Published in final edited form as:
Addiction. 2007 December ; 102(12): 1863–1870. doi:10.1111/j.1360-0443.2007.02011.x.

Self-administration of drugs in animals and humans as a model and an investigative tool

Leigh V. Panlilio and **Steven R. Goldberg**
Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, National Institute on Drug Abuse, NIH/DHHS, 5500 Nathan Shock Drive, Baltimore, MD 21224, FAX: (410) 550-1648, e-mail: sgoldber@intra.nida.nih.gov

Abstract

Aim—To briefly review the methods, assumptions, models, accomplishments, drawbacks, and future directions of research using drug self-administration in animals and humans.

Background—The use of drug self-administration to study addiction is based on the assumption that drugs reinforce the behavior that results in their delivery. A wide range of drug self-administration techniques have been developed to model specific aspects of addiction. These techniques are highly amenable to being combined with a wide variety of neuroscience techniques.

Conclusions—The identification of drug use as behavior that is reinforced by drugs has contributed greatly to the understanding and treatment of addiction. As part of a program of preclinical research that also involves screening with a variety of simpler behavioral techniques, drug self-administration procedures can provide an important last step in testing potential treatments for addiction. There is currently a concerted effort to develop self-administration procedures that model the extreme nature of the behavior engendered by addiction. As advances continue to be made in neuroscience techniques, self-administration should continue to provide a means of applying these techniques within a sophisticated and valid model of human drug addiction.

Keywords

addiction; animal models; reinforcement; operant behavior

This review is intended as a brief survey of how drug self-administration procedures are used in the laboratory as a model of addiction. The goals are to identify the core methods, assumptions and models; the triumphs, limitations and failures; the new directions and the possible interfaces with other disciplines. It is not intended to provide an encyclopedic statement for those readers already familiar with the basic procedures. Rather, we have attempted to provide a more general audience with an overview of the many ways in which these procedures have been applied and also an appreciation of how new applications are continually developed to address different aspects of addiction. Although drug self-administration procedures are used with both animal and human research subjects, and human research has many unique aspects, it should be pointed out that our personal experience has primarily involved animal research, and the review is therefore written from this perspective.

Correspondence to: Steven R. Goldberg.

Core methods and assumptions

Drug self-administration procedures provide a means for studying addiction under controlled conditions in the laboratory. Under these procedures, an animal subject or human volunteer performs a response, such as pressing a lever, that delivers a dose of a drug, such as cocaine or heroin. The drug is typically delivered via an intravenous catheter, although other routes (e.g., oral, insufflation, inhalation) are sometimes used, particularly with humans. Compared to other models of addiction, these procedures provide the most direct point-to-point correspondence with addictive behavior that occurs in the natural environment. For this reason, these methods have a high degree of face validity. Furthermore, this close correspondence allows the details of the procedure to be modified in a variety of ways to model specific aspects of addiction. The behavior observed under these various models is highly sensitive to manipulations of specific environmental and pharmacological variables. Thus, these models can be used to provide a better understanding of the factors that influence addiction, and they can also provide a means of testing potential therapeutic treatments.

The drug self-administration paradigm extends from the field of operant conditioning. Thus, it is built on a venerable scientific system that provides a powerful means of understanding and controlling behavior. Although it might be possible to use drug self-administration procedures to study addiction without making the assumptions inherent in the conditioning and learning approach, much more can be achieved by taking full advantage of this rich background. The most basic assumption of this approach is that drugs function as reinforcers; that is, they increase the likelihood of the behavior that produces them. Thus, drug self-administration is viewed as an operant response reinforced by the effects of the drug. As such, drugs have functional similarities with other reinforcers, such as food, that have traditionally been studied in the field of operant conditioning. Perhaps the most striking of these similarities involves the exquisite sensitivity of behavior to the nature of the relationship between response and reinforcer. This relationship is known as the schedule of reinforcement and describes requirements such as how many responses are required to produce a reinforcer, how much time must pass before the next reinforcer becomes available, and what cues, if any, signal the availability of reinforcement. Many schedules of reinforcement originally developed with food reinforcement have been adapted to the study of drug reinforcers, modeling specific aspects of addiction.

Whenever an operant response is reinforced, there is also the potential for classical conditioning. That is, stimuli present in the environment that are predictive of the onset of the drug's effects come to have conditioned effects of their own. It is assumed that this classical conditioning contributes to addiction in two important ways. First, stimuli that have been associated with the drug can become conditioned reinforcers, capable of reinforcing the response that produces them and maintaining tremendous amounts of behavior. Second-order and chained schedules of reinforcement (as described below) are used to study this phenomenon in the laboratory and provide a model of the long and complex sequences of behavior that are often required for humans to obtain, prepare, and consume a drug. Second, stimuli associated with drug effects can produce conditioned responses that are motivational in nature, inducing the person to seek the drug. These incentive-motivational effects are presumably what is being described when humans report craving for a drug.

Models

Continuous reinforcement, in which each response is reinforced by drug delivery, is the most simple schedule of reinforcement and has been used extensively because it provides the most direct relationship between the subject's behavior and drug intake. The most striking aspect of drug self-administration under this schedule is its temporal regularity, which has led to the

hypothesis that the response occurs whenever the level of drug effect drops below a specific threshold (see [1]). Under this schedule, the rate of self-injection is highly dose-dependent, with higher doses maintaining less frequent injections.

Basic intermittent schedules of reinforcement

In natural environments, it is extremely rare for a response to be reinforced each time it occurs. Usually, there is a certain amount of work that must occur or a certain amount of time that must pass before a reinforcer can be obtained. These respective situations are formalized in the laboratory as r*atio* schedules (which stipulate the number of responses required) and *interval* schedules (which stipulate the amount of time that must pass before the response will produce a reinforcer). These requirements can be constant (in *fixed-ratio and fixed-interval* schedules) or vary from reinforcer to reinforcer (in *variable-ratio* and *variable-interval* schedules). Importantly, each of these schedules tends to maintain a characteristic pattern of responding, and each of these patterns has its uses in behavioral research. For example, fixed-ratio schedules are often used to detect reinforcing effects of a long-lasting drug that may be self-administered infrequently over time. Under a continuous reinforcement schedule with such a drug, the low number of responses on the drug-delivery lever may not differ from the number that occurs on a lever that delivers only a placebo. If a fixed-ratio schedules is used instead, the number of injections over time may still be low, but the number of responses will be much higher on the lever that produces the drug. The control of behavior by simple schedules is an important area of behavioral research in general, with many implications and practical applications for drug self-administration, beyond the scope of this review. In addition, it should be noted that basic schedules can be used as building blocks to create complex schedules, like the second-order, chained, and multiple schedules described below.

Progressive-ratio schedules are used to assess the effectiveness of a reinforcer (i.e., reinforcing efficacy (see [2]). Under this schedule, the number of responses required for drug delivery increases with repeated injections until the subject ceases responding for a certain amount of time. The highest response requirement that is satisfied at a specific dose is termed the breakpoint. The breakpoint is typically an ascending function of dose per injection. Since self-administered drugs often alter rates of operant responding, and these effects are not directly related to reinforcing efficacy, an important feature of progressive-ratio schedules is that they measure the persistence of responding independently of the rate of responding.

Behavioral economics procedures provide another method for measuring reinforcing efficacy (see [3]). These procedures involve manipulating the unit price of a drug (i.e., the number of responses required for delivery of a specified amount of drug) and measuring the level of consumption across a range of prices. The same unit price could be arranged in many ways. For example, if 20 responses were required for 1 mg/kg of cocaine, or if 10 responses were required for 0.5 mg/kg, the unit price would be the same (i.e., 20 responses/mg/kg). Typically, these equivalent prices will maintain similar levels of consumption. Behavioral economics procedures are highly valuable for measuring the elasticity of demand (i.e., how sensitive consumption is to price) and the effects of alternative sources of reinforcement (e.g., a second drug or non-drug reinforcer).

Choice

Behavioral economics studies often involve a choice between self-administering a drug and receiving a non-drug reinforcer. Choice schedules can also be used to compare the reinforcing effects of two different drugs, two different doses of the same drug, or one drug with versus without the addition of another drug. For example, Negus [4] has developed an innovative choice schedule in which monkeys can choose between a lever that delivers drug injections

and a lever that delivers food pellets. Over the course of the session, the available dose is varied, allowing a dose-effect function for choice to be obtained within each session.

Second-order schedules provide a model of how drug-associated stimuli help to maintain responding that is ultimately reinforced by delivery of the drug (see [5,6]). Under a typical version of this schedule, every tenth response on a lever produces a brief presentation of a colored light. After 30 minutes have passed, the next light presentation is accompanied by a drug injection. Thus, through being paired with the drug, the light becomes a conditioned reinforcer. Under these schedules, responding typically occurs at very low rates if the brief stimulus presentations are discontinued, but very high rates when the presentations are resumed, demonstrating that the stimulus functions as a conditioned reinforcer. In this model of drug abuse, the stimulus is presumed to be analogous to features of the drug-abuse environment that are encountered when the drug is consumed, such as the physical features of the prepared drug and related paraphernalia. One valuable feature of second-order schedules is that behavior can be studied prior to the reinforcing drug being delivered (see [7]), or even delivering only one injection at the end of the daily session (e.g., see [5,8]). This allows the effects of a potential therapeutic treatment on drug seeking to be assessed independently of its interaction with the self-administered drug, and it also allows substantial amounts of drug-seeking behavior to be generated with drugs that interfere with responding once they are delivered.

Chained schedules can also model sequences of drug-seeking and how this behavior is affected by environmental stimuli present in the drug abuse environment. Under a chained schedules of drug self-administration, there is a sequence of different conditioned reinforcers that must be obtained before the drug is obtained [9]. These stimuli are presumed to be analogous to conditioned reinforcers such as the stimuli associated with obtaining money, and purchasing, preparing and consuming the drug. An important way that chained schedules are currently being applied is to explicitly separate the drug-seeking response from the drug-taking response [10]. This is accomplished by requiring a certain number of responses on one lever (the drug-seeking lever) to obtain access to a second lever (the drug taking lever), which delivers the drug.

Multiple schedules are used to model the effects of environmental cues that signal when a response will be reinforced and when it will not. These cues can gain powerful control of self-administration behavior. For example, Panlilio et al. [11] used a multiple schedule with two cues, in which responding on a lever was reinforced with cocaine only when a light or a tone is presented. Once the rats learned to respond when either one of the stimuli was present and cease responding when the stimuli were absent, a test was performed by presenting the tone and light together. This caused robust increases in drug seeking and intake, suggesting a potential mechanism by which drug use may become escalated in the drug abuse environment.

Reinstatement procedures are used to model relapse following a period of abstinence. Subjects are trained to self-administer a drug, and then drug delivery is discontinued until responding occurs very infrequently, which typically requires 10 sessions or more. Then, various treatments are tested to determine whether they cause the response to resume. Three major types of treatment have been found to induce reinstatement, and each of these is clearly analogous to the events that can trigger relapse in human drug abusers: priming by re-exposure to the self-administered drug or another reinforcing drug, exposure to drug-associated cues, or exposure to footshock stress in the self-administration environment (see [12]). An alternative version of this procedure [12,14] reduces the self-administration response by delivering response-dependent footshock instead of discontinuing drug delivery; under this procedure, a fourth kind of trigger has been identified, exposure to an anxiolytic drug.

Route of administration and speed of delivery

Although the intravenous route of administration is typically used to study drug self-administration studies, the procedure can also involve intramuscular injection, oral administration (in liquid or pill form), smoking (tobacco, cocaine), or insufflation (cocaine). The faster routes of delivery (iv and smoked) tend to produce stronger reinforcing effects, and it has been shown in monkeys that slow iv infusions, with delivery rates comparable to routes such as oral administration, are also less reinforcing (e.g., see [15]). Interestingly, the duration of effect of the self-administered drug, at least with opioids, does not seem to influence its reinforcing efficacy (see [16]).

Controls for specificity of effect

There are several ways to determine whether a treatment specifically affects drug self-administration. For example, in humans, questionnaires can be used to detect general sedative or depressant effects. In animals, the effects of the treatment on general locomotor activity and feeding can be measured. A widely-used procedure for demonstrating specificity of effect during drug self-administration sessions with animals is to include a control condition in which responding is reinforced by delivery of food pellets. This can be accomplished in a separate group of subjects, or in the same subjects during a different part of the experimental session or a different phase of the study. In testing experimental therapeutics, this control condition is important because it may detect treatments that not only reduce drug self-administration, but may cause a general, depression-like decrease in reinforcement. However, in light of the fact that overeating may be viewed as a form of substance abuse, it might be more important to demonstrate that a treatment only reduces extreme or excessive behavior, rather than selectively reducing drug-reinforced behavior.

Triumphs, limitations, and failures

As described above, drug self-administration procedures can model many of the features of human drug abuse. Drug self-administration in animals has been used quite successfully to predict the abuse liability of novel compounds in humans. Furthermore, in the cases where comparable procedures have been used to study human and animal subjects, the resulting behavior has been strikingly similar. For example, when human volunteers were given relatively free access to cocaine in a laboratory setting, they self-injected at regular temporal intervals, with the duration of the interval determined by dose [17]. As another example, when human volunteers were given experience self-administering cocaine in the laboratory under a second-order schedule, presentation of the drug-paired stimulus functioned as a powerful conditioned reinforcer, maintaining thousands of drug-seeking response even when cocaine delivery was discontinued [18]. Thus, the self-administration paradigm is highly reliable and exhibits both face validity and species generality. However, due to the fact that there are so few positive controls (e.g., methadone, Antabuse®) for an effective pharmacological treatment for addiction, it is difficult to assess the predictive validity of self-administration procedures (or any other preclinical assay) for detecting therapeutic effects of experimental treatments. Furthermore, there remains a general need for further validation of these models, verifying that the results obtained with animals can be generalized to humans, and that results obtained with humans in the laboratory generalize to the actual drug abuse environment.

A drawback of self-administration procedures is that they are relatively expensive in terms of time and other resources. Due to ethical and safety concerns [19], it is necessary to go to great lengths to ensure that human volunteers are carefully screened, then closely monitored for potential adverse effects during and after the study. In rodents, self-administration techniques are limited by the fact that intravenous catheters last a few months at most, precluding long-term studies and the use of complex training schedules that can be studied with food

reinforcement or in non-human primates. This problem of maintaining catheters is especially acute in mice, but this preparation is becoming increasingly viable [20]. Furthermore, because they attempt to mirror the complexity of human behavior, self-administration procedures may actually be less productive than some simpler alternatives for screening novel therapeutic compounds or relating addiction-related behavior to specific neural circuitry. Therefore, self-administration procedures are often used as part of a program of research involving several different methods. A common strategy is to use self-administration to test the efficacy of treatments that have been discovered or developed using simpler behavioral procedures, such as drug-induced locomotor activity, conditioned place-preference, and drug discrimination.

As part of the general behavioral pharmacology approach to drug abuse, studies of drug self-administration have historically helped lead to some of the most significant advances in the understanding and treatment of addiction. For example, at a time when tobacco smoking was widely considered to be simply a "habit," these procedures were instrumental in demonstrating that nicotine is a reinforcing drug used for its pharmacological properties (e.g., see [21]). Replacement therapy (e.g., methadone), antagonist therapy (e.g., naltrexone), and more recently, partial agonist therapy (e.g., buprenorphine) also arose from this field. In addition, contingency management is solidly based on the principles of operant conditioning and has had unparalleled clinical success in achieving and maintaining drug abstinence (see [22]).

Although there were some earlier studies in which human subjects were allowed to self-administer drugs at the Addiction Research Center in Lexington, Kentucky, the systematic study of drug self-administration did not become widespread until effective techniques were developed for use in animals in the early 1960's [23,24,25]. To a large extent, drug self-administration studies conducted in humans today still tend to be linked to the techniques and basic findings from animal research. In evaluating potential therapeutic treatments — and also in studying changes in the brain that underlie addiction — an efficient allocation of resources is to use rodents for the more broad screening procedures, followed by studies in non-human primates, and finally with human subjects in the laboratory. Increasingly, the final assessment before starting clinical trials involves using the subjective effects of a novel compound to predict its abuse liability or treatment efficacy. However, these self-report data do not always agree with the results of parallel drug self-administration studies in humans, even when these measures are obtained simultaneously (see Lamb *et al.* [26]). Although self-administration data may be more difficult and expensive to obtain than self-report data, they are worthwhile because they may provide a more reliable prediction of clinical efficacy.

New directions

In recent years, there has been a concerted effort to develop animal models that more clearly focus on addiction, per se, as opposed to just drug reinforcement. In the past, it was often assumed that studying low-level drug use in animals with limited access to drugs would provide information about addiction. However, many researchers have begun to question this assumption and have developed methods for inducing and assessing more addiction-like behavior in animals.

A basic technique that is increasingly used to induce addiction-like behavior in rats is to provide extended access to the drug during long training sessions. Somewhat ironically, the current interest in these extended-access treatments actually represents a return to the kind of procedure used in some of the earliest studies of drug self-administration in animals, in which constant access to drugs was provided for extended periods, sometimes leading to severe, addiction-like consequences [23]. Thus, the most innovative aspect of the contemporary extended-access studies is not the level of access, per se, but the variety of measures that are being applied to model specific aspects of addiction. In general, all of these procedures attempt to model the

compulsive nature of addiction, as exemplified by the classic aspects of addiction in humans, as described briefly below.

Escalation of use

Rats given extended access to drugs typically increase their rates of drug intake over time in a manner that is not simply attributable to tolerance. Rather, this escalation appears to be related to a loss of control over intake [27]. Interestingly, Liu *et al.* [28] found that rats given extended access to cocaine showed escalated intake, but not increased breakpoints under a progressive-ratio schedule. Thus, escalated intake is not necessarily a result of an increase in the reinforcing effects of the drug.

Relapse is considered a central characteristic of addiction, and possibly the most important to overcome. Work with the reinstatement procedure (described above) has repeatedly demonstrated that reinstatement is more likely in rats given extended access to drugs, and this is true of re-exposure to the training drug (priming; [29]), exposure to response-contingent drug-paired cues [30], and exposure to stress [31].

Difficulty stopping

Rats given extended access to drugs may take longer to cease drug-seeking when drug delivery is discontinued [31,32]. The self-administration responding of rats given extended access to cocaine also shows resistance to suppression by a stimulus paired with footshock that is delivered independently of the rat's behavior [33].

Continued use despite adverse consequences

When rats are allowed to self-administer cocaine even under relatively limited-access conditions, a small proportion of them develop behaviors that resemble human addiction in several important ways, including escalated intake and increased breakpoints under a progressive-ratio schedule [34]. Another interesting aspect of the behavior shown by these rats is that it is resistant to punishment (i.e., suppression by footshock that is only delivered when the rat performs the self-administration response). Thus, the drug-seeking response is less sensitive to aversive consequences in this subgroup of rats. Another example of continued use despite adverse consequences is that rats given extended access to heroin continue to self-administer the drug even when it induces self-injury behavior [29].

Use to the exclusion of other behaviors

It has long been known that rats or monkeys given continuous access to cocaine or other stimulants may overdose or neglect feeding and other normal behavior [23,35]. However, it does not appear that behavioral economics techniques — such as studying the elasticity of demand for cocaine when food is offered as an alternative reinforcer — have been implemented yet to study the effects of extended access condition.

Habitual use despite devaluation of the drug reinforcer

Drug use in addicted individuals may become extremely habitual. With regards to conditioning and learning, habitual behavior can be described as insensitive to changes in the value of the reinforcer. Habit is often measured using devaluation procedures such as those used to study ethanol [36] and cocaine [37] self-administration in rats. In these procedures, after animals were trained to self-administer food or a drug, the reinforcer was devalued by pairing it with an aversive injection of lithium. (Note that during the devaluation treatment, the operant response was not available, differentiating this procedure from punishment procedures, in which the response produces the aversive consequence.) When food was devalued by pairing it with lithium, rats subsequently reduced their food-reinforced operant responding, indicating

that responding was sensitive by the current value of the reinforcer. In contrast, when ethanol or cocaine was paired with an aversive injection of lithium, rats did not reduce their subsequent self-administration responding, indicating that responding had become more habitual and was no longer controlled by the current value of the reinforcer. This resistance to devaluation was evident even without extended access to the drug. Furthermore, cocaine-sensitized rats showed resistance to devaluation of food pellets [38], suggesting that exposure to cocaine makes even food-reinforced behavior more compulsive. These results indicate that the drug-seeking habit may continue at high levels in addicted individuals even if the reinforcing effects of the drug have been diminished.

Interfaces with other disciplines

Drug self-administration is highly amenable to being studied with many contemporary techniques of neuroscience (see [39]), such as neuro-imaging, single-unit recording, temporary lesioning of specific brain circuits, microdialysis, microinjection into discrete brain areas, and genetic knockouts of specific receptor systems. The availability of mice with a wide variety of targeted gene mutations has led to important findings concerning the influence of genetics on addiction. All of these techniques are being used to elucidate the mechanisms involved in each of the aspects of addiction described in the “Models” and “New directions” sections, above. For example, Wise et al. [40] used microdialysis to measure dopamine levels in the nucleus accumbens of rats that were self-administering cocaine, supporting the hypothesis that responding occurs when the dopamine level falls below a certain level. As another example, Martinez et al. [41], performed PET in cocaine-dependant humans as they were given a choice of self-administering cocaine or receiving money, demonstrating changes in dopamine function that were predictive of self-administration. As surely as neuroscience and genetic techniques will continue to be developed and refined, they will continue to be applied within the drug self-administration paradigm.

Conclusion

Drug self-administration is a highly adaptable technique for modeling various aspects of drug addiction in the laboratory using human or animal subjects. Its assumptions follow from the field of operant conditioning. The most important of these assumptions is that drugs function as reinforcers that maintain drug-seeking and drug-taking behavior. Due to their relative difficulty and expense, self-administration procedures are often used as the last part of a program of research in which the effects of treatments are first screened using simpler methods. As part of the area of behavioral pharmacology, the use of self-administration techniques has led to many highly important findings concerning addiction and has contributed to some of the most effective treatment strategies available today. A recent trend in addiction research is to develop self-administration procedures that model the extreme qualities that separate addiction from more “casual” drug use. Self-administration techniques can easily be combined with a variety of neuroscience techniques to further our understanding of addiction and self-administration behavior. Self-administration techniques represent one of the oldest methods for studying addiction, but it seems certain they will continue to provide valuable contributions to the science of addiction well into the future.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute on Drug Abuse.

References

1. Lynch WJ, Carroll ME. Regulation of drug intake . Exp Clin Psychopharmacol 2001;9:131–43. [PubMed: 11518086]
2. Arnold JM, Roberts DC. A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement . Pharmacol Biochem Behav 1997;57:441–7. [PubMed: 9218268]
3. Bickel WK, DeGrandpre RJ, Higgins ST. Behavioral economics: a novel experimental approach to the study of drug dependence . Drug Alcohol Depend 1993;33:173–92. [PubMed: 8261882]
4. Negus SS. Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with d-amphetamine and flupenthixol. Neuropsychopharmacology 2003;28:919–31. [PubMed: 12637948]
5. Goldberg SR, Kelleher RT, Morse WH. Second-order schedules of drug injection . Fed Proc 1975;34:1771–6. [PubMed: 1149889]
6. Schindler CW, Panlilio LV, Goldberg SR. Second-order schedules of drug self-administration in animals . Psychopharmacology 2002;163:327–44. [PubMed: 12373434]
7. Everitt BJ, Robbins TW. Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour . Psychopharmacology 2000;153:17–30. [PubMed: 11255926]
8. Yasar S, Gaal J, Panlilio LV, Justinova Z, Molnar SV, Redhi GH, et al. A comparison of drug-seeking behavior maintained by D-amphetamine, L-deprenyl (selegiline), and D-deprenyl under a second-order schedule in squirrel monkeys. Psychopharmacology 2006;183:413–21. [PubMed: 16292593]
9. Thompson T, Schuster CR. Morphine self-administration, food-reinforced, and avoidance behaviors in rhesus monkeys . Psychopharmacologia 1964;5:87–94. [PubMed: 14137126]
10. Olmstead MC, Parkinson JA, Miles FJ, Everitt BJ, Dickinson A. Cocaine-seeking by rats: regulation, reinforcement and activation . Psychopharmacology 2000;152:123–31. [PubMed: 11057515]
11. Panlilio LV, Weiss SJ, Schindler CW. Cocaine self-administration increased by compounding discriminative stimuli . Psychopharmacology 1996;125:202–8. [PubMed: 8815954]
12. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings . Psychopharmacology 2003;168:3–20. [PubMed: 12402102]
13. Panlilio LV, Thorndike EB, Schindler CW. Reinstatement of punishment-suppressed opioid self-administration in rats: an alternative model of relapse to drug abuse . Psychopharmacology 2003;168:229–35. [PubMed: 12845420]
14. Panlilio LV, Thorndike EB, Schindler CW. Lorazepam reinstates punishment-suppressed remifentanil self-administration in rats . Psychopharmacology 2005;179:374–82. [PubMed: 15821953]
15. Balster RL, Schuster CR. Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration . J Exp Anal Behav 1973;20:119–29. [PubMed: 4197505]
16. Ko MC, Terner J, Hursh S, Woods JH, Winger G. Relative reinforcing effects of three opioids with different durations of action . J Pharmacol Exp Ther 2002;301:698–704. [PubMed: 11961075]
17. Sughondhabirom A, Jain D, Gueorguieva R, Coric V, Berman R, Lynch WJ, et al. A paradigm to investigate the self-regulation of cocaine administration in humans. Psychopharmacology 2005;180:436–46. [PubMed: 15726333]
18. Panlilio LV, Yasar S, Nemeth-Coslett R, Katz JL, Henningfield JE, Solinas M, et al. Human cocaine-seeking behavior and its control by drug-associated stimuli in the laboratory. Neuropsychopharmacology 2005;30:433–43. [PubMed: 15536497]
19. College on Problems of Drug Dependence. Human subject issues in drug abuse research. Drug Alcohol Depend 1995;37:167–75. [PubMed: 7758406]
20. Thomsen M, Caine SB. Intravenous drug self-administration in mice: practical considerations. Behav Genet 2007;37:101–18. [PubMed: 17226102]
21. Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine . Science 1981;214:573–5. [PubMed: 7291998]
22. Rawson RA, McCann MJ, Flammino F, Shoptaw S, Miotto K, Reiber C, et al. A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. Addiction 2006;101:267–74. [PubMed: 16445555]

23. Deneau G, Yanagita T, Seevers MH. Self-administration of psychoactive substances by the monkey . Psychopharmacologia 1969;16:30–48. [PubMed: 4982648]
24. Thompson T, Schuster CR. Morphine self-administration, food-reinforced and avoidance behaviors in rhesus monkeys. Psychopharmacologia 1964;5:817–894.
25. Weeks JR, Collins RJ. Factors affecting voluntary morphine intake in self-maintained addicted rats . Psychopharmacologia 1964;6:267–79. [PubMed: 5890552]
26. Lamb RJ, Preston KL, Schindler CW, Meisch RA, Davis F, Katz JL. The reinforcing and subjective effects of morphine in post-addicts: a dose-response study. J Pharmacol Exp Ther 1991;259:1165–73. [PubMed: 1762068]
27. Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev 2004;27:739–49. [PubMed: 15019424]
28. Liu Y, Roberts DC, Morgan D. Effects of extended-access self-administration and deprivation on breakpoints maintained by cocaine in rats . Psychopharmacology 2005;179:644–5. [PubMed: 15650844]
29. Lenoir M, Ahmed SH. Heroin-induced reinstatement is specific to compulsive heroin use and dissociable from heroin reward and sensitization . Neuropsychopharmacology 2007;32:616–24. [PubMed: 16641938]
30. Kippin TE, Fuchs RA, See RE. Contributions of prolonged contingent and noncontingent cocaine exposure to enhanced reinstatement of cocaine seeking in rats . Psychopharmacology 2006;187:60–7. [PubMed: 16598453]
31. Ahmed SH, Walker JR, Koob GF. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 2000;22:413–21. [PubMed: 10700660]
32. Perry JL, Morgan AD, Anker JJ, Dess NK, Carroll ME. Escalation of iv. cocaine self-administration and reinstatement of cocaine-seeking behavior in rats bred for high and low saccharin intake . Psychopharmacology 2006;186:235–45. [PubMed: 16596398]
33. Vanderschuren LJ, Everitt BJ. Drug seeking becomes compulsive after prolonged cocaine self-administration . Science 2004;305:1017–9. [PubMed: 15310907]
34. Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. Science 2004;305:1014–7. [PubMed: 15310906]
35. Bozarth MA, Wise RA. Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat . JAMA 1985;254:81–3. [PubMed: 4039767]
36. Dickinson A, Wood N, Smith JW. Alcohol seeking by rats: action or habit? Q J Exp Psychol B 2002;55:331–48. [PubMed: 12350285]
37. Miles FJ, Everitt BJ, Dickinson A. Oral cocaine seeking by rats: action or habit? Behav Neurosci 2003;117:927–38. [PubMed: 14570543]
38. Adams CD. Variations in the sensitivity of instrumental responding to reinforcer devaluation. Q J Exp Psychol 1982;34:77–98.
39. Spanagel R, Heilig M. Addiction and its brain science. Addiction 2005;100:1813–22. [PubMed: 16367982]
40. Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JB. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats . Psychopharmacology 1995;120:10–20. [PubMed: 7480530]
41. Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang DR, Broft A, et al. Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. Am J Psychiatry 2007;164:622–9. [PubMed: 17403976]