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Impulsivity in Animal Models for Drug Abuse Disorders

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Abstract

Different conceptual frameworks have been generated to explain substance abuse; of relevance to this article, dysfunction of impulse control systems that are required for avoiding or stopping drug-seeking and –taking may play a key role in addiction. This review summarizes work in animal models that explains the pervasive association between impulse control and substance abuse. It further underscores the concept that impulse control may be a critical target for pharmacological intervention in the treatment of addictions and suggests that further developments in animal models for impulsivity may be useful in expanding our understanding and treatment of drug abuse.

Introduction

Drug dependence is characterized by risky drug-taking behavior, repeated failures to reduce drug-taking and evidence of tolerance or physical or psychological withdrawal. It is proposed to involve alterations in systems that govern reinforcement-based learning and incentive processing [1] such that drug-induced neuroadaptations within the circuitry mediating these processes leads to greater control over behavior by drugs and drug-related cues. Beyond this, certain aspects of addiction suggest that other processes should be the focus of research, including the study of mechanisms by which individuals actively inhibit drug taking behavior. Until recently, animal models have focused on the mechanisms that support drug-taking, not on the mechanisms mediating its inhibition (but see [2,3]).

The active suppression of drug-taking behavior is thought to involve the recruitment of neural systems involved in “cognitive control”, a set of abilities related to the voluntary modulation of impulsive thoughts, feelings and actions. These are processes that an individual would need to call on in order to willfully inhibit impulsive drug-seeking and –taking actions. The focus on this article, therefore, is on animal models for impulse control, with a particular emphasis on the ways in which these models have already contributed to our understanding for the role of impulsive behavior, and its suppression, in addiction.

Main Body

In Vivo Models

As described above, individuals who are dependent upon drugs of abuse, particularly stimulants or alcohol, routinely exhibit significant and robust impairments in measures of cognitive control, including tasks that require stopping, withholding or changing responses (e.g.,

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response inhibition/control), working memory maintenance and/or manipulation and control over attention or emotion. It is thought that weakened control over impulsive thoughts and behavior is a phenotype that directly contributes to failure to "cut down" drug-taking behavior [4], as indicated by the Diagnostic and Statistical Manual [5]. Moreover, these deficits in cognition turn out to be reasonably predictive of the prognosis of drug-dependent individuals in treatment [6], suggesting that they are linked to recidivism. For these reasons, animal models of loss of impulse control have potentially significant value in the process of understanding the neurobiology of addiction, as well as in identifying maximally effective interventions.

A range of behavioral tests are used to evaluate impulse control/cognitive control deficits in laboratory animals. A number of tests measure the ability to stop or withhold a pre-potent response; these include the go/no-go and stop-signal reaction time tasks [7–9]. Additionally, choice reaction time tasks [10–13] and reinforcement of low rates of responding schedules [14–17] can be used to assess the ability to temporarily delay a reward-directed response over an interval. Other tests measure the ability to adaptively inhibit one response in favor of another when contingencies are adjusted during performance, i.e. reversal of a learned discrimination [18–22]. Collectively, these procedures, along with others, are used to measure the ability to cognitively control responding or behavior.

Another set of tasks have been used to examine some of the "reasoning" or choice processes that contribute to certain aspects of impulsivity; these tasks are thought to measure aspects of impulsive decision-making, rather than impulsive behavior. Discounting tasks are common examples of these sets of tasks; humans and animals discount reinforcers when they are delayed, require greater effort to obtain or are probabilistic/uncertain. Evidence of impulsive decision-making is conceived of as reduced sensitivity to increased delay/effort/uncertainty, i.e. less discounting in impulsive subjects.

Importantly, while all measuring some aspect of cognitive control, these various tests rely upon only partially over-lapping neural circuitry, and their individual relationships to addiction may, therefore, vary. For example, poor adaptation of responding, measured using a reversal learning task, depends upon orbitofrontal cortex and its efferent targets in the medial striatum [18,23–27]. Conversely, impulsive choice is linked to the anterior cingulate cortex, medial prefrontal cortex and nucleus accumbens core [28,29]. Stemming from these non-overlapping neural substrates, the associations of these domains of impulsivity with addiction to stimulants vs. alcohol vs. nicotine, etc., may be different. These issues are partially addressed in the following sections.

Impulsive Action/Decision-Making and Addiction: Drug Effects

As noted above, the relationship between addiction and impulsivity cannot be tested in humans, so some of the first studies in animals on this topic addressed the question of whether exposure to illicit drugs, *per se*, affects impulsivity/aspects of cognitive control. It is important to note that many studies have examined the effects of acute administration of drugs of abuse on impulsive action and decision-making in rats, but this manuscript focuses on studies utilizing chronic drug exposure, given the greater relevance for drug addiction. The first study on this topic examined how repeated, intermittent cocaine exposure affected the ability of monkeys to adaptively modify a behavioral response in a discrimination reversal task; we showed that even short-term exposure to cocaine (twice-daily injections for 2 weeks) produced relatively long-lasting impairments in response updating [20]. Our group has extended these results by showing that cocaine-exposed monkeys exhibit perseverative deficits in a number of variations on the reversal task [30]. Subsequently, similar effects have been shown in rats that self-administer cocaine [31] and in humans who abuse cocaine [32,33], indicating that this is a robust impairment that is caused by exposure to cocaine. Consistent with the idea that this

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deficit is one of failed inhibition of behavior/responses, cocaine self-administration also produces persistent increases in premature responding in a choice reaction time task [11]. A question arises as to whether this effect is specific to cocaine or also applies to other drugs; notably, the study by Ersche and colleagues (*ibid*.) did not identify similar deficits in individuals who abuse illicit substances other than cocaine, suggesting that not all drugs are alike, either due to their different pharmacological properties or due to differences in the severity of the addiction caused by various illicit drugs.

Similarly, chronic intake (voluntary or otherwise) to drugs of abuse can impair impulsive choice in rats. As compared to saline-treated controls, rats chronically exposed to cocaine transiently exhibit less ability to delay gratification [34,35]; differences in ambulatory activity did not explain these effects. In an olfactory discrimination task, cocaine-exposed rats exhibit hypersensitivity to changes in both reward delay and magnitude [36]. This effect is not specific to cocaine in that steeper delay discounting gradients have also been found after chronic treatment with methamphetamine [37] and nicotine [38]. Again, each of these effects mimics an observed impairment of impulsive choice, using analogous procedures, in humans that abuse cocaine [39–41], methamphetamine [42] or nicotine [43].

Collectively, these data provide direct evidence that the direct pharmacological actions of drugs of abuse produce, particularly after chronic administration, changes in impulsive responding and choice in laboratory animals and that these effects mirror (and perhaps partially explain) similar deficits in performance in drug-dependent individuals measured using analogous or homologous behavioral instruments. Perhaps most importantly, a number of studies are beginning to describe the molecular neuroadaptations within frontostriatal regions that likely explain these persistent changes in impulsivity [11,30], underscoring the utility of developing animal models of drug abuse behavior that capture aspects of loss of cognitive control.

Impulsive Action/Decision-Making and Addiction: Risk Indicator?

Although the previously described studies implicate alterations in impulsive action and choice as a consequence of exposure to drugs of abuse (at some drugs of abuse, under some circumstances), this does not invalidate the potential for naturally-occurring variation in these traits to influence risk for the disorders and, therefore, to co-segregate with them. Indeed, individual variation in impulse control capabilities, in part programmed by genetic variation in dopamine system-related genes, may represent a key quantitative indicator of drug abuse liability [4].

Several recent studies suggest that this is the case. Using a measure of premature responding in a choice reaction-time task, Dalley et al. showed that rats screened as exhibiting greater impulsive action would subsequently take more cocaine (they were “abuse prone”) and that this effect was associated with lower dopamine D2-like receptor availability within the ventral striatum [44]; a similar phenotypic relationship holds between impulsive action and the acquisition of nicotine self-administration in rats [13]. Notably, in a separate study in monkeys, we showed that blockade of D2/D3 receptor function caused impulsive responding in a reversal learning task [45], suggesting that there is a causal relationship between D2-like receptor function and poor impulse control. What is more, animals with high impulsivity are more likely to transition to inflexible cocaine-taking that becomes resistant to punishment, a hallmark of compulsive actions [3].

A high degree of naturally-occurring impulsive choice is also known to relate to liability to self-administer drugs of abuse in rats. Animals exhibiting the steepest delay discounting effects self-administer more ethanol or cocaine than their low impulsive choice counterparts [46,47]. Furthermore, impulsive delay discounting performance predicts resistance to extinction and susceptibility to conditioned-cue reinstatement in rats self-administering nicotine [13].

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Together, these studies in animal models that measure aspects of impulsive responding or choice are useful in defining a substance abuse "vulnerable" phenotype that should be used to further explore the nature of addiction risk in humans, particularly the genetic or molecular basis of this susceptibility.

Model Comparison

Two aspects of impulsivity related to drug abuse have been described above: namely, impulsive action and impulsive choice. Furthermore, there are multiple behavioral models that measure these two domains of function. At present, the data described suggests that different behavioral models have partially non-overlapping neural circuits and bear differently upon the dimensions of drug-taking behavior in rats. In that sense, they are complementary, and further work is required to specify the mechanistic bases of the relationships between measures of impulsive action and choice and the variable facets of drug self-administration (acquisition of drug-taking behaviors, differences in drug sensitivity, extinction of responding and its reinstatement, drug-seeking despite adverse, contingent consequences of taking). The presence of multiple positive relationships between these measures is inspiring for future research, but clearly, it is not yet clear what models afford the best traction with respect to understanding drug abuse liability and progression in non-human animals.

Model Translation to Humans

While the translatability of individual behavioral measures in rats to humans can be fraught with problems, this is not always the case. Animal models of drug (cocaine, methamphetamine, nicotine) self-administration often appear face valid for the human disorder, but it is obvious that non-humans do not suffer from the same psychosocial consequences of drug-taking behavior that often lead human subjects to seek treatment to achieve abstinence. In that sense, the active suppression of impulsive drug-taking may not play an equivalent role in drug-taking in rats, as it does in humans. Because evidence does relate impulse control to drug-taking in rats, this criticism may be constrained, but it should nevertheless be factored into understanding the ultimate validity of animal models of drug abuse behavior.

Conclusions

Impulsive behavior, and its suppression by cognitive control mechanisms, plays a highly important role in our concepts of drug abuse. Animal models are increasingly demonstrating the nature of these relationships (the chronic drug exposure causes impulsivity but that impulsivity also represents a liability factor for substance use), and these models are also offering new insights into the underlying biology. New pharmacological treatments selected according to their ability to enhance impulse control in animal models should, therefore, be increasingly the focus on future drug treatment trials in humans.

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