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Review

Imbalance between drug and non-drug reward availability: A major risk factor for addiction

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Abstract

Laboratory animals self-administer most, though not all, drugs of abuse. Recent evidence shows that with increased drug availability, most laboratory rats develop all the major behavioral signs of addiction, including: 1) drug intake escalation, 2) increased motivation for the drug, 3) difficulty to abstain, 4) decreased reward function, and 5) inflexible drug use. The large prevalence of addicted rats may suggest that they are particularly vulnerable to develop compulsive drug use. I review evidence showing that this apparent vulnerability results in large part from the lack of positive (i.e., alternative non-drug rewards) and negative (i.e., costs) incentives capable of turning animals away from the pursuit of drugs. In particular, most animals seem to take drugs and eventually become addicted, not because drugs are intrinsically addictive, but more likely because drugs are the only significant sources of reward available in the laboratory. Laboratory animals would therefore represent more of a model of high-risk human groups than of the general population. Consequently, they should be more suited for searching factors that protect from, rather than predispose to, drug addiction. Reconsidering the environmental background of drug self-administration experiments in laboratory animals raises intriguing implications for understanding the initial demand for drug consumption and the transition to drug addiction, and for extrapolation from laboratory animals to humans.

Keywords: Addiction; Dependence; Behavioral economics; Choice; Dopamine; Lateral hypothalamus; Cocaine; Heroin; Prefrontal cortex

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1. Drug addiction as compulsive drug use

1.1. Definition and behavioral criteria

Definitions of drug addiction have considerably evolved over the past 40 years, as illustrated by the multiple revisions of the Diagnostic and Statistical Manual (DSM) for Mental Disorders of the American Psychiatric Association (for interesting discussion, see Grant, 1989; Heather, 1998; Jaffe, 1992). Our views of drug addiction will probably continue to change with further clinical and experimental advances (Helmuth, 2003). Today, drug addiction or dependence (both terms are used interchangeably in the text) is consensually defined – at least within the biomedical community – as compulsive drug use, as opposed to controlled drug use, such as, for instance, episodic smoking in tobacco chippers (Shiffman, 1989; for other medical and non-medical cases of controlled drug use, see Chapman and Hill, 1989; Sloan and Melzack, 1999; Zinberg, 1984). Several behavioral criteria have been defined to distinguish compulsive from controlled drug use (DSM-IV, American Psychiatric Association, 1994; ICD-10, World Health Organization, 1992) (Table 1). The most important diagnostic criteria – at least from a preclinical perspective – include: 1) drug tolerance and/or escalation of drug dosage to maintain the desired effects; 2) drug withdrawal whose physiological and behavioral characteristics vary with the drug; 3) persistent (or overwhelming) desire to take the drug; 4) neglect of alternative rewards; 5) difficulty to abstain or to curtail drug use, despite the firm resolution to quit; 6) finally, and perhaps the most perplexing aspect of drug addiction from a rational choice perspective, indifference to the negative consequences of drug use.

1.2. Experimental modeling of drug addiction in animals

A critical goal of the neuroscience of drug addiction is to explain the neurobiological mechanisms underlying the transition from controlled to compulsive drug use, with the hope to discover more effective and durable treatments (Koob et al., 1998). Despite tremendous advances in behavioral, cellular and molecular neurobiology of drug reinforcement and drug-induced neuroplasticity, the pathophysiology of compulsive drug use is still poorly understood (Berke and Hyman, 2000; Kalivas et al., 2005; Koob et al., 1998; Nestler, 2001; Robbins and Everitt, 1999; Wise, 2000). This paradoxical situation may have resulted in large part from the lack of valid animal models of the differences between controlled and compulsive drug use that permit invasive neurobiological interventions not feasible in humans. Until rather recently, most, though not all, preclinical researchers have tended to conflate these different patterns of drug use. Mere drug use by laboratory animals was and still is widely considered as analogous to drug addiction in humans (Tecott and Nestler, 2004). As initially argued by Jochen Wolffgramm, however, mere drug use is not sufficient evidence for addiction (Ahmed and Koob, 1998; Wolffgramm, 1991; Wolffgramm and Heyne, 1995). Animal drug users must satisfy to other behavioral criteria before being considered as genuinely dependent on a drug, such as, for instance, drug intake escalation and relapse after abstinence (Ahmed and Koob, 1998).

Table 1
Behavioral distinction between controlled and compulsive drug use in humans (left column) and laboratory animals (right column)

Controlled vs. compulsive drug users	ShA vs. LgA rats
Tolerance, escalation	Tolerance, escalation
Persistent desire	Increased motivation
Difficulty to abstain	Resistance to extinction
Neglect of alternative rewards	Decreased reward function, decreased demand elasticity
Indifference to negative effects	Increased risk-taking, behavioral inflexibility

In addition, in most previous studies, drug self-administration has been studied in animals with restricted access to drug self-administration, probably to prevent drug toxicity associated with more prolonged access to the drug (see below). Restrictions of drug accessibility do not, however, promote escalating patterns of drug use characteristic of addiction, but instead favor highly stable and regular patterns of drug consumption (Koob et al., 1987; Pickens et al., 1978; Yokel, 1987). Most neurobiological findings related to drug addiction have been gathered from animals with restricted access to the drug, a fact that should considerably limit their relevance to the pathophysiology of drug addiction. Thus, developing and validating an animal model of the differences between controlled and compulsive drug use seem indispensable to establish the foundations of a "science of drug abuse", and not merely of drugs of abuse (Bloom, 1997).

Based on previous research on unlimited access to drug self-administration in both animals and humans, we and others have developed and begun to validate an animal model of the transition from drug use to drug addiction (Ahmed and Koob, 1998; Liu et al., 2005; Mantsch et al., 2001; Paterson and Markou, 2003; Roth and Carroll, 2004; Vanderschuren and Everitt, 2004). Increasing drug access time precipitates a rapid escalation of drug self-administration as opposed to the stable pattern of drug self-administration classically seen in animals with restricted access to the drug (Ahmed and Koob, 1998). Additional investigations showed that most individuals with prolonged drug exposure develop all the major behavioral signs of addiction. The relatively high prevalence of addicted animals probably results from the lack of alternative, non-drug rewards

during prolonged access to the drug. We began to study the neurobiological differences between individuals with escalating drug use and those with stable drug use to discover cellular and molecular markers specific to compulsive drug use. Overall, our results indicate that prolonged drug use induces a profound decrease in reward function that is mediated by a remodelling of lateral hypothalamic circuitry (Ahmed et al., 2002, 2005). The reduction or correction of this brain reward disruption would drive the compulsion to take the drug in addicted individuals, as was originally hypothesized by Koob and Le Moal (1997, 2001).

2. Inducing and assessing compulsive drug use in animals

2.1. Drug availability as a major risk factor

Genetic, developmental and environmental factors are thought to contribute to the transition from drug use to drug addiction (Altman et al., 1996; Glantz and Pickens, 1992; Higgins et al., 2004; Koob and Le Moal, 2001; Uhl et al., 1995). Among environmental factors, drug availability represents a major risk factor. Increased drug availability can precipitate the transition to addiction, especially, as we will discuss later, when no or little non-drug rewards are concurrently available (Gawin and Ellinwood, 1989; Kramer et al., 1967; Robins et al., 1975; Siegel, 1984; Wikler, 1952; White, 1988). Differences in drug accessibility also explain why the prevalence of dependent individuals in the general population is generally larger for legal products, such as tobacco and alcohol beverages, than for illegal substances (Pouletty, 2002; WHO, 2004). Interestingly, availability of other non-drug commodities, such as energy-dense foods, is also a major risk factor for other consumption-related pathology, such as certain forms of obesity and type-2 diabetes (Hill and Peters, 1998; Zimmet et al., 2001).

Similarly, earlier experimental studies have shown that increased accessibility to drug self-administration can induce maladaptive patterns of drug use in laboratory animals. With unlimited access to stimulant drugs, such as, for instance, methamphetamine and cocaine, animals develop a binge-like pattern of drug self-administration, with periods of heavy drug intake alternating with periods of spontaneous abstinence (Bozarth and Wise, 1985; Deneau et al., 1969; Johanson et al., 1976). This periodic up-and-down pattern of stimulant use often ends up, but not always, with death (Bozarth and Wise, 1985; Deneau et al., 1969; Johanson et al., 1976). This lethal pattern of stimulant use has been observed in several animal species, including rats, dogs, cats and monkeys (Balster et al., 1976; Bozarth and Wise, 1985; Deneau et al., 1969; Risner and Jones, 1976). In contrast, with unlimited access to opiates, animals escalate drug intake but not to the point of serious ill effects or death (Bozarth and Wise, 1985; Woods and Schuster, 1971).

Though these earlier studies suggested that laboratory animals could develop maladaptive patterns of drug use with unlimited access to the drug, most subsequent researches were conducted in animals with drug access restricted to a few hours per day (generally, less than 3 h) and/or to a few doses per day, such as in intermittent schedules of drug reinforcement. These conditions of drug accessibility are not favorable to the development of escalating patterns of drug use characteristic of drug dependence; on the contrary, they tend to promote the development of highly stable and regular patterns of drug use (Koob et al., 1987; Pickens et al., 1978; Yokel, 1987). Based on these initial studies from the literature, we began to systematically examine the effects of different drug access times on the pattern of drug self-administration in laboratory rats, with the general aim to model the transition from drug use to drug addiction.

2.2. General experimental procedure

Rats (young adult, male, Wistar strain, group-housed) were prepared with a chronic catheter in the right jugular. After recovery from surgery, they were allowed to self-administer cocaine (or heroin) under a continuous schedule of reinforcement whereby each bar press is rewarded by a fixed drug dose. The delivery of each drug dose is signaled by a light and initiates a short refractory period (no greater than 20 s) during which bar pressing has no programmed effect. In these conditions, there is virtually no external limitation on the frequency of injections; the only limiting factor to drug intake is the individual itself (Ahmed and Koob, 1999). Such conditions of drug availability are admittedly artificial; nevertheless, they uniquely allow the study of how animals regulate, and eventually lose control over, drug intake (Ahmed and Koob, 1999).

It is also important to note that rats were supplied with a relatively high unit dose of cocaine (about 0.75 mg/kg). Using a high unit dose allows one to circumvent initial individual differences in drug reward detection during acquisition of drug self-administration. Previous studies have shown that the proportion of animals that learns to self-administer cocaine increases with the unit dose available (Carroll and Lac, 1997). Even so-called addiction-resistant animals readily acquire the self-administration behavior with a sufficiently high unit dose of cocaine (Piazza et al., 2000). After acquisition of drug self-administration, the size of the unit dose is less of a problem because animals have learned to expect the rewarding effects of the drug. As a result, they can adjust the frequency of injections to changes in the dose to maintain the expected effects (Lynch and Carroll, 2001; Yokel, 1987), even at very low doses that non-trained animals would fail to learn to self-administer. In this context, it is important to recall that in humans, naïve drug users have prior knowledge about drug effects before any drug experience (generally from their peers) and thus they can choose to increase the dose if the initial dose does not meet their expectations (see also, Wise, 2000). In this respect, animals trained with relatively high drug doses seem to better model human drug beginners (as well as subsequent habitual drug users) than drug-naïve animals do.

2.3. Increased availability precipitates drug intake escalation

Using this general experimental procedure, we measured the effects of differential access time to cocaine on the pattern of

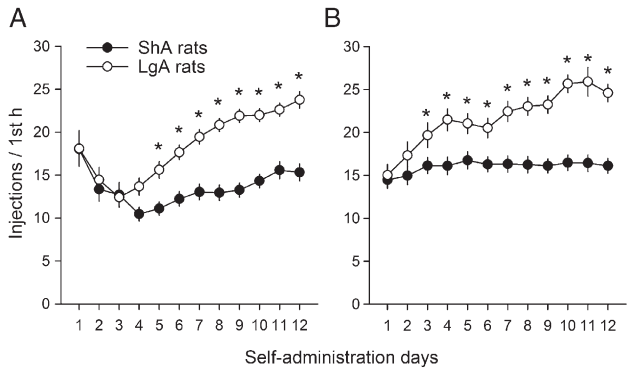

Fig. 1. Effects of access time to cocaine self-administration on the pattern of drug consumption. Data represent the mean number±S.E.M. of cocaine injections during the first hour of each daily self-administration session. Rats had access to cocaine (unit dose=0.25 mg, i.v.) for either 1 h (ShA rats) or 6 h per day (LgA rats). In the first set of experiments (A), rats (57 ShA rats; 53 LgA rats) were initially trained to press a lever for food on a fixed-ratio 1 schedule of reinforcement before having differential access to cocaine self-administration. In the second set of experiments (B), rats (28 ShA rats; 25 LgA rats) were first allowed to self-administer cocaine during 1 or 2 h per day for at least 10 days before having differential access to the drug. *Different from ShA rats ($P<0.05$, Newman–Keuls test).

drug self-administration. As expected, with 1 h of access per day (short access or ShA), drug intake is low and remains stable over a long period of time (i.e., during at least 6 months; Ahmed and Koob, 1998, 1999) (Fig. 1). In contrast, with 6 or more hours of access per day (long access or LgA), cocaine intake gradually escalates above control levels. Cocaine intake escalation is observed regardless of the behavioral history of the subjects before exposure to the drug (i.e., with [Fig. 1A] or without [Fig. 1B] prior operant training with food as the reinforcer). Escalation of cocaine intake in LgA rats is not associated with changes in brain cocaine kinetics or metabolism (Ahmed et al., 2003). Finally, once established, escalated levels of drug consumption persist several weeks, despite reduced drug availability (Ahmed and Koob, 1999).

A total of 163 rats were tested with differential access to intravenous cocaine self-administration for at least 12 days (corresponding to a total of 9 independent experiments). In ShA rats ($n=85$), the distribution of cocaine injections is normal, as shown in Fig. 2A by the fit with a Gaussian curve. This distribution is shifted to the right in LgA rats ($n=78$) after cocaine intake escalation, without changes in symmetry or dispersion. This parallel shift suggests that most of the factors that contribute to the random variation in cocaine self-administration in outbred rats are homogenously altered during prolonged drug exposure. To assess the prevalence of rats with an excessive level of cocaine consumption, we counted the number of individuals whose cocaine intake is above the mean intake of ShA rats by at least one standard deviation. One standard deviation corresponds to more than 6 cocaine doses and to about 40% of the mean drug intake of ShA rats. According to this statistical criterion, about 70% of LgA animals develop an excessive level of drug intake compared to less than 12% of ShA rats (Fig. 2B). In brief, increasing access time to intravenous cocaine self-administration precipitates in most individuals the development of an excessive level of consumption.

The effects of drug availability on consumption have been recently reproduced by other laboratories (Liu et al., 2005; Mantsch et al., 2001; Roth and Carroll, 2004; Terry Robinson, personal communication) and with other drugs of abuse, such as heroin (Ahmed et al., 2000), methamphetamine (George Koob, personal communication) and phencyclidine (Carroll et al., 2005). In the latter case, experimental subjects were male and female rhesus monkeys, suggesting that the effects of drug accessibility on the pattern of drug use are generalizable across sexes and animal taxa. Few recent studies suggest that availability can also affect the pattern of other, non-drug rewarding activities, such as sugar intake (Colantuoni et al., 2002; Avena et al., 2005) and wheel-running (Lattanzio and Eikelboom, 2003), a putative animal model of behavioral addiction (Holden, 2001). Surprisingly, however, increasing drug availability has an opposite effect on intravenous nicotine self-administration (Paterson and Markou, 2004). Rats with a long access to nicotine self-administration do not increase, but decrease, their hourly intake of nicotine compared to rats with a short access to the drug. This perplexing observation may suggest that nicotine is not the main active alkaloid in tobacco smoke and/or that it needs to act with a tobacco co-factor to support drug intake escalation (Berlin and Anthenelli, 2001; Fowler et al., 2003). Thus, studying the effects of drug availability on the pattern of drug intake could represent an additional means to assess the abuse liability of a psychoactive substance.

2.4. Animals with increased drug access develop the major signs of addiction

Additional behavioral investigations indicate that the differences between stable and escalating patterns of drug consumption parallel the differences drawn by clinicians

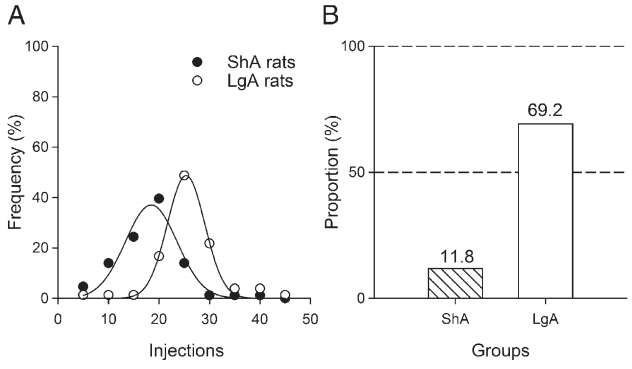

Fig. 2. Effects of access time to cocaine self-administration on the prevalence of excessive drug users. (A) Distribution of first hour cocaine consumption in both ShA rats ($n=85$) and LgA rats ($n=78$). For each individual, first hour intake corresponds to the average of the last 3 days (for other details, see legend of Fig. 1). In both groups, cocaine consumption followed a normal distribution, as shown by the superimposed Gaussian curve. (B) Percentage of animals whose first hour intake is 1 S.D. (i.e., 6.1 injections) above the mean cocaine intake of ShA rats (i.e., 15.5 injections).

between controlled and compulsive drug use in humans. First, regardless of the dose tested, LgA rats are more motivated than ShA rats to work to obtain cocaine, as shown by increased breakpoints in a progressive ratio (PR) schedule of drug self-administration (Paterson and Markou 2003; but see, Liu et al., 2005). In a more recent experiment, we have extended this observation to rats with differential access to intravenous heroin self-administration. After heroin intake escalation in LgA rats, all animals were tested under a PR3 schedule during 5 days. LgA rats maintain higher breakpoints than ShA rats throughout the duration of the experiment (Ahmed and Lenoir, in preparation) (Fig. 3A). Further, the demand for heroin is less elastic in LgA rats than in ShA rats, as assessed by within-session increases in heroin unit price (i.e., fixed-ratio) (Fig. 3B). Decreased price-elasticity of demand for drug consumption has been hypothesized to distinguish dependent from non-dependent drug users (Heyman, 1998; Heyman et al., 1999; see also, Miron and Zwiebel, 1995). Together, these findings indicate that LgA rats have an increased motivation to take the drug and a decreased sensitivity to available substitutes. Second, LgA rats have a greater difficulty to abstain from seeking the drug than ShA rats during extinction. LgA rats persist longer than ShA rats (4 versus 10 days) in responding on the drug-paired lever despite the fact that this behavior is not rewarded (i.e., they present a resistance to extinction; Ahmed et al., 2000). Third, Vanderschuren and Everitt (2004) have recently shown that after prolonged exposure to cocaine self-administration, LgA rats become less sensitive to a danger signal that normally deters animals from seeking the drug

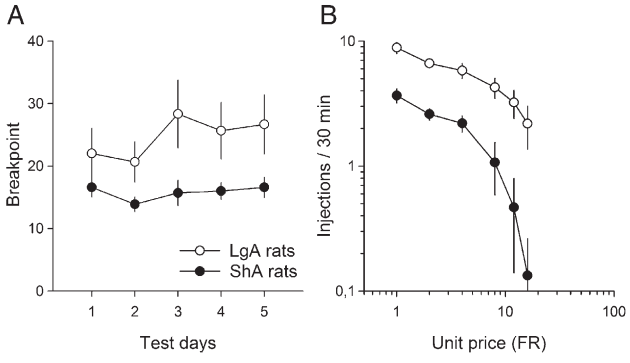

Fig. 3. Effects of access time to heroin self-administration on the motivation (A) and demand (B) for drug consumption. The motivation to self-administer heroin was assessed by measuring breakpoints under a progressive-ratio 3 schedule of reinforcement. Breakpoints were measured every other day after escalation of heroin self-administration in LgA rats. Between testing days, rats self-administered the drug under a fixed-ratio 1 schedule of reinforcement (1 or 6 h, depending on the group). LgA rats had greater breakpoints than ShA rats ($F_{1,17}=6.43$, $P<0.05$). The demand curve for heroin was established by increasing heroin unit price (i.e., fixed-ratio or FR) every 30 min within a 3-h self-administration session. Data represent mean heroin consumption ± S.E.M. (averaged over 3 testing sessions). A demand curve analysis using Hursh's equation (Hursh et al., 1988; see also, Lea, 1978) shows that elasticity of demand for heroin consumption increases slowly in LgA rats ($a=0.09$) than in ShA rats ($a=0.18$) with increasing price. In addition, the value of P_{max} (the price at maximum responding) was higher in LgA rats (11.0) than in ShA rats (5.6), a result that confirms the PR data. Hursh's equation accounted for about 70% of the variance in both ShA and LgA rats.

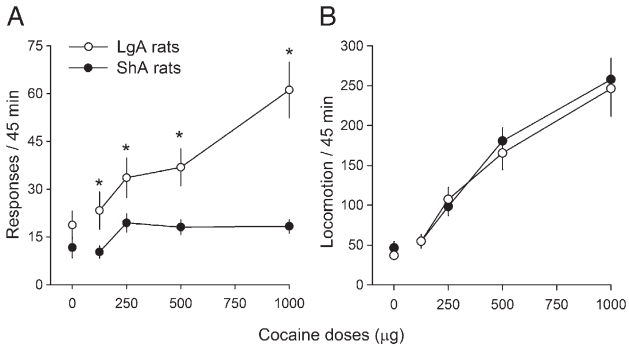

Fig. 4. Effects of access time to cocaine self-administration on cocaine-induced reinstatement (A) and stimulation of locomotion (B). The effects of cocaine on extinguished drug-seeking behavior and on locomotion were concurrently assessed on three occasions (for other details, see Ahmed and Cador, in press). For simplicity, data obtained during these 3 tests were averaged. During all tests, rats passively received increasing doses of cocaine (0.125–1 mg, i.v.), one dose every 45 min with the first 45-min interval corresponding to behavioral extinction. Note that during testing, lever pressing had no programmed consequence. *Different from ShA rats ($P<0.05$, Newman–Keuls test).

during extinction (see the contribution of these authors in this special issue). This observation suggests that LgA rats accept to take increased risks to seek the drug and that their drug-seeking behavior has become inflexible. This conclusion concurs with previous studies of oral drug self-administration showing that rats with an escalating drinking pattern become indifferent to the deterring effects of a bitter tasting compound (i.e., quinine) added to the drug solution (Wolffgramm, 1991; Heyne and Wolffgramm, 1998). Overall, these data strongly suggest that rats with prolonged access to drug self-administration develop all the major behavioral signs of drug dependence (see Table 1).

More recently, we discovered that rats with escalating cocaine use respond considerably more to the motivational effects of the drug, as assessed in a modified within-session, reinstatement model of drug-induced craving (Ahmed and Cador, in press; see also, Sutton et al., 2000; Mantsch et al., 2004). In this model, after 45 min of extinction, both ShA and LgA rats were challenged every 45 min with several doses of cocaine (0.125–1 mg, i.v.). After each dose, lever responding was recorded but had no programmed consequence. In most ShA rats, cocaine fails to reinstate cocaine-seeking behavior, regardless of the dose tested (Fig. 4A). In contrast, in LgA rats, cocaine induces a dose-dependent reinstatement of drug-seeking behavior. The responsiveness of LgA rats to the motivational effects of cocaine is not due to an increased behavioral sensitization to the drug, since LgA rats are not more sensitive than ShA rats to the psychomotor effects of cocaine (Fig. 4B). Similar results were observed in rats with different access time to i.v. heroin self-administration (Ahmed and Lenoir, in preparation). These findings suggest the existence of some threshold duration below which most individuals readily learn to take cocaine without becoming responsive to its motivational effects and above which they become dependent and responsive to these effects. Thus, responsiveness to the motivational effects of the drug would represent a specific behavioral marker of the transition to compulsive cocaine use

(see also, Sutton et al., 2000). In humans too, the ability of cocaine or cocaine-like compounds to induce craving appears to constitute a specific marker of cocaine addiction (Jaffe et al., 1989; Volkow et al., 2005).

3. Neurobiological disruptions in the transition to compulsive drug use

Several different neurobiological mechanisms have been proposed to explain the transition from controlled to compulsive drug use in animals with extended access to the drug (Zernig et al., 2004 and associated commentaries). According to the hedonic allostasis hypothesis of drug addiction (Koob and Le Moal, 1997), which is a neurobiological elaboration on Solomon and Corbit's (1974) classical opponent–process theory of motivation, the precipitation of compulsive drug use would result from a chronic decrease in reward system responsivity that is produced by an overactivation of brain anti-reward processes. The correction or reduction of this reward deficit would drive escalation of drug consumption (Koob and Le Moal, 1997; 2001).

3.1. The reward allostasis hypothesis of drug addiction

Structurally, the brain reward system corresponds to the neural circuitry involving the extended amygdala and its anatomical links with the lateral hypothalamus (Koob and Le Moal, 2001; Heimer, 2003). Functionally, this system is hypothesized to assign positive or negative affective valences to incoming sensory stimuli depending on the current state and past experience of the subject. The responsivity of the reward system to the environment would be regulated by pro- and anti-reward neurotransmitters (Koob, 1996). Pro-reward neurotransmitters increase while anti-reward neurotransmitters decrease reward system responsivity. It is the dynamic equilibrium between these "rein control" neurotransmitters that would maintain hedonic stability (Ahmed and Koob, 2005; Saunders et al., 1998). Dopamine is the most studied pro-reward neuromodulator; anti-reward neuromodulators are less studied but they may include corticotropin-releasing factor (CRF), a major stress neuropeptide, and probably dynorphin, an endogenous agonist of κ-opioid receptors (Koob and Le Moal, 2001).

By directly acting on dopamine transmission, cocaine would boost reward system responsivity outside the normal range, thereby increasing the hedonic impact of sensory stimuli. This abnormal facilitation of brain reward function, however, would be followed rapidly by an opposing reaction (Solomon and Corbit's *b*-process) that tends to slowly return the system to the initial level of hedonic responsivity (Koob, 1996). Under increasingly frequent drug demand, such as in animals with prolonged access to cocaine, the counter-reaction fails to return the system within the normal range of functioning before drug-taking begins again, thereby gradually decreasing brain reward function (residual hysteresis) (Koob and Le Moal, 2001). This stabilized new level of reward system responsivity represents an allostatic decrease in reward function (Koob and Le Moal, 1997, 2001). The correction or reduction of this reward deficit would drive increased drug consumption which in turn would aggravate the deficit. Thus, all the ingredients of a vicious cycle seem to be mixed together.

3.2. Evidence for reward allostasis in animals with compulsive cocaine use

Brain reward homeostasis is suggested by previous studies that measured directly brain reward responsiveness by means of the intracranial self-stimulation (ICSS) procedure (Kornetsky and Esposito, 1979; Markou and Koob, 1992). Under normal conditions, ICSS reward thresholds remain stable over a long period of time, supporting the hypothesis that brain reward systems are under homeostatic control (Markou and Koob, 1992). However, during acute drug withdrawal, ICSS thresholds increase above baseline and then slowly return to baseline levels hours afterward (Leith and Barrett, 1976; Markou and Koob, 1991; Schulteis et al., 1994, 1995; Wise and Munn, 1995; Epping-Jordan et al., 1998). This after-reaction is opposite in direction to the well-documented lowering effects of drugs of abuse on ICSS thresholds (Gardner and Lowinson, 1993; Wise, 1996) and is associated with a dysphoric-like effect in both animals (Ettenberg et al., 1999; Mutschler and Miczek, 1998) and humans (Gawin, 1991; Uslaner et al., 1999). These observations demonstrate that the reward-facilitating effects of the drug are effectively counterbalanced by a slow-decaying after-reaction.

More recently, we observed that this transient counter-reaction fails to return to normal between days in LgA animals, thereby producing a progressive and persistent elevation in reward thresholds (i.e., decreased reward system responsivity; Ahmed et al., 2002) (Fig. 5A). The establishment of this new level of reward system responsivity precedes and is highly correlated with escalation of cocaine use (Fig. 5B). No change

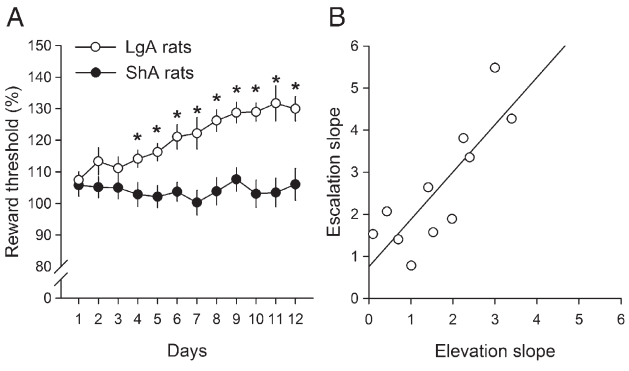

Fig. 5. Effects of access time to cocaine self-administration on brain reward function (A). Brain reward function was assessed by measuring intracranial self-stimulation (ICSS) thresholds using a modified version of the psychophysical method of limits (Markou and Koob, 1991). ICSS reward thresholds were measured two times a day in rats with electrodes in the lateral hypothalamus: 1 h before and 3 h after each daily self-administration session. Only the first measurement is shown here (for other information, see Ahmed et al., 2002). (B) Correlation between the slope of cocaine intake escalation and the slope of ICSS threshold elevation in LgA rats. *Different from ShA rats ($P<0.05$, Newman–Keuls test).

in reward thresholds is observed in ShA animals. According to the reward allostasis hypothesis of drug addiction, this escalation-selective elevation in brain reward threshold would reflect the chronic overactivation of brain anti-reward neurotransmitters (Koob and Le Moal, 2001). The correction or reduction of this chronic overactivation by drug-induced facilitation of pro-reward processes would add a novel source of negative reinforcement, thereby further increasing the motivation to take cocaine (Koob, 1996). We have tested this prediction by directly measuring dopamine levels in the nucleus accumbens during cocaine self-administration. As predicted, LgA animals maintain higher levels of dopamine than ShA rats (Ahmed et al., 2003). Importantly, increased dopamine levels in LgA rats are directly related to the amount of self-administered cocaine, not to an increase in the neurochemical efficacy of the drug (Ahmed et al., 2003).

An allostatic decrease in reward function also induces tolerance to the rewarding effect of cocaine. Due to the persistent elevation in basal reward threshold, cocaine fails to lower thresholds – and thus facilitate reward function – to the same level as prior to escalation (Ahmed et al., 2002). As a result, more cocaine is needed to maintain the same level of reward facilitation, thereby explaining drug intake escalation. Similar baseline shifts also induce tolerance to the discriminative cues of amphetamine (Barrett et al., 2004) and tolerance to the analgesic effects of heroin (Celerier et al., 2001). Using a pharmacokinetic/pharmacodynamic model of intravenous cocaine self-administration, we recently demonstrated that simulation of the baseline shift in reward system responsivity seen in animals after prolonged cocaine exposure suffices to induce a dramatic increase in the rate of drug self-administration (Ahmed and Koob, 2005). Note that this simulated effect was obtained without programmed changes in pharmacokinetics (e.g., elimination rate) or pharmacodynamics (e.g., drug potency or efficacy) parameters (Ahmed and Koob, 2005). Thus, an allostatic decrease in reward function appears to provide a satisfactory and parsimonious explanation of tolerance to, and increased motivation for, the rewarding effects of cocaine associated with compulsive levels of cocaine consumption.

To begin to identify specific molecular markers of compulsive drug use, Pietro Sanna and co-workers recently used high-density oligonucleotide arrays to profile gene expression in several reward-related brain regions of rats with prolonged cocaine exposure (Ahmed et al., 2005). Of the numerous gene transcripts responsive to cocaine self-administration, the expression of only a small fraction (less than 10%) is specifically modified in animals with compulsive cocaine intake. The lateral hypothalamic area shows by far the largest transcriptional response to cocaine intake escalation. Most escalation-selective genes in this brain region are up-regulated and code for both pre- and post-synaptic proteins (see Table 1 in Ahmed et al., 2005). This latter finding suggests that the lateral hypothalamic area has undergone a profound reorganization of its intrinsic circuitry that would explain the reward deficit seen in animals with prolonged cocaine exposure (Ahmed et al., 2002). We speculated that these animals maintain higher levels of dopamine in the nucleus accumbens during self-administration to somehow correct this lateral hypothalamic dysfunction (Ahmed et al., 2003). The lateral hypothalamus receives GABAergic inputs from nucleus accumbens medium-spiny neurons (Heimer et al., 1991; Mogenson et al., 1983; Usuda et al., 1999). Many of these neurons are tonically inhibited during cocaine self-administration, presumably by a self-sustained increase in dopamine levels (Carelli and Deadwyler, 1994; Carelli and Deadwyler, 1996; Chang et al., 1998; Peoples et al., 1999; Nicola and Deadwyler, 2000). This self-inhibition should in turn disinhibit lateral hypothalamic neurons (Kelley, 2004), a phenomenon that could contribute to the rewarding effects of the drug. This complex dopamine-mediated disinhibition of lateral hypothalamic function would become deficient during prolonged drug exposure, thereby driving increased drug consumption. Further studies are needed to test this hypothesis.

4. Origins of vulnerability to drug addiction in laboratory animals

We have shown that below a certain level of drug availability, most rats can repeatedly take cocaine without developing brain reward dysfunction and without showing signs of drug dependence. Above this level, however, the large majority of rats (about 70%) develop alterations in brain reward function that lead to compulsive drug use. This large prevalence of drug-addicted rats associated with increased drug availability seems excessive compared to current estimates in human drug users. Though prevalence estimations are delicate in humans, epidemiologists estimate that depending on the drug, 7% to 32% of those who experiment with drugs eventually become dependent (Anthony, 2002). With legal products, such as tobacco and alcohol beverages, whose availability more closely approximates drug availability in laboratory experiments, the lifetime prevalence of dependent individuals is lower than one third of drug-exposed individuals. This crude cross-species comparison suggests that laboratory rats would be at increased risk to develop drug addiction (Alexander and Hadaway, 1982; Ahmed and Koob, 2005), a conclusion that may have profound implications for the interpretation of drug self-administration data. A critical issue for future research will be to determine the factors responsible for this apparent vulnerability to drug addiction in laboratory animals.

4.1. Poorly evolved prefrontal inhibitory mechanisms

At least two broad, non-mutually exclusive, categories of factors can be envisioned to account for the difference in vulnerability to addiction between laboratory animals and drug-exposed humans. First, this difference could result from phylogenetic differences. Due to the divergent brain evolution between the *Rodentia* family – to which the wild ancestor of all laboratory rat strains belonged – and the *Primates* family — to which humans belong, rats would not have evolved powerful cortical (chiefly prefrontal) inhibitory mechanisms that allow most humans today to resist the rewarding effects of drugs (Allman, 1999; Preuss, 1995; Preuss and Kaas, 1999; but see, Uylings et al., 2003). Inherited and/or acquired deficits in

prefrontal inhibitory control are currently thought to contribute to drug addiction in humans (Bechara and Damasio, 2002; Bickel and Marsch, 2001; Bolla et al., 2003; Volkow and Fowler, 2000; Garavan and Stout, 2005; Rogers and Robbins, 2001). In other words, the lack of strong prefrontal inhibitory mechanisms in laboratory animals would explain why with increased drug availability, most of them would self-expose to the drug to the point of disrupting brain reward pathways and, therefore, of losing control over drug use.

This evolutionary view fails, however, to consider large differences in environmental backgrounds between laboratory animals and drug-exposed humans. Contrary to ecological and/or social environments, the laboratory environment generally provides no positive (i.e., rewards and benefits) and negative (i.e., punishments and costs) incentives capable of turning animals away from the pursuit of drugs. In particular, and contrary to human drug users who have access to a large spectrum of social and non-social alternative reinforcers, experimental animals have no other choice during drug access but to take the available drug to obtain some level of satisfaction. This lack of alternative, non-drug rewards would explain why the demand for drug consumption is generally inelastic in laboratory animals (see Heyman, 1998; Hursh, 1991; Lea, 1978) and why most animals develop compulsive drug use with increased drug availability (Ahmed and Koob, 2005). Thus, even if laboratory rats had evolved sufficiently strong cortical inhibitory capacities, they would not have the solicitations to recruit them in the laboratory environment. Experimental animals are probably more of a model of human populations at increased risks to drug addiction than of the general population, as commonly assumed (Ahmed and Koob, 2005). From this perspective, laboratory animals appear particularly well-suited for the study of factors that protect from, rather than predispose to, drug dependence.

4.2. Imbalance between drug and non-drug reward availability

The above analysis suggests that the transition from drug use to addiction would ultimately depend, not on drug availability per se, but on an imbalance between drug and non-drug reward accessibility (current and expected) (see also, Heyman, 1996; Higgins, 1997; Hursh, 1991). This hypothesis predicts that supplying non-drug reward during drug access should prevent or reduce drug use and eventually drug addiction in naive animals. Marylin Carroll and her co-workers were among the first to directly test the effects of an alternative non-drug reward on drug self-administration in laboratory animals (for review, Campbell and Carroll, 2000). They showed that providing concurrent access to a highly palatable drink (i.e., containing glucose and saccharin) during drug access considerably reduces the proportion of rats that learn to self-administer cocaine (Carroll et al., 1989; Carroll and Lac, 1993). In addition, supplying the same alternative reinforcer after animals had acquired the self-administration behavior also decreases cocaine intake, especially when the unit price of the drug is high (Carroll et al., 1989; Carroll et al., 1995; Rodefer and Carroll, 1997). Other non-food alternatives have also been shown to reduce stimulant intake or preference, such as, for instance, access to a wheel for running (Cosgrove et al., 2002; Kanarek et al., 1995) or to pups in dams (Mattson et al., 2001). Finally, the discovery that male subordinate animals take more drugs than dominant ones may arise from their restricted access to non-drug rewards, such as space, food resources and females (Wolffgramm, 1991; Morgan et al., 2002).

In these experiments, the subject's preference could not be determined because both drug and non-drug rewards were concurrently available, not mutually exclusive. Using a discrete-trials choice procedure in which one choice excludes the other, several researchers have demonstrated that an alternative reinforcer can considerably decrease drug preference in non-dependent monkeys (Nader and Woolverton, 1991, 1992; Negus, 2003; Paronis et al., 2002). Due to the necessarily small number of subjects used, however, these initial studies do not allow an estimation of the impact of an alternative reward on the prevalence of spontaneous drug preference. To begin to address this issue, we recently developed a discrete-trials choice procedure in rats similar to that validated in monkeys (Ahmed and Lenoir, in preparation). Briefly, twenty-two drug-naïve and non-food-restricted rats were allowed to choose between a sweet, but non-caloric, drink (water containing 0.2% saccharin) and heroin at a dose (0.015 mg, i.v.) that is readily self-administered by most rats under a continuous schedule of reinforcement (Ahmed and Lenoir, in preparation). During choice, less than 10% of rats prefers heroin over the sweet drink (percent of heroin choices greater than 60%) (Fig. 6). In contrast, when no alternative reward is available, most rats shift their preference to the drug. Thus, providing an alternative to heroin protects most, though not all, individuals from the progression toward excessive drug choice, a finding that extends previous results from the literature. These observations suggest that the

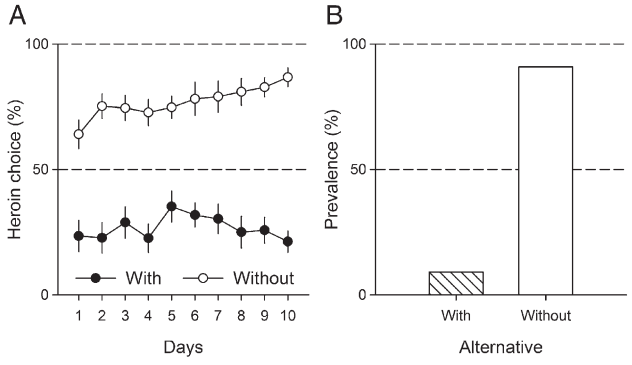

Fig. 6. Effects of an alternative, non-drug reward on heroin choice. Rats (n=22) were allowed to choose between heroin (0.015 mg, i.v.) and a palatable, but non-caloric, sweet drink (water containing 0.2% saccharin) on a discrete-trials choice procedure. After an initial sampling period during which rats learned to associate one lever to heroin delivery and the other to saccharin delivery, both levers were presented concurrently and rats had to respond two times in a row on one of the two levers to earn the corresponding reward. Immediately after the choice, both levers simultaneously retracted during 15 min until the next choice trial. After 10 testing days with the alternative reward available, rats were tested during 10 additional days with no alternative reinforcer. (A) Mean percent drug choice±S.E.M. (B) Proportion of rats that prefer heroin (i.e., frequency of heroin choice greater than 60%).

high prevalence of drug-addicted rats associated with increased availability largely result from a lack of alternative non-drug rewards. By extrapolation, these data imply that environmental variations in non-drug reward availability may contribute to variations in the prevalence of drug addiction within and across human societies.

A critical issue for the treatment of drug addiction is to determine the degree to which non-drug rewards conserve their protective efficacy in addicted individuals (i.e., after the transition to addiction in environments with no or little alternatives to the drug). According to the reward allostasis hypothesis of drug addiction, increasing the availability of alternative non-drug rewards should only have a marginal therapeutic effect in drug dependent individuals because they have compromised brain reward function (Ahmed, 2004; Ahmed et al., 2002; Ahmed and Koob, 2005; see also, Heyman, 1996). In support of this hypothesis, animals withdrawn from prolonged drug exposure are less sensitive to the rewarding and/or motivational effects of non-drug rewards, such as food (Carroll and Lac, 1987; Harris and Aston-Jones, 2003; Lieblich et al., 1991; Lynch and Taylor, 2005; Silva and Heyman, 2001). Further, Spragg (1940) has shown in the first experiment demonstrating "the presence of desire for the drug" in animals that morphine-dependent chimpanzees (one female and one male) prefer the drug over a normally highly palatable food, even if hungry. In contrast, several clinical studies have shown that alternative rewards can significantly increase the duration of abstinence and thus retard relapse in drug addicts who want to quit (Higgins et al., 2004). In these clinical studies, however, non-drug rewards were made contingent upon voluntary abstinence (i.e., upon negative urine tests). It is not clear at present how such higher-order behavioral contingencies can be applied to laboratory animals (i.e., rewarding voluntary abstinence). Nevertheless, understanding the neurobehavioral factors that influence the protective efficacy of alternative reinforcers in dependent individuals may lead to the discovery of more effective and durable treatments of drug addiction.

5. Summary

It is proposed that an environmental imbalance between drug and non-drug reward availability represents a major causative factor in drug addiction. The prevalence of drug addiction is expected to be high in environments that do not provide enough alternatives to drugs of abuse, such as in the environment of laboratory animals with extended access to drug self-administration, and low in environments that provide abundant non-drug reinforcers. Thus, reducing drug availability together with increasing access to non-drug reward should prove a powerful, though difficult to implement, societal mean to contain drug addiction (Heyman, 1996; Hursh, 1991; Jarvik, 1990). Nevertheless, as suggested above, this strategy is unlikely to reduce to zero the prevalence of drug addiction because few vulnerable individuals (about 10% in our experiment) prefer to take the drug despite the availability of a highly rewarding alternative. Future studies are needed to study how alternative reinforcers protect most individuals from drug addiction and why few individuals escape this protection.

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References

Ahmed, S.H., 2004. Addiction as compulsive reward prediction. Science 306, 1901–1902.

Ahmed, S.H., Cador, M., in press. Dissociation of psychomotor sensitization from compulsive cocaine consumption. Neuropsychopharmacology.

Ahmed, S.H., Koob, G.F., 1998. Transition from moderate to excessive drug intake: change in hedonic set point. Science 282, 298–300.

Ahmed, S.H., Koob, G.F., 1999. Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology 146, 303–312.

Ahmed, S.H., Koob, G.F., 2005. Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. Psychopharmacology 180, 473–490.

Ahmed, S.H., Walker, J.R., Koob, G.F., 2000. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22, 413–421.

Ahmed, S.H., Kenny, P.J., Koob, G.F., Markou, A., 2002. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat. Neurosci. 5, 625–626.

Ahmed, S.H., Lin, D., Koob, G.F., Parsons, L.H., 2003. Escalation of cocaine self-administration does not depend on altered cocaine-induced nucleus accumbens dopamine levels. J. Neurochem. 86, 102–113.

Ahmed, S.H., Lutjens, R., van der Stap, L., Lekic, D., Romano-Spica, V., Morales, M., Koob, G.F., Repunte-Canonigo, V., Sanna, P.P., 2005. Gene expression evidence for remodeling of lateral hypothalamic circuitry in cocaine addiction. Proc. Natl. Acad. Sci. U. S. A. 102, 11533–11538.

Alexander, B.K., Hadaway, P.F., 1982. Opiate addiction: the case for an adaptative orientation. Psychol. Bull. 92, 367–381.

Allman, J., 1999. Evolving Brain. Scientific American Library, New York, NY.

Altman, J., Everitt, B.J., Glautier, S., Markou, A., Nutt, D., Oretti, R., Phillips, G.D., Robbins, T.W., 1996. The biological, social and clinical bases of drug addiction: commentary and debate. Psychopharmacology 125, 285–345.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth edition. American Psychiatric Association, Washington, D.C.

Anthony, J.C., 2002. Epidemiology of drug dependence. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C. (Eds.), Neuropsychopharmacology: the Fifth Generation of Progress. Lippincott Williams and Wilkins, Philadelphia, pp. 1557–1573.

Avena, N.M., Long, K.A., Hoebel, B.G., 2005. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol. Behav. 84, 359–362.

Balster, R.L., Kilbey, M.M., Ellinwood Jr., E.H., 1976. Methamphetamine self-administration in the cat. Psychopharmacologia 46, 229–233.

Barrett, R.J., Caul, W.F., Smith, R.L., 2004. Evidence for bidirectional cues as a function of time following treatment with amphetamine: implications for understanding tolerance and withdrawal. Pharmacol. Biochem. Behav. 79, 761–771.

Bechara, A., Damasio, H., 2002. Decision-making and addiction (part I: impaired activation of somatic states in substance dependent individuals

when pondering decisions with negative future consequences). Neuropsychologia 40, 1675–1689.
Berke, J.D., Hyman, S.E., 2000. Addiction, dopamine, and the molecular mechanisms of memory. Neuron 25, 515–532.
Berlin, I., Anthenelli, R.M., 2001. Monoamine oxidases and tobacco smoking. Int. J. Neuropsychopharmacol. 4, 33–42.
Bickel, W.K., Marsch, L.A., 2001. Toward a behavioral economic understanding of drug dependence: delay discounting processes. Addiction 96, 73–86.
Bloom, F.E., 1997. The science of substance abuse. Science 278, 15.
Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R., Ernst, M., 2003. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. NeuroImage 19, 1085–1094.
Bozarth, M.A., Wise, R.A., 1985. Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. J. Am. Med. Assoc. 254, 81–83.
Campbell, U.C., Carroll, M.E., 2000. Acquisition of drug self-administration: environmental and pharmacological interventions. Exp. Clin. Psychopharmacol. 8, 312–325.
Carelli, R.M., Deadwyler, S.A., 1994. A comparison of nucleus accumbens neuronal firing patterns during cocaine self-administration and water reinforcement in rats. J. Neurosci. 14, 7735–7746.
Carelli, R.M., Deadwyler, S.A., 1996. Dose-dependent transitions in nucleus accumbens cell firing and behavioral responding during cocaine self-administration sessions in rats. J. Pharmacol. Exp. Ther. 277, 385–393.
Carroll, M.E., Lac, S.T., 1987. Cocaine withdrawal produces behavioral disruptions in rats. Life Sci. 40, 2183–2190.
Carroll, M.E., Lac, S.T., 1993. Autoshaping i.v. cocaine self-administration in rats: effects of nondrug alternative reinforcers on acquisition. Psychopharmacology 110, 5–12.
Carroll, M.E., Lac, S.T., 1997. Acquisition of i.v. amphetamine and cocaine self-administration in rats as a function of dose. Psychopharmacology 129, 206–214.
Carroll, M.E., Lac, S.T., Nygaard, S.L., 1989. A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology 97, 23–29.
Carroll, M.E., Rodefer, J.S., Rawleigh, J.M., 1995. Concurrent self-administration of ethanol and an alternative nondrug reinforcer in monkeys: effects of income (session length on demand for drug). Psychopharmacology 120, 1–9.
Carroll, M.E., Batulis, D.K., Landry, K.L., Morgan, A.D., 2005. Sex differences in the escalation of oral phencyclidine (PCP self-administration under FR and PR schedules in rhesus monkeys). Psychopharmacology 180, 414–426.
Celerier, E., Laulin, J.P., Corcuff, J.B., Le Moal, M., Simonnet, G., 2001. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. J. Neurosci. 21, 4074–4080.
Chang, J.Y., Janak, P.H., Woodward, D.J., 1998. Comparison of mesocorticolimbic neuronal responses during cocaine and heroin self-administration in freely moving rats. J. Neurosci. 18, 3098–3115.
Chapman, C.R., Hill, H.F., 1989. Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit. Cancer 63, 1636–1644.
Colantuoni, C., Rada, P., McCarthy, J., Patten, C., Avena, N.M., Chadeayne, A., Hoebel, B.G., 2002. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes. Res. 10, 478–488.
Cosgrove, K.P., Hunter, R.G., Carroll, M.E., 2002. Wheel-running attenuates intravenous cocaine self-administration in rats: sex differences. Pharmacol. Biochem. Behav. 73, 663–671.
Deneau, G., Yanagita, T., Seevers, M.H., 1969. Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16, 30–48.
Epping-Jordan, M.P., Watkins, S.S., Koob, G.F., Markou, A., 1998. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 393, 76–79.
Ettenberg, A., Raven, M.A., Danluck, D.A., Necessary, B.D., 1999. Evidence for opponent–process actions of intravenous cocaine. Pharmacol. Biochem. Behav. 64, 507–512.
Fowler, J.S., Logan, J., Wang, G.J., Volkow, N.D., 2003. Monoamine oxidase and cigarette smoking. Neurotoxicology 24, 75–82.
Garavan, H., Stout, J.C., 2005. Neurocognitive insights into substance abuse. Trends Cogn. Sci. 9, 195–201.
Gardner, E.L., Lowinson, J.H., 1993. Drug craving and positive/negative hedonic brain substrates activated by addicting drugs. Semin. Neurosci. 5, 359–368.
Gawin, F.H., 1991. Cocaine addiction: psychology and neurophysiology. Science 251, 1580–1586.
Gawin, F.H., Ellinwood Jr., E.H., 1989. Cocaine dependence. Annu. Rev. Med. 40, 149–161.
Glantz, M.D., Pickens, R.W., 1992. Vulnerability to Drug Abuse. American Psychological Association, Washington DC.
Grant, B.F., 1989. DSM III-R and ICD 10 classifications of alcohol use disorders and associated disabilities: a structural analysis. Int. Rev. Psychiatry 1, 21–39.
Harris, G.C., Aston-Jones, G., 2003. Altered motivation and learning following opiate withdrawal: evidence for prolonged dysregulation of reward processing. Neuropsychopharmacology 28, 865–871.
Heather, N., 1998. A conceptual framework for explaining drug addiction. J. Psychopharmacol. 12, 3–7.
Heimer, L., 2003. A new anatomical framework for neuropsychiatric disorders and drug abuse. Am. J. Psychiatry 160, 1726–1739.
Heimer, L., Zahm, D.S., Churchill, L., Kalivas, P.W., Wohltmann, C., 1991. Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41, 89–125.
Helmuth, L., 2003. In sickness or in health? Science 302, 808–810.
Heyman, G.M., 1996. Resolving the contradictions of addiction. Behav. Brain Sci. 19, 561–610.
Heyman, G.M., 1998. An economic approach to animal models of alcoholism. Alcohol Res. Health 24, 132–139.
Heyman, G.M., Gendel, K., Goodman, J., 1999. Inelastic demand for alcohol in rats. Psychopharmacology 144, 213–219.
Heyne, A., Wolffgramm, J., 1998. The development of addiction to D-amphetamine in an animal model: same principles as for alcohol and opiate. Psychopharmacology 140, 510–518.
Higgins, S.T., 1997. The influence of alternative reinforcers on cocaine use and abuse: a brief review. Pharmacol. Biochem. Behav. 57, 419–427.
Higgins, S.T., Heil, S.H., Lussier, J.P., 2004. Clinical implications of reinforcement as a determinant of substance use disorders. Annu. Rev. Psychol. 55, 431–461.
Hill, J.O., Peters, J.C., 1998. Environmental contributions to the obesity epidemic. Science 280, 1371–1374.
Holden, C., 2001. 'Behavioral' addictions: do they exist? Science 294, 980–982.
Hursh, S.R., 1991. Behavioral economics of drug self-administration and drug abuse policy. J. Exp. Anal. Behav. 56, 377–393.
Hursh, S.R., Raslear, T.G., Shurtleff, D., Bauman, R., Simmons, L., 1988. A cost–benefit analysis of demand for food. J. Exp. Anal. Behav. 50, 419–440.
Jaffe, J.H., 1992. Current concepts of addiction. In: O'Brien, C.P., Jaffe, J.H. (Eds.), Addictive States (Association for Research in Nervous and Mental Disease Research Publications), vol. 70. Raven Press, New York, NY, pp. 1–21.
Jaffe, J.H., Cascella, N.G., Kumor, K.M., Sherer, M.A., 1989. Cocaine-induced cocaine craving. Psychopharmacology 97, 59–64.
Jarvik, M.E., 1990. The drug dilemma: manipulating the demand. Science 250, 387–392.
Johanson, C.E., Balster, R.L., Bonese, K., 1976. Self-administration of psychomotor stimulant drugs: the effects of unlimited access. Pharmacol. Biochem. Behav. 4, 45–51.
Kalivas, P.W., Volkow, N., Seamans, J., 2005. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 45, 647–650.
Kanarek, R.B., Marks-Kaufman, R., D'Anci, K.E., Przypek, J., 1995. Exercise attenuates oral intake of amphetamine in rats. Pharmacol. Biochem. Behav. 51, 725–729.
Kelley, A.E., 2004. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci. Biobehav. Rev. 27, 765–776.
Koob, G.F., 1996. Drug addiction: the yin and yang of hedonic homeostasis. Neuron 16, 893–896.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.
Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.
Koob, G.F., Vaccarino, F., Amalric, M., Bloom, F.E., 1987. Positive reinforcement properties of drugs: search for neural substrates. In: Engel, J., Oreland, L. (Eds.), Brain Reward Systems and Abuse. Raven Press, New York, pp. 35–50.
Koob, G.F., Sanna, P.P., Bloom, F.E., 1998. Neuroscience of addiction. Neuron 21, 467–476.
Kornetsky, C., Esposito, R.U., 1979. Euphorigenic drugs: effects on the reward pathways of the brain. Fed. Proc. 38, 2473–2476.
Kramer, J.C., Fischman, V.S., Littlefield, D.C., 1967. Amphetamine abuse: pattern and effects of high doses taken intravenously. J. Am. Med. Assoc. 201, 305–309.
Lattanzio, S.B., Eikelboom, R., 2003. Wheel access duration in rats: I. Effects on feeding and running. Behav. Neurosci. 117, 496–504.
Lea, S.E.G., 1978. The psychology and economics of demand. Psychol. Bull. 85, 441–466.
Leith, N.J., Barrett, R.J., 1976. Amphetamine and the reward system: evidence for tolerance and post-drug depression. Psychopharmacologia 46, 19–25.
Lieblich, I., Yirmiya, R., Liebeskind, J.C., 1991. Intake of and preference for sweet solutions are attenuated in morphine-withdrawn rats. Behav. Neurosci. 105, 965–970.
Liu, Y., Roberts, D.C., Morgan, D., 2005. Effects of extended-access self-administration and deprivation on breakpoints maintained by cocaine in rats. Psychopharmacology 179, 444–451.
Lynch, W.J., Carroll, M.E., 2001. Regulation of drug intake. Exp. Clin. Psychopharmacol. 9, 131–143.
Lynch, W.J., Taylor, J.R., 2005. Decreased motivation following cocaine self-administration under extended access conditions: effects of sex and ovarian hormones. Neuropsychopharmacology 30, 927–935.
Mantsch, J.R., Ho, A., Schlussman, S.D., Kreek, M.J., 2001. Predictable individual differences in the initiation of cocaine self-administration by rats under extended-access conditions are dose-dependent. Psychopharmacology 157, 31–39.
Mantsch, J.R., Yuferov, V., Mathieu-Kia, A.M., Ho, A., Kreek, M.J., 2004. Effects of extended access to high versus low cocaine doses on self-administration, cocaine-induced reinstatement and brain mRNA levels in rats. Psychopharmacology 175, 26–36.
Markou, A., Koob, G.F., 1991. Postcocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 4, 17–26.
Markou, A., Koob, G.F., 1992. Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations. Physiol. Behav. 51, 111–119.
Mattson, B.J., Williams, S., Rosenblatt, J.S., Morrell, J.I., 2001. Comparison of two positive reinforcing stimuli: pups and cocaine throughout the postpartum period. Behav. Neurosci. 115, 683–694.
Miron, J., Zwiebel, J., 1995. The economic case against drug prohibition. J. Econ. Perspect. 9, 175–192.
Mogenson, G.J., Swanson, L.W., Wu, M., 1983. Neural projections from nucleus accumbens to globus pallidus, substantia innominata, and lateral preoptic-lateral hypothalamic area: an anatomical and electrophysiological investigation in the rat. J. Neurosci. 3, 189–202.
Morgan, D., Grant, K.A., Gage, H.D., Mach, R.H., Kaplan, J.R., Prioleau, O., Nader, S.H., Buchheimer, N., Ehrenkaufer, R.L., Nader, M.A., 2002. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nat. Neurosci. 5, 169–174.
Mutschler, N.H., Miczek, K.A., 1998. Withdrawal from i.v. cocaine "binges" in rats: ultrasonic distress calls and startle. Psychopharmacology 135, 161–168.
Nader, M.A., Woolverton, W.L., 1991. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. Psychopharmacology 105, 169–174.
Nader, M.A., Woolverton, W.L., 1992. Choice between cocaine and food by rhesus monkeys: effects of conditions of food availability. Behav. Pharmacol. 3, 635–638.
Negus, S.S., 2003. Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with D-amphetamine and flupenthixol. Neuropsychopharmacology 28, 919–931.
Nestler, E.J., 2001. Molecular basis of long-term plasticity underlying addiction. Nat. Rev. Neurosci. 2, 119–128.
Nicola, S.M., Deadwyler, S.A., 2000. Firing rate of nucleus accumbens neurons is dopamine-dependent and reflects the timing of cocaine-seeking behavior in rats on a progressive ratio schedule of reinforcement. J. Neurosci. 20, 5526–5537.
Paronis, C.A., Gasior, M., Bergman, J., 2002. Effects of cocaine under concurrent fixed ratio schedules of food and IV drug availability: a novel choice procedure in monkeys. Psychopharmacology 163, 283–291.
Paterson, N.E., Markou, A., 2003. Increased motivation for self-administered cocaine after escalated cocaine intake. NeuroReport 14, 2229–2232.
Paterson, N.E., Markou, A., 2004. Prolonged nicotine dependence associated with extended access to nicotine self-administration in rats. Psychopharmacology 173, 64–72.
Peoples, L.L., Uzwiak, A.J., Gee, F., West, M.O., 1999. Tonic firing of rat nucleus accumbens neurons: changes during the first 2 weeks of daily cocaine self-administration sessions. Brain Res. 822, 231–236.
Piazza, P.V., Deroche-Gamonent, V., Rouge-Pont, F., Le Moal, M., 2000. Vertical shifts in self-administration dose–response functions predict a drug-vulnerable phenotype predisposed to addiction. J. Neurosci. 20, 4226–4232.
Pickens, R., Meisch, R.A., Thompson, T., 1978. Drug self-administration: an analysis of the reinforcing effects of drugs. In: Iversen, L.L., Iversen, S.D., Snyder, S.H. (Eds.), Affective Disorders: Drug Actions in Animals and Man (Handbook of Psychopharmacology Series), vol. 14. Plenum Press, New York, NY, pp. 1–37.
Pouletty, P., 2002. Drug addictions: towards socially accepted and medically treatable diseases. Nat. Rev. Drug Discov. 1, 731–736.
Preuss, T.M., 1995. Do rats have prefrontal cortex? The Rose–Woolsey–Akert program reconsidered. J. Cogn. Neurosci. 7, 1–24.
Preuss, T.M., Kaas, J.H., 1999. Human brain evolution. In: Zigmond, M.J., Bloom, F.E., Landis, S.C., Roberts, J.L., Squire, L.R. (Eds.), Fundamental Neuroscience. Academic Press, San Diego, CA, pp. 1283–1311.
Risner, M.E., Jones, B.E., 1976. Characteristics of unlimited access to self-administered stimulant infusions in dogs. Biol. Psychiatry 11, 625–634.
Robbins, T.W., Everitt, B.J., 1999. Drug addiction: bad habits add up. Nature 398, 567–570.
Robins, L.N., Helzer, J.E., Davis, D.H., 1975. Narcotic use in Southeast Asia and afterwards. Arch. Gen. Psychiatry 32, 955–961.
Rodefer, J.S., Carroll, M.E., 1997. A comparison of progressive ratio schedules versus behavioral economic measures: effect of an alternative reinforcer on the reinforcing efficacy of phencyclidine. Psychopharmacology 132, 95–103.
Rogers, R.D., Robbins, T.W., 2001. Investigating the neurocognitive deficits associated with chronic drug misuse. Curr. Opin. Neurobiol. 11, 250–257.
Roth, M.E., Carroll, M.E., 2004. Sex differences in the escalation of intravenous cocaine intake following long- or short-access to cocaine self-administration. Pharmacol. Biochem. Behav. 78, 199–207.
Saunders, P.T., Koeslag, J.H., Wessels, J.A., 1998. Integral rein control in physiology. J. Theor. Biol. 194, 163–173.
Schulteis, G., Markou, A., Gold, L.H., Stinus, L., Koob, G.F., 1994. Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose–response analysis. J. Pharmacol. Exp. Ther. 271, 1391–1398.
Schulteis, G., Markou, A., Cole, M., Koob, G.F., 1995. Decreased brain reward produced by ethanol withdrawal. Proc. Natl. Acad. Sci. U. S. A. 92, 5880–5884.
Shiffman, S., 1989. Tobacco "chippers"—individual differences in tobacco dependence. Psychopharmacology 97, 539–547.
Siegel, R.K., 1984. Changing patterns of cocaine use: longitudinal observations, consequences, and treatment. In: Grabowski, J. (Ed.), Cocaine: Pharmacology, Effects, and Treatment of Abuse (NIDA Research Monograph), vol. 50. National Institute on Drug Abuse, Rockville, MD, pp. 92–110.

Silva, M.T., Heyman, G.M., 2001. Chronic morphine consumption decreases wheel running and wheel running-reinforced behavior in rats. Pharmacol. Biochem. Behav. 69, 51–57.

Sloan, P., Melzack, R., 1999. Long-term patterns of morphine dosage and pain intensity among cancer patients. Hosp. J. 14, 35–47.

Solomon, R.L., Corbit, J.D., 1974. An opponent process theory of motivation: I. Temporal dynamics of affect. Psychol. Rev. 81, 119–145.

Spragg, S.D., 1940. Morphine addiction in chimpanzees. Comp. Psychol. Monogr. 15, 1–132.

Sutton, M.A., Karanian, D.A., Self, D.W., 2000. Factors that determine a propensity for cocaine-seeking behavior during abstinence in rats. Neuropsychopharmacology 22, 626–641.

Tecott, L.H., Nestler, E.J., 2004. Neurobehavioral assessment in the information age. Nat. Neurosci. 7, 462–466.

Uhl, G.R., Elmer, G.I., LaBuda, M.C., Pickens, R.W., 1995. Genetic influences in drug abuse. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: the Fourth Generation. Raven Press, New York, pp. 1793–1806.

Uslaner, J., Kalechstein, A., Richter, T., Ling, W., Newton, T., 1999. Association of depressive symptoms during abstinence with the subjective high produced by cocaine. Am. J. Psychiatry 156, 1444–1446.

Usuda, I., Tanaka, K., Chiba, T., 1999. Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. Brain Res. 797, 73–93.

Uylings, H.B., Groenewegen, H.J., Kolb, B., 2003. Do rats have a prefrontal cortex? Behav. Brain Res. 146, 3–17.

Vanderschuren, L.J., Everitt, B.J., 2004. Drug seeking becomes compulsive after prolonged cocaine self-administration. Science 305, 1017–1019.

Volkow, N.D., Fowler, J.S., 2000. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb. Cortex 10, 318–325.

Volkow, N.D., Wang, G.J., Ma, Y., Fowler, J.S., Wong, C., Ding, Y.S., Hitzemann, R., Swanson, J.M., Kalivas, P., 2005. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. J. Neurosci. 25, 3932–3939.

White, H.R., 1988. Longitudinal patterns of cocaine use among adolescents. Am. J. Drug Alcohol Abuse 14, 1–15.

World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, Tenth Revision. World Health Organization, Geneva.

World Health Organization, 2004. Neuroscience of Psychoactive Substance Use and Dependence: Summary. World Health Organization, Geneva.

Wikler, A., 1952. A psychodynamic study of a patient during experimental self-regulated re-addiction to morphine. Psychiatr. Q 26, 270–293.

Wise, R.A., 1996. Addictive drugs and brain stimulation reward. Annu. Rev. Neurosci. 19, 319–340.

Wise, R.A., 2000. Addiction becomes a brain disease. Neuron 26, 27–33.

Wise, R.A., Munn, E., 1995. Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. Psychopharmacology 117, 130–136.

Wolffgramm, J., 1991. An ethopharmacological approach to the development of drug addiction. Neurosci. Biobehav. Rev. 15, 515–519.

Wolffgramm, J., Heyne, A., 1995. From controlled drug intake to loss of control: the irreversible development of drug addiction in the rat. Behav. Brain Res. 70, 77–94.

Woods, J.H., Schuster, C.R., 1971. Opiates as reinforcing stimuli. In: Thompson, T., Pickens, R. (Eds.), Stimulus Properties of Drugs. Appleton-Century-Crofts, New York, NY, pp. 163–175.

Yokel, R.A., 1987. Intravenous self-administration: response rate, the effects of pharmacological challenges, and drug preference. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer-Verlag, New York, NY, pp. 117–141.

Zernig, G., Wakonigg, G., Madlung, E., Haring, C., Saria, A., 2004. Do vertical shifts in dose–response rate-relationships in operant conditioning procedures indicate “sensitization” to “drug wanting”? Psychopharmacology 171, 349–351.

Zimmet, P., Alberti, K.G., Shaw, J., 2001. Global and societal implications of the diabetes epidemic. Nature 414, 782–787.

Zinberg, N.E., 1984. Drug, Set, and Setting: the Basis for Controlled Intoxicant Use. Yale University Press, New Haven, Connecticut.