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What is This?
Drug Tolerance, Drug Addiction, and Drug Anticipation

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ABSTRACT—Environmental cues associated with drugs often elicit withdrawal symptoms and relapse to drug use. Such cues also modulate drug tolerance. The contribution of drug-associated stimuli to withdrawal and tolerance is emphasized in a Pavlovian-conditioning analysis of drug administration. Conditional responses occur in the presence of cues that have been associated with the drug in the past, such as the setting in which the drug was taken. These conditional responses mediate the expression of tolerance and withdrawal symptoms. Recently, it has become apparent that internal predrug cues, as well as environmental cues, elicit pharmacological conditional responses that contribute to tolerance and withdrawal. Such internal cues include cognitive or proprioceptive cues incidental to self-administration, drug-onset cues that are experienced shortly after administration, and emotional cues. According to the conditioning analysis, addiction treatment should incorporate learning principles to extinguish the association between stimuli (environmental and internal) present at the time of drug administration and the effects of the addictive drug.

KEYWORDS—addiction; drug tolerance; Pavlovian conditioning; withdrawal symptoms

When drug-control legislation was first implemented in 1915, it became clear that drug use could not be ended simply by legislative fiat. Lawrence Kolb, the first superintendent of the “Narcotics Treatment Farm” in Lexington, Kentucky, noted that treated addicts experienced drug-withdrawal symptoms and craving, and often relapsed, when confronted with situations that had been paired with their drug use: “We see this plainly exemplified in the cured tobacco smoker . . . A cured smoker who usually does not crave tobacco may feel an intense desire resembling hunger when he gazes on a box of cigars or sits in the company of friends who are smoking” (Kolb, 1927, p. 39). Other researchers subsequently described examples of patients who displayed withdrawal symptoms and who craved drugs when confronted with cues that had signaled the drug—e.g., seeing the paraphernalia of addiction such as a syringe and tourniquet, discussing drugs with others, or even seeing actors injecting heroin in a movie. The results of many experiments with animals support clinical observations that predrug cues are powerful elicitors of withdrawal symptoms (see reviews by McDonald & Siegel, 2004; Siegel & Ramos, 2002).

In summary, drug users respond in anticipation of drugs with withdrawal symptoms. The study of anticipatory responding to biologically significant effects is the study of Pavlovian conditioning.

PAVLOVIAN CONDITIONING AND DRUG EFFECTS

Events occurring during drug administration correspond to a Pavlovian conditioning trial. Using the usual conditioning terminology, cues accompanying the primary drug effect function as conditional stimuli. The direct effect of the drug constitutes the unconditional stimulus. Prior to any learning, this pharmacological stimulation elicits responses that compensate for the drug-induced disturbances (unconditional responses). After some pairings of the predrug conditional stimuli and pharmacological unconditional stimuli, drug-compensatory responses are elicited as conditional responses. These conditional compensatory responses mediate the development of tolerance by counteracting the drug effect. For example, in rats tolerant to the hypothermic (temperature-lowering) effect of alcohol, administration of an inert substance in the presence of alcohol-associated cues results in a rise in body temperature (hyperthermia; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). This hyperthermia is a conditional compensatory response that attenuates the hypothermic effect of alcohol administered in the presence of alcohol-paired stimuli.

Pavlovian Conditioning and Drug Tolerance

To understand the role of drug-associated cues in drug addiction we first must understand the role of these cues in drug tolerance.
Tolerance is said to occur when the effect of a drug decreases over the course of repeated administrations. Pavlovian conditioning contributes to tolerance. After some pairings of the pre-drug conditional stimulus and pharmacological unconditional stimulus, conditional compensatory responses counteracting the drug effect develop, producing tolerance. As the drug is administered more and more often, and the conditional compensatory response grows in strength, the attenuation of the drug effect becomes more pronounced.

A phenomenon that highlights the contribution of Pavlovian conditioning to drug tolerance has been termed the situational specificity of tolerance. The simplest design to illustrate situational specificity of tolerance is illustrated in Figure 1. During the tolerance-development phase, the drug is repeatedly administered in a distinctive environment. On the tolerance test, the drug is administered in either the same environment in which it had previously been administered, or in an alternative environment. Greater tolerance is seen in subjects who are administered the drug in the same environment than in subjects administered the drug in a different environment.

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A phenomenon that highlights the contribution of Pavlovian conditioning to drug tolerance has been termed the situational specificity of tolerance. The simplest design to illustrate situational specificity of tolerance is illustrated in Figure 1. During the tolerance-development phase, an organism is administered a drug in a particular environment (schematically depicted as a gray box) on a number of occasions, sufficient for tolerance to be apparent. On a final tolerance-test session, if the drug is administered in the usual drug-administration environment tolerance is apparent (i.e., the drug effect is smaller than it was at the start of the tolerance-development phase). However, tolerance is attenuated (i.e., the drug effect is partially or completely reinstated) if the drug is administered in a different environment (the white box in Fig. 1). Situational specificity of tolerance has been seen with respect to tolerance to a variety of effects—including lethal effects—of various drugs, in many species (see Siegel et al., 2000).

Situational specificity of tolerance has been demonstrated in studies involving explicit pairing of a cue with a drug effect, as well as studies using opportunistic designs that rely on subjects’ extraexperimental conditioning histories. College students display greater tolerance to the intoxicating effects of alcohol when the alcohol is consumed in the presence of the usual alcohol cues—a beer-flavored beverage—than if the same amount of alcohol is consumed in a novel blue, peppermint-flavored beverage. Tolerance to the cardiac effect of caffeine is more pronounced if the caffeine is administered in the context of the usual caffeine-administration cues (i.e., consumed in coffee) than if the same blood level of caffeine is obtained with an administration procedure that does not incorporate these cues (i.e., intravenous administration; see Siegel et al., 2000; Siegel, Kim, & Sokolowska, 2003).

Situational specificity is expected on the basis of the conditioning analysis of tolerance. That is, drug-associated cues elicit the conditional compensatory responses that attenuate the drug effect; thus tolerance is greater when tolerance is assessed in the presence of drug-associated cues than when it is assessed elsewhere.

**Pavlovian Conditioning and Drug-Withdrawal Symptoms**

According to the conditioning analysis, tolerance and withdrawal symptoms are both manifestations of the same conditional compensatory responses. When the drug is administered in the context of the usual drug-administration cues, such responses attenuate the drug effect and contribute to tolerance. However, if the usual drug is not administered in the presence of the usual cues for drug administration, conditional compensatory responses achieve full expression because they are not modulated by a drug effect. Such responses, displayed in such circumstances, are termed withdrawal symptoms: “It is the anticipation of the drug, rather than the drug itself, that is responsible for these symptoms . . . some drug 'withdrawal symptoms' are, more accurately, drug 'preparation symptoms'” (Siegel & Ramos, 2002, p. 171). Conditional compensatory responses elicited in such circumstances include the readily observable drug-compensatory responses and less readily observable neurochemical responses that are interpreted as craving.

**INTEROCEPTIVE CUES FOR DRUGS**

Studies of conditioning effects on tolerance and withdrawal typically have manipulated exteroceptive cues. Exteroceptive cues are external and public—they are apparent both to the organism experiencing the drug effect and to the experimenter.
studying the drug effect. Distinctive visual, auditory, or olfactory cues present at the time of drug administration all are examples of exteroceptive cues. In contrast, some cues for a drug are internal and private—they are apparent only to the drug taker. There is evidence that such interoceptive cues become associated with a drug (see Siegel et al., 2000). Two types of interoceptive cues that recently have been studied are self-administration cues and drug-onset cues.

Self-Administration Cues
The effects of both licit (e.g., alcohol, caffeine, and nicotine) and illicit (e.g., heroin, cocaine, marijuana) drugs are experienced following the act of self-administration. Interoceptive cues arising from the act of self-administration modulate the expression of both tolerance and withdrawal symptoms.

Self-Administration and Tolerance
Typically, people experience the effects of drugs only after engaging in some self-administration ritual. There is some internal process that motivates the drug taker to smoke a cigarette, or inject heroin, or pour a glass of scotch. Additionally, engaging in the behaviors that are precursors to these drug effects gives rise to many response-initiating (or response-produced) cues. These interoceptive, self-administration cues are paired with the drug effect. If these self-administration cues function as other conditional stimuli, they should come to elicit conditional compensatory responses. Moreover, if self-administration cues elicit conditional compensatory responses, it would be expected that self-administered drugs should have a smaller effect than do passively received drugs. Indeed, people do display greater tolerance to alcohol and opiates when they self-administer the drugs than when they receive the same doses in a pattern determined by the experimenter. Furthermore, animals that self-administer a drug by making a designated response (e.g., pressing a lever in an operant chamber) are more tolerant to the drug than are “yoked” animals that receive the same drug doses at the same time, but not contingent on their behavior. Thus, self-administration cues function as conditional stimuli, and the fact that tolerance is especially pronounced when the drug effect occurs following the usual self-administration cue is but another demonstration of the situational specificity of tolerance (Weise-Kelly & Siegel, 2001).

Self-Administration and Withdrawal Symptoms
On the basis of a conditioning analysis, self-administering subjects should not only display more tolerance than passive-receipt subjects, but should also display more withdrawal symptoms when the instrumental response no longer leads to pharmacological reinforcement. Alcohol-experienced people (Mello & Mendelson, 1970) and morphine-experienced rats (MacRae & Siegel, 1997), when denied access to drugs, display more severe withdrawal symptoms if they had previously self-administered the drug than if they had passively-received the drug. These results would be expected if withdrawal symptoms in response to self-administration cues are another manifestation of the conditional compensatory responses that mediate tolerance when the drug is administered.

Drug-Onset Cues
When a drug is administered, people experience its initial effects prior to experiencing the full effect of the drug. The warmth experienced when starting to consume alcohol may be followed by the intoxicating effect of the drug. The short-term rush experienced immediately after intravenous heroin administration may be followed by a general sense of euphoria. That is, within each drug administration, drug-onset cues reliably precede the later, larger drug effect; thus there is the potential for the formation of associations whenever a drug is administered. Functionally, a small drug dose, sensed shortly after administration, is paired with a larger drug dose, sensed some time after administration as the peak effect of the drug is experienced. Greeley, Lé, Poulos, and Cappell (1984) provided evidence that drug-onset cues serve as conditional stimuli. They demonstrated that a small dose of alcohol could serve as a conditional stimulus for a larger dose of alcohol. Paired rats consistently received a low dose of alcohol 60 minutes prior to a high dose of alcohol. Unpaired rats received the low and high doses on an unpaired basis. When tested for the tolerance to the hypothermic effect of the high dose following the low dose, paired rats, but not unpaired rats, displayed tolerance. There also is evidence that a small dose of morphine may serve as a cue for a larger dose of the opiate and control the display of morphine tolerance (Cepeda-Benito & Short, 1997).

Drug-Onset Cues and Tolerance
The type of association that potentially forms within each administration has been termed an intra-administration association. Results of several experiments indicate that such associations do form when a drug is administered, and that drug-onset cues, in common with exteroceptive cues, contribute to drug tolerance (see Sokolowska, Siegel, & Kim, 2002).

Drug-Onset Cues and Withdrawal Symptoms
On the basis of the conditioning analysis, withdrawal symptoms—a manifestation of a pharmacological conditional compensatory response—should be elicited not only by drug-associated environmental cues, but also by drug-associated pharmacological cues. Recently, McDonald and I (McDonald & Siegel, 2004) reasoned that if an intra-administration association was formed during a series of morphine administrations, presenting a small dose of the opiate might be expected to reproduce the early effect of the drug—an effect that had become associated with the subsequent, larger effect. Typically, for the organism with a history of morphine administration,
administration of the opiate prevents withdrawal symptoms from occurring. In contrast, we suggested that a small dose of the drug should actually elicit the symptoms in rats previously administered larger doses of the drug. As we predicted, rats with a history of administration of large morphine doses (50 mg/kg of body weight) displayed behavioral and thermic evidence of morphine withdrawal when administered small (5 mg/kg) doses of the opiate. Such a finding would be expected if, during administrations of the large dose of morphine, the rats had formed an association between drug-onset cues and the subsequent larger drug effect.

**Drug-Onset Cues and Relapse**

Demonstrations that drug-onset cues elicit withdrawal symptoms are consistent with clinical observations. It is well established that drug-withdrawal symptoms and a relapse to drug use frequently are precipitated by exposure to small drug doses (see McDonald & Siegel, 2004). For example, the long-abstinent alcoholic may experience a “loss of control” if he or she tastes alcohol. This small-dose effect may be attributable to the addict’s association of the initial effect of the drug (i.e., drug-onset cues experienced soon after administration) with subsequent larger amounts of the drug.

**IMPLICATIONS FOR TREATMENT**

Appreciation of the contribution of learning to drug tolerance and withdrawal has led to the development of conditioning-based, behavioral therapies for addiction. Such cue-exposure therapies are designed to extinguish the association between predrug cues and the systemic effects of the drug (so that these cues will no longer elicit conditional compensatory responses). The patient is presented with drug-associated stimuli while denied access to the drug. Typically such treatment involves presentation of exteroceptive drug-associated cues; however, the treatment protocol should be more effective if it incorporates extinction of drug-onset cues and self-administration cues, as well as exteroceptive cues. That is, the patient should be exposed to small amounts of the addictive substance and be permitted to engage in self-administration rituals (Siegel & Ramos, 2002).

Research concerning two types of interoceptive cues—self-administration cues and drug-onset cues—has been summarized. Further research can elucidate other important interoceptive cues such as memories and emotions. Merely thinking about their preferred drug elicits withdrawal distress and craving in cigarette smokers, alcoholics, and heroin addicts (Greeley & Ryan, 1995; Siegel & Ramos, 2002). Emotions, especially negative emotions, are frequent elicitors of withdrawal distress and craving. As summarized by Greeley and Ryan (1995): “A good case exists, then, for making cognitions per se a pivotal concern of conditioning models, allowing the possibility of cognitions as interoceptive cues” (p. 133). The effectiveness of cue-exposure treatment may be enhanced if it incorporates systematic elicitation of such cognitive drug-associated stimuli (Siegel & Ramos, 2002).

The purpose of cue-exposure treatments is to enable the addict to confront drug-associated stimuli without experiencing the conditional compensatory responses evoked by these stimuli prior to treatment, and thus maintain abstinence. Autobiographical accounts of addiction typically describe difficulties authors face in maintaining long-lasting abstinence. As Jean Cocteau noted in his description of his own addiction, “the dead drug leaves a ghost behind. At certain hours it haunts the house” (Cocteau, 1958, p. 60). The “ghost” is the conditional compensatory response elicited by drug-associated cues. It “haunts the house” when the addict is confronted with conditional stimuli that have been paired with drug use. These stimuli may be exteroceptive cues that have been paired with the drug in the past, such as the time the drug was usually taken, the people usually present when the drug was administered, the places where the drug was used, and tastes or odors present at the time the drug was used. More importantly, conditional compensatory responses may be elicited by highly salient interoceptive cues that have been associated with the drug. Understanding addiction requires an understanding of the conditioning history that causes this ghost to materialize. Effective treatment requires an appreciation of how conditioning may be used to exorcise the ghost.

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**Recommended Reading**

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