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How to make a rat addicted to cocaine

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Abstract

Procedures have been developed which provide extremely stable patterns of cocaine self-administration in rats and these have been useful in lesion and drug pretreatment studies aimed at understanding the neurobiology of cocaine reinforcement. The issue now is whether studying the neurobiology of reinforcement is the same as studying the neurobiology of addiction. If the goal is to understand a progressive and deteriorating disorder, then the self-administration procedures should model specific aspects of the progressive stages of the addiction process. Here we review theoretical strategies for modeling the addiction process and present data from a series of experiments from our laboratory showing conditions which produce a progressive change in the motivation to self-administer cocaine in rats. This phenomenon is revealed by an escalation in breakpoints on a progressive ratio schedule. The effect, which is robust and persistent, depends on dose and speed of injection. Interestingly, high drug intake can retard the development of this effect, which we argue indicates that the addiction process has a developmental sequence. Finally, we suggest that specific parameters (dose, price and availability) can be used to examine the transition from recreational use to binge-like intake.

Keywords

Animal models; Motivation; Sensitization; Addiction

1. Introduction

Cocaine addiction is a process which generally starts with recreational use and deteriorates over time into a compulsive and chronically-relapsing drug taking disorder (O'Brien, 2001). The position of the National Institute on Drug Abuse (NIDA) is that addiction is a brain disease¹ and that the disorder can and should be understood through a coordinated analysis of brain function and behavior.

Recent advances in molecular biology and in neural-imaging techniques have provided opportunities to study the neurobiology of addiction in human cocaine addicts. Advances in functional magnetic resonance imaging (fMRI) and Positron Emission Tomography (PET) technology have provided ways to identify brain structures associated with drug craving (see

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¹It should be noted that not all clinicians and researchers agree that addiction is a brain disease. Some would argue, for example, that addiction is mainly a matter of moral turpitude and the culmination of 'bad choices'. If one takes the latter position, we are a long way from understanding the neurobiology of moral reasoning – and it would be hard to conceive of animal models of immoral behavior.

reviews, Gatley et al., 2005; Magalhaes, 2005). In addition, advances in imaging of cocaine addicts have helped document changes in brain structure and function following chronic drug exposure (see reviews, Goldstein and Volkow, 2002; Rojas et al., 2005; Borne et al., 2005). Furthermore, new techniques in molecular biology have helped provide meaningful post-mortem analysis of brain tissue from addicts (see reviews, Bannon et al., 2005; Hemby, 2006). However there are considerable challenges involved with human addiction research. It is often difficult to separate out the influences of genetics, socioeconomic histories, and poly-drug use. There are also strict ethical limitations when dealing with administration of drugs to recovering addicts or first time users.

The use of animal models provides enormous potential. A growing number of laboratories are now examining receptors, enzymes, gene expression and metabolic markers in animals exposed to cocaine. The relevance of the results from these sophisticated neurobiological studies will depend, to a large extent, on the quality of the animal models used.

Self-administration procedures are now a standard tool. Much has been learned about the neurobiological consequences of cocaine exposure from studies that have used experimenter-administered cocaine. Various patterns of chronically administered drug – typically using systemic injections - have been developed. However, there is growing evidence that self-administered drugs may produce different effects relative to either experimenter-administered or “yoked” procedures (Porrino, 1993; Dworkin et al., 1995; Hemby et al., 1997; McFarland et al., 2003; Stefanski et al., 2007). Therefore self-administration procedures are becoming the *de facto* standard for studying the neurobiology of cocaine addiction.

A great many studies have examined the neurobiological consequences of cocaine self-administration. At issue is the extent to which typical cocaine self-administration studies model specific aspects of the addiction process. If the question is limited to whether a given amount of cocaine intake can produce a specific effect on brain chemistry, then fairly simple self-administration procedures are all that is required. If, however, one wishes to draw conclusions related to an addiction process, then greater demands are placed on the behavioral model.

2. Reinforcement vs Addiction

Thus, the issue is whether studying the neurobiology of reinforcement is the same as studying the neurobiology of addiction. Because of the experimental questions that were being asked, limited access self-administration procedures evolved to provide extremely stable patterns of responding allowing an assessment of the effects of various treatments. These procedures along with standardized training protocols have resulted in behavioral assays that are ideally suited to study receptor pharmacology, neurotoxic lesions, or hormonal effects (Roberts, 1989; Roberts et al., 1994; Brebner et al., 2000). Limited access self-administration procedures have also allowed neurochemical, epigenetic or electrophysiological effects to be linked to acute cocaine reinforcement (see reviews, White and Kalivas, 1998; Nestler, 2001; Nestler and Landsman, 2001; Everitt and Wolf, 2002). However, it is becoming increasingly clear that such self-administration procedures have failed to model fundamental characteristics of *the addiction process*. The very fact that cocaine self-administration under limited access conditions is extraordinarily stable precludes its use as a model of a progressive disease state. Associating neuroadaptive changes with an addictive process necessarily requires robust animal models which reflect a deteriorating (or at least changing) behavioral profile. Partly through the urging of NIDA (Leshner, 2000), a greater emphasis has been placed on addiction (rather than reinforcement) and it is now a priority to understand the ‘neuroadaptations’ which occur in conjunction with this process. This of course begs the question, “To what extent do self-administration procedures model an addiction process”? Obviously the fact that laboratory

animals and humans voluntarily self-administer drugs of abuse is an important parallel; but can a rat really become addicted to cocaine?

What aspects of the addiction process can be modeled? The definition/diagnosis of cocaine addiction has changed over time. Addiction was at one point confused with physical dependence. In fact, a recent paper by Nutt et al. (2007) seems to suggest that the idea is still firmly held. Since cocaine did not appear to produce classic withdrawal symptoms, it was questioned whether cocaine was addicting at all.

Over time, the Diagnostic and Statistical Manual (DSM) has changed to reflect the evolving concept of drug addiction. The current edition describes in detail the symptoms associated with drug dependence in general and cocaine addiction in particular. The DSM-IV lays out 7 categories of symptoms (See Table 1). The DSM-IV has provided guidance for self-administration laboratories attempting to address specific aspects of the addiction process (e.g. Deroche-Gamont et al., 2004). For example, a growing literature has concentrated on self-administration conditions which increase the rate of drug intake (Ahmed and Koob, 1998; 2005; Ahmed et al., 2002). This work has drawn attention to the fact that longer daily self-administration sessions (e.g. 6 hrs/day) produce a progressive increase in the rate of drug intake. A second area has focused on 'relapse', which seeks to understand how environmental or interoceptive events cause drug-seeking (see reviews, Lu et al., 2004; Schmidt et al., 2005; Epstein et al., 2006). The dependent variable in these studies is the number of responses on a lever previously associated with drug delivery. The effect of drug pretreatments or other stimuli (e.g. foot shock) are assessed on lever responding. Others have addressed continued drug taking in the face of aversive consequences (Di Chiara et al., 2004; Vanderschuren and Everitt, 2004) or changes in attention or impulsivity after extended cocaine intake (Dalley et al., 2005; Perry et al., 2005; Dalley et al., 2007). Each of these approaches has demonstrated that some dependent measures which appear to reflect addiction-like symptoms change over time.

3. Changes in the motivation to self-administer cocaine

Our laboratory has focused on a different characteristic of the addiction process. A defining feature of addictive behavior (DSM-IV) is the increase in time and energy spent in gaining access to drugs. We have attempted to specifically examine this aspect of addiction through the use of Progressive Ratio (PR) schedules. The term "progressive ratio" has been used to describe a variety of schedules employed in self-administration experiments involving primates (Griffiths et al., 1975; Griffiths et al., 1978; Griffiths et al., 1979) and dogs (Risner and Silcox, 1981; Risner and Goldberg, 1983). It originally described a fixed ratio schedule that was increased from one day to the next. Thus "breakpoints" were defined as the ratio in effect on the day on which responding fell below some set level. It therefore took many days to establish a breakpoint. In the first implementation of the PR schedule for drug self-administration in rats (Roberts et al., 1989), the response requirements were increased after the delivery of each reinforcement (i.e. within a session) as originally suggested by Hodos (1961) and later adapted by Bedford (1978) for studies in rhesus monkeys. This procedure yields a daily assessment of breakpoint. The early studies by Hodos originally used an arithmetic function (e.g. 2, 4, 6, 8...) with sweetened milk reinforcement, although an exponential function (1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95 ...) has gained acceptance in drug self-administration studies (Richardson and Roberts, 1996).

Figure 1 shows an example of the pattern of cocaine self-administration on a PR schedule. Presumably the initial breakpoints obtained under this procedure would reflect the acute reinforcing effects of the drug (i.e. the reinforcing effects during initial exposure to the drug). Our focus has been to document the conditions which lead to increases in breakpoints

maintained by cocaine. The figure illustrates our premise that such an augmentation would reflect the addiction process.

Cocaine self-administration on a PR schedule can be affected by experimenter-administered pretreatments. Rats receiving prior exposure to stimulants acquire self-administration faster and/or at lower doses (Horger et al., 1990; Horger et al., 1992; Piazza et al., 1989; Pierre and Vezina, 1997, 1998; Schenk et al., 1991; Vezina et al., 1999). Prior treatment with experimenter-administered stimulants also results in higher breakpoints when rats are subsequently tested on a PR schedule (Covington, III and Miczek, 2001; Lorrain et al., 2000; Suto et al., 2002; Suto et al., 2003; Vezina et al., 2002; see Li et al., 1994 for an example of tolerance). Such data clearly show that the motivation to self-administer cocaine can be manipulated (see review, Vezina, 2004). Since dose (Roberts et al., 1989), injection speed (Liu et al., 2005a; Woolverton and Wang, 2004), and drug deprivation (Morgan et al., 2002, 2005) can all interact and influence breakpoints that are obtained, it cannot be assumed that the phenomena demonstrated in experiments using experimenter-administered drug exposure protocols will necessarily have relevance to studies in which drug exposure consists solely of drug self-administration. The challenge for us has been to find the self-administration conditions which alter breakpoints.

4. Binge-Abstinence Self-Administration Increases Cocaine-reinforced Breakpoints

Our initial efforts focused on binge self-administration conditions based on the notion that cocaine use in humans is best characterized by periods of binge self-administration followed by abstinence periods (O'Brien, 2001). One series of studies examined the effects of continuous access to cocaine for varying durations, and these studies have been summarized previously (Morgan and Roberts, 2004) and are described in Table 2. Some of these experimental conditions included 24-hour or 72-hour access on an FR1 schedule, or 3 "bouts" of 24-hour access each separated by 24 hours. In order to increase the overall length of the "binge" period (as greater than 72-hour continuous access typically results in death), we provided access to cocaine on a discrete-trials procedure (DT5; 5 trials per hour, 24 hours per day; each trial provides a 10-minute opportunity to self-administer a single injection of cocaine; Roberts et al., 2002) for 5 days. Following each of these "binge" self-administration episodes, abstinence (i.e. forced deprivation) was introduced before reassessment of self-administration on a PR schedule. Under each of these conditions, breakpoints maintained by cocaine decrease shortly after the "binge" and returned to control levels by approximately 1 week of abstinence (Morgan and Roberts, 2004; Roberts et al., 2002).

In an effort to further increase the duration of the "binge" period of self-administration, access conditions were restricted to 4 trials per hour (DT4) for 10 days. During this period overall intake was similar to the conditions described above. Under these conditions, when a 7–10 day deprivation period was imposed – but not following a 1-day deprivation period – there were dramatic increases in breakpoints maintained by cocaine (Morgan et al., 2002; Morgan and Roberts, 2004; Morgan et al., 2005). Interestingly, when the same total cocaine intake was self-administered via an FR1 schedule over the 10 days (a control group for the DT4 rats) and followed by a deprivation period, increases in breakpoint were not observed (Morgan et al., 2005). These data suggest that the particular access conditions or the pattern of self-administration were critical to changing breakpoints. At this point, the particular history, experimental protocol, and parameters that are necessary and/or sufficient for producing increased breakpoints are not known. As described below however, we believe that limiting access in some manner (e.g. making the drug available less often, increasing the "price" of the reinforcer, introducing extended periods of deprivation) contributes to the phenomenon.

More recent experiments have attempted to identify neurobiological correlates of these changes in breakpoint. The first system targeted was the dopaminergic system, as increases in responsiveness in this system could potentially account for increases in breakpoint. In contrast to our expectations, in rats given a history of DT4 self-administration and 7 days of deprivation, basal levels of dopamine in the nucleus accumbens were decreased, cocaine was essentially ineffective in changing dopamine levels (assessed via microdialysis), and electrically-stimulated dopamine release was decreased while DA uptake was increased (assessed via fast-scan voltammetry) (Mateo et al., 2005). Ongoing experiments have begun examining changes in gene and protein expression following DT4 self-administration and abstinence.

5. Escalation of Cocaine-reinforced Breakpoints

The experiments examining DT4 for 7–10 days coupled with 7–10 day of deprivation suggested that *limiting* access to cocaine was potentially responsible for the increases in breakpoint. Under DT4 conditions, a single drug reinforcer is available every 15 minutes (i.e. 4 trials per hour) when the rats would typically self-administer this dose every ~8 minutes under FR1 schedule conditions (see for example, Liu et al, 2005b) – this is a restriction that is not present under typical training (FR1) conditions. The next series of experiments limited access to cocaine in another manner - providing access to cocaine on a PR schedule immediately after training. This limits access by increasing the work requirement (i.e. price) associated with obtaining reinforcers. Somewhat surprisingly, these conditions resulted in a progressive increase in cocaine self-administration over time as illustrated in Figure 2. Daily testing on a PR schedule produced a steady increase in the breakpoints over a two-week period. Note that on the second day of testing, the average final ratio of the group was about 118. After two weeks of testing, this had increased on average to 268. Across these sessions, the total number of responses emitted within a session had increased from 568 to 1378.

6. Dose Dependence

The escalation of cocaine-reinforced breakpoints described above has been studied extensively and found to depend on the unit injection dose, the speed of the drug injection, and training conditions. Figure 3 illustrates that a progressive increase in breakpoints is dose-dependent. In a replication of previous results, a dose of 1.5 mg/kg/inj produced a robust increase in breakpoint across days. This effect was weaker or absent at lower doses of cocaine. Note that the 1.5 mg/kg/inj cocaine dose is near the top of the dose-response curve suggesting that doses with the highest acute reinforcing efficacy may result in the greatest escalation in breakpoints (Liu et al., 2005a). Presumably this indicates that the dose most likely to push the addiction process forward is also the dose that rats would gravitate toward if given a choice (see for example, Ward et al., 2005).

The effect of higher unit injections doses (~ 3.0 mg/kg/inj) depends on whether rats have had extensive prior cocaine self-administration experience. For example, experiments (Liu et al., 2005b; Morgan et al., 2006) using rats with more extensive cocaine self-administration experience (e.g. training with the relatively high cocaine dose of 1.5 mg/kg/inj) have shown that breakpoints supported by 3.0 mg/kg/inj are the same or sometimes higher than those supported by 1.5 mg/kg/inj; that is, the 3.0 mg/kg/inj dose could support the highest breakpoints if the rats have several weeks of cocaine self-administration experience, or can be on the descending limb of the curve (i.e. “over the top”) in rats with little experience. Such a difference is evident by comparing Figures 3 and 4. In rats with little cocaine self-administration history (Fig. 3), the 3.0 mg/kg/inj cocaine dose supported very low breakpoints with little escalation over time. Figure 4 illustrates a different effect in experienced rats that had already shown a significant increase in breakpoints with a cocaine dose of 1.5 mg/kg/inj. In this situation, breakpoints supported by the high dose (3.0 mg/kg/inj) were significantly higher than the 1.5

mg/kg/inj values. These data demonstrate that the effect of a high dose of cocaine on escalation of breakpoints depends on the prior self-administration experience.

7. Importance of Injection Speed

Figure 5 illustrates that speed of drug injection significantly affects the escalation of breakpoints, but may not be important to the acute reinforcing effects. The baseline breakpoints determined on Day 1 of testing were not statistically significant between the groups receiving cocaine injections delivered over 5, 25 or 50 seconds. These data are consistent with those of Crombag et al. (2003) who demonstrated that injection speeds (i.e. 5 vs. 100 sec) failed to affect the rate of acquisition for cocaine or amphetamine self-administration, response rates maintained using an FR schedule, breakpoints on a PR schedule, or reinstatement of extinguished responding. This is also consistent with unpublished data from our laboratory showing that in rats with relatively extensive histories of cocaine self-administration, there is generally no effect of manipulating injection speed on the cocaine dose–effect curve assessed with a PR schedule. Despite the fact that injection speed may not affect acutely determined breakpoints, Figure 5 shows that the group which received each cocaine infusion delivered over 5 seconds showed a progressive increase in breakpoints. This replicates previous results. By contrast, groups that received the same dose delivered over 25 or 50 seconds failed to demonstrate a change over time.

The fact that rapid delivery of cocaine is important for sensitizing the reinforcing effects of cocaine has important parallels with the literature on sensitization of locomotor activity. Samaha et al. (2002; 2004; Samaha and Robinson, 2005) reported that the rate of intravenous cocaine delivery significantly affected sensitization of cocaine-induced locomotor activity, rotational behavior as well as neurochemical markers associated with locomotor sensitization (e.g. expression of the immediate early genes *c-fos* and *arc* mRNA). Together, these studies demonstrate that while the development of sensitization is dependent on injection speed, the baseline responses are not – that is, the acute locomotor and reinforcing effects may not depend on speed of injection, however sensitization of the responses is.

It is widely held that speed of drug onset is an important factor which influences a drug's abuse liability (Zernig et al., 2003). We have previously reported the dose–response relationship for various psychostimulant drugs on a PR schedule (Richardson and Roberts, 1996). These curves allowed comparisons between drugs on such factors as relative reinforcing potency and efficacy. With our recent observations that the cocaine dose–effect curve can be shifted leftward and/or upward (i.e. sensitized) by a number of exposure regimens (Morgan and Roberts, 2004; Morgan et al., 2005; Morgan et al., 2006), it would appear that acutely determined dose–effect curves may underestimate the reinforcing efficacy of cocaine and perhaps other drugs. If the maximal breakpoint is taken to reflect abuse liability, then clearly the values following sensitization should be taken as the best estimate. Whether all reinforcing drugs will show sensitization remains to be determined; however, the data regarding speed of injection suggests that differences in abuse liability between drugs (or routes of administration) might be accounted for by rates of sensitization in addition to differences in acute reinforcement.

8. Training Procedures Can Affect Escalation of Breakpoints

We were somewhat surprised to find that escalation of breakpoints can be influenced by certain types of training procedures. In Figure 2, a dotted horizontal line represents the mean ($\pm$ SEM) for the breakpoints of eight consecutive publications from our laboratory. Note that breakpoints were much lower and did not escalate over time. The difference between the previous studies which produced stable and lower breakpoints, and more recent studies in which an escalation

is observed, appears to lie in the training procedures used. In our earlier studies, rats received longer training experience on an FR1 schedule, usually a minimum of 5 days access to 40 injections/day (1.5 mg/kg/inj) (for a total intake of 300 mg/kg cocaine). In retrospect, it appears that this training protocol evolved to provide stable response patterns which were useful for testing drug pretreatments, lesions, and hormonal cycles. It now appears that such training procedures prevent the escalation of breakpoints. Initially this was puzzling, but we will argue below that these data reveal something interesting about how the addiction sequence unfolds.

We have explicitly tested whether training procedures interfere with the expression of escalated breakpoints. Figure 6 shows groups of rats that received different levels of cocaine exposure during 5 days of training. Rats in Group A (20 mg/kg/day) showed the escalation effect. Groups of rats in either Group B or C (60 or 100 mg/kg/day) failed to show an escalation in breakpoints. It appears that “more is not better”, at least as far as producing an increase in the motivation to self-administer cocaine.

Our high dose training procedures produce similar daily intakes to those observed with the 6 hr procedures described by Ahmed and Koob (1998). We have tested whether these procedures which produce an escalation in cocaine intake also produce an escalation in breakpoints. Consistent with the data described above, rats given high cocaine intake failed to produce increases in breakpoints on a PR schedule (Liu et al. 2005b), but see Paterson and Markou (2003).

It may seem paradoxical that access to high daily doses of cocaine appears to inhibit the escalation of breakpoints. After all, high drug intake is a hallmark of cocaine addiction and it seems to make little sense that high drug intake should prevent an important aspect of the addiction process. However, we believe that the data can be reconciled if one posits that the addiction process has a specific sequence. First, a change in the motivation to take cocaine must develop and our data show that this can occur during small self-administration bouts. The process begins to affect the motivation to self-administer cocaine in small increments, with each exposure. In our view, this change is what guarantees that the individual will ‘pay the necessary price’ later on to sustain a binge. The second stage is an escalation in drug intake, which might well involve behavioral and neurochemical tolerance.

Morgan et al. (2006) have supplied compelling data in support of the idea that the sequence of events is important. In Figure 7, Group E (open symbols) were initially given 5 days of exposure to 40 daily injections of cocaine, followed by PR testing. This group showed breakpoints at a level traditionally expected and showed no escalation. Group D (closed symbols) were given less cocaine experience (5 days of exposure to 13 daily injections of cocaine) and these rats showed the expected escalation from PR testing day 1 to 14. The breakpoints maintained by these groups are significantly different on days 12, 13 and 14 of testing. Both groups of rats were then given high access to cocaine on an FR 1 schedule for five days. As shown in Figure 7, the two groups merged temporarily. The escalated group (Group D) then returned to a level of significantly higher breakpoints. The data demonstrate that if high access to cocaine is given before the PR testing, then breakpoints do not escalate. If, however, the breakpoints have already escalated then high access to cocaine has only transient effects. We conclude from these data that the addiction process develops in stages, beginning when intake is relatively small. Under the PR schedule used in our laboratory, the number of injections would normally be limited to less than 20 per day. After the motivation to self-administer has escalated then intake could rise without affecting the process. Much more work is needed before we understand how high drug intake and abstinence interact with the motivation to seek and take cocaine.

What do higher breakpoints mean in the context of drug seeking and drug taking? It is important to note that breakpoints reflect the motivation to obtain the next injection in a series - at a time when high drug levels are on board. To be clear, breakpoints do not reflect the price an animal would pay for the first injection. In spite of the fact that animals will respond upwards of several hundred times for a single injection on a PR schedule, it is in fact difficult to coax rats to respond for the first injection of the session at ratios much higher than an FR20 (Ranaldi and Roberts, 1996). In fact, rats will often decline the opportunity to self-administer cocaine altogether, even on an FR1 schedule, if access is given in their inactive part of the day/light cycle (see below; Roberts et al., 2002). We have concluded therefore that breakpoints reflect the motivation to continue a binge. Continuing a binge versus starting a binge are different phenomena.

9. “Recreational” cocaine use in the rat

A key turning point in the addiction process is the transition from recreational drug use to binge-abstinence patterns of cocaine intake. It may seem almost absurd to propose that the switch from recreational to binge patterns of cocaine use can be modeled in the rat; however this would seem to be a fundamental aspect that should be addressed. We will argue here that principles of behavioral economics can be applied to self-administration procedures that induce patterns of intake (i.e., frequency, total intake) similar to different stages of human drug taking.

It is well documented that, if given unlimited access, rats will self-administer cocaine in ‘binge’ patterns, often resulting in lethal overdose (Johanson et al., 1976; Risner and Jones, 1976; Bozarth and Wise, 1985). These data seem to have spawned the misperception that rats will take cocaine whenever offered, which is certainly not the case. It must be emphasized that the propensity to binge is greatly affected by factors such as price, dose and availability. For example, Carroll et al (1987) have shown that rats do not overdose if small unit doses are offered.

Our laboratory has studied the effects of manipulating the frequency of available injections by using a discrete trials procedure. Rats are given opportunities to self-administer cocaine during trials which are separated by various inter-trial intervals (ITIs). Binge-type responding is seen when rats have access to 5 trials/hr (i.e. access to an injection every 12 min) throughout the day and night (Roberts et al. 2002). Interestingly, however, the pattern of self-administration changes dramatically when the ITI is lengthened by just a few minutes. Figure 8 shows an example of a typical pattern of cocaine self-administration when access is given every twenty minutes (3 trials/hour). Rats self-administer cocaine almost exclusively during the dark (active) phase of the day/night cycle. It is important to emphasize that rats routinely declined to self-administer especially during the light cycle. These data show that when access to cocaine is restricted only slightly there is an inherent circadian rhythm much like there is for other consumptive behaviors. Intake of most drugs of abuse (e.g. caffeine, alcohol, and nicotine) is circadian in humans.

Dose, price and availability all interact in a predictable way to affect the propensity to binge. Binge-like patterns of self-administration, which may last several days, are seen when high doses are made available with short ITIs (Roberts et al., 2002). These patterns become predictably more circadian when the dose is reduced or the ITI is lengthened. The propensity to binge is also suppressed by increasing the ratio requirements (Arnold et al., unpublished data). These data suggest that under many conditions a ‘binge’ is not normally sustained. In fact, it might be argued that a circadian (recreational) pattern of cocaine intake is ‘normal’ behavior for a rat.

The propensity to binge can be modeled by an ascending dose-response function (see Figure 9) - actually a family of curves which depend on the frequency of availability and price. We propose that the transition from recreational to binge-like drug taking is essentially a shift of

this ‘propensity to binge’ curve to the left. Given a circadian pattern of drug intake under specified conditions of dose, price and availability, Figure 9 illustrates how a small shift to the left would result in a dramatic increase in intake and a transition toward drug taking throughout the day/night cycle. We propose that the so-called addiction ‘switch’ can be characterized as a lawful process which shifts this robust dose-response curve to the left. Studies are presently underway to examine whether self-administration procedures which have been proposed to model the addiction process (Roberts et al., 2002; Morgan and Roberts, 2004; Ahmed and Koob, 2005) will in fact shift the ‘propensity to binge’ curve. It is our prediction – but it remains to be seen – that conditions which increase breakpoint or escalate drug use will also affect the propensity to binge.

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Abbreviations

DSM	Diagnostic and Statistical Manual
DT	Discrete-trial
fMRI	Functional magnetic resonance imaging
FR	Fixed Ratio
ITI	Inter-trial Interval
NIDA	National Institute on Drug Abuse
PET	Positron Emission Tomography
PR	Progressive Ratio

Figure 1.

Cumulative records for a representative rat self-administering cocaine (1.5 mg/kg/inj) on a PR schedule of reinforcement. The record on the left represents the acute reinforcing effects of cocaine. Presumably if the breakpoint were to escalate over time this would reflect an addiction process, as represented in the record on the right. Tick marks on the records indicate a drug infusion in this and subsequent figures.

Figure 2.

Cocaine self-administration induced increases in cocaine's reinforcing effects. The left panel represents mean ($\pm$ SEM) breakpoints maintained by cocaine (1.5 mg/kg/inj) delivered on a PR schedule across sessions. The right panel shows an event record from experimental day 0 (FR schedule; this shows 14 hours of a session) and cumulative records from days 1, 6 and 14 (PR schedule; the scale goes to 5 hours) for a representative rat. Horizontal lines represent breakpoints ($\pm$ SEM) from the previous published papers from this laboratory. Adapted from Morgan et al. (2006)

Figure 3.

The increases in cocaine's reinforcing effects are dose-dependent. Data are expressed as mean ($\pm$ SEM) breakpoints. Animals self-administered 20 injections of cocaine (0.75 mg/kg/inj) during the initial exposure. Breakpoints maintained by 0.75 and 1.5 mg/kg/inj significantly increased across days; in contrast, 0.38 or 3.0 mg/kg/inj failed to induce such changes. Adapted from Liu et al. (2005a).

Figure 4.

Breakpoints supported by a high dose of cocaine (3.0 mg/kg/inj) depend on drug history. Points represent mean ($\pm$ SEM) breakpoints maintained by cocaine 1.5 mg/kg/inj (open symbols) or 3.0 mg/kg/inj (closed symbols). The higher dose supported significantly higher breakpoints after a period of escalation on the lower dose.

Figure 5.

Injection speed significantly influences escalation of cocaine-reinforced breakpoints. Mean ($\pm$ SEM) breakpoints maintained by cocaine (1.5 mg/kg/inj) delivered over 5, 25 and 50 seconds. The fastest injection speed (5s) resulted in progressive increases in breakpoints, whereas longer durations of drug delivery (25 and 50s) failed to result in escalation. Adapted from Liu et al. (2005a).

Figure 6.

Cocaine intake during initial exposure is critical to the escalation of cocaine-reinforced breakpoints. In the left panel, event records of representative rats having different levels of cocaine intake during FR testing are shown. The right panel represents mean ($\pm$ SEM) breakpoints maintained by cocaine (1.5 mg/kg/inj) delivered on a PR schedule across sessions. Limited intake during initial access to cocaine resulted in increases in breakpoints over sessions. High levels of cocaine consumption prevented such increases. Adapted from Morgan et al. (2006).

Figure 7.

High levels of cocaine intake only transiently alter the escalated breakpoints. The left panel shows the mean ($\pm$ SEM) breakpoints produced by rats receiving limited (Group D) or extended exposure (Group E) during baseline. The middle panel shows event records for two representative rats with high levels of cocaine intake (60 mg/kg/day) for 5 days. The right panel shows the mean ($\pm$ SEM) breakpoints produced by Group D or E following high levels of cocaine self-administration. High levels of cocaine consumption only transiently influence the reinforcing effects of cocaine after escalation. Adapted from Morgan et al. (2006).

Figure 8.

Circadian pattern of cocaine self-administration (1.5 mg/kg/inj) appears when access is limited to 3 discrete trials per hour. Each row represents one 24 hour period. Injections are denoted by an upward line. A dot denotes a trial in which the rat declined to self-administer. Cocaine was provided for 21 consecutive days. The horizontal line at the top indicates the dark phase of the cycle.

Figure 9.

Increasing the number of trials per hour resulted in a significant increase in the duration of the binge. Data represent the mean ($\pm$ SEM) length in hours of the first cocaine binge (defined as a series of injections with periods of cocaine abstinence no longer than 1 h).

Table 1
DSM-IV diagnostic Criteria for Substance Dependence

Adapted from Mendelson and Mello (1996).

Categories	Symptoms
Tolerance	1. A need for markedly increased amount of the substance to achieve intoxication or desired effects; Markedly diminished effects with continued use of the same amount of the substance
Withdrawal	2. Criteria for withdrawal from the specific substance; The same as (or closed related to) substance taken to relieve or avoid withdrawal symptoms
Binge	3. The substance often taken in larger amounts or over a longer period than was intended
Frequent relapse	4. A persistent desire or unsuccessful efforts to cut down or control substance use
Drug seeking and taking	5. A great deal of time spent in activities necessary to obtain substance, use the substance, or recover from its effects
	6. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
Social activity disruption	7. Important social, occupational, or recreational activities given up or reduced because of substance use

Table 2

Effects of various self-administration histories on breakpoints maintained by cocaine on a progressive ratio schedule.

Procedure	Experimental session	Duration	Deprivation	Effects on breakpoints	References
FR1	24 hr; unlimited access	1 day	1 day	Decrease	Morgan et al. (2002, 2005), Morgan and Roberts (2004)
	72 hr; unlimited access	3 days	1 day	Decrease	
	3 "bouts" of 24 hr access each separated by 24 hr	6 days	1 day	Decrease	
	72 hr; unlimited access	3 days	7 days	No change	
DT5	Extended intake in rats with similar daily intake to that observed on DT4	10 days	7 days	No change	Roberts et al. (2002)Morgan and Roberts (2004)
	24 hr; 5 trials per hr	5 days	1 day	Decrease	
DT4	24 hr; 4 trials per hr	10 days	3 days	No change	Morgan et al. (2002, 2005)Morgan and Roberts (2004)
			7 days	No change	
			1 day	No change	
			7 days	Increase	