



## Animal Studies of Addictive Behavior

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## Animal Studies of Addictive Behavior

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It is increasingly recognized that studying drug taking in laboratory animals does not equate to studying genuine addiction, characterized by loss of control over drug use. This has inspired recent work aimed at capturing genuine addiction-like behavior in animals. In this work, we summarize empirical evidence for the occurrence of several DSM-IV-like symptoms of addiction in animals after extended drug use. These symptoms include escalation of drug use, neurocognitive deficits, resistance to extinction, increased motivation for drugs, preference for drugs over nondrug rewards, and resistance to punishment. The fact that addiction-like behavior can occur and be studied in animals gives us the exciting opportunity to investigate the neural and genetic background of drug addiction, which we hope will ultimately lead to the development of more effective treatments for this devastating disorder.

Drug addiction is an enormous medical problem, not least because of the ensuing unhealthy lifestyle and the comorbidity with other neuropsychiatric disorders. Moreover, because of its socioeconomic and legal impact on society, it affects many more people than the addicts themselves. It has been calculated that drug addiction accounts for more than 40% of the financial cost to society of all major neuropsychiatric disorders (Uhl and Grow 2004).

Addiction is a chronic relapsing disorder characterized by loss of control over drug taking. Over the course of the addiction process, drug use escalates from casual consumption to inappropriate use (“abuse”), and the subject ultimately loses control over drug seeking and

taking, which is characterized by, among others, the occurrence of drug-related activities at the expense of previously important social and professional activities and continued drug use despite awareness of its adverse consequences.

Although recent years have seen progress in this regard (O’Brien 2008; Koob et al. 2009; van den Brink 2011; Pierce et al. 2012), there is still a pressing need for more effective pharmacotherapies for drug addiction, especially those that target the loss of control over drug intake which constitutes the core of the disorder. To facilitate the development of such a therapy, elucidation of the neural substrates of compulsive drug use is essential. However, the neurobiological factors that distinguish casual from compulsive drug

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use are not known, not least because of the difficulties in establishing loss of control over drug use in animal studies. During the last two decades, several investigators have been successful in emulating the addicted phenotype in laboratory animals, and we are beginning to understand the neurobiological factors that distinguish casual from compulsive drug use (e.g., Hollander et al. 2010; Im et al. 2010; Kasanetz et al. 2010; Zapata et al. 2010).

In the present review, we will describe recent progress that has been made in studying aspects of addictive behavior in animal studies. During the last five decades, studies on drug self-administration, conditioned place preference, and intracranial self-stimulation have resulted in an enormous body of data concerning the neural substrates of drug reward and reinforcement (e.g., Wise 1996; Tzschentke 2007; O'Connor et al. 2011). This knowledge has been invaluable in our understanding of why people start using drugs, and to some extent why drug use is continued after initial exposure. However, there is increasing awareness that investigating mere drug taking in animals does not equate to studying genuine addiction, characterized by loss of control over drug use. Recognition of this fact within the field has inspired research in the last decade or two, in which researchers have attempted (and, as we wish to argue, have succeeded to a considerable degree) to capture genuine aspects of addiction-like behavior in laboratory animals (Ahmed 2005, 2012; Vanderschuren and Everitt 2005; Kenny 2007). Below, we will discuss the evidence for the occurrence of addiction-like phenotypes in animal studies. Because the DSM-IV criteria for addiction (Table 1) (American Psychiatric Association 2000) are widely accepted as a touchstone to define and characterize addiction-like behavior, we will use these as a guideline to describe the animal studies. In particular, we identify several ways in which these DSM-IV criteria can be studied in an animal model (Table 2) (Wolffgramm and Heyne 1995; Ahmed and Koob 1998; Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004; Ahmed 2012), and will then describe the evidence that these phenomena can be observed in laboratory animals after repeated or prolonged drug use.

**Table 1.** DSM-IV criteria for drug addiction

Pattern of drug abuse causing significant harm or suffering, as characterized by three or more of the following:

1. Tolerance
2. Withdrawal symptoms
3. Drug use in larger amounts or during longer periods than initially intended
4. Difficulty in restricting drug use
5. Great deal of time devoted to procuring and consuming drugs, and recovery from drug use
6. Important social or professional activities given up in favor of drug-related activities
7. Drug use continued despite knowledge of adverse consequences

## ANIMAL STUDIES OF ADDICTIVE BEHAVIOR

### Escalation of Drug Use

Escalation of drug use is a hallmark stage in the transition to addiction (Ahmed 2012). In almost all cases of addiction, the loss of control over drug use is preceded or accompanied by a dramatic increase in drug intake, which is likely to induce an array of neural adaptations that facilitate the descent into the addicted state (Vanderschuren and Everitt 2005; Kalivas and O'Brien 2008). Traditionally, increases in drug use over time have been attributed to the occurrence of tolerance (i.e., decrease in the positive or negative subjective effects of the drug) or withdrawal symptoms (whereby drug use not only serves to achieve positive subjective effects,

**Table 2.** Appearance of DSM-IV criteria in animal studies of drug addiction

DSM-IV criterion	Behavioral equivalent
1. and 2. Tolerance, withdrawal	Tolerance, escalation of drug use
3. Using more than intended	Impaired control, neurocognitive deficits
4. Difficulty restricting	Resistance to extinction
5. Great deal of time spent	Increased motivation for drug
6. Other activities given up	Drug preference over nondrug rewards
7. Continued use despite problems	Resistance to punishment



but also to ameliorate the negative state of withdrawal). These two factors, that are the first two symptoms of addiction in DSM-IV, can clearly contribute to escalation of drug use. However, one should not equate escalation of drug use to tolerance because other medical, psychological, societal, and economic factors can also contribute to escalation of drug use (Ahmed 2011).

In animal studies, escalation of drug intake has been most widely investigated in cocaine and ethanol self-administration settings. In the context of cocaine self-administration, a landmark study by Ahmed and Koob (1998) showed that rats with extended access to cocaine self-administration (i.e., 6 h/d) gradually increased their cocaine intake across days, whereas with more limited drug access (i.e., 1 h/d), it remained remarkably stable, even after several months of testing (Ahmed and Koob 1999). The escalation of cocaine intake with extended access to the self-administered drug has been independently replicated many times (e.g., Ben-Shahar et al. 2008; Mantsch et al. 2008; Oleson and Roberts 2009; Quadros and Miczek 2009; Hao et al. 2010; Hollander et al. 2010; Pacchioni et al. 2011; for review, see Ahmed 2011, 2012). Rats with a history of escalated cocaine self-administration have also been shown to display other behavioral characteristics of addictive behavior, such as increased motivation for the drug (Paterson and Markou 2003; Lenoir and Ahmed 2008; Wee et al. 2008; Orio et al. 2009; but see Liu et al. 2005a), an increased sensitivity for reinstatement of cocaine seeking after extinction (Mantsch et al. 2004; Ahmed and Cadore 2006; Kippin et al. 2006; Knackstedt and Kalivas 2007), and reduced sensitivity to punishment of cocaine seeking (Vanderschuren and Everitt 2004; Ahmed 2012). Escalation of self-administration after extended access to the self-administered drug has subsequently also been found for other drugs of abuse, including methamphetamine (e.g., Kitamura et al. 2006), heroin (Ahmed et al. 2000), and methylphenidate (Marusich et al. 2010), but, remarkably, not for nicotine (Paterson and Markou 2004; Kenny and Markou 2005).

In a somewhat different setting, it has been repeatedly shown that oral ethanol ingestion in

rats and mice also increases over time. In a pioneering study, Wise (1973) showed that rats that received intermittent access to ethanol (i.e., every other day) gradually increased their alcohol intake over time. Subsequently, Wolffgramm and Heyne (Wolffgramm 1991; Wolffgramm and Heyne 1991, 1995) showed that after several months of relatively stable ethanol intake, rats increase their levels of ethanol drinking, which was associated with other signs of addiction-like behavior (e.g., resistance to punishment, see below). Interestingly, they showed a comparable increase over time of oral drug ingestion for other drugs, such as amphetamine (Heyne and Wolffgramm 1998), the opiate etonitazene (Wolffgramm and Heyne 1995, 1996), but less so for nicotine (Galli and Wolffgramm 2011). Consistent with these findings, Spanagel and Höltter (Höltter et al. 1998; Spanagel and Höltter 1999) showed that rats with access to different concentrations of ethanol in their home cages increased their intake after long-term ethanol exposure with repeated periods of withdrawal. In addition, these animals developed a preference to drink higher ethanol concentrations, and also showed signs of reduced sensitivity to punishment. In an operant setting, repeated deprivation from ethanol was also shown to increase responding for ethanol under both fixed-ratio and progressive-ratio schedules, suggesting an increase in the motivation to self-administer ethanol (Rodd et al. 2003). Extending these studies to another species, Lesscher et al. (2009) have showed that in a limited access choice paradigm, in which mice had access to ethanol for 2 h/d, these animals gradually escalated their ethanol intake over 4 wk of testing.

### Impaired Control over Behavior: Neurocognitive Deficits

The occurrence of neurocognitive deficits in drug addiction is well documented (Bechara 2005; Garavan and Stout 2005; Paulus 2007; Robbins et al. 2008; Chambers et al. 2009; Goldstein et al. 2009). By and large, the cognitive deficits in addiction are relatively mild, and affect a variety of functions, such as attention, working memory, memory, planning, impulse

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control, and decision-making. These deficits contribute to the addiction in several ways. For example, impaired impulse control, in the sense of difficulty to inhibit prepotent drug-taking actions or to wait for future gratification, i.e., to weigh the delayed benefits of a drug-free lifestyle against an immediate drug reward, likely plays a critical role in the maintenance of addictive behavior. In addition, cognitive deficits in the realm of attention, working memory and memory functions may limit the success of rehabilitation programs, if participants have trouble attending to, or remembering what was learned during a counseling session. Indeed, impaired decision making on a gambling task has been shown to predict the risk of relapse in alcoholics (Bowden-Jones et al. 2005), and lack of impulse control is associated with poor treatment retention in cocaine addicts (Moeller et al. 2001) and earlier relapse in alcoholics (Charney et al. 2010).

Clearly, it is difficult to discern from studies in humans whether these neurocognitive deficits are the cause or the consequence of addictive behavior, although there is some evidence to show that impulse control deficits predisposes adolescents for smoking, alcoholism, and substance abuse (Nigg et al. 2006; Audrain-McGovern et al. 2009). Interestingly, there is an emerging body of animal studies to investigate the relationship between addictive behavior and neurocognitive function. In general, these studies support both cause and consequence notions. Thus, high impulsivity in rats predicts the vulnerability to alcohol consumption, nicotine self-administration, cocaine self-administration, and signs of cocaine addiction (Poulos et al. 1995; Perry et al. 2005; Dalley et al. 2007a; Belin et al. 2008; Diergaarde et al. 2008), although impulsive behavior does not appear to predict heroin self-administration (McNamara et al. 2010; Schippers et al. 2012). Conversely, a period of self-administration of cocaine, methamphetamine, MDMA, or heroin has been shown to affect a variety of cognitive functions in rats, including attention, working memory, cognitive flexibility, object recognition memory, and impulsive behavior (Dalley et al. 2005, 2007b; Calu et al. 2007; Briand et al. 2008; Rogers

et al. 2008; Gipson and Bardo 2009; Winstanley et al. 2009; Mendez et al. 2010; Parsegian et al. 2011; Schenk et al. 2011; Schippers et al. 2012). Interestingly, some of these deficits were specifically observed (or more prominently so) in animals with a history of escalated drug taking (Briand et al. 2008; George et al. 2008; Rogers et al. 2008; Gipson and Bardo 2009). A recent study in primates also showed cognitive inflexibility and working memory deficits after a lengthy history of cocaine self-administration (Porter et al. 2011). Interestingly though, opposite findings have also been reported, as a period of cocaine self-administration was shown to reduce impulsivity in high-impulsive rats and to improve learning and memory in a water maze (Dalley et al. 2007b; del Olmo et al. 2007), a paradoxical effect that may explain certain forms of drug self-medication.

### Resistance to Extinction

Difficulty abstaining from drugs can be studied in laboratory animals by assessing drug seeking when the drug is no longer available (i.e., responding in extinction). Indeed, resistance to extinction has been observed in heroin-withdrawn rats with a history of extended access to heroin self-administration (Ahmed et al. 2000; Lenoir and Ahmed 2007; Doherty et al. 2009). However, escalation of self-administration does not seem to be a prerequisite for resistance to extinction because extended access to cocaine or methamphetamine self-administration does not result in increased responding in extinction (e.g., Mantsch et al. 2004; Sorge and Stewart 2005; Kippin et al. 2006; Allen et al. 2007; Knackstedt and Kalivas 2007; Rogers et al. 2008). Interestingly though, gradual increases in responding for cocaine during periods of explicit non-availability of the drug have been observed in subgroups of rats that also display other signs of addiction-like behavior after prolonged cocaine self-administration experience (Deroche-Gamonet et al. 2004; Belin et al. 2009). Furthermore, it was recently shown that lengthy training to respond for cocaine availability under a random interval schedule (that promotes the development of an associative structure of behavior



in which operant responding is less sensitive to the value of its outcome; [Dickinson 1985]) led to persistent responding after extinction of the cocaine taking response (Zapata et al. 2010). In this study (see also Olmstead et al. 2001), responding for a cocaine taking opportunity was sensitive to extinction in animals with a short training history, consistent with the studies described above (Deroche-Gamonet et al. 2004; Belin et al. 2009), that showed that persistent responding in extinction develops with increasing cocaine self-administration experience.

Another factor that seems to determine the sensitivity to extinction is length of withdrawal from self-administration. Thus, the degree of resistance to extinction of cocaine and heroin seeking increased with the length of withdrawal from extended drug self-administration (Ferrario et al. 2005; Zhou et al. 2009). This incubation of responding for drugs with prolonged withdrawal has been extensively studied by Shaham and colleagues (Grimm et al. 2001; for reviews, see Lu et al. 2004; Pickens et al. 2011). These studies have shown that the sensitivity to extinction of operant responding for drugs, or drug-associated cues is time-dependent. With prolonged withdrawal, responding in extinction increases, peaks (depending on the self-administered drug) between 1 wk and 3 mo post-withdrawal, and declines thereafter. Although dissipation of the response-suppressing effects of acute drug withdrawal can explain some of the rises in responding in the first few days postwithdrawal, the temporal profiles of the incubation effect, and the neural adaptations involved—the majority of which is likely not associated with the response-suppressant or anhedonic properties of drug withdrawal (Lu et al. 2004; Pickens et al. 2011)—suggest that incubation of responding for drugs also involves behavioral mechanisms related to motivation for the drug, or cognitive control over behavior.

### Increased Motivation for Drugs

Motivation to take drugs in animals is most often studied using a progressive ratio schedule of reinforcement, in which animals have to make an increasing number of responses for every

subsequent reward (Hodos 1961; Richardson and Roberts 1996). Using this schedule, it has been reported many times that after a period of drug self-administration, the motivation of the animals for drugs can increase. Thus, animals with a history of escalated cocaine use were found to respond at higher levels than animals that had limited cocaine access (Paterson and Markou 2003; Allen et al. 2007; Larson et al. 2007; Wee et al. 2008, 2009; Orio et al. 2009; Hao et al. 2010, but see Quadros and Miczek 2009). This effect has subsequently also been found for other drugs of abuse, including methamphetamine (Wee et al. 2007) and heroin (Lenoir and Ahmed 2007). Remarkably, Roberts and colleagues also showed that a period of drug (cocaine or heroin) self-administration leads to increased break-points under a progressive ratio schedule of reinforcement (Liu et al. 2005b, 2007; Morgan et al. 2005, 2006; Ward et al. 2006), but this increase in the motivation for cocaine appeared to be more pronounced in animals with limited drug self-administration experience (Liu et al. 2005b; Morgan et al. 2006). A subsequent study from this laboratory (Oleson and Roberts 2009) showed that escalation of cocaine intake increased the motivation for cocaine at high unit doses, but reduced the rate of responding at a threshold dose of cocaine, suggesting that after a history of escalated cocaine intake, animals take more of the drug if large amounts are available, but are not willing to pay a high price for a low amount of the drug (Oleson and Roberts 2009). In contrast, escalation of heroin self-administration was shown to increase the value of the drug, as the maximum price animals were willing to pay for heroin was increased (Lenoir and Ahmed 2008). Increases in the motivation for cocaine have also been found in a subgroup of rats with prolonged cocaine self-administration experience (Deroche-Gamonet et al. 2004; Belin et al. 2009).

Additional evidence for increased motivation for cocaine after escalated self-administration was obtained using the operant runway procedure. In this procedure, rats with extended cocaine use ran faster than controls to reach a goal box to receive an intravenous bolus of cocaine (Ben-Shahar et al. 2008). Somewhat

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consonant with this observation, Deroche et al. (1999) previously found that the motivational properties of the drug were augmented in the animals with the long cocaine taking history, as these animals took less time to traverse a runway for cocaine reinforcement.

### Drug Preference over Nondrug Rewards

As mentioned earlier, one of the core behavioral symptoms of drug addiction is a progressive neglect of alternative pleasures or interests in favor of continued drug use. As a result of drug preference, important social, occupational, or recreational activities are given up, resulting in turn in severe opportunity costs (e.g., poor education and associated long-term negative consequences). One of the most challenging obstacles facing addiction treatments is to replace this maladaptive preference for drug use by alternative nondrug activities or behaviors.

In animal studies of addiction, drug preference can be studied by giving access to other behavioral options or choices during drug access—an opportunity lacking in standard experimental settings (Ahmed 2005, 2010). In a typical choice experiment, animals face two behavioral options: responding for a drug or for a nondrug reward, generally a small piece of food (Aigner and Balster 1978). The first choice study—which was also the first study to show drug self-administration in nonhuman animals—was conducted in adult chimpanzees (one male, one female) rendered physically dependent on morphine by passive drug administration (Spragg 1940). Chimpanzees preferred morphine over a piece of fresh fruit (orange, banana) during drug withdrawal but otherwise preferred food (see also Negus 2006). Subsequent research showed that drug preference in animals was dose-dependent (e.g., Nader and Woolverton 1991; Paronis et al. 2002; Negus 2003) and surmountable by increasing the value of the alternative nondrug reinforcer (e.g., by increasing its magnitude; Nader and Woolverton 1991). Only a subgroup of animals persisted in preferring the drug despite the opportunity of making a different choice (Nader and Woolverton 1991; Lenoir et al. 2007; Cantin et al.

2010; Kerstetter et al. 2010; Augier et al. 2011; Norman et al. 2011; Perry et al. 2011; for recent reviews, Ahmed 2010, 2012).

For instance, in a recent series of experiments, rats were offered a choice between cocaine and a nondrug reward (i.e., water sweetened with saccharin or sucrose). Facing this choice, rats preferred cocaine or were indifferent when the expected value of sweet water was low but reversed their preference toward the alternative reinforcer when its value was sufficiently high. This preference shift occurred regardless of the dose of cocaine available and even following a long history of extended access to cocaine self-administration (Lenoir et al. 2007; Cantin et al. 2010). These findings are generally consistent with previous research (Carroll et al. 1989; Carroll and Lac 1993) and with recent behavioral economics studies showing that food (or sucrose) demand was more inelastic than cocaine demand (Christensen et al. 2008; Koffarnus and Woods 2011; for review, see Kearns et al. 2011). They are also congruent with a recent study showing that mice preferred drinking sucrose over direct optostimulation of midbrain dopamine neurons (Domingos et al. 2011). After extended access to cocaine self-administration, however, a subgroup of rats (i.e., roughly 15%–20%) continued to prefer cocaine over the alternative option—a behavior that could not be attributed to a mere disinterest in, or aversion to, sweet water. Indeed, when sweet water was the only option available, cocaine-preferring rats drank as much and as fast as nondrug-preferring rats (Cantin et al. 2010). Most importantly, this subgroup of cocaine-preferring rats continued to take cocaine even when hungry and offered sucrose to relieve their need of calories (Cantin et al. 2010). The persistence of cocaine preference despite its opportunity costs strongly suggests loss of control and compulsive cocaine use in these rats (see also below). The subgroup of cocaine-preferring rats may thus represent the most advanced and severe stage in the transition to cocaine addiction. This conclusion was recently generalized to other food rewards (Kerstetter et al. 2010; Perry et al. 2011) and to other drugs of abuse, including heroin (M Lenoir, L Cantin, F Serre, et al., unpubl.) and nicotine

(Le Sage 2009; Norman et al. 2011). Finally, it is consistent with other methodological approaches that have also identified subgroups of rats resistant to the suppressive effects of punishment on cocaine, amphetamine, or nicotine self-administration (Deroche-Gamonet et al. 2004; Galli and Wolffgramm 2004, 2011; Peloux et al. 2007; Belin et al. 2008).

### Resistance to Punishment

Recent years have seen a considerable amount of studies that have tried to emulate drug use continued despite knowledge of adverse consequences in an animal experiment. These studies have in common that they have used punishment setups, in which seeking or taking drugs was paired with a negative stimulus. In studies using oral ingestion of drugs (for the most part ethanol), this has been performed by adulterating the drug solution with the bitter tastant quinine. In addition, other studies have punished drug seeking or taking with post-ingestion illness using lithium chloride, or using footshocks or shock-associated stimuli (e.g., Grove and Schuster 1974; Bergman and Johanson 1981; Kearns et al. 2002).

The quinine model was first published by Wolffgramm and Heyne (Wolffgramm 1991; Wolffgramm and Heyne 1991). This study, as well as subsequent work, showed that after a lengthy period of ethanol drinking followed by a period of forced abstinence, ethanol ingestion became insensitive to the addition of quinine. That is, if quinine was added to the ethanol that was available to rats that drank ethanol for 6–9 mo before, their intake was not, or was only to a limited extent, reduced by the bitter taste of quinine. In contrast, rats with limited ethanol experience did considerably reduce their intake. Comparable insensitivity to quinine adulteration after prolonged drug intake was subsequently found for the opiate etonitazene (Wolffgramm and Heyne 1995; Heyne 1996), amphetamine (Heyne and Wolffgramm 1998; Galli and Wolffgramm 2004), and nicotine (Galli and Wolffgramm 2011). Interestingly, the latter two studies (Galli and Wolffgramm 2004, 2011) reported that insensitivity to qui-

nine adulteration developed with lengthy amphetamine and nicotine experience in a subgroup of rats only.

The quinine adulteration model was recently followed up in two separate studies (Hopf et al. 2010; Lesscher et al. 2010). Hopf et al. (2010) showed that rats that had been allowed to drink ethanol intermittently (3 d/wk) for 3–4 mo were insensitive to the addition of quinine to ethanol when their motivation to self-administer ethanol under a progressive ratio schedule of reinforcement was assessed. Interestingly, sensitivity to quinine was found after shorter ethanol experience (1.5 mo). In a home cage drinking setup, rats with intermittent ethanol experience were less sensitive to quinine than animals that had continuous ethanol access, echoing, for example, the findings of Wise (1973) that intermittent ethanol access leads to larger amounts of ethanol ingestion than continuous access. In a limited access choice paradigm, Lesscher et al. (2010) showed that mice became insensitive to quinine adulteration after only 2 wk of ethanol experience. Thus, whereas quinine addition did suppress acquisition of ethanol drinking, adding an aversive quinine concentration to ethanol failed to reduce drinking in mice with 2 wk of ethanol experience, when this was their only source of ethanol. Remarkably, a further sign of insensitivity to quinine emerged after 6 more weeks of ethanol experience, in that mice with an ethanol drinking history of 8 wk became indifferent to quinine, as they drank equal amounts from bottles of ethanol with and without quinine at an aversive concentration.

In a series of studies designed to assess habitual aspects of drug seeking, Dickinson and colleagues (Dickinson et al. 2002; Miles et al. 2003) tested whether devaluation of orally ingested ethanol or cocaine, by pairing its consumption with lithium chloride-induced illness, reduced responding for these drugs. Whereas the operant responding for food appeared sensitive to devaluation, responding in extinction for ethanol or cocaine was not. Remarkably, both during taste aversion conditioning with lithium and during reacquisition of responding for the drug, responding for and



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intake of the drug solution associated with lithium-induced malaise was markedly decreased (Dickinson et al. 2002; Miles et al. 2003). This shows that drug intake can be sensitive to devaluation whereas responding for the drug in extinction is not. Given that other studies, summarized above (Wolffgramm 1991; Wolffgramm and Heyne 1991, 1995; Heyne 1996, 1998; Galli and Wolffgramm 2004, 2011; Hopf et al. 2010; Lesscher et al. 2010), clearly show that intake of the drug itself can become insensitive to punishment after prolonged drug experience, it may be possible that development of inflexible drug use occurs in a staged manner. Distal drug cues or drug-related actions become insensitive to punishment before intake of the drug itself do, perhaps representing a gradual worsening of the addiction syndrome with increasing drug experience.

Consistent with this notion, it has been shown that operant responding for drugs is initially sensitive to punishment, but that this behavioral flexibility is gradually lost after prolonged drug experience (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004; Pelloux et al. 2007; Belin et al. 2009). In these studies, cocaine seeking in rats was punished with footshock, or assessed in the presence of a footshock-associated conditioned stimulus (CS). In animals with limited cocaine self-administration experience, the aversive CS markedly suppressed cocaine seeking. In contrast, the footshock-associated CS had no effect on cocaine seeking in rats with a prolonged cocaine self-administration history (Vanderschuren and Everitt 2004). Following punishment by footshock (rather than a footshock-associated CS), rats with extended access to cocaine resumed drug self-administration more rapidly than animals with limited cocaine access (Ahmed 2012). Likewise, punishment of cocaine seeking with footshock also markedly suppressed responding for cocaine in animals with limited drug experience, but a subgroup of animals subsequently displayed insensitivity to punishment (Pelloux et al. 2007). In keeping with these results, Deroche-Gamonet and colleagues (Deroche-Gamonet et al. 2004; Belin et al. 2009) observed that pairing intravenous delivery of

cocaine with footshock dramatically suppressed cocaine in animals with limited drug experience, but that this sensitivity to punishment was lost in a subgroup of rats after lengthy cocaine experience.

Last, in a setup based on the classic “Obstruction Box,” in which rats have to cross an electrified grid to reach a reward (Jenkins et al. 1926), Cooper et al. (2007) showed that increasing the shock intensity of the grid led rats with a limited cocaine self-administration history to abstain from the drug, although the intensity needed to achieve this varied between animals. Interestingly, presentation of cocaine-associated cues then evoked reinstatement of responding for those cues, but only in a subgroup of rats. Together, these data show that with sufficient drug-taking experience, drug seeking and taking can become insensitive to punishment. However, there are marked differences between drug-experienced individuals regarding the development of this resistance to adverse consequences.

## CONCLUDING REMARKS

Here we have summarized empirical evidence for the occurrence of symptoms of drug addiction in animals. Based on the DSM-IV criteria for drug addiction (Table 1) (American Psychiatric Association 2000), several symptoms of addictive behavior have been shown to occur in laboratory animals, i.e., escalation of drug use, neurocognitive deficits, resistance to extinction, increased motivation for drugs, preference for drugs over nondrug rewards, and resistance to punishment. These data indicate that addictive behavior can occur and be studied in animal models, showing that the neural machinery that underlies drug seeking and taking is present and can become dysregulated in non-human animals as it does in humans. This gives us the exciting opportunity to study the neural and genetic background of drug addiction in animal studies. In the case of cocaine intake escalation, this research is already underway and is beginning to reveal important neurobiological insights. For instance, it has recently culminated in the breakthrough discovery of

entirely new molecular pathways in the dorsal striatum that controls escalation of cocaine self-administration (Hollander et al. 2010; Im et al. 2010; for a recent review, see Ahmed and Kenny 2011). We hope that this research will, in the end, lead to the development of more effective treatments for this devastating disorder.

The summary presented here also identifies several outstanding questions that need to be addressed in future research. First, it should be recognized that occurrence of one symptom of addiction in an animal model does not equate to a model of drug addiction. Clearly, DSM-IV criteria state that three or more of seven criteria need to be met (American Psychiatric Association 2000). Therefore, one important issue is to determine whether the separate expressions of addictive behavior discussed here occur together in certain individuals or under certain conditions. There is some empirical evidence to suggest that various aspects of addictive behavior indeed co-occur (e.g., Wolffgramm 1991; Deroche-Gamonet et al. 2004). For instance, escalation of cocaine use has been shown to co-occur in the same group of individuals with increased motivation, neurocognitive deficits, drug preference, or resistance to punishment (for a recent review, see Ahmed 2012). One subsequent major challenge to the field is to elucidate the circumstances that determine the co-occurrence of various aspects of addictive behavior, and the relevant underlying neural changes. Another related challenge for future research will be to determine whether all symptoms of addiction can occur in animals or whether some symptoms are specific to humans. The latter possibility will raise interesting brain evolution issues. In addition, we need to remain aware that drug addiction, even after prolonged drug exposure, only occurs in a subgroup of individuals. Therefore, it is imperative to determine the genetic, neural, and environmental factors that render an individual vulnerable to the development of addictive behavior. These include, but are certainly not limited to, preexisting temperamental features such as impulsivity (Dalley et al. 2007b; Belin et al. 2008), sex (Anker and Carroll 2011), and social status (e.g., Wolffgramm 1991; Morgan et al. 2002).

For instance, two recent independent choice studies in rats showed that cocaine preference over palatable food was about 2–3 times more frequent in females than in males, suggesting that females may be more vulnerable to cocaine addiction (Kertstetter et al. 2009; Perry et al. 2011). Last, addictive drugs come from widely variant pharmacological classes, such as psychostimulants (cocaine, amphetamine, methamphetamine), opiates (heroin), ethanol, and nicotine. Even though each of these drugs is known to be highly addictive, their relative addictive potential varies, and their reinforcing strength depends on environmental factors (e.g., Caprioli et al. 2009; Solinas et al. 2011). Therefore, we need to identify the extent to which the occurrence of addictive behavior and its underlying neural, genetic, and environmental factors hold true for addictive drugs in general, or whether they are drug specific (Badiani et al. 2011). For instance, it was recently found that escalation of cocaine self-administration did not generalize to heroin self-administration and vice versa, suggesting that drug differences do indeed matter (Lenoir et al. 2011).

Even with these unresolved issues and outstanding questions in mind, we think that the last five decades of preclinical addiction research have generated an excellent body of information, and that the recent interest in studying genuine addiction-like behavior in animal experiments has resulted in the development of a launching pad for exciting further research that will help us to better understand the nature of the addiction syndrome.

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