversing the aberrant neuroplasticity underlying addiction.

Keywords

addiction; alcohol; cocaine; escalation; heroin; self-administration

Drug addiction: defining the disease state to model

Drug addiction is a chronic, relapsing disorder that has been characterized by compulsive seeking and escalated intake of drugs. Excessive drug use promotes both a tolerance to the rewarding effects of drugs along with a manifestation of negative emotional states (e.g. dysphoria, anxiety, irritability) to drive a loss of control over intake. Limited recreational drug use is clinically separable from escalated drug use and the emergence of compulsive drug-seeking behavior that characterizes addiction. In fact, a certain resilience to drug addiction may be the norm in both rodents and humans (Ahmed, 2010, 2012; Swendsen and Le Moal, 2011), further highlighting the critical distinction between simple drug exposure and the transition to addiction in vulnerable individuals (George and Koob, 2010). Recognizing distinct stages of the addiction timeline is important in terms of preclinical

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Conflicts of interest
There are no conflicts of interest.

modeling (Edwards and Koob, 2012) and clinical treatment (Heilig and Egli, 2006), although discriminating innocuous drug use from aberrant pathology can be difficult. To address this challenge, multiple groups have put forward multifaceted addiction models/conceptualizations in rodents (e.g. Ahmed and Koob, 1998; Piazza *et al.*, 2000; Sutton *et al.*, 2000; Deroche-Gamonet *et al.*, 2004; Roberts *et al.*, 2007).

Our view is that the motivation for pathological drug seeking involves the interplay of two distinct sources of reinforcement that separate initial drug use from drug addiction: positive and negative reinforcement. Positive reinforcement occurs when presentation of a stimulus increases the probability of subsequent response and is typically associated with a state of reward. One prominent conceptual framework for addiction is that drugs usurp brain incentive salience systems (Robinson and Berridge, 1993; Hyman *et al.*, 2006), leading to a narrowing of the behavioral repertoire toward the goal of obtaining and using drugs at the expense of natural or more adaptive goals such as career and family (Volkow *et al.*, 2011). In contrast, negative reinforcement involves the use of drugs to either self-medicate an existing aversive state or to alleviate negative emotional symptomatology, often induced by withdrawal, including dysphoria, anxiety, and sleep disturbances. Solomon and Corbit (1974) postulated that the development of hedonic or affective states is instantaneously tempered by the central nervous system to reduce the intensity of hedonic feelings; this mechanism was termed an opponent process. From a drug abuse perspective (with brain motivational circuitry as an example), the initial positive hedonic response resulting from drug use is thought to be counterbalanced by a negative hedonic response for the purpose of homeostatic balance within brain motivational systems. This affective regulatory system was conceptualized as a negative feedback or opponent process loop or multiple feedbacks that oppose the stimulus-aroused affective state to suppress or reduce significant departures from hedonic homeostasis (Poulos and Cappell, 1991; Koob and Le Moal, 2001).

Recently, the opponent process theory has been extended to study the biology of drug addiction from a neuro-circuitry perspective, including elements of molecular neuroscience. An allostatic model of interacting brain motivational systems has been proposed to explain the persistent changes in motivation associated with the persistence of dependence in addicted states (Koob and Le Moal, 2008). Within this hypothesis, addiction is conceptualized as a cycle of increasing dysregulation of brain reward/antireward systems resulting in the generation and sensitization of negative emotional states that contribute to the compulsive seeking and intake of abused drugs, despite adverse consequences encountered in the natural environment (e.g. job loss, divorce). Normal counteradaptive processes that are a part of the homeostatic attenuation of reward function fail to return the organism to within the natural homeostatic range, leading to a pathological state. Two types of changes are hypothesized to drive these processes: within-system neuroadaptations and between-system neuroadaptations (Koob and Bloom, 1988). As part of a within-system opponent neuroadaptation, ‘the primary cellular response element to the drug would itself adapt to neutralize the drug’s effects; persistence of the opposing effects after the drug disappears would produce the withdrawal response’ (Koob and Bloom, 1988). Therefore, a within-system opponent neuroadaptation is a molecular or cellular change within a given reward circuit designed to blunt overactivity of reward processing associated with drug use, resulting in decreased reward function. A relevant example of a potent reward homeostasis neuroadaptation is the drug-induced activation of the cAMP response element-binding protein/dynorphin axis in the nucleus accumbens (Carlezon *et al.*, 1998; Pliakas *et al.*, 2001; Choi *et al.*, 2006; Nestler and Carlezon, 2006; Larson *et al.*, 2011; Chartoff *et al.*, 2012). Dynorphin typically acts to blunt local dopamine and glutamate signaling (Di Chiara and Imperato, 1988; Hjelmstad and Fields, 2001), and this system may become potentiated in response to chronic stress or drug exposure (Fig. 1; Bruchas *et al.*, 2010; Wee and Koob, 2010; Nealey *et al.*, 2011; Schlosburg *et al.*, 2011; Whitfield *et al.*, 2011). In a between-

system neuroadaptation, neurochemical systems other than those involved in the initial positive rewarding effects of drugs of abuse are recruited after chronic or excessive activation of the reward system (Koob and Bloom, 1988). Thus, a between-system neuroadaptation is a circuitry change in which a separate, distinct neural substrate (essentially an antireward circuit; Koob and Le Moal, 2008) is triggered by the original reward circuit to oppose or limit reward function. Potentiation of corticotropin-releasing factor signaling in the extended amygdala represents one critical antireward neuroadaptation driving negative reinforcement in addiction- related behaviors (Logrip *et al.*, 2011). Previous reviews from our laboratory have discussed numerous neuroadaptive changes in brain reward systems (within-system adaptations) and brain stress systems (between-system adaptations), both of which contribute to the pathology of dysregulated motivational systems in addiction after excessive drug exposure (Edwards and Koob, 2010; George *et al.*, 2012). Given their role in the modulation of complex behaviors, we particularly believe that a greater understanding of the interactions of neuropeptide signaling within brain reinforcement circuitry may shed additional light on biobehavioral mechanisms underlying the addiction process (Koob, 2008; Martin-Fardon *et al.*, 2010; Schank *et al.*, 2012).

Escalation of drug self-administration: interpretation and relevance to addiction

Although a preponderance of studies on the neuro-pharmacology of drug addiction have focused on the acute biological effects of drug exposure, more attention is now shifting to chronic administration models and investigations into the long-term neuroadaptive changes in the brain that may define an addicted state or predispose vulnerable individuals to relapse. The purpose of ongoing research in our field is to reveal the genetic, biochemical, cellular, and circuitry mechanisms underlying the transition from recreational drug use to the uncontrolled drug-taking and drug-seeking behaviors associated with addicted populations. In this sense, the data generated by preclinical models are limited in validity to the soundness of the model itself. Animal models for a complete syndrome of a psychiatric disorder as complex as drug addiction are highly unlikely to be attainable either conceptually or practically. Thus, although there are no perfect animal models of addiction, models do exist for distinct elements underlying important stages of the disorder: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (described in Edwards and Koob, 2012).

Intravenous drug self-administration has served as a valid and tractable model of drug use as it typically produces stable individual behavior allowing for the reliable interpretation of data generated by within-subject designs. However, a progressive increase in the frequency and intensity of drug use (uncontrolled intake) is a hallmark of addiction and more directly models criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (‘The substance is often taken in larger amounts and over a longer period than was intended’; American Psychiatric Association, 2000). As an attempt to explore the possibility that differential access to abused drugs may confer greater face validity related to the compulsive-like intake behavior observed in addiction, Ahmed and Koob (1998) published a seminal article 15 years ago describing an animal model of cocaine intake escalation after transition from limited to extended-access conditions. When animals were allowed differential access (1 vs. 6 h) to different doses of cocaine, both the long access (6 h/day) and short access (1 h/day) animals titrated their cocaine intake, but the long access rats exhibited an escalation in intake and consistently self-administered almost twice as much cocaine at any dose tested, suggesting a vertical/upward shift in the set point for cocaine reward associated with escalation (Ahmed and Koob, 1998). Subsequent studies have shown that rodents increase intravenous or oral self-administration with extended access to

numerous abused drugs and during withdrawal from the dependent state. Such increased self-administration in dependent animals has been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol (Ahmed and Koob, 1998; Ahmed *et al.*, 2000; Roberts *et al.*, 2000; Kitamura *et al.*, 2006; O'Dell *et al.*, 2007). It should be noted that extended drug access typically, but not always, generates an escalation of intake (Kippin *et al.*, 2006). The relationship between these two conditions may depend on numerous variables, including unit drug dose and animal strain.

In addition to intake escalation, evidence of compulsivity associated with extended drug access is provided by the fact that animals work much harder to obtain the drug under these conditions (as evidenced by progressive ratio schedules; Paterson and Markou, 2003; Walker and Koob, 2007; Wee *et al.*, 2008). Progressively greater work requirements not only lead to motivational alterations in animals but also represent an adverse barrier to drug acquisition that the animal must overcome. Additional models evidencing a transition to compulsivity, following long access conditions and/or intake escalation, include enhanced drug-induced and stress-induced reinstatement of drug seeking, decreased latency to reach a goal in the runway model of drug reward, and persistent responding despite concomitant punishment (Deroche *et al.*, 1999; Deroche-Gamonet *et al.*, 2004; Mantsch *et al.*, 2004; Vanderschuren and Everitt, 2004; Kippin *et al.*, 2006; Pelloux *et al.*, 2007; Ben-Shahar *et al.*, 2008; Mantsch *et al.*, 2008; Jonkman *et al.*, 2012; Vendruscolo *et al.*, 2012).

An underlying theme of the original Ahmed and Koob model was the assumption that a minimum threshold of drug exposure might be necessary to establish and/or sustain aberrant, addiction-related behavioral and molecular neuroadaptations (Ahmed, 2012). Excessive drug intake was originally hypothesized to promote (or reflect) neurophysiological changes associated with newly established hedonic set points (Ahmed and Koob, 1998). Further experimentation has produced extensive data complementing this original conceptualization, whereby intake escalation models have been paired with measures of brain stimulation reward thresholds utilizing intracranial self-stimulation methodology. For example, differential exposure to cocaine self-administration produces marked effects on reward thresholds that progressively increase in long access rats but not in short access rats across successive self-administration sessions (Ahmed *et al.*, 2002). Importantly, baseline reward threshold elevations temporally precede and are highly correlated with cocaine intake escalation. Similar results have been observed with extended access to heroin (Kenny *et al.*, 2006) and methamphetamine (Jang *et al.*, 2013) self-administration.

Persistent molecular neuroadaptations after intake escalation

Drugs of abuse elicit complex physiological responses that can produce rapid and, in some cases, long-lasting neuronal plasticity. In pathological addition to drugs themselves, subjective responses to drugs also act as visceral cues to promote associations with paired cues and environments. Together, conditioned and unconditioned neuroadaptations are hypothesized to underlie the development and maintenance of escalated drug intake and a heightened propensity for relapse (Self and Nestler, 1998). However, the precise determination of which drug-induced neuroadaptations in turn drive specific components within the multifaceted psychopathology of addiction (e.g. intake escalation vs. relapse) is of utmost importance (Kalivas, 2005).

In addition to early withdrawal studies, much recent interest has focused on long-term plasticity remaining long after the termination of extended-access drug exposure. Such studies attempt to model the persistence of propensity to relapse (Shaham and Hope, 2005; Wolf and Ferrario, 2010) and further underscore the challenges that abstinent addicts face. Indeed, normalization of neuroadaptations that emerge as a consequence of withdrawal may

be of greater importance than targeting drug-induced changes that quickly dissipate. Recruitment and/or potentiation of brain stress circuitry (e.g. corticotropin-releasing factor, dynorphin, and norepinephrine systems) occur in the extended amygdala and are believed to drive negative motivational states associated with the development of addiction. Importantly, changes in brain stress circuitry, particularly within the central amygdala, are hypothesized to contribute not only to the increased motivation to take drugs in the dependent state but also to maintenance of allostatic sensitization during postacute dependence, thereby contributing to the heightened vulnerability for future relapse (Fig. 1). The quality (but not necessarily intensity, depending on the dependent variable) of negative affective changes is distinct between early and protracted drug withdrawal (Sinha and Li, 2007). An accumulation of intermittent withdrawal episodes (common to intake escalation and addiction) is thought to engender a stress sensitization, either in intensity or salience, that may account for the endurance of negative emotionality in protracted abstinence (Valdez *et al.*, 2002, 2003; Breese *et al.*, 2005; Heilig and Koob, 2007; Heilig *et al.*, 2010; Huang *et al.*, 2010).

Although several behavioral changes associated with dysregulated motivation for drugs are evident, the precise neurobiological mechanisms underlying the aberrant persistence of these phenomena remain unknown. Animal models of relapse have recapitulated a clinical phenomenon of craving (Gawin and Kleber, 1986), whereby drug seeking persists (or even increases) well into withdrawal (Fig. 1; Tran-Nguyen *et al.*, 1998; Grimm *et al.*, 2001; Edwards *et al.*, 2011). Importantly, withdrawal-induced increases in relapse behavior are thought to directly relate to the intensity of drug exposure, with the phenomenon most consistently being observed in drug-escalated animals (Lu *et al.*, 2004). Specific molecular neuroadaptations in mesolimbic circuitry resulting from protracted abstinence from extended access to cocaine self-administration have been discovered, including changes in ionotropic glutamate receptor channel subunits in the amygdala (30-day withdrawal, Lu *et al.*, 2005a) and accumbens (30–90-day withdrawal, Lu *et al.*, 2003; also see Conrad *et al.*, 2008). Changes in excitatory signaling potential are paralleled by cocaine withdrawal time-dependent increases in the brain-derived neurotrophic factor in both the amygdala and the accumbens (Grimm *et al.*, 2003), and these findings suggest an interaction between positive and negative reinforcement circuitry in this phenomenon. One critical neuroadaptation implicated in mediating heightened cocaine-seeking behavior in protracted withdrawal from escalated drug intake is a recruitment of central amygdala excitatory signaling and extracellular signal-regulated kinase phosphorylation (Lu *et al.*, 2005b), and this mechanism may also extend to opiate craving (Li *et al.*, 2008). In addition to potentiated relapse behavior, these molecular neuroadaptations may also influence the more rapid escalation of intracranial self-stimulation thresholds observed during a second exposure to extended-access methamphetamine self-administration (conducted ~1 month after the end of a first extended-access period; Jang *et al.*, 2013). As noted earlier, strategies for medication development should take into account that these biobehavioral changes emerge as a result of protracted drug withdrawal rather than excessive drug use *per se*, and in some cases only after re-exposure to the drug-paired context, necessitating the tailoring of therapeutic strategies for this component of the addiction timeline. For example, drugs exhibiting preclinical efficacy that target extracellular signal-regulated kinase-coupled, stress-related neuropeptide receptors (e.g. V1b receptor antagonists; Zhou *et al.*, 2008; Edwards *et al.*, 2012) may be even more effective at protracted withdrawal times.

Another emerging mechanism attempting to explain the more enduring addiction-related neuroadaptations is epigenetic regulation (Robison and Nestler, 2011), whereby new, stable changes in gene expression result from biochemical modifications of genetic elements. Although epigenetic marking typically represents an adaptive component of brain plasticity (Siegmund *et al.*, 2007), specific epigenetic alterations have also been described in multiple

psychiatric disorders (Tsankova *et al.*, 2007). Gene expression is tightly regulated by the balance of enzymatic control of protein scaffolds surrounding the DNA, in addition to the DNA itself. These factors include covalent histone modifications (e.g. acetylation and phosphorylation), as well as direct methylation of DNA nucleotides. Alterations in chromatin structure can facilitate or inhibit the transcriptional potential of specific genes by filtering transcription factor accessibility. As one example of the power of epigenetic regulation, modifying total histone deacetylase (HDAC) activity in the nucleus accumbens can make cocaine either more rewarding (HDAC inhibition) or less rewarding (HDAC5 overexpression) to rats, as measured by conditioned place preference (Renthal *et al.*, 2007). In addition to its effects on cocaine reward, loss of HDAC5 function causes an exacerbation of negative affective-like behaviors, such as chronic social defeat stress (Renthal *et al.*, 2007). Thus, it is very likely that epigenetic modifications act through both positive and negative motivational systems to influence addiction-related behaviors. An important question is whether manipulation of HDAC activity modifies escalation of drug self-administration in an animal. In addition, many of the initial studies on epigenetic influences on drug reward have been limited to the ventral striatum, although stable changes in gene expression across additional brain reinforcement circuitry would also be likely to impact intake escalation. For example, recent investigations by Pandey *et al.* (2008) report architectural remodeling of chromatin in the central amygdala to be a key driver of negative reinforcement mechanisms underlying excessive alcohol drinking (Starkman *et al.*, 2012). Further elucidation of epigenetic mechanisms within and between motivational circuits will shed light on how these systems respond to and persistently change after drug intake escalation to promote a reconstruction of gene expression, and may also provide an additional biochemical endpoint to determine the potential efficacy of new therapeutics for addiction.

As a temporal complement to the study on persistent neuroadaptations after intake escalation, there also remains considerable interest in the field as to whether it is possible to uncover behavioral or molecular predictors of intake escalation. The critical question here is whether some preceding genetic or environmental element can significantly influence pathological behavior that is likely heavily driven by the requisite, direct impact of excessive drug exposure on neuronal elements of reinforcement. It does appear that factors related to the initiation of drug use may be more easily predictable, including drug sensitivity, acquisition of self-administration, or self-administration of low drug doses (Piazza *et al.*, 1989; Mantsch *et al.*, 2001; Perry *et al.*, 2005, 2008). However, in accordance with the hypothesis that drug addiction may represent progression along an impulsive–compulsive axis (Fig. 1; Koob, 2009), greater trait impulsivity (as measured by impulsive choice in a delay discounting task or impaired inhibition in a five-choice serial reaction time test) has been shown to predict future indices of compulsive-like intake, including intake escalation (Dalley *et al.*, 2007; Belin *et al.*, 2008; Anker *et al.*, 2009). At the neurobiological level, continuing advances in microPET and other small-animal imaging technologies will facilitate the elucidation of pre-existing neurocircuitry characteristics forecasting intake escalation (Virdee *et al.*, 2012). Nevertheless, excessive drug exposure likely remains an indispensible element driving the development of addiction and particularly its persistence when escalated drug use is discontinued.

Conclusion

Escalation of drug self-administration represents one critical symptom of uncontrolled drug use associated with a break from brain reward homeostasis. In addition, behavioral and molecular neuroadaptations produced in concomitance with escalating intake produce a manifestation of additional symptomatology that is closely related to the establishment and maintenance of the addicted phenotype. These include the development of persistent and

sensitized negative emotional states, heightened motivation for drug use, and compulsive drug seeking in withdrawal, each of which corresponds with measurable perturbations in brain reward and stress circuitry (Fig. 1). The continued use of intake escalation models will yield valuable information related to mechanisms underlying the transition to addiction and will also reveal the most suitable strategies for therapeutic intervention.

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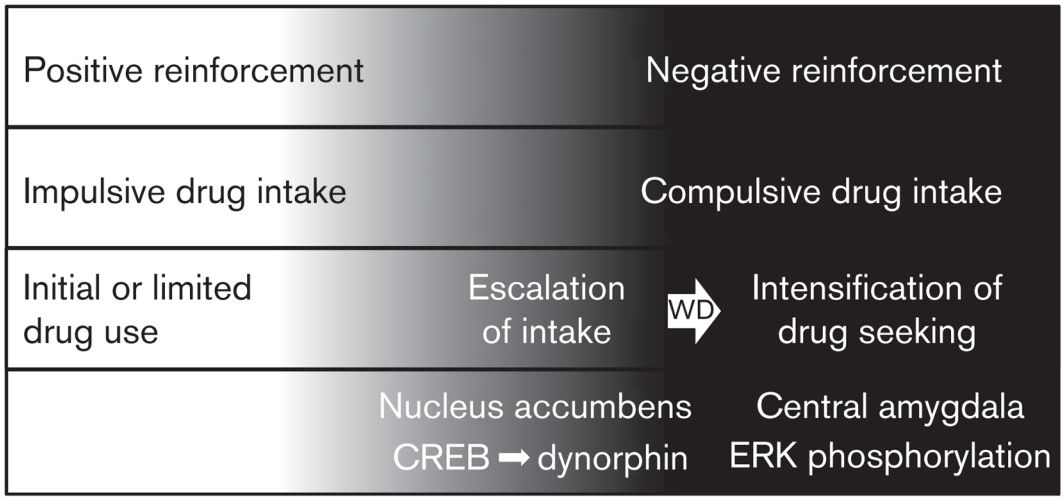

Fig. 1.

Parallel timelines for biobehavioral transitions associated with the establishment and maintenance of the addicted state. Overall, drug addiction can be conceptualized as a transition from positive to negative reinforcement mechanisms, whereby drug use becomes compulsive along this same timeline. The transition from initial or limited drug use to addiction can be modeled in rodents through extended access to drug self-administration (Ahmed and Koob, 1998). Extended access typically produces escalation of intake and, in turn, a constellation of other addiction-related effects, including negative emotional states and an intensification of drug seeking during abstinence. Escalation of intake in animals is associated with a recruitment of the CREB/dynorphin axis in the nucleus accumbens. Excessive drug use also produces increases in excitatory signaling potential throughout mesolimbic circuitry, as well as a withdrawal time-dependent activation of ERK phosphorylation in the central amygdala (possibly downstream of CRF receptor activation) that drives compulsive drug-seeking behavior upon re-exposure to the drug-paired context, underscoring the persistence of relapse potential. Therapeutic reversal of these neuroadaptations at relevant points along this timeline may alleviate the negative motivational processes underlying drug addiction, whereas further use of intake escalation models will continue to reveal additional neural substrates for targeting. CRF, corticotropin-releasing factor; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinase; WD, withdrawal.