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# A Review of Preclinical Research Demonstrating that Drug and Non-Drug Reinforcers Differentially Affect Behavior

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## Abstract

This review describes and summarizes current preclinical research revealing important differences between drug and non-drug reinforcers in terms of their effects on behavior. Despite research showing that drugs are not especially strong reinforcers in animals, a number of other behavioral differences potentially relevant to addiction have been reported in studies that have compared drug and non-drug reinforcers. Several of these effects appear only after long-term access to drugs. These include an escalation of drug intake, an increased persistence in responding for the drug, and a decreased sensitivity to the effects of punishers or other suppressors of drug seeking. Further differences between drug and non-drug reinforcers include the effects that reinforcer-paired stimuli have on behavior. Drug cues, as compared to food cues, have been shown to exert greater control over reinforcer-seeking behavior after periods of abstinence. Similarly, behavior previously reinforced by drugs, but not food, has been shown to be susceptible to stress-induced reinstatement after extinction. The behavioral differences between drug and non-drug reinforcers reviewed here may identify special features of drugs that lead to addiction.

### Keywords

animal models of drug abuse; addiction; reinforcer; reward; drug self-administration; cocaine; food

## 1. INTRODUCTION

The purpose of this review is to describe and summarize current preclinical research demonstrating important ways in which drug reinforcers and non-drug reinforcers affect behavior differently. If drug reinforcers are especially “addictive” in ways that non-drug reinforcers are not, then identifying situations where these reinforcers differ could provide insight into addiction. Many studies using drug reinforcers do not include comparisons to non-drug reinforcers. It is therefore often unclear whether the results of such studies reflect general reinforcement processes common to all reinforcers or the unique properties of drug reinforcers. To avoid this kind of interpretational difficulty, the present review will focus on those studies where drug and non-drug reinforcers have been compared *and* have been shown to function differently. Cocaine and food (or similar ingestive reinforcers like saccharin or sucrose) will be the most discussed drug and non-drug reinforcers, respectively, since these have been the most commonly used reinforcers in preclinical studies. Whether behavioral differences observed between cocaine and food are also observed between other drug reinforcers and food, or between cocaine and other non-drug reinforcers, will have to be determined by future research.

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## 2. REINFORCER STRENGTH

It is commonly believed that that drugs lead to addiction because they are extremely powerful reinforcers. In contrast to this popular view, animal research indicates that cocaine is not an especially strong reinforcer as compared to non-drug reinforcers such as food or saccharin. In fact, several recent studies with rats have suggested that cocaine is actually a relatively weak reinforcer. Ahmed and colleagues [1–3] have performed a series of experiments with rats involving a choice between cocaine and saccharin or sucrose. In these studies, rats' responses on one lever led to a cocaine infusion and responding on another, simultaneously available lever resulted in a drop of saccharin- or sucrose-sweetened water. A great majority of rats (~85%) consistently preferred the sweet drink over cocaine. This occurred even though the rats were not food- or water-deprived. Only when the concentration of saccharin was reduced to a very low level did rats become indifferent between saccharin and cocaine [2]. Furthermore, preference for saccharin could not be overcome by increasing the dose of self-administered cocaine [3]. Rats only switched their preference to cocaine when they had to make approximately 8 times as many responses to obtain a saccharin reinforcer [2]. These results led Ahmed (2010) to suggest that drug self-administration may only be valid as a model of addiction for those 15% of rats that choose the drug over sweetened water [1].

Further evidence suggesting that cocaine is a relatively weak reinforcer in rats comes from studies comparing economic demand curves for cocaine and food. Christensen et al. (2008, 2009) trained separate groups of rats to lever press for a food pellet or for a cocaine infusion [4,5]. The number of lever presses required per reinforcer, or fixed-ratio (FR) value, was then varied within subjects over sessions. As the price (FR value) of food went up (to as high as FR-560), rats were persistent in continuing to lever press in an effort to maintain baseline food intake levels. In contrast, rats more quickly stopped lever pressing for cocaine as the price increased. These results showed that demand for food is relatively inelastic while demand for cocaine is more elastic. It should be noted however, that rats in these studies were food-deprived to 85% or less of their free-feeding weights. It is unclear whether demand for food would still be more inelastic than demand for cocaine in less food-deprived rats.

A somewhat different picture emerges from studies where rhesus monkeys, rather than rats, were the subjects. A number of operant choice experiments have shown that preference for cocaine over food is relatively easy to establish in monkeys if the cocaine dose is sufficiently high [7–12]. Preference for cocaine has been observed even when monkeys were food-deprived to 90% of their free-feeding weights [9]. In contrast to results obtained with rats [2,3], exclusive choice of cocaine over food in monkeys has been reliably demonstrated when the number of responses required to receive each reinforcer was the same [7,13]. It should be noted, however, that even in monkeys, cocaine is not an overwhelmingly powerful reinforcer. Preference for cocaine over food in monkeys is sensitive to factors such as dose of cocaine, size of the alternative (food) reinforcer, and the FR value associated with each reinforcer [9,10,13]. (Similar sensitivity to variables such as cocaine dose and alternative reinforcer magnitude have been found in human choice studies [14,15]).

Before concluding that there may be a species difference in cocaine preference, procedural factors that could potentially affect choice behavior must be considered. For example, the palatability of the food alternative could influence choice. The rat studies [2,3] used saccharin- or sucrose-sweetened water as the non-drug alternative, while the monkey studies typically used food pellets [e.g., 7–9]. It is difficult to know whether saccharin is as palatable to a rat as a food pellet is to a monkey. Perhaps weaker preference for cocaine would be observed in monkeys if a more palatable food alternative were used. Type of

economy – open versus closed – is another factor that could influence choice. In both the rat and monkey studies reviewed, cocaine was available within a closed economy since it was only available during experimental sessions. In the rat studies, the sweetened drink alternative reinforcer was also available within a closed economy. In some monkey studies [e.g., 10, 13], food pellets may be considered to be part of an open economy, since monkeys received other foods (e.g., monkey chow, fresh fruit) outside of experimental sessions. This would be expected to promote preference for cocaine. However, even when all food availability was limited to the experimental session, strong preference for cocaine over food has still been observed in monkeys [7]. Another factor that could influence choice is direct drug effects. With relatively short inter-trial intervals, the effects of previous drug infusions may not have dissipated before the next choice trial starts. This could be problematic if, for example, the appetite-suppressing effects of previous cocaine infusions produce a bias against food (or saccharin) choice. The rat studies used a 10-min inter-trial interval, which the investigators that performed these studies described as being a long enough period for the stimulant effects of cocaine to dissipate [2]. That rats overwhelmingly preferred saccharin suggests that direct effects did not interfere with saccharin preference. The monkey studies [e.g., 7, 9] typically used a 10–15 min inter-trial interval, which is substantially shorter than the approximately 45–60 min half-life of i.v. cocaine in rhesus monkeys [16]. It would be interesting to see whether greater choice for food over cocaine would be observed in monkeys trained on a choice procedure with very long inter-trial intervals.

In conclusion, results of pre-clinical research are not consistent with the popular conception that drugs like cocaine cause addiction because they are extraordinarily powerful reinforcers whose temptations are impossible to resist. Instead, results of animal studies suggest that cocaine is, at best, a very ordinary reinforcer. Thus, if drugs like cocaine are especially addictive as compared to non-drug reinforcers like food or sweetened fluid, the pre-clinical research described above suggests that this difference between reinforcers must lie in something other than reinforcer strength.

## 3. EFFECTS OF LONG-TERM ACCESS

### 3.1. Escalation of intake

Ahmed and Koob (1998, 1999) found that extended access (daily 6-h sessions) to self-administered cocaine in rats led to an escalation of cocaine intake over sessions [17,18]. In contrast, rats given limited access to cocaine (1-h daily self-administration sessions) displayed stable rates of cocaine intake over many weeks [18]. These results have been replicated a number of times with different drugs of abuse, including cocaine [17–23], heroin [24], and methamphetamine [25,26]. Ahmed and Koob argue that this escalation of intake is not due to a tolerance or sensitization to the drug, since it is not associated with a rightward or leftward shift in the self-administration dose-response function, but instead results in an upward shift of the curve [17,18]. Others have argued that escalation of intake may reflect tolerance to the rate-decreasing effects of cocaine [27,28] or sensitization to the reinforcing effects of cocaine [29] or sensitization of incentive-salience [30]. (See Zernig et al. [2007] for a review of potential explanations of escalation of drug intake [31]).

In a recent study that compared cocaine vs. sucrose self-administration during extended access conditions (6-h sessions for 21 days), a robust escalation of intake was observed in rats self-administering cocaine, but there was no change in intake over the 21 sessions for rats self-administering sucrose [32]. In mice it has been reported that extended, but not limited, access to a non-drug reinforcer (vanilla-flavored fluid) produces an escalation of intake [33]. It is worth noting, however, that the escalated intake of vanilla-flavored fluid in mice appears to be somewhat idiosyncratic and parameter-bound, as it depends on the

particular operant response used and the particular type of ingestive reinforcer used [33]. Escalation was not observed when a nose-poke was the operant or when a food pellet served as the reinforcer, but was only observed when lever pressing was the operant and vanilla-flavored fluid was the reinforcer. This study did not include comparison groups of mice self-administering drugs, so it is impossible to know whether similar or even greater escalation of drug intake would occur on this procedure. Similarly, in studies using procedures different from those originally used by Ahmed and Koob, escalation of sucrose [34] or saccharin [35] consumption and escalation of wheel running [36] has been observed in rats. But these studies did not include comparison groups that self-administered drugs. Therefore it is not known whether even greater escalation of intake would be observed with drug reinforcers under the conditions used in these experiments.

### 3.2 Changes in reinforcer strength

Consistent with the escalation of intake data, experiments have shown that long-term exposure increases the reinforcer value of cocaine, but not of food. Christensen et al. (2008) performed demand analyses before and after long-term access to self-administration of either cocaine or food in separate groups of rats [6]. They found that demand for cocaine became more inelastic after long-term access. That is, as the number of responses per reinforcer increased (i.e., the “price” of cocaine increased), rats were more persistent in responding after long-term access as compared to before. This result is consistent with those of studies reporting that rats show increased perseverance in responding on progressive ratio schedules (where the number of lever presses required for reinforcement increases within-session) after long access to cocaine self-administration [37,38]. Lenoir and Ahmed (2008) also found increased inelasticity of demand for heroin after extended heroin access [39]. In contrast to the increased demand for cocaine, Christensen et al. (2008) found that there was no change in the elasticity of demand for food after long-term experience lever pressing for food [6]. It should be noted, however, that even though the value of the cocaine reinforcer increased after long-term self-administration in the Christensen et al. (2008) study, it still did not surpass the value of food [6]. Similarly, in the studies by Ahmed and associates [2,3], extended access to cocaine self-administration did not reverse rats’ preference for sweetened water over cocaine.

### 3.3 Resistance to conditioned suppression and punishment

After chronic exposure to self-administered cocaine, rats show a decreased sensitivity to aversive stimuli that normally suppress drug seeking [37,40,41]. In contrast, behavior maintained by sucrose does not decrease in sensitivity to the suppressive effects of aversive stimuli after long-term access to sucrose. For example, Vanderschueren and Everitt (2004) looked at the effects of extended access to cocaine self-administration within a conditioned suppression procedure [41]. (This is also known as the conditioned emotional response [CER] procedure [42]). A tone was established as a conditioned aversive stimulus by pairing it with footshock. The tone was then presented for brief periods while rats lever pressed for cocaine infusions. The tone produced near complete suppression of lever pressing in rats that had limited access to cocaine, replicating results of a previous study that investigated conditioned suppression of cocaine seeking after limited cocaine access [43]. After extended cocaine self-administration access, however, the tone no longer produced conditioned suppression. That is, extended access made rats’ cocaine self-administration more resistant to the suppressive effects of an aversive CS. In contrast, in a parallel group trained under identical conditions but with sucrose (instead of cocaine) as the reinforcer for lever pressing, the tone still suppressed sucrose seeking even after extended access to sucrose. Using a different procedure, Johnson and Kenney (2010) have recently shown that extended access to a highly palatable cafeteria-style diet (cheesecake, bacon, chocolate, etc.) can result in resistance to an aversive CS’s suppressive effects on eating highly palatable food [44]. It

may be the case that access to a varied and energy-rich diet produces effects similar to those of cocaine while access to sucrose alone does not. This can only be a tentative conclusion because Johnson and Kenney's study did not include a comparison group that self-administered cocaine under the same experimental conditions.

Results similar to those found by Vanderschueren and Everitt (2004) have been reported with punishment, as opposed to conditioned suppression. (In punishment, an aversive stimulus such as footshock is presented contingent on the subject's response; in conditioned suppression, a CS and aversive US are presented independently of the subject's behavior.) Pelloux, Everitt, & Dickinson (2007) trained different groups of rats to lever press for cocaine or sucrose reinforcers [40]. After either limited or extended access to the reinforcer (in separate groups), a punishment contingency was introduced where lever presses occasionally resulted in footshock. This eliminated lever pressing in rats that received limited access to either cocaine or sucrose as well as in rats that received extended access to sucrose. Punishment also reduced lever pressing in approximately 75% of rats that received extended access to cocaine self-administration. However, a subset of extended-access cocaine rats (approximately 25% of the sample) were resistant to the effects of punishment. After an initial suppression of cocaine seeking when the punishment contingency was first introduced, cocaine seeking in this subset of rats returned to baseline (pre-punishment) levels. Resistance to the effects of punishment after long-term exposure to self-administered cocaine was also reported by Deroche-Gamonet et al. (2004), though their study did not have a comparison group that responded for a non-drug reinforcer [37].

The decreased sensitivity to conditioned suppressors or punishers is consistent with the hypothesis that extended access to the drug enhances motivation for the drug. Earlier studies with food reinforcement showed that increased food motivation (produced by either increasing the level of food deprivation or by increasing reinforcer magnitude) resulted in less conditioned suppression of food seeking [45]. Similarly, punishers were less effective if motivation for food was increased [46,47]. The results of the studies showing that extended cocaine access produces resistance to the behavioral effects of aversive stimuli [37,40,41] suggest that the effect of extended cocaine access on motivation for cocaine may be functionally analogous to the effect of increasing food deprivation level (or reinforcer magnitude) on motivation for food.

## 4. EFFECTS OF CUES PAIRED WITH THE REINFORCER

Many animal studies have investigated the effects of drug-paired environmental cues on behavior. Fewer studies have directly compared the behavioral effects of drug cues with those of cues paired with a non-drug reinforcer within the same paradigm. The following section specifically focuses on pre-clinical research showing that drug and non-drug reinforcers differ with respect to how environmental cues associated with those reinforcers control behavior. The studies described below involve different types of drug cues, defined by their functional relationship to behavior. Discriminative stimuli ($S^D$s) signal when an operant response will be followed by reinforcement. For example, a light $S^D$ may signal the availability of cocaine self-administation. When the light is presented, lever presses are followed by cocaine infusions. When the light is off, lever presses are not reinforced. Because cocaine is only presented when the light is on, the light becomes associated with cocaine. Another commonly studied drug cue is a CS that is paired with drug infusion. For example, when a rat presses the lever, a light CS is turned on simultaneously with the infusion pump. This CS signals that an infusion has been earned. Such CSs can function as conditioned reinforcers [48]. That is, after a number of pairings of the CS with the drug, animals will perform an operant response to produce the CS alone (without a drug infusion). Drug cues have also been studied as traditional Pavlovian CSs, where both the CS and the

drug infusion are presented independently of the subject's behavior. As will be seen, the manner in which the drug cue is presented is an important determinant of its effect on behavior.

Cicciocioppo, Martin-Fardon, and Weiss (2004) performed a study that illustrates the power of drug cues to control behavior and how drug cues may importantly differ from food cues [49]. Rats that had previously learned to lever press for food pellets were exposed to a single 2-h cocaine self-administration session. A novel white noise stimulus was presented during this cocaine self-administration session and thus served as an $S^D$ signaling that cocaine was available for lever pressing. After this single session where rats self-administered a mean of approximately 40 cocaine infusions, lever pressing was extinguished (i.e., not reinforced) in the absence of the white noise $S^D$ for several sessions. The white noise $S^D$ was tested for its ability to control cocaine seeking at the end of extinction and again at 3-month intervals over the course of a year. No cocaine was available during these test sessions, and thus each test session subjected the white noise to extinction. Interestingly, the white noise $S^D$ significantly increased cocaine-seeking behavior over baseline levels for up to 9 months. That is, only a single experience of cocaine being paired with a cue was sufficient for that cue to have long-lasting and persistent motivating effects on cocaine-seeking behavior. In contrast, in a separate group of rats trained on the same procedure but with sweetened condensed milk as the reinforcer instead of cocaine, the white noise had no significant energizing effect on reinforcer-seeking behavior when tested immediately after extinction or at later points.

Results similar to that described above have been reported in studies investigating the incubation of craving [50,51]. In this phenomenon, the power of drug cues to control drug-seeking behavior grows with the simple passage of time (i.e., without any further exposure to the cues or the drug). In the original report of the effect [50], rats were first trained to self-administer cocaine in the presence of a light $S^D$ over the course of several days. Each self-administered cocaine infusion was accompanied by presentation of a tone-light compound CS (the CS light was different from the $S^D$ light). After acquiring self-administration, rats were divided into separate groups and then subjected to abstinence periods of either 1, 2, 4, 7, 15, 29, or 60 days. During the abstinence period, rats were not presented with the lever or with the $S^D$ or CS associated with cocaine. At the end of the abstinence period, rats were given a test where the light $S^D$ was presented and rats were allowed to lever press. Lever pressing did not result in presentation of the cocaine or the tone-light CS. The amount of cocaine seeking (i.e., lever pressing) controlled by the $S^D$ was found to be an increasing function of the length of the abstinence period. That is, the most cocaine seeking was observed in the group given 60 days of abstinence and the least cocaine seeking was observed in the group given only one day of abstinence. Rats were then given a test of the conditioned reinforcing properties of the tone-light CS. On this test, lever presses resulted in presentation of the CS (but no cocaine). Again, lever pressing was a linear function of the length of time since the last cocaine self-administration session, suggesting that the conditioned reinforcing effects of a cocaine cue grow with time. Incubation of craving has also been observed using the same procedure with sucrose as the reinforcer instead cocaine, but the effect is notably weaker and peaks after about 1 month of abstinence as compared to 3 months when cocaine is the reinforcer [50–53].

The results of the studies described above suggest that the effects of cocaine cues are stronger and more enduring than the effects of cues paired with a non-drug reinforcer like sucrose. These results are especially interesting in light of the studies described earlier suggesting that cocaine is not an especially powerful reinforcer for animals and, at least for rats, cocaine may even be weaker than natural reinforcers such as food or saccharin [1–6]. That conditioned cues associated with cocaine are more persistent in controlling reinforcer-

seeking behavior than cues associated with sucrose or sweetened milk could represent an important difference between drug and non-drug reinforcers that is relevant to addiction. It may be the case that while abused drugs are not very strong reinforcers, they are able to create stimulus-reinforcer associations that are especially well "stamped in" or that are more persistent than the associations between environmental stimuli and natural reinforcers [54,55].

In the studies described above, the drug-paired cues functioned as operant $S^D$s signaling drug availability or as conditioned reinforcers presented contingent upon performance of an operant response. Reinforcer-paired cues can also serve as Pavlovian CSs that elicit conditioned responses (CRs). Kearns and Weiss (2004) performed a study that compared cocaine- and food-paired cues in their ability to elicit a commonly studied CR called sign-tracking, also known as autoshaping [56]. Traditionally, sign-tracking procedures have involved pairings of a discrete CS, such as 15-s insertions of a retractable lever, with non-contingent presentations of an appetitive unconditioned stimulus (US). When food is the US, rats quickly come to approach and contact the lever CS, even though their behavior has no effect on the delivery of food. Sign-tracking has also been demonstrated with a variety of other reinforcers serving as the US, including water [57], electrical brain stimulation [58], and even warmth in heat-deprived subjects [59].

Kearns & Weiss (2004) investigated the ability of a lever CS paired with cocaine to elicit sign-tracking in rats [56]. Separate groups of rats were subjected to pairings of retractable lever insertions with one of three doses of cocaine within a range of commonly self-administered doses (0.125, 0.25, and 0.5 mg/kg/infusion, i.v.). A comparison group received pairings of the lever CS with a food pellet US. As expected, rats trained with the food US quickly learned the sign-tracking response and after just a few sessions came to physically contact the lever CS on close to 100% of trials (well above control levels of approximately 10–15%). In contrast, sign-tracking was not observed in any of the cocaine groups even after 20 sessions. Insertions of the cocaine-paired lever had no discernible effect on rats' approach behavior. Since this study, Uslaner et al. (2006) have reported sign-tracking to a lever paired with i.v. cocaine in rats with a procedure involving very long inter-trial intervals, but the quantity and quality of the elicited behavior greatly differed from that typically observed when food is the US instead of cocaine [60]. In Uslaner et al.'s (2006) study, slightly (but significantly) more approach behavior (defined as being within 1 cm of the lever) was observed in a group that had the lever paired with cocaine as compared to a control group that had lever insertions and cocaine infusions explicitly unpaired. Neither group contacted the lever much. In contrast, when food is the US, rats contact the lever on almost every trial and this contacting is quite vigorous, with rats often biting, gnawing, and pulling the lever [56,61]. (In a later study using the same conditioning procedure (but with a 0.2 mg/kg cocaine dose instead of 0.3 mg/kg), Uslaner et al. (2008) found no difference between a group receiving lever insertions paired with cocaine infusions and a group receiving lever insertions and cocaine infusions explicitly unpaired [62]. Only a group that received lever-cocaine pairings *plus* lesions of the subthalamic nucleus showed significant sign-tracking behavior.)

The finding that when cocaine is the US, little to no sign-tracking behavior occurs is somewhat surprising given that sign-tracking has been observed when a diverse number of other appetitive USs have been used [for review see 61]. Earlier research has shown that sign-tracking is very dependent on the topography of responding elicited by a particular US. For example, Jenkins and Moore (1973) found that when food was the US, pigeons pecked at the keylight CS with a topography resembling the way that they peck at food. When water was the US, in contrast, pigeons contacted the keylight CS with a slurping response that resembled the movements involved in drinking [57]. Receipt of a noncontingent i.v. cocaine

infusion does not require any particular response on the part of the subject. Given that the sign-tracking CR usually resembles the response to the US, it is perhaps less surprising that cocaine does not foster strong sign-tracking behavior.

As the studies described above show, the effects of drug cues on behavior depend on a number of factors, including the type of cue, how it is presented, and the behavior being measured. Cocaine CSs presented as conditioned reinforcers (i.e., contingent on lever-pressing) and cocaine $S^D$s (which previously signaled cocaine availability) have long-lasting effects in controlling cocaine seeking and in this respect differ from cues associated with non-drug reinforcers like sweetened condensed milk or sucrose [49,50]. Cocaine CSs presented non-contingently, in contrast, had little to no ability to elicit sign-tracking behavior, while CSs paired with food elicited robust responding [56,60,62]. Other research (which did not include comparisons with cues associated with non-drug reinforcers) has similarly shown that non-contingently presented drug CSs have little influence on ongoing self-administration or on extinguished drug seeking [63–65]. Thus, the way in which a drug CS is presented (contingently vs. non-contingently) plays a major role in determining its effect on behavior [63]. Given the potential importance of drug cues in driving addiction, it will be important for animal research to model as closely as possible the kinds of cues that drug users encounter in the real world [66].

## 5. REINSTATEMENT

Relapse is perhaps the most difficult challenge in addiction [67,68]. Identifying the factors that cause an individual to resume using drugs after a period of abstinence will be important for the understanding of addiction and for the development of effective addiction treatments. Animal studies have modeled relapse with the use of the reinstatement procedure [69–71]. In this paradigm, animals are first trained to self-administer a drug. After the drug-taking response is well established, extinction is implemented. During extinction, the drug-taking response is no longer followed by the drug reinforcer. This causes drug-seeking behavior to decrease in frequency. Stressful experiences, presentation of drug cues, and priming injections of the drug have been shown to cause a reappearance of drug seeking after it has been extinguished [70,71]. Identifying situations where drug and non-drug reinforcers differ within the reinstatement model could help understand why drug-seeking behavior might be especially sensitive to relapse.

Ahmed and Koob (1997) demonstrated an important difference between cocaine and food as reinforcers within the stress-induced reinstatement paradigm [72]. Rats in separate groups were first trained to lever press for either cocaine infusions or for food pellets. Then, in a second phase, cocaine- and food-seeking behavior was subjected to extinction. Lever pressing declined to low levels. Animals were then exposed to unpredictable footshock. This caused a strong reappearance of lever pressing in the rats that had previously lever pressed for cocaine. In contrast, no recovery of lever pressing was observed in the rats that had been trained to respond for food. The selective shock-induced reinstatement of drug seeking, but not food seeking, has since been replicated in studies where the drug was cocaine [73], nicotine [74], or alcohol [75].

Shelton and Beardsley (2005) found that shock-induced reinstatement of cocaine seeking depended on whether injection-paired cues were presented during the reinstatement test [76]. They first trained rats on the commonly used self-administration procedure where lever presses resulted in a cocaine infusion and the simultaneous presentation of a tone-light CS. Rats were divided into groups prior to the extinction phase. For one group, lever presses during extinction and during the reinstatement test did not result in cocaine, but continued to produce the CS that previously accompanied infusions. For rats in the other group, lever

presses during extinction did not result in cocaine infusions or presentation of the CS. A robust reinstatement of cocaine seeking was observed in the group that continued to receive presentations of the CS. No reinstatement was observed in the group that did not receive presentations of the CS. This result suggests that the footshock does not directly reinstate the lever-press response, but instead reinstates the effects of the cocaine cue, which then acts as a conditioned reinforcer for lever pressing on the test. The finding that drug cues play a critical role in stress-induced reinstatement further highlights the importance of drug cues in controlling drug-seeking behavior.

In addition to stress-induced relapse, the two other commonly studied reinstaters are non-contingent presentation of the reinforcer ("priming") and contingent presentation of reinforcer-paired cues. Noncontingent reinforcer presentation reinstates both drug seeking and food seeking behavior after extinction [77–80]. Contingent presentation of reinforcer-paired cues has also been shown to be an effective reinstater of both drug- and food-seeking behavior, though the effect is often stronger with drug cues than with food cues [50–53]. That stress and cues are reinstaters that are especially effective in re-invigorating animals' drug seeking after extinction or abstinence is consistent with results of human studies showing that both stress and drug cues play a major role in drug relapse [81].

## 6. SUMMARY

Pre-clinical research has shown that there are a number of situations where cocaine and non-drug reinforcers such as food or saccharin differ in their effects on behavior. Several important differences only appear after extended exposure to the reinforcer. As noted previously [17,37], these behavioral effects of long-term exposure to drugs bear a strong resemblance to human behaviors meeting diagnostic criteria for substance abuse and dependence disorders [82]. For example, the escalation of intake and the increased persistence in responding parallel substance dependence disorder criteria pertaining to using the drug in greater amounts than intended and spending increasing amounts of time using or procuring the drug. The decreased sensitivity to punishment parallels the criterion pertaining to continued use despite negative consequences. The similarity between these animal behaviors induced by extended drug (but not food) access and those human behaviors meeting substance dependence criteria suggests that drugs may indeed possess special properties that can contribute to addiction.

The effects that reinforcer-paired cues have on behavior is another area where drug and non-drug reinforcers importantly differ. Cocaine cues, as compared to cues paired with food reinforcers, have been shown to have more persistent and enduring effects on behavior. Further, the control of cocaine cues over behavior increases (incubates) over time to a greater extent than is seen with food-associated cues. The special power of drug cues in influencing behavior, even long since the last exposure to the drug itself, may be especially relevant to relapse, which may be the most difficult obstacle in treating addiction [67,68]. The differential susceptibility of drug seeking to stress-and cue-induced relapse is another feature that distinguishes drugs from non-drug reinforcers like food in terms of potential addiction liability.

The preclinical literature reviewed above suggests that there are number of special characteristics of drug reinforcers that may contribute to addiction. But these factors are certainly not the sole determinants of addiction. After all, the vast majority of users who try drugs like cocaine do not become addicted [1]. Characteristics of the individual likely play a major role in determining which drug users become addicted and which users do not. For example, impulsivity is a trait that is strongly associated with addiction in humans [for reviews, see 83,84]. Drug addicts score higher on questionnaire measures of impulsivity

[85,86] and have greater delay discounting rates (a measure of delay intolerance) than non-addicts [85,87,88]. With human studies, it is not known whether high impulsivity is a trait that precedes drug use or whether high impulsivity is caused by drug use. Recent studies with rats, however, suggest that trait impulsivity precedes and predicts addiction-like drug seeking and taking [89,90]. Research with rats has also shown that exposure to cocaine self-administration can cause an increase in impulsivity [91]. Thus, a vicious circle may be involved with drug reinforcers like cocaine, where impulsivity leads to drug taking and drug taking increases impulsivity [77]. Adding to this cycle all of the special features of drug reinforcers (as compared to non-drug reinforcers) reviewed above may help to explain how a drug user's behavior can spiral out of control with the end result being addiction.

This review has focused on research where drug and non-drug reinforcers, primarily food or similar ingestive reinforcers, have been shown to differ in terms of their effects on behavior. A number of potentially important differences were identified. However, we do not intend to deny the possibility of food addiction or other non-drug addictions. Indeed, there is growing recent behavioral and neurobiological evidence for food addiction (e.g., [44]; for reviews see [92,93]). Rather, our goal has been to highlight situations where, under the same experimental conditions, drugs and non-drug reinforcers have been shown to differ in an effort to identify features of drug reinforcers that may contribute to their potential to produce addiction.

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