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REVIEW

THE SCIENCE OF MAKING DRUG-ADDICTED ANIMALS

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Abstract—Research involving animal models of drug addiction can be viewed as a sort of reverse psychiatry. Contrary to clinicians who seek to treat addicted people to become and remain abstinent, researchers seek to make drug-naïve animals addicted to a drug with known addictive properties in humans. The goals of this research are to better understand the neuroscience of drug addiction and, ultimately, to translate this knowledge into effective treatments for people with addiction. The present review will not cover the vast literature that has accumulated over the past 50 years on animal models of drug addiction. It is instead more modestly devoted to recent research spanning the past decade on drug self-administration–based models of addiction in the rat (the animal species most frequently used in the field), with a special focus on current efforts to model compulsive cocaine use as opposed to nonaddictive use. Surprisingly, it turns out that modeling compulsive cocaine use in rats is possible but more difficult than previously thought. In fact, it appears that resilience to cocaine addiction is the norm in rats. As in human cocaine users, only few individual rats would be vulnerable. This conclusion has several important implications for future research on the neuroscience of cocaine addiction and on preclinical medication development.

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Key words: addiction, abstinence, choice, prefrontal cortex, cocaine, heroin.

Contents

Although drug self-administration by rodents has provided important information, it is difficult to argue that it truly models compulsion, when the alternative to self-administration is solitude in a shoebox cage.

–Hyman and Malenka, 2001

The transition to drug addiction is characterized by a progression toward compulsive drug use to the detriment of other socially valued behavioral choices (O'Brien et al., 2006; Saunders, 2006; Martin et al., 2008). The neglect of alternative behaviors in favor of drug-related activities can result in severe, sometimes irreversible opportunity costs (e.g. poor education and associated long-term negative consequences), particularly during critical developmental stages (i.e. adolescence, early adulthood) (Volkow et al., 2011). Drug addiction is currently thought to reflect a loss of volitional and/or rational control over recurrent impulses to use drugs that are reported as unwanted (e.g. the addicted person who seeks help and wants to quit does not want to crave the drug) (McLellan et al., 2000; Bechara, 2005; Kalivas et al., 2005; Koob, 2006; Hyman, 2007a; Goodman, 2008; Martin et al., 2008; Redish et al., 2008). According to current epidemiological evidence, the transition to drug addiction only affects a minority of drug users, which nevertheless represents a sizeable population with disproportionately major medical and social problems (Uhl and Grow, 2004; Nutt et al., 2007). The remaining majority of people who regularly use psychoactive drugs, even highly addictive ones such as cocaine, do not go on to develop addiction (Anthony et al., 1994; Anthony, 2002; Degenhardt et al., 2008). A long-standing problem in addiction research is to understand why only few people who use drugs eventually transition to a state of addiction, while the remaining majority seems to be resilient (i.e. resistant to addiction regardless of drug exposure) (Anthony et al., 1994; Anthony, 2002; Swendsen and Le Moal, 2011).

Human brain imaging studies have discovered addiction-related metabolic changes in several prefrontal cortical regions involved in normal reward evaluation and choice-making processes, notably in the orbitofrontal cortex—a phylogenetically conserved brain region that is also dysfunctional in other compulsive disorders (Volkow et al., 1991, 2005; Volkow and Fowler, 2000). However, because of limitations in the spatial and temporal resolution of brain imaging technologies and in the correlational design of human studies, the origin, nature, and causal effectiveness of these cortical changes remain largely undetermined. As a result, there is currently no or little hope to exploit this

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Abbreviations: CTA, conditioned taste avoidance; DSM, Diagnostic and Statistical Manual; ITI, inter-trial interval; PR, progressive ratio.

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neurobiological knowledge to inform and improve the diagnosis, prognosis, and/or treatment of drug addiction—a situation common to other psychiatric conditions (Hyman, 2007b). Further scientific advancement in our understanding of the neurobiological basis of addiction will thus continue to require parallel experimental research on laboratory animals, which permit invasive neurobiological investigations not feasible in humans.

Over the past 50 years, several efforts were made to model the transition to drug addiction in nonhuman animals, particularly in rats, which is by far the most frequently used animal species in experimental addiction research (Olmstead, 2011). Overall, this research can be conceptualized as reverse psychiatry (or reverse addiction medicine). Contrary to clinicians who seek to treat people with a diagnosis of addiction to become and remain abstinent, preclinical researchers who use nonhuman animals (designed as animals thereafter) work in the opposite direction. They start with nonaddicted animals, generally initially drug-naïve, and try to make them addicted to a drug that has known addictive properties in humans. The immediate goals of this research are to gain insight into the etiology and neurobiology of drug addiction and, ultimately and hopefully, to translate this knowledge into effective treatments for people with addiction. The aim of the present review is not to cover the vast literature that has accumulated over the past 50 years on animal models of drug addiction. This review is instead more modestly devoted to recent research (i.e. roughly spanning the past decade) on drug self-administration–based models of addiction in the rat, with a special focus on current efforts to better model compulsive cocaine use as opposed to nonaddictive use.

Before embarking on this review, some preliminary comments on terminologies and concepts that are currently particularly controversial are in order (see "Conclusions and perspectives" below). First, as explained in detail elsewhere, the term "addiction" will be preferred over the term "dependence" throughout the review (Ahmed, 2010). Though the latter term is currently used as a diagnostic label in influential international nomenclatures (e.g. Diagnostic and Statistical Manual (DSM)-IV-TR), it should eventually be dropped in future nomenclatures (Maddux and Desmond, 2000; O'Brien et al., 2006, 2011; Miller and Holden, 2010). Second, addiction is conceptualized here as a mental disorder, though there is still considerable debate surrounding this concept (Falk, 1983; Becker and Murphy, 1988; Goodman, 1990; Heyman, 1996; Heather, 1998; Ainslie, 2000; Orford, 2001; Skog, 2003; Bechara, 2005; Foddy and Savulescu, 2006; Hyman, 2007a; Alexander, 2008). Following the DSM-III-R and DSM-IV-TR, one can roughly define a mental disorder as a harmful behavioral or psychological condition that reflects an underlying dysfunction in the individual, particularly in its brain. Though this relatively old definition is far from being perfect (e.g. how does one define objectively a dysfunction? (Wakefield, 1992)), it will be only slightly modified in the next DSM revision (Helmuth, 2003; Stein et al., 2010). Importantly, excluded from this definition is any negative behavioral or psychological condition that is "a result of social deviance or conflicts with society" or that can be considered an "expectable response" to common situations or events (Stein et al., 2010). For instance, in the case of addiction, such exclusion clause was recently applied to redefine the status of certain symptoms that have historically played a major role in the initial diagnosis of drug addiction. For instance, as argued vividly by O'Brien, physical dependence should no longer be considered a core symptom of addiction but rather a normal or expectable physiological reaction to chronic drug exposure (O'Brien et al., 2006). In this definition, a heroin-withdrawn baby born from a mother addicted to heroin is no doubt physically dependent on, but not addicted to, heroin (O'Brien, 2011). In addition, on this view, people who use a substance to avoid physical withdrawal would not be compulsive users but functional, rational, and voluntary users. As explained below in "Compulsion and loss of control over drug self-administration" and "Conclusions and perspectives," the same exclusion clause can be fruitfully used to potentially exclude nonaddictive drug use in animal models (Ahmed, 2005, 2010). Finally, as already mentioned above, though there are neurobiological correlates of drug addiction, they are not currently sufficiently expressive and selective to serve in the inclusive diagnosis of addiction. To cope with this fundamental problem, psychiatrists and clinicians have progressively over the years redefined and refined inclusive behavioral criteria and decision rules (e.g. diagnostic threshold) to better discriminate between addictive and nondisordered drug use (see Table 1) (Saunders and Schuckit, 2006; Schuckit and Saunders, 2006; Martin et al., 2008). The multiple revi-

Table 1. Correspondence between effects of extended drug use and addiction diagnostic criteria

Effects of extended drug access	Frequency (%)	Relevant diagnostic criteria
Escalation of drug use	70	Escalation of drug use, tolerance
Increased motivation	nd	Persistent desire, increased time spent
Resistance to extinction	nd	Difficulty to cut down, persistent desire
Resistance to punishment	100	Continued use despite problems
Neurocognitive deficits	nd	Impaired control, more than intended
Increased drug reinstatement	80	Possibly craving (in DSM V)
Drug preference over other choices	15	Neglect of other activities
		Continued use despite problems

Frequency data were obtained by estimating the percentage of rats positive for the corresponding effect. The method of estimation for each effect can be found in the original publications (escalation: Ahmed, 2005; drug reinstatement: Ahmed and Cador, 2006; Lenoir and Ahmed, 2007; drug preference: Cantin et al., 2010; resistance to punishment: Ahmed, 2011). The diagnostic criteria correspond to those defined in the fourth revision of the American Psychiatric Association Diagnostic and Statistical Manual (DSM) for Mental Disorders. Craving should appear in the forthcoming fifth revision of the DSM. nd, not determined yet.

sions of the DSM of Mental Disorders of the American Psychiatry Association are probably the best example of this progress, and, though it was originally developed by US clinicians, the next revision will be a truly international achievement (Schuckit and Saunders, 2006; Miller and Holden, 2010; O'Brien, 2011). One prominent feature of the next revision is that it will put more emphasis on psychosocial consequences of addictive drug use (e.g. recurrent substance use resulting in a failure to fulfill major role obligations; important social, occupational, or recreational activities are given up or reduced because of substance use), which explains the definition of addiction given above. Despite this evolution in diagnosis, however, there remain long-standing controversies that need to be briefly mentioned here. There is still some dispute about whether the clinical manifestations of addiction qualify as obsessions, compulsions, or cravings (Kozlowski and Wilkinson, 1987; Goodman, 1990; Heyman, 1996; Heather, 1998; Orford, 2001; Foddy and Savulescu, 2006; Hyman, 2007a; Redish et al., 2008). For example, in humans, the concept of craving for a drug can be distinguished from the concept of an obsession based on what the patient is seeking out. Thus, contrary to a patient with cravings, a patient with obsessions does not seek out the object of obsession. The concept of compulsion in psychiatry raises a similar problem. Namely, a patient with a compulsion often receives no primary reward (though he/she obtains some acute relief), while a patient with an addiction clearly does (Lasagna et al., 1955). However, one could argue that in both cases, the patient does not want to act in the way he/she eventually acts and/or to have the desire he/she happens to have. In other words, in both cases, the individual does not identify with parts of his/her own motivations and experiences a psychological conflict between his/her different motivations (e.g. between immediate versus long-term goals, between lower-order and higher-order goals, between local and global goals). This brief conceptual overview shows that fine-grained psychological distinctions can be made, at least in theory, between different psychiatric concepts that look similar at first glance. Clearly, such fine-grained distinctions can hardly be matched in animal models of addiction. For instance, the concept of addiction as compulsive drug use is difficult to model in a valid manner in rats because it would imply a hierarchy of motivations that is apparently absent or difficult to evidence in these animals (Roberts, 2002; Suddendorf and Corballis, 2007). This limitation should be constantly kept in mind when interpreting the crosswalk between animal models and humans that is proposed throughout this review.

THE SCIENCE OF MAKING DRUG-ADDICTED ANIMALS

Until recently, it was generally believed that making cocaine-addicted rats was relatively straightforward, a presumption that contrasts with the known epidemiology of this disorder, which only affects a fraction of regular drug users and with the difficulty of reversing it once acquired or expressed. Accordingly, it would suffice to expose animals to cocaine—the supposed primary disease-causing agent—to turn them into addicted-like animals or, at least, into animals sensitized or vulnerable to cocaine addiction. Then the comparison of cocaine-exposed animals to drug-naïve controls would reveal what are the neuropathological alterations hypothesized to underlie cocaine addiction. Over the past 30 years, this paradigm has inspired and stimulated a productive and creative line of research, which led to the successful identification of many significant cocaine-induced neuroplastic changes, both short and long term, in relevant functional brain circuits (e.g. corticostriatal circuits). However, without independent, reliable, and valid evidence for addiction-like behavior in cocaine-exposed rats, it is difficult to univocally interpret these numerous changes in terms of addiction-causing neuropathological dysfunctions (Ahmed, 2011). This relative confusion may explain, at least partly, why despite much progress in understanding the neurobiology of cocaine actions (e.g. cocaine-induced perturbation of reinforcement learning), research involving animal models of cocaine addiction has had so far little significant translational impact for both medical diagnosis and treatment (Hyman, 2007b; Koob et al., 2009). For instance, most advances in current treatments for cocaine addiction, if any, still come from the bedside, and not yet from the laboratory bench (Potenza et al., 2011).

Fortunately, this situation has recently evolved. It is now acknowledged by many researchers in the field that mere cocaine exposure or self-administration is necessary, but not sufficient, for inducing and identifying an addiction-like profile or phenotype in laboratory animals (Wolffgramm and Heyne, 1995; Ahmed and Koob, 1998; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004; Roberts et al., 2007; Belin et al., 2008). Such recognition directly follows from a greater awareness of the multifactorial nature of cocaine addiction and of its medical diagnosis, which, in the current absence of objective neuropathological criteria, has defined reliable behavioral criteria, both inclusive and exclusive, to draw a dividing line with other nondisordered, nonaddictive forms of drug use (e.g. occasional or controlled use) (Edwards and Gross, 1976; Saunders, 2006; Roberts et al., 2007; Martin et al., 2008). Thus, to be considered having an addiction-like behavior, animals must, in addition to self-administering cocaine, develop or present an array of behavioral changes that recapitulate important behavioral features of cocaine addiction (e.g. escalation of cocaine intake, continued drug use despite punishment). Ideally, however, one should search for direct evidence that rats have lost control over cocaine self-administration, and that that they take cocaine by compulsion (i.e. in response to an uncontrollable impulse to take cocaine) (Ahmed, 2010) and not because of other nonpathological causes.

Several different approaches can be envisioned to model the clinical distinction between cocaine addiction and other nondisordered, nonaddictive forms of cocaine use in rats (Ahmed and Koob, 1998; Deroche-Gamonet et al., 2004; Roberts et al., 2007). Notably, among these different approaches, one modeling strategy has gathered

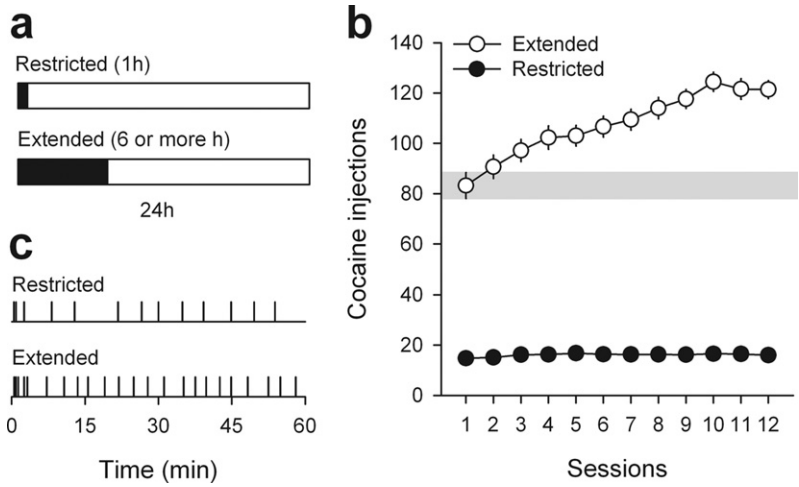

Fig. 1. Effects of restricted versus extended drug access on cocaine self-administration over time. (a) Experimental design. After acquisition of cocaine self-administration under a fixed-ratio 1 schedule of reinforcement, rats were assigned to at least two drug intake-matched groups. One group of control rats has restricted access to cocaine during only 1 h per day (n=30), while the other experimental group has extended access to cocaine during six or more hours per day (n=28). (b) Escalation of cocaine intake in rats with extended drug access. Data represent the mean number (±SEM) of cocaine injections (0.25 mg, i.v.) per session. The horizontal grey box indicates the mean number (±SEM) of drug injections during the first day. (c) First-hour distribution of cocaine injections (upward ticks) by two representative individual rats: one with restricted drug access, the other with extended drug access. This example shows that escalation of cocaine intake is largely due to acceleration in the rate of cocaine self-administration. Adapted from Ahmed (2005, 2011).

increasing momentum in recent years. It consists of comparing and contrasting rats with a history of extended versus limited access to cocaine self-administration (Ahmed, 2011). In a typical experiment implementing such a strategy, at least two matched groups of rats are allowed to self-administer cocaine intravenously for several days or weeks. The only difference between groups is daily access time to the drug; one group of control rats has access to cocaine during only 1 h per day, while the other experimental group has its access to cocaine extended to six or more hours per day (Ahmed and Koob, 1998) (Fig. 1a). The original rationale behind this approach was based on the assumption that extended drug use plays an etiological, though not necessarily exclusive, role in triggering the transition to cocaine addiction in humans. Specifically, it was hypothesized that addiction-causing neuropathological processes could be set in motion only when rats can expose themselves sufficiently to cocaine to cross the "threshold of addiction"—the minimum level of drug exposure required for inducing addiction (Benowitz and Henningfield, 1994). Conversely, below this critical level of cocaine exposure, there would be no drug-induced neuropathological changes, and drug use would remain under control, at least in the majority of drug-exposed individuals.

As reviewed in detail in "Recapitulation of the behavioral features of addiction in animals," this general hypothesis is consistent with numerous recent findings showing that rats with a history of extended access to cocaine self-administration develop unique behavioral alterations that are not observed in controls with a more restricted drug access. At the surface level, these behavioral changes can be interpreted as recapitulating some of the behavioral expressions of addiction or, at the very least, as indication that the motivation to self-administer cocaine is increased after extended drug use. However, despite all the appearances, there is currently little direct evidence that this increased motivation for cocaine reflects a genuine loss of control or compulsion, except perhaps in a minority of vulnerable individual rats. As explained in detail in "Compulsion and loss of control over drug self-administration," regardless of the cocaine exposure, most rats cannot apparently be turned into compulsive-like drug users, suggesting the existence of a biological resilience against cocaine addiction. Obviously, if confirmed, it should have important implications for future animal research on the neurobiology of cocaine addiction and on medication development (see "Conclusions and perspectives" below).

RECAPITULATION OF THE BEHAVIORAL FEATURES OF ADDICTION IN ANIMALS

This section summarizes what is currently known about the behavioral effects of extended versus restricted access to self-administration in rats (see Table 1). Overall, there is now strong evidence showing that following a history of extended access to cocaine self-administration, rats present behavioral features that recapitulate important behavioral criteria of addiction. They are more likely to escalate cocaine intake, to work harder and to accept increased costs to seek and/or to obtain the drug. In addition, they become more vulnerable to stress- and drug-primed reinstatement of cocaine seeking after extinction—a well-established animal model of precipitated craving and/or relapse. Finally, they also present alterations in executive functions (e.g. working memory) that

may compromise effective self-regulation of cocaine consumption.

Escalation of cocaine self-administration

Escalation of drug use—a hallmark stage in the transition to addiction (Ahmed, 2011)—was one of the first features of addiction demonstrated in rats with extended access to cocaine, but not in control rats with limited access to the drug (Ahmed and Koob, 1998) (Fig. 1b, c). Specifically, with extended access to cocaine self-administration, cocaine self-administration gradually increased across days, while, with more limited drug access, it remained remarkably stable, even after several months of testing (Ahmed and Koob, 1999). It has been estimated that the large majority of individual animals with a history of extended access to cocaine show escalation of cocaine intake (i.e. about 70%), while this phenomenon is observed only in a subset of controls (i.e. about 12%) (Ahmed, 2005). This outcome strongly suggests that mere, repeated cocaine self-administration is necessary, but not sufficient, to cause escalating patterns of cocaine use. A certain critical level of drug self-exposure is thus required to precipitate escalation of cocaine use in most animals. Importantly, the differential effect of drug access on cocaine self-administration (i.e. stability of drug use versus escalation of drug use) has now been replicated numerous times (Ben-Shahar et al., 2004, 2006, 2008, 2009; Mantsch et al., 2004, 2008a,b; Ferrario et al., 2005; Kenny et al., 2005; Perry et al., 2006; Allen et al., 2007a,b; Dalley et al., 2007; Ferrario and Robinson, 2007; Hansen and Mark, 2007; Madayag et al., 2007; Wee et al., 2007a, 2008; Aujla et al., 2008; Briand et al., 2008a,b,c; Anker et al., 2009; Oleson and Roberts, 2009; Quadros and Miczek, 2009; Gipson et al., 2010; Hao et al., 2010; Hollander et al., 2010; Jin et al., 2010; Wakabayashi et al., 2010). This effect also generalizes to a variety of other drugs of abuse belonging to different pharmacological classes [methamphetamine: (Kitamura et al., 2006; Mandyam et al., 2007; Wee et al., 2007b; Schwendt et al., 2009); heroin: (Ahmed et al., 2000; Kenny et al., 2006; Lenoir and Ahmed, 2007, 2008; McNamara et al., 2011; Vendruscolo et al., 2011)], including methylphenidate, a dopamine reuptake blocker that is used orally in the symptomatic treatment of attention-deficit hyperactivity disorder (Marusich et al., 2010) (Fig. 2). The only remarkable exception to this overall picture is nicotine for reasons that have not been entirely elucidated yet (Paterson and Markou, 2004; Kenny and Markou, 2006) but that are probably related to the strong aversive effects of this drug in animals (Fowler et al., 2011). Finally, when offered the opportunity to choose the dose per injection, rats also progressively shifted preference to higher cocaine doses during extended access to cocaine self-administration (Picetti et al., 2010). Escalation of the size of the unit dose was previously documented in an old case study of opioid re-addiction in humans (Wikler, 1952).

Increased motivation for cocaine

Rats with extended access to cocaine self-administration also show an enhanced motivation for cocaine compared

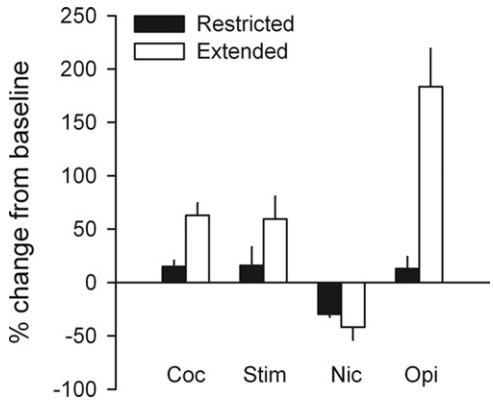

Fig. 2. Meta-analysis of published research on the effects of extended drug access on drug intake in rats. A total of 49 separate studies have looked at the effects of drug access time on the pattern of self-administration. These studies amount to a total of 74 independent experiments (cocaine: 55; amphetamine, methamphetamine: 7; nicotine: 2; heroin, morphine, fentanyl: 11). Most, though not all, experiments compared the effects of restricted (1 h per day) versus extended access (six or more hours per day) to the drug on the evolution of drug consumption. Coc, cocaine; Stim, other stimulant drugs (i.e. amphetamine and methamphetamine); Nic, nicotine; Opi, opiates (i.e. morphine and heroin). For additional information, see (Ahmed, 2011). Adapted from (Ahmed, 2011).

with controls with a more limited access to the drug. This increase in motivation for cocaine was originally suggested by the upward shift in the peak of the dose-effect function for cocaine self-administration seen following extended drug access (Ahmed and Koob, 1998; Mantsch et al., 2004; Roth and Carroll, 2004; Allen et al., 2007a; Wee et al., 2007a). Such shift shows that rats make more effort to maintain the same drug effect (Ahmed and Koob, 2005; Christensen et al., 2008b). More direct evidence for increased drug motivation following extended access to cocaine was obtained using the classic progressive ratio (PR) procedure (Hodos, 1961; Richardson and Roberts, 1996). Paterson and Markou (2003) reported that rats with a history of extended cocaine use maintain a higher breakpoint than controls, regardless of the dose available. This observation was subsequently confirmed by other teams or laboratories (Allen et al., 2007b; Larson et al., 2007; Wee et al., 2008, 2009; Orio et al., 2009; Hao et al., 2010) and was recently extended to other drugs of abuse, including methamphetamine (Wee et al., 2007b) and heroin (Lenoir and Ahmed, 2008). Note, however, that several researchers failed to find evidence for an increase in breakpoint following extended cocaine use (Li et al., 1994; Liu et al., 2005; Oleson and Roberts, 2009; Quadros and Miczek, 2009). Additional evidence for a post-escalation enhancement in the motivation for cocaine was also recently 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 i.v. bolus of cocaine (Ben-Shahar et al., 2008). Finally, using a conditioned emotional suppression procedure, Vanderschuren and Everitt (2004) found that rats with a history of extended cocaine self-administration were more likely to continue to seek cocaine despite the presence of a danger signal that

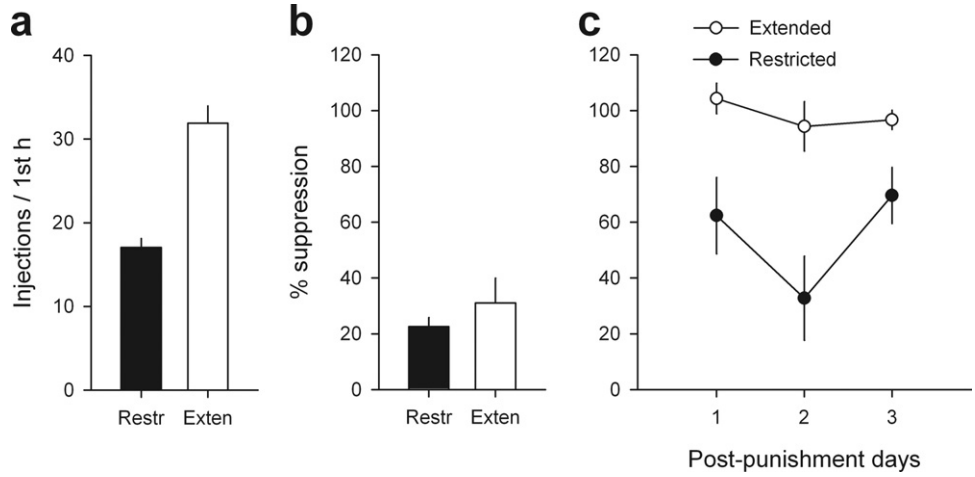

Fig. 3. Effects of extended drug access on punishment-induced suppression of cocaine self-administration. (a) Mean number of first-hour cocaine injections averaged over the last three baseline sessions of self-administration preceding the punishment day. (b) Unconditioned punishment-induced suppression of cocaine self-administration expressed as percent change from pre-punishment baseline. (c) Delayed effects of punishment on subsequent days expressed as percent change from pre-punishment baseline. Percent values below 100% indicate suppression of cocaine intake. For additional information, see (Ahmed, 2011). Reproduced from (Ahmed, 2011).

normally suppresses operant behavior. Similarly, we recently found that following punishment by footshock, rats with extended access to cocaine resumed drug self-administration more rapidly than controls, which refrained from self-administering cocaine during at least three consecutive days (Ahmed, 2011) (Fig. 3). Overall, following a history of extended access to cocaine self-administration, rats are more likely to accept a greater cost, either in terms of effort or negative consequences, to continue to seek and/or to obtain cocaine, suggesting an increased motivation for the drug.

Resistance to extinction of drug seeking

Difficulty of abstaining from drug seeking—another addiction-like feature—can be operationalized in laboratory animals by continued drug seeking even when the drug is no longer available (i.e. resistance to extinction) (Ahmed et al., 2000). The first evidence for resistance to extinction was obtained 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). The degree of resistance to extinction of heroin seeking increased with the length of withdrawal from extended heroin self-administration, suggesting an incubation effect (Zhou et al., 2009). Surprisingly enough, however, no resistance to extinction has so far been demonstrated following extended access to cocaine self-administration (Mantsch et al., 2004, 2008b; Sorge and Stewart, 2005; Kippin et al., 2006; Allen et al., 2007a; Knackstedt and Kalivas, 2007; Jin et al., 2010; Madayag et al., 2010) or methamphetamine self-administration (Rogers et al., 2008; Schwendt et al., 2009). This lack of evidence for resistance to extinction may be due to the short period of drug withdrawal preceding extinction of cocaine seeking (i.e. 24–72 h compared with several days with heroin), presumably preventing a possible incubation effect (Grimm et al., 2001). Consistent with this hypothesis, when the withdrawal interval from cocaine self-administration was longer (i.e. 3 weeks), rats with extended cocaine use responded more during extinction, than controls (Ferrario et al., 2005). Alternatively, it is also possible that the increase in cocaine seeking following prolonged abstinence from cocaine use reflects the dissipation of some early withdrawal effects that directly interfered with drug seeking (e.g. general suppression of behavior and/or decreased hedonic state). In summary, extended drug use is associated with an increased difficulty of abstinence from drug seeking. However, in the case of cocaine self-administration, the expression of this behavioral feature seems to require a relatively long incubation period. More research is clearly needed here to clarify the origin of these differences between cocaine and heroin.

Increased vulnerability to reinstatement of drug seeking

Though drug-induced craving is not a current diagnostic criterion of addiction, it nevertheless represents a rather selective feature of addiction as it is not present in nondependent cocaine users (Jaffe et al., 1989; Volkow et al., 2005). In fact, a craving criterion should be included in the next revision of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Substance-Use Disorders (Miller and Holden, 2010). Craving-like behavior can be modeled in laboratory animals by reinstatement of drug seeking after extinction (Epstein and Preston, 2003). Briefly, in this well-established model, responding for the drug is first extinguished by discontinuing drug delivery and then reinstated by exposure either to a priming dose of drug, a conditioned stimulus, or a stressor. Importantly, during reinstatement testing, responses continue to be unrewarded as during extinction and, therefore, reflect genuine drug-seeking behavior. Using this model, Mantsch et al. (2004) reported that a history of extended, but not limited, access to cocaine self-administration was

associated with an increase in cocaine-primed reinstatement of drug seeking. This finding was subsequently reproduced several times (Ahmed and Cador, 2006; Kippin et al., 2006; Knackstedt and Kalivas, 2007; Mantsch et al., 2008b) and extends to other drugs of abuse, including heroin (Lenoir and Ahmed, 2007) and methamphetamine (Rogers et al., 2008; Schwendt et al., 2009). Importantly, sensitivity to stress-primed reinstatement is also increased following a history of extended access to cocaine self-administration (Mantsch et al., 2008a), an effect that confirms previous research with heroin self-administration (Ahmed et al., 2000). However, whether reactivity to cue-primed reinstatement is also altered following a history of extended access to cocaine or other stimulant drugs is currently less clear. Some studies report no change in sensitivity to cue-primed reinstatement (Rogers et al., 2008; Doherty et al., 2009; Schwendt et al., 2009; Zhou et al., 2009), while others report a significantly increased sensitivity (Kippin et al., 2006; Jin et al., 2010).

Decreased neurocognitive functions

Long-term drug users addicted to cocaine present a variety of neurocognitive deficits, generally mild in severity, that can affect a range of higher-order functions, from attention to memory to complex decision-making (Bechara, 2005; Garavan and Stout, 2005; Paulus, 2007; Robbins et al., 2008; Chambers et al., 2009; Goldstein et al., 2009). For instance, people with cocaine addiction have some difficulty to inhibit prepotent motor responses (motor impulsivity) and to wait for future gratification (cognitive impulsivity). Whether and how such relatively mild deficits are a cause or consequence of drug addiction has not been fully elucidated at present (Setlow et al., 2009). Recent research has begun to document similar deficits in animals following extended cocaine use. Using a delayed non-matching to sample task in a T-maze, George and colleagues (2008) have observed a dramatic decrease in working memory in rats following extended cocaine self-administration. Importantly, in this study, controls with more restricted access to cocaine were cognitively indistinguishable from drug-naïve rats (George et al., 2008). Similarly, Briand and coworkers have shown that rats with extended cocaine use develop a selective deficit in object recognition memory that was again not present in controls (Briand et al., 2008c). This selective deficit has also been seen in rats following extended access to methamphetamine self-administration (Rogers et al., 2008). In addition, prolonged cocaine self-administration can also cause some transient alterations in visual attention in rats (Dalley et al., 2005). More surprisingly, however, extended access to cocaine has also been shown to reduce motor impulsivity in high-impulsive rats, a paradoxical effect that is currently poorly understood but that may represent the basis of some sort of cognitive self-medication (Dalley et al., 2007). To sum up, in addition to triggering escalation of cocaine use and other addiction-like behavioral changes, extended access to cocaine self-administration can also directly cause different cognitive deficits in animals (George et al., 2008). Though these deficits should in theory impact negatively the regulation of cocaine self-administration, this has not been directly demonstrated yet.

COMPULSION AND LOSS OF CONTROL OVER DRUG SELF-ADMINISTRATION

Overall, it is now clear that following extended, but not limited, access to cocaine self-administration, rats develop a number of behavioral changes that are reminiscent of some of the behavioral symptoms of cocaine addiction. They are more likely to escalate cocaine consumption; they work harder and take more risk to seek and to obtain the drug; and finally, they are more responsive to drug- and stress-primed reinstatement of drug seeking. All these changes indicate that the motivation to take cocaine is increased following a history of extended drug use. Systematically comparing and contrasting animals with a history of extended access to cocaine with control animals with more limited drug access should thus reveal important insights into the neurobiology underlying enhanced drug motivation (Ahmed et al., 2002, 2003, 2005; Orio et al., 2009; Ahmed and Kenny, in press). This research strategy has recently culminated in the breakthrough discovery of a new molecular pathway in the dorsal striatum that controls escalation of cocaine self-administration (Hollander et al., 2010; Im et al., 2010). Future research will be needed to spell out the detailed mechanisms through which extended cocaine self-administration causally increases the motivation to take cocaine.

However, whether and to what extent the behavioral changes associated with extended drug use also represent *bona fide* evidence for loss of control over cocaine self-administration—which is quintessential to the concept of addiction as a psychiatric disorder—remain uncertain at present. This incertitude is largely because in all studies that have explored the behavioral effects of extended drug use, rats had no choice than drug use (Ahmed, 2005). Arguably, without the possibility of alternative choice, it is difficult, not to say intractable, to determine whether rats take cocaine by compulsion (i.e. an uncontrollable impulse to take cocaine) or by default of other rewarding options (Ahmed, 2010). To begin to address this problem, we recently conducted a long series of experiments where rats could choose between cocaine self-administration and a nondrug alternative activity. If rats prefer to self-administer cocaine despite the opportunity of making a different choice, then one has ground to hypothesize a state of addiction that could then be confirmed by increasing the costs associated with drug preference.

A digression on methodology

The general design of the choice procedure used in rats is inspired from seminal research on monkeys and humans (Aigner and Balster, 1978; Nader and Woolverton, 1991; Negus, 2003; Haney, 2009). In the standard version of this procedure, rats face a daily choice between two rewarding behaviors or actions: pressing one lever to receive an i.v. dose of cocaine or pressing a second lever to have access

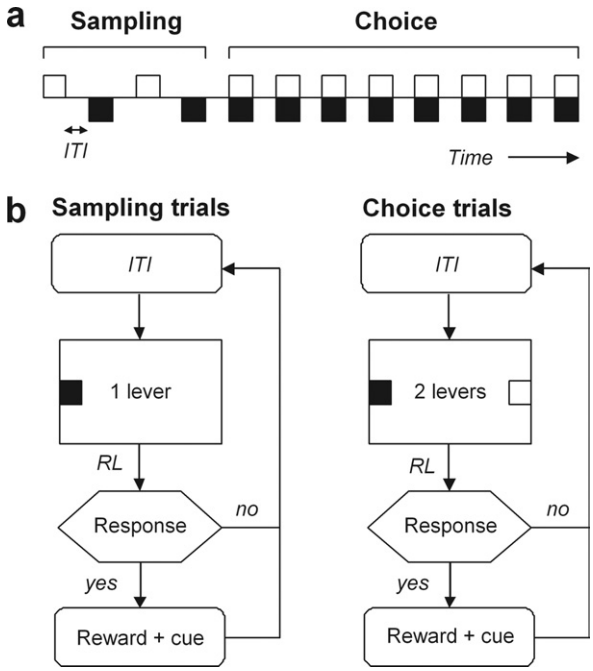

Fig. 4. Discrete-trials choice protocol. (a) Each testing session consists of two successive periods: sampling (four alternating cocaine or saccharin trials) and choice (eight or more trials). All trials are separated by a fixed inter-trial interval (ITI, generally 600 s). (b) Sampling trials (left panel) begin by the insertion of one single lever (alternatively cocaine- or saccharin-paired lever). If the animal completes the FR requirement before the time imparted (generally 300 s), the following events occurs simultaneously: the lever is automatically retracted, the cue light above it is turned on, and the corresponding reward is delivered. A new ITI is initiated when the reward-paired cue is turned off (generally after 20–40 s). If the rat does not respond within the imparted time, the trial ends unrewarded, and a new ITI is initiated. In general, response latencies (RL) are much shorter than 300 s. The sequence of events during choice trials (right panel) is identical to that during sampling trials, except that two levers are simultaneously presented before choice making or simultaneously retracted after choice making.

to a potent nondrug alternative (Ahmed, 2005; Lenoir et al., 2007). Though one can envision a variety of possible nondrug rewards in rats, we opted for a brief access to sweet water (i.e. sweetened with an optimal concentration of saccharin [0.2%]; Vendruscolo et al., 2010). Sweet-tasting water (or food) is a potent innate rewarding sensation in most mammals, including humans, that does not require any prior restriction or learning and is easy to control in the laboratory (compared with perhaps more relevant nondrug options, such as social reinforcers; Fritz et al., 2011). Each daily choice session is made up of a minimum of 12 discrete trials, spaced by a dose-dependent inter-trial interval (ITI) and divided into the following two successive phases: sampling and choice (Fig. 4a). During sampling (four trials), each lever is presented alone twice, alternatively with the other lever, and animals are free to respond on it to obtain the available reward (Fig. 4b). The sampling period allows animals to separately learn the respective value of each operant behavior or action (i.e. pressing the cocaine or saccharin lever) before making their choice. It also allows experimental checking of whether (and to what extent) each option is rewarding when presented alone and whether cocaine sampling interferes negatively with sweet consumption (see below). During choice (eight trials), the two levers are presented simultaneously, and rats are free to choose among them to obtain the corresponding reward (Fig. 4b). Each choice trial is mutually exclusive or either/or, meaning that choosing one reward excludes the other option until the next trial, compelling animals to express their preference at the cost of renouncing to the other option. It is hypothesized that this architecture of choice roughly corresponds to what people with addiction face when choosing between using drugs, particularly illegal ones, and engaging in other incompatible social activities (e.g. going to school, job occupation, family care). In addition, each type of reward is available in a closed economy, meaning that, except during choice sessions, rats have no other opportunity to access either type of reward (Hursh, 1980; Collier and Johnson, 1997). Thus, choosing one reward cannot be compensated later by subsequent access to the nonchosen reward.

Though sweet water presents several methodological advantages compared with other possible alternatives to cocaine, it has some specific limitations that need to be taken into account in the implementation of choice experiments and in the interpretation of the resulting data. The value attached to the action leading to consumption of sweet water can be affected by the pharmacological effects of cocaine in at least two different ways that are specific to food-related rewards and not necessarily generalizable to other types of nondrug reward (e.g. social rewards) and/or relevant to understand cocaine addiction in humans. First, cocaine, particularly at high doses, can induce behavioral effects (e.g. hyperactivity or focused motor stereotypies) that directly compete with drinking behavior and/or that acutely inhibit sweet appetite (Wolgin, 2000). Obviously, if these effects occur, they should eventually lead to a decrease in the value attached to the lever associated with sweet water, thereby biasing choice toward the cocaine lever and preventing accurate assessment of its relative value. To avoid this potential bias, the inter-trial interval must be equal or preferably longer than the duration of effects of the available dose of cocaine. This can be directly confirmed by demonstrating that cocaine sampling does not interfere with saccharin sampling (i.e. latency to respond for and consumption of sweet water). Second, rats can also learn to avoid ingestion of sweet water if it is followed by cocaine intoxication (Riley, 2011). Following this conditioned taste avoidance (CTA), consumption of sweet water does no longer increase dopamine levels in the nucleus accumbens but instead decreases it. This outcome shows that sweet water has acquired aversive properties (Wheeler et al., 2011). Though there is no evidence that cocaine-induced CTA occurs in our standard choice procedure, it could manifest in some other choice settings involving sweet-tasting water and, if so, bias choice toward cocaine. For instance, in one unpublished study, we found that prior acquisition of cocaine CTA shifted preference to cocaine (Dubreucq

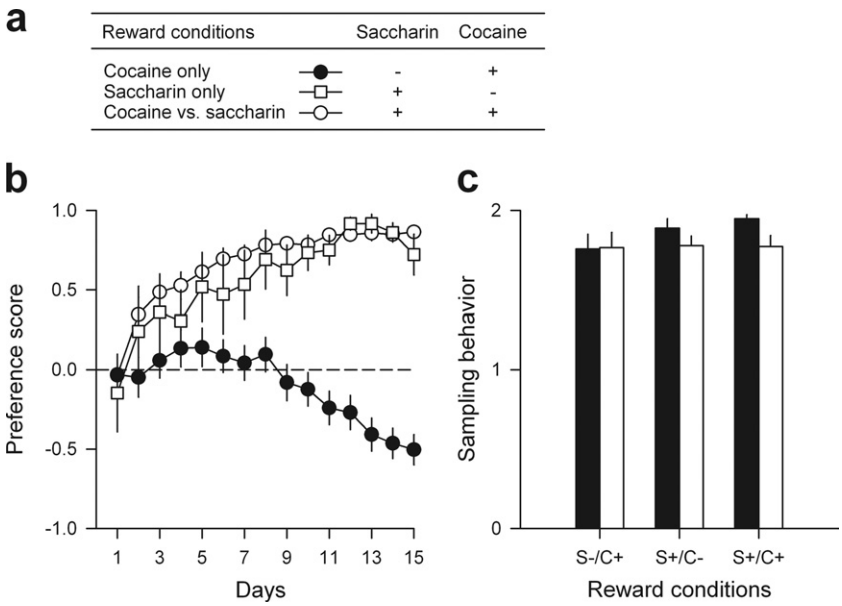

Fig. 5. Choice between saccharin and cocaine. (a) Table showing the three reward conditions tested during choice. Under the S−/C+ condition (n=30), only responding on the cocaine lever (C) was rewarded (+) by cocaine delivery; responding on the other lever was not rewarded (−). Under the S+/C−condition (n=9), only responding on the saccharin lever (S) was rewarded by saccharin access; responding on lever C was not rewarded. Finally, under the S+/C+ condition (n=43), both levers were rewarded by their corresponding rewards. (b) Choice between levers C and S (mean±SEM) across reward conditions and as a function of time (open circle: S−/C+ condition; closed triangle: S+/C−condition; closed circle: S+/C+ condition). The horizontal gray line at 0 indicates the indifference level. Values above 0 indicate a preference for lever S, while values below 0 indicate a preference for lever C. (c) Sampling (mean±SEM of the last 3 d) of lever S (black bars) and lever C (white bars) across reward conditions. Adapted from (Lenoir et al., 2007).

et al., unpublished observations). Thus, cautions should be exercised when designing choice experiments to prevent the development of CTA and/or to reduce the unconditioned aversive effects of cocaine (e.g. by preexposing rats to cocaine self-administration before choice testing) (Riley, 2011). Finally, it is important to note that the two biases discussed above are likely to be specific to food-like nondrug options and should not be generalized *a priori* to other options that are more difficult to test in an operant choice setting (e.g. social interactions, sex). In addition, it is unlikely and there is currently no evidence that these biases play a major role in the progression toward excessive cocaine choices in humans. Thus, ruling out their possible intervention in choice experiments involving food-like reinforcers in animals should therefore further increase, rather than decrease, comparability to humans.

Alternative choice promotes abstinence from cocaine self-administration

Drug choice was first studied in naïve animals with no prior experience with either cocaine or sweet water (Lenoir et al., 2007). Rats were tested under three distinct reward conditions (Fig. 5a). The first two conditions were control conditions that verified the reinforcing effectiveness of each option. In those control conditions, only responding on one lever was rewarded by the corresponding reward (cocaine or saccharin); responding on the other lever remained unrewarded. In the third experimental condition, responding on one lever was rewarded by cocaine, and responding on the alternate lever was rewarded by saccharin. As expected, when only one reward was available, rats preferred the rewarded lever and ignored the nonrewarded lever (Fig. 5b). This result demonstrates that each behavioral option effectively and selectively reinforced and maintained responding. In the case of cocaine, this result confirms previous research showing that rats do self-administer cocaine when no other choice is available. Surprisingly, however, cocaine preference (i.e. number of days to reach a stable preference) emerged more slowly than sweet preference, suggesting that cocaine is less reinforcing than saccharin (Fig. 5b). This interpretation is supported by the outcome of the experimental condition. When responding on either lever was rewarded, rats preferred sweet water and almost completely ignored cocaine (Fig. 5b). This finding is generally consistent with previous research in rats showing that an alternative behavior can reduce operant responding for cocaine during acquisition, maintenance, extinction, and reinstatement (Carroll et al., 1989; Carroll and Lac, 1993; Liu and Grigson, 2005; Quick et al., 2011). Finally, after stabilization of preference, the latency to choose cocaine was greater than the latency to choose sweet water. Since response latencies are generally inversely related to the magnitude of the forthcoming reward, this result provides additional, independent confirmation that cocaine is less reinforcing than sweet water in rats. Since rats choose to refrain from cocaine for another pursuit and not because they are forced to do so, we consider thereafter this choice as a form of voluntary abstinence.

Interestingly, sweet preference was acquired and persisted despite near maximal sampling of cocaine reward (i.e. about two drug sampling before choice trials) (Fig. 5c). Though low, cocaine sampling is nevertheless sufficient to learn the value of the cocaine lever before making their choice as rats develop a preference of this lever when they have no other choice (see control reward conditions above). Moreover, it is sufficient to induce a robust sensitization to the stimulant effects of cocaine that is indistinguishable from that seen in control rats that only had access to cocaine during choice and that eventually chose almost exclusively the cocaine lever (Lenoir et al., 2007). Cocaine sensitization is a well-documented behavioral change associated with persistent alterations in brain dopamine and glutamate synapses (Vanderschuren and Kalivas, 2000; Hyman et al., 2006), and it is generally associated with an increased incentive or motivational value of the drug, as measured using different methods (Robinson and Berridge, 2008). However, though sensitization undeniably occurred in rats that had the choice between cocaine and sweet water, it was not sufficient to override sweet preference in favor of cocaine preference (Lenoir et al., 2007).

The above findings strongly suggest that cocaine is less attractive and reinforcing than sweet water even for cocaine-sensitized rats. In addition, they indicate that rats retain the ability to abstain from cocaine self-administration when offered a different choice. However, before reaching these startling conclusions, one must rule out some potential alternative explanations. First, it could be argued that the dose of cocaine, though behaviorally effective, was nevertheless too low to compete with the reward value of the alternative option. To address this issue, after stabilization of sweet preference, rats were tested with increasing doses of cocaine. Cocaine doses were increased from 0.25 up to the subconvulsive dose of 1.5 mg per infusion (or about 3.3 mg/kg). Surprisingly, though the stimulant effects of cocaine increased with the dose, rats nevertheless continued to prefer sweet water (Lenoir et al., 2007). This lack of dose-dependent effect on cocaine choice shows that for most cocaine self-administering rats, the value of cocaine is bounded with a maximum lower than the value of the available option. In support of this interpretation, we recently found that cocaine choice increases when the magnitude of the nondrug option (i.e. concentration of sweet water) is decreased or when its relative cost is increased (Cantin et al., 2010). However, for most rats, it takes a large decrease in magnitude or a large increase in cost to shift preference to cocaine.

Cocaine abstinence could also be explained by some sort of behavioral inertia unrelated to the difference in value between the two rewards. Specifically, since rats quickly learned to prefer sweet water almost exclusively, this subsequently limited their experience with cocaine (except during drug sampling) and thus their opportunity to shift preference to the drug. To address this issue, rats were first trained in the choice procedure with cocaine as the only available reward. Once they developed a stable preference for the cocaine-rewarded lever, they were then allowed to choose between cocaine and sweet water. Rats rapidly shifted their preference from cocaine to sweetened water, suggesting that behavioral inertia is unlikely a significant factor in the maintenance of sweet preference (Lenoir et al., 2007). To further address this issue, rats were tested in a modified choice procedure where the sampling period preceding choice trials was replaced by a 1-h period of exclusive access to cocaine self-administration. If behavioral inertia played a significant role in choice behavior, then one should expect that rats will continue—at least transiently—to respond on the cocaine lever during choice. Contrary to this prediction, however, rats that responded on the cocaine lever (on average 15 injections per hour) during the first hour almost immediately shifted to the saccharin lever during choice (Lenoir et al., 2007). This rapid, within-session reorientation of behavior clearly demonstrates that the persistence of sweet preference is not attributable to behavioral inertia. This experiment also demonstrates that the same rats that self-administer cocaine when there is no other choice can readily abstain from it when another pursuit is available.

Cocaine abstinence could also be explained by some unique ambivalent or conflictual effects of cocaine. Several lines of evidence indicate that in addition to its well-established rewarding action, cocaine can also have significant anxiogenic effects in rats (e.g. Ettenberg and Geist, 1991). Thus, it is possible that rats choose to refrain from cocaine for sweet water to avoid its anxiogenic effects. However, the anxiogenic effects are typically seen in initially cocaine-naïve rats but are no longer present following a history of cocaine self-administration, presumably because of tolerance development (Ben-Shahar et al., 2008). Thus, though cocaine initially has some anxiogenic effects in drug-naïve rats, these effects are unlikely to significantly influence cocaine choice in drug-experienced animals. In support of this interpretation, we recently found that diazepam—a broad spectrum anxiolytic—did not increase cocaine choice, as one would expect if rats avoided the anxiogenic effects of cocaine, but instead decreased it, thereby further increasing sweet preference (Augier et al., in press). This increase in sweet preference is not surprising since diazepam as well as other benzodiazepine anxiolytics are known to potentiate sweet palatability in rats (Berridge and Treit, 1986; Treit et al., 1987; Treit and Berridge, 1990; Berridge and Peciña, 1995; Peciña and Berridge, 1996) through a mechanism that involves brain mu-opioid receptor signaling (Richardson et al., 2005). Incidentally, these pharmacological findings further confirm that rats' choice is mainly driven by the palatability of sweet water.

Finally, one could also argue that rats do not choose to take cocaine because during choice they are not free to regulate the rate of cocaine intake (which is limited by a fixed inter-trial interval) and thus to achieve their preferred level of drug intoxication (Ahmed and Koob, 2005). To directly test this hypothesis, we developed a variant of the choice procedure allowing rats to regulate the moment and rate of choice trials (Augier et al., unpublished observations). Briefly, rats were trained to nose-poke a hole located at equal distance between the cocaine and saccha-

rin levers to trigger their presentation and thus the onset of choice trials. Rats could then respond on either lever to obtain the corresponding reward as described in the discrete-choice procedure. Under this operant chain schedule, rats were entirely free to choose to self-administer cocaine on their own self-paced rate; yet, they continued to choose almost exclusively sweet water, thereby confirming and extending to a different choice setting the above findings. Intriguingly, inspection of the within-session pattern of sweet choices revealed another striking phenomenon. After having selected sweet water continuously early during the session, rats typically marked long pauses (>5 min) before resuming sweet consumption. During these relatively long satiety pauses, they could have chosen to take cocaine but they refrained from doing so. Note that when sweet water was not available, the same rats self-administered cocaine under the same operant chain schedule at an average rate of about 10 infusions per hour. This outcome clearly demonstrates that cocaine self-administering rats have the ability to refrain from cocaine self-administration when the drug is available and when they are not currently interested and/or engaged in a different competing rewarding behavior.

Resilience to cocaine addiction in rats

All the evidence for sweet preference described above was found in either initially cocaine-naïve rats or in rats with a relatively limited exposure to cocaine self-administration. As explained in "Recapitulation of the behavioral features of addiction in animals," however, there is now substantial behavioral evidence showing that the reinforcing and incentive value of cocaine increases following extended access to cocaine self-administration. Thus, one key remaining issue is whether and to what extent this increase in cocaine value can suffice to override initial saccharin preference and shift preference toward cocaine use. To answer this question, rats were initially allowed to have daily extended access to cocaine self-administration during several weeks, as described above in "Recapitulation of the behavioral features of addiction in animals," before choice testing. As expected, following extended access to cocaine self-administration, most rats escalated their consumption of cocaine. Surprisingly, however, when facing a choice between cocaine and saccharin, most rats rapidly exhibited a strong preference for the saccharin lever regardless of the cocaine dose available (i.e. 0.25–1.5 mg per injection) (Lenoir et al., 2007). Sweet preference was obvious as soon as the second day of choice testing, a rate of preference acquisition not different from that seen in initially naïve rats. Thus, the increase in drug value known to occur following extended exposure to cocaine self-administration was apparently not sufficient to override initial sweet preference, further indicating that the maximal value of cocaine is bounded below the value of sweet water. Using a different approach based on demand curve analysis, Christensen and colleagues have also reached the same conclusion (Christensen et al., 2008b).

Vulnerability to cocaine addiction in rats

In all the experiments summarized above, though the large majority of rats refrained from cocaine self-administration when offered a different choice, few individuals nevertheless continued to take cocaine despite the opportunity of making a different choice. Out of a total of 184 rats tested in the discrete-trials choice procedure over the past 5 years, only 16 individuals (i.e. 8.7%) preferred cocaine (i.e. cocaine choices >50% of completed trials) (Fig. 6a). Preference for cocaine was not attributable to a mere disinterest in or aversion to saccharin-sweetened water since during sampling trials; cocaine-preferring rats drank sweet water as much as the majority of other rats (Cantin et al., 2010). To assess the effects of cocaine exposure on the frequency of cocaine-preferring individuals, the total amount of self-administered cocaine before choice testing was calculated for each individual. Cocaine consumption ranged from 0 to 486 mg and defined five levels of severity (Cantin et al., 2010), with the most severe levels corresponding to those shown previously to induce several unique neuroplastic changes in relevant brain regions (Ahmed et al., 2002, 2003, 2005; Ferrario et al., 2005; Edwards et al., 2007; Madayag et al., 2007; Briand et al., 2008a,b; George et al., 2008; Ben-Shahar et al., 2009; Orio et al., 2009; Hollander et al., 2010; Wakabayashi et al., 2010). Surprisingly, however, the rate of cocaine-preferring individuals remained stable between 10 and 20% (Fig. 6b). Thus, no matter how intense was the level of past cocaine self-administration, cocaine preference remains a rare and exceptional phenotype in rats. Importantly, cocaine-preferring rats continued to prefer cocaine, even when hungry and offered a natural sugar (i.e. sucrose) that could relieve their need of calories. Persistence of cocaine use and preference despite choice and increasing stakes or opportunity costs strongly suggests compulsive cocaine use (i.e. continued drug use at the expense of other im-

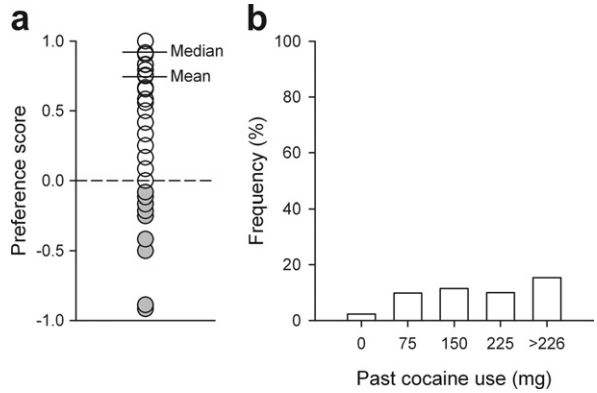

Fig. 6. Effects of severity of past cocaine use on cocaine choice. (a) Distribution of individual preferences regardless of past cocaine use. Only 16 individuals out of a total of 184 rats tested in the choice procedure preferred cocaine over water sweetened with saccharin (closed circles). (b) Histograms represent the frequency of cocaine-preferring individuals (i.e. cocaine choices >50% of completed trials over the last three stable testing sessions) as a function of past cocaine use (i.e. amount of self-administered cocaine prior to choice testing). Adapted from (Cantin et al., 2010).

portant activities or occupations) and is generally consistent with human laboratory research on cocaine-dependent users who clearly prefer cocaine over money when offered a choice (Haney, 2009; Walsh et al., 2010).

CONCLUSIONS AND PERSPECTIVES

Previous research has amply demonstrated that when no other choice is available, most rats learn to self-administer cocaine or other available drugs of abuse. More recent evidence has shown that with extended access to cocaine self-administration, most rats also develop an array of changes in drug self-administration demonstrating that they are increasingly motivated to take and to seek cocaine. The study of the cellular and molecular correlates of these behavioral changes in relevant brain circuits promises to provide unique insights on the neurobiology of increased cocaine intake and motivation. For instance, a recent series of breakthrough experiments revealed the existence of a new molecular pathway in the dorsal striatum that causally and selectively controls escalation of cocaine intake in rats. This pathway involves homeostatic interactions between microRNAs—a class of nonprotein coding RNAs—and some key molecular regulators of neuronal plasticity (e.g. methyl CpG binding protein 2 and brain-derived neurotrophic factor) (Hollander et al., 2010; Im et al., 2010). There is thus now some reasonable hope that the neurobiological code of cocaine intake escalation may soon be cracked or, at least, this long-standing goal seems now to be within reach (Welberg, 2010; Ahmed and Kenny, in press).

Relatively surprisingly, however, efforts to induce, through extended drug exposure, loss of control over cocaine consumption in rats (i.e. continued cocaine preference despite the possibility to make a different choice and despite severe opportunity costs) have so far failed, at least in the large majority of rats (Ahmed, 2010). Even following a long history of extended access to cocaine self-administration and evidence for increased drug motivation, most rats (i.e. roughly 90%) do not apparently loose control over drug self-administration as they retain the ability to choose to abstain from cocaine for another nondrug pursuit when it is available. Importantly, abstinence in humans also generally involves the act of refraining from drug use to engage in other nondrug activities. Thus, contrary to what was previously believed (including by this author), not many can be turned into compulsive-like users with extended drug use. Only few individual rats continue to take cocaine despite the possibility to choose otherwise and despite severe opportunity costs. These few individuals are all the more remarkable because their behavior clearly deviates from the norm, and their low frequency apparently remains unchanged regardless of the cocaine exposure (Cantin et al., 2010). Everything happens as if most cocaine self-administering rats would be resilient or resistant to addiction, taking cocaine only by default of other valuable options, while only a minority of individuals would be predisposed to addiction. This conclusion is generally consistent with recent research that used a DSM-based multicriteria approach for identifying compulsive drug users in rats (Deroche-Gamonet et al., 2004; Belin et al., 2008). The opportunity to choose otherwise during access to cocaine self-administration therefore represents a reliable and valid mean to screen compulsive cocaine users among resilient rats.

Extrapolation of data obtained in laboratory animals to real-world humans is always delicate and possibly misleading. Yet, one cannot refrain from noting that the distribution of cocaine preference seen in rats fits the epidemiological pattern of individual variation in cocaine addiction. Most people who regularly use cocaine do not go on to develop addiction. Only a minority of cocaine users eventually become addicted (Anthony, 2002). A long-standing question in addiction research, with critical consequences for prevention and policy, is how to interpret this individual variation, particularly the absolute high rate of nonaddictive cocaine use. Do environmental circumstances (e.g. economic constraints, societal regulations, cultural norms) prevent people from exposing themselves sufficiently to cocaine to cross the “threshold of addiction” (Benowitz and Henningfield, 1994)? Or, alternatively, are most cocaine users somehow biologically resilient to addiction (e.g. genetically resistant to addiction regardless of drug exposure)? Epidemiology of cocaine addiction alone has been so far unable to univocally resolve this apparent dilemma (Anthony, 2011). This limitation is largely because people have no equal access and exposure to cocaine (see also below). This lack of firm evidence probably explains why the prevailing default view in drug prevention and policy has always been to consider each one of us as a potential addict. Given sufficient drug exposure, each one of us could be turned into a cocaine addict. A biological resilience against cocaine addiction would not exist, or such resilience would exist only in rare individuals. The findings showing that most rats—a mammalian species that diverged from the lineage leading to humans about 60 millions years ago—are resilient to cocaine addiction may provide some scientific ground to begin to reconsider the addiction resilience issue in humans. Interestingly, such a conclusion is entirely consistent with current theorizing about the evolutionary origin of psychoactive drug use in humans (Pollan, 2001; Sullivan and Hagen, 2002; Ahmed, in press; Müller and Schumann, in press).

One of the relative strengths of animal models regarding the issue of addiction resilience is that they allow one to approach the ideal situation where each randomly selected individual has equal access and exposure to cocaine. In this ideal situation, it is possible to determine what proportion of animals develops cocaine addiction-like behavior, and what proportion is resilient. In contrast, people in the real world have no equal access and exposure to cocaine. The pool of humans who have access to cocaine and who eventually experiment with it is not drawn at random from the general population. The drug exposure and experimentation process is influenced by a variety of individual and environmental factors that can themselves vary as a function of time and place (Anthony et al., 1994; Anthony, 2002; Swendsen and Le Moal, 2011). As aptly reminded

by O'Brien, it takes an agent (the drug), a host, and the environment to yield a case of drug addiction (O'Brien, 2008). As a result, current estimates of the proportion of human cocaine users who become addicted to cocaine nowadays in a given country should not necessarily be conceived as universal to humans, as suggested here. A thought experiment may help to better convey this important point. One could hypothesize that the proportion becoming addicted to cocaine estimated nowadays in the United States (where the best estimated rates of cocaine addiction are produced), when there is a relative trough in the rate of cocaine users, must exceed estimates obtained near the peak of the cocaine epidemic years during the late 1970s and early 1980s. Indeed, during these trough years, there should be an overrepresentation of vulnerable, young people among newly occurring drug users, whereas during the peak years of an epidemic interval, the association with vulnerable youth would be much weaker (Robins, 1998; Anthony, 2002). Similarly, the proportion currently becoming addicted to cocaine in the United States should not necessarily be generalized to other countries, say France. If cautions should be exercised when generalizing epidemiological estimations across time and place in humans, then even more cautions should be exercised when extrapolating data from animals to humans. Notwithstanding this important reservation, it remains that available evidence suggests that like humans, the majority of rats are likely resilient to cocaine addiction. Only a minority of rats would be vulnerable to cocaine addiction.

At first glance, however, the observed distribution of individual drug preferences in rats seems to contradict what is known from laboratory choice experiments involving human and nonhuman primates (Aigner and Balster, 1978; Woolverton and Balster, 1979; Nader and Woolverton, 1991; Paronis et al., 2002; Negus, 2003; Banks and Negus, 2009; Haney, 2009; Walsh et al., 2010). Those experiments have established beyond doubt that the availability of alternative reinforcers can reduce cocaine choices, particularly at low doses; yet at sufficiently high doses, virtually all subjects choose cocaine almost exclusively. This apparent discrepancy could point to an unsuspected species-specific difference between rodents and primates (Lenoir et al., 2007). There are however other possible explanations. First, for obvious ethical reasons, most human laboratory studies involve preselected samples of people with a pre-existing diagnosis of cocaine abuse or addiction. These samples are not representative of the whole spectrum of human drug users, including the majority of those who use the drug in a controlled manner. This selection bias explains why human choice studies overwhelmingly report evidence for drug preference. There is thus no contradiction between the human and rat data. In both species, drug-preferring individuals represent only a relatively small nonrepresentative fraction of the population of drug users. Interestingly, this interpretation is supported by an early human laboratory study on the subjective effects of heroin. Among 20 initially drug-naïve, healthy human volunteers, only four wished to repeat the heroin experience. The remaining majority was not willing to repeat the experience or was indifferent. In contrast, the proportion who wanted to repeat the experience was much higher in heroin-addicted individuals (Lasagna et al., 1955). Second, the distribution of individual drug preferences in rats is more difficult to reconcile with the distribution generally seen in nonhuman primates allowed to choose between cocaine and food. However, primate choice experiments are generally designed to favor cocaine preference to study its pharmacological basis. In most studies, the alternative reinforcer generally has a low value, consisting of a small pellet of dry food (1 g) with no or little palatable value, and is generally also available between choice sessions (i.e. available in an open economy). It is thus possible that monkeys' preference for high doses of cocaine reflect the low value of the alternative reinforcer more than the high value of the drug. In support of this interpretation, when the value of food is increased (i.e. by increasing the number of food pellets), most monkeys (three out of four) prefer food over the maximal dose of cocaine, an outcome that fits the distribution of drug preference seen in rats (Nader and Woolverton, 1991). This outcome is also consistent with research in hungry rats showing that cocaine has less value than food (Christensen et al., 2008a). Other procedural factors could also have contributed to cocaine preference in primate choice studies, including a lower cost of cocaine compared with that of food, drug priming before choice trials and/or presence of drug direct effects during choice making due to short inter-trial intervals. More research is clearly needed to determine the origin of the apparent discrepancy between rodents and primates in the distribution of individual cocaine preferences at high cocaine doses.

From a methodological standpoint, the choice-based approach advocated here may be useful to screen out compulsive drug users among animals that take the drug for other causes (e.g. by default of other options). One can envision a wide array of future possible applications for future research on the neuroscience of addiction, only a few are enumerated below. First, by characterizing animals before selecting them through the choice-based method of selection, one should be able to discover behavioral and biological predispositions that predict vulnerability to compulsive drug use. This predictive approach may help to resolve current controversy concerning the causal role of some psychological traits (e.g. different forms of impulsivity) in cocaine addiction (Dalley et al., 2007; Belin et al., 2008; Hogarth, 2011). Second, by comparing and contrasting cocaine-preferring animals with other drug self-administering animals, one should be able to define the neurobiological correlates of compulsive drug use at different levels of neural organization, from the circuit level down to the intracellular molecular level in specific neuronal populations. By combining this comparative neurobiological approach with the predictive approach outlined above, one should also be able to determine whether and to what extent the neurobiological correlates of compulsive drug use pre-exist to drug use and/or result from the interaction of a vulnerable substrate with drug use. After identification of the neurobiological corre-

lates of compulsive drug use, one can then test causality by checking whether their reversal by specific neurobiological interventions can reverse drug preference in favor of the alternative option. Third, the proposed choice-based method of selection of compulsive drug users in animals could also be applied to promote pharmacological treatment development. Specifically, by screening medications for their unique ability to shift drug preference in compulsive drug users, one should increase the chance to discover novel effective pharmacological treatments for drug addiction (Koob et al., 2009; Potenza et al., 2011). Fourth, this method of selection could also be applied to objectively assess and rank the addictive potential across different drugs of abuse. For instance, by measuring the frequency of compulsive drug users as a function of the type of drugs, one should be able to generate an objective hierarchy of addictive drugs (i.e. the higher the frequency, the more addictive would be the corresponding drug). Using this approach, we recently obtained evidence suggesting that heroin is more addictive than cocaine in rats (Magalie Lenoir et al., unpublished observations), a finding that corroborates epidemiological data in humans (Anthony, 2002). Fifth, the proposed choice-based method of selection could also be used to test the causal contribution of different possible factors (genetic, developmental/epigenetic, and environmental) to the etiology of compulsive drug use. For instance, if one factor increases the proportion of animals that prefer the drug, then it is likely that it is causally involved in the etiology of compulsive drug use. One could also envision using this approach to generate through selective breeding a strain of rat (or mice) that takes the drug compulsively. Note, however, that the strain of rats used in the choice experiments described in "Compulsion and loss of control over drug self-administration" (i.e. Wistar strain) is known to be highly sensitive to cocaine self-administration (Ahmed, 2010). Finally and more generally, the choice protocol is sufficiently versatile at the parametric level for a broad application to other scientific questions or domains. For instance, the choice procedure can be profitably applied to study more generally how the brain uses a common valuation scale to represent and compare the values of actions associated with "incommensurable" outcomes before making "its" choice (i.e. that not only differ quantitatively, but also qualitatively). Interestingly, though progress was made recently on this important issue (Chib et al., 2009; FitzGerald et al., 2009; Hare et al., 2009; Lebreton et al., 2009), little is known about how the brain "chooses" between a drug of abuse and a nondrug reinforcer as a function of the addiction state of the individual.

Strictly speaking, there is currently no other comparable methods for the objective identification and selection of compulsive drug users in drug self-administering rats. The only possible exception is perhaps the multicriteria method of identification of cocaine addiction-like behavior recently developed in rats (Deroche-Gamonet et al., 2004; Belin et al., 2008). This method takes its inspiration directly from the DSM-IV-based diagnosis of cocaine addiction. Briefly, animals that present extreme scores (i.e. above the 66th percentile) on three cocaine self-administration–related behaviors are considered compulsive-like drug users. Though innovative and interesting, this frequency-dependent method of identification of addiction-like behavior is limited by its circularity. It limits *a priori* and arbitrarily the maximum frequency of rats with an addiction-like behavior to 33%. As a result, the application of this method should always return the same pre-defined narrow range of frequencies of compulsive drug users, which should considerably limit its domain of application (as defined above). In addition, the constructive validity of each behavioral criterion has not been established separately and can be challenged on empirical and theoretical grounds. For instance, regarding the resistance-to-punishment criterion (i.e. continued drug use despite footshock punishment), little empirical research has determined whether it reflects *bona fide* compulsive drug use. For instance, resistance to punishment could merely result from an increased motivation for the drug (i.e. resistant rats may choose cocaine despite punishment because the benefit of cocaine is worth its cost) and/or a reduced sensitivity to footshock-induced pain (i.e. resistant rats may be less sensitive to the painful effects of footshock). Similarly, individual differences in PR responding could reflect not only individual variation in drug motivation but also variation in sensitivity to the drug direct stimulant effects on operant performance. The latter effect was recently shown to influence PR performance with a degree that was unsuspected in rats (Cantin et al., 2010). All these limitations do not apply to the choice-based method of selection. First, this method does not define in advance the frequency of drug-preferring animals. In theory, this frequency could range between 0 and 100%. Second, continued drug use to the detriment of other rewarding behaviors and despite great opportunity costs unambiguously recapitulates the core feature of compulsive drug use. Third, the choice procedure is relatively easy to implement and is not time-consuming. Once trained for drug self-administration, it takes less than 10 daily sessions to obtain a stable preference. These latter methodological features make the choice-based method of selection of compulsive drug users in animals particularly well-suited for future high-throughput research on the neuroscience of drug addiction.

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