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Pavlovian Psychopharmacology: The Associative Basis of Tolerance

Shepard Siegel, Marco A. S. Baptista, Joseph A. Kim, Robert V. McDonald, and Lorraine Weise-Kelly
McMaster University

The Pavlovian conditioning analysis of drug tolerance emphasizes that cues present at the time of drug administration become associated with drug-induced disturbances. These disturbances elicit unconditional responses that compensate for the pharmacological perturbation. The drug-compensatory responses eventually come to be elicited by drug-paired cues. These conditional compensatory responses (CCRs) mediate tolerance by counteracting the drug effect when the drug is administered in the presence of cues previously paired with the drug. If the usual predrug cues are presented in the absence the drug, the unopposed CCRs are evident as withdrawal symptoms. Recent findings elucidate intercellular and intracellular events mediating CCRs and indicate the importance of internal stimuli (pharmacological cues and interoceptive cues inherent in self-administration) to the acquisition of drug tolerance and the expression of withdrawal symptoms.

Early chroniclers of drug effects noted that responsivity to drugs often decreased as a function of experience with the drug. For example, in 1612, Jean Mousin, physician to the King of France, wondered why individuals sometimes became progressively more sober while they were continuing to drink alcoholic beverages. Although the term *tolerance* was not used until some years later, it appears that Mousin observed the phenomenon now termed *acute tolerance*—decreased responsiveness to a drug within the course of a single administration (Kalant, 1998).

Acute Tolerance and Withdrawal

Acute tolerance has been investigated extensively with respect to ethanol (e.g., see LeBlanc, Kalant, & Gibbins, 1975) as well as other drugs, such as opiates. For example, over the course of a single, long administration of morphine, accomplished by gradual infusion via an implanted morphine pellet, the analgesic effect of the drug decreases (e.g., see Tilson, Rech, & Stolman, 1973; Wei & Way, 1975).

The existence of acute tolerance is evidence that pharmacological stimulation initiates adaptive responses that compensate for the primary drug effect (Haefely, 1986; Ramsay & Woods, 1997; Siegel & Allan, 1998). The observed effect of a drug is therefore the net result of primary, drug-induced changes and these secondary, compensatory responses. Further evidence for drug-compensatory responses may be seen when the drug effect is abruptly terminated (e.g., by cessation of the delivery of ethanol vapor to the environment or by removal of a morphine pellet). The compensatory response, having little to compensate for, may now be seen. Thus, on termination of an ethanol effect (and the anticonvulsant effect of the drug), a decrease in seizure threshold is noted (e.g., see McQuarrie & Fingl, 1958). Similarly, on termination of a morphine infusion (and the analgesic effect of the drug), an increased sensitivity to painful stimuli is noted (e.g., see Tilson et al., 1973; Wei & Way, 1975). Such compensatory responses seen following termination of drug administration are termed *acute withdrawal symptoms*.

Chronic Tolerance and Withdrawal

Typically, drugs are not administered via constant long infusions. Rather, administration is by means of a brief injection, and the effects are measured following the termination of the injection. It has been known for many years that when such measurements are made following each of a series of drug administrations, the drug effect frequently is noted to become progressively smaller over the course of these administrations. This decreasing effect seen following each successive administration of a drug is termed *chronic tolerance* (for historical reviews of chronic tolerance to ethanol and opiates, see Kalant, 1998, and DuMez, 1919, respectively). The term *tolerance*, as it is generally used, refers to such chronic tolerance.

Chronic tolerance, like acute tolerance, is mediated by compensatory responding. That is, at some time following a series of drug administrations, if the drug no longer is administered, pharmacological aftereffects may be seen. These withdrawal symptoms seen after chronic administration may be termed *chronic withdrawal symptoms* but generally are referred to simply as *withdrawal symptoms*.

Shepard Siegel, Marco A. S. Baptista, Joseph A. Kim, Robert V. McDonald, and Lorraine Weise-Kelly, Department of Psychology, McMaster University, Hamilton, Ontario, Canada.

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Correspondence concerning this article should be addressed to Shepard Siegel, Department of Psychology, McMaster University, Hamilton, Ontario, Canada L8S 4K1. Electronic mail may be sent to siegel@mcmaster.ca.

Acute tolerance results from drug-compensatory processes reflexively elicited by a drug (e.g., Haefely, 1986). [1] Chronic tolerance (hereinafter termed *tolerance*) results, at least in part, from drug-compensatory processes elicited not only by the drug effect, but also by cues that, in the past, have been associated with the drug effect. That is, learning contributes to tolerance.

Tolerance and Learning

As early as the 1960s, some investigators proposed that a complete analysis of tolerance requires an appreciation of associative principles. For example, Cohen, Keats, Krivoy, and Ungar (1965) suggested that "the development of tolerance can be considered a form of learning" (p. 383), because actinomycin D, an inhibitor of protein synthesis, retarded the development of tolerance (much as it retards the acquisition of other learned responses). Results of subsequent research demonstrated that many metabolic inhibitors impede the development of morphine tolerance, as do several other manipulations that retard learning (e.g., electroconvulsive shock or frontal cortical stimulation). Moreover, several pituitary peptides that antagonize metabolic inhibitors and facilitate learning also facilitate the acquisition of tolerance (see Siegel, 1983, for a historical summary of research concerning the relationship between learning and tolerance).

In addition, some researchers proposed that learning contributes to tolerance because tolerance often is very well retained. That is, if an organism has acquired tolerance to a drug, this tolerance may be manifest even after a prolonged drug-free period. For example, tolerance to the analgesic effect of morphine in rats persists over a drug-free period of months—indeed, perhaps even a year (Cochin & Kornetsky, 1964; Kornetsky & Bain, 1968). Because learned responses typically display very substantial retention (e.g., see Kimble, 1961, p. 281), some investigators have suggested that tolerance is "a reaction analogous to memory" (Cochin, 1970, p.19).

The contribution of learning to tolerance and the importance of drug-associated environmental cues to tolerance are incorporated in an analysis of tolerance that emphasizes Pavlovian conditioning principles.

Pavlovian Conditioning and Tolerance

Pavlov (1927, pp. 35–37) suggested that the administration of a drug could be viewed as a conditioning trial; the drug effect serves as the unconditional stimulus (US), and the immediately antecedent environmental cues served as the conditional stimulus (CS). Some years ago, we suggested that "conditioned drug responses are commonly opposite in direction to the unconditioned effects of the drug" (Siegel, 1975, p. 499), and these "compensatory" conditional responses (CRs) attenuated the drug effect and mediated tolerance. The pharmacological CR, then, was conceived as being opposite in direction to the pharmacological unconditional response (UR)—at least in instances in which tolerance occurred—a position contrary to Pavlov's view that the CR was similar to the UR.

The conditioning analysis of drug administration has subsequently undergone several important modifications, primarily as a result of critical analyses of pharmacological conditioning by several authors (B. R. Dworkin, 1993; Eikelboom & Stewart, 1982; Poulos & Cappell, 1991; Ramsay & Woods, 1997; Wikler, 1973). It is now apparent that the initial application of the Pavlovian conditioning paradigm to drug administration was somewhat superficial. The UR to a pharmacological stimulus, in common with reflex responses to other stimuli, consists of responses generated by the central nervous system (CNS). The drug effect that initiates these CNS-mediated responses is the US (not the UR). For many effects of drugs, the UR consists of responses that compensate for drug-induced perturbations. These unconditionally-elicited compensatory responses are responsible for acute tolerance (Ramsay & Woods, 1997). After some pairings of the predrug CS and pharmacological US, drug-compensatory responses can be elicited by predrug cues. These conditional compensatory responses (CCRs) mediate the development of tolerance by counteracting the drug effect. As noted by B. R. Dworkin (1993), the analysis now closely follows Pavlov's (1927) conceptualization of conditioning: "Conditioned drug responses, when adequately isolated, dissected, and understood, exemplify in an uncomplicated way the phenomenon first described by Pavlov: The conditioned reflex resembles the unconditioned reflex, and as it develops, it augments the effect of the unconditioned reflex" (B. R. Dworkin, 1993, p. 38).

Typically, CCRs are observed by presenting the usual predrug cues in the absence of the drug. Perhaps the first demonstration of a CCR was provided by Subkov and Zilov more than 60 years ago. They injected dogs with epinephrine (adrenaline) on a number of occasions (one injection every few days) and noted that the tachycardiac effect of the drug decreased over the course of repeated injections (i.e., tolerance developed). On a final test session, they placed the dog in the injection stand and administered an inert substance (Ringer's solution). On this test, a decrease in heart rate was observed: "It follows that the mere reproduction of the experimental conditions in which the animal is accustomed to receive adrenaline is alone sufficient to set in motion the mechanism, by means of which the animal counteracts the high vascular pressure produced by adrenaline" (Subkov & Zilov, 1937, p. 295).

Subsequently, CCRs have been demonstrated with many drugs (see Siegel, 1991, 1999a), including commonly abused drugs, such as opiates (e.g., see Grisel, Wiertelak, Watkins, & Maier, 1994; Krank, Hinson, & Siegel, 1981;

[1] Although acute tolerance typically is attributed to drug-compensatory responses unconditionally elicited by the drug, there is a potential role for instrumental learning in acute tolerance (B. R. Dworkin, 1993; Ramsay & Woods, 1997). During the early part of an initial drug infusion, organisms may acquire a behavioral strategy that is negatively reinforced by a reduction in the drug-induced disturbance. For example, when administered a drug that induces hypothermia, subjects may learn to make postural adjustments that conserve body heat (Ramsay & Woods, 1997).

Raffa & Porreca, 1986), ethanol (e.g., see Larson & Siegel, 1998; Siegel, 1987), and caffeine (Andrews, Blumenthal & Flaten, 1998; Rozin, Reff, Mark, & Schull, 1984).

The original phenomenon implicating CCRs in tolerance has been termed the "situational-specificity of tolerance" (Siegel, 1978, p. 345). After tolerance is established by repeatedly administering the drug in a particular environment, tolerance often is more pronounced in that drug-paired environment than in an alternative environment.

Situational Specificity of Tolerance

Situational specificity of tolerance has been demonstrated in experiments that have cues explicitly paired with a drug effect or that have used *opportunistic designs* that rely on the subjects' extraexperimental conditioning histories.

Experimental designs. There are several experimental designs that have been used to demonstrate situational specificity of tolerance (see Siegel, 1983). For example, the *paired–unpaired* design was used both by Siegel, Hinson, and Krank (1978), to demonstrate the situational specificity of tolerance, and by Baptista, Siegel, MacQueen, and Young (1998), to evaluate the neurochemical basis of the phenomenon. In these experiments, rats were assigned to paired or unpaired conditions. For paired rats, pretest morphine injections were signaled by an audiovisual cue. Unpaired rats received their pretest drug injections and cue presentations in an unpaired manner. Following the last pretest injection, analgesia was assessed in the presence of the audiovisual cue. Despite the fact that paired and unpaired rats received the same number of morphine injections, at the same doses, at the same intervals, paired rats were more tolerant to morphine-induced analgesia than were unpaired rats.

Opportunistic designs. An example of an opportunistic design is that used by McCusker and Brown (1990). In their experiment, one group of (human) participants was given alcohol in a familiar context (beer in a simulated bar, the beer-bar group), and another group was administered the same dose of alcohol in an unusual form and context (alcohol mixed in carbonated water and consumed in an office setting, the alcohol-office group). Participants in the beer-bar group were less impaired on cognitive and motor tasks than were the subjects in the alcohol-office group. More recently, Remington, Roberts, and Glautier (1997) reported that the same amount of alcohol induced less impairment when college students consumed the alcohol in an alcohol-associated beverage (beer) rather than in a novel liquid (a blue, peppermint-flavored beverage).

Situational specificity of tolerance to the lethal effects of drugs. The most dramatic demonstrations of the situational specificity of tolerance concern tolerance to the lethal effects of drugs. Following a series of drug administrations involving escalating doses, each in the context of the same cues, tolerance develops to the potentially lethal effect of that drug as long as it is administered in the usual context. Altering the context of drug administration increases the lethality of several drugs, including heroin (Siegel, Hinson, Krank, & McCully, 1982), pentobarbital (Vila, 1989), and alcohol (Melchior, 1990; Melchior & Tabakoff, 1982; but see Neumann & Ellis, 1986; Tsibulsky & Amit, 1993). There are clinical reports suggesting that an alteration in predrug cues may be responsible for some instances of opiate overdoses experienced by drug addicts (Siegel, 1984) and by patients that receive drugs for pain relief (Siegel & Ellsworth, 1986; Siegel & Kim, 2000).

Generality of the situational specificity of tolerance. Situational specificity has been demonstrated with respect to tolerance to many effects of a variety of drugs: opiates (reviewed by Siegel, 1991), naloxone (Goodison & Siegel, 1995b), ethanol (e.g., see Lê, Poulos, & Cappell, 1979; Seeley, Hawkins, Ramsay, Wilkinson, & Woods, 1996), nicotine (e.g., see Cepeda-Benito, Reynosa, & McDaniel, 1998; Epstein, Caggiula, & Stiller, 1989), pentobarbital (e.g., see Cappell, Roach, & Poulos, 1981), phencyclidine (Smith, 1991), immunoenhancing drugs (Dyck, Driedger, Nemeth, Osachuk, & Greenberg, 1987), cholecystokinin (CCK; Goodison & Siegel, 1995a), carisoprodol (Flaten, Simonsen, Waterloo, & Olsen, 1997), haloperidol (Poulos & Hinson, 1982) and several benzodiazepines (Greeley & Cappell, 1985; King, Bouton, & Musty, 1987; Siegel, 1986b). It has been reported in many species, from snails (Kavaliers & Hirst, 1986) to humans (e.g., see Dafters & Anderson, 1982). Situational specificity is also typically seen with respect to cross-tolerance. Thus, rats tolerant to Drug A in a particular context also display cross-tolerance to Drug B if Drug B is administered in that context, but not if Drug B is administered in an alternative context (e.g., see El-Ghundi, Kalant, Lê, & Khanna, 1989; Goodison & Siegel, 1995b; but see Carter & Tiffany, 1996).

The fact that tolerance displays situational specificity is consistent with the conditioning analysis of tolerance. That is, drug-associated cues elicit CCRs that attenuate the drug effect, thus tolerance is greater when assessed in the presence of drug-associated cues than when it is assessed elsewhere.

Parallels Between Pavlovian Conditioning and Tolerance

If conditioning processes contribute to tolerance, it would be expected that nonpharmacological manipulations of putative CSs (cues present at the time of drug administration), known to affect the course of Pavlovian conditioning, should similarly affect the course of CCR acquisition and thus tolerance. The results of many such manipulations have been assessed. Because these data are extensively reviewed elsewhere (e.g., see Goudie, 1990; Ramsay & Woods, 1997; Siegel, 1989, 1991), we summarize them only briefly here.

Extinction of tolerance. The magnitude of established CRs is decreased by *extinction*, that is, repeated presentations of the CS without the US, or unpaired presentations of both the CS and US. Similarly, tolerance to both the lethal (Siegel, Hinson, & Krank, 1979) and analgesic (e.g., see Siegel, Sherman, & Mitchell, 1980) effects of morphine is attenuated by repeated presentation of the predrug cues. Once tolerance to the behaviorally sedating effect of morphine is established by repeated presentation of the drug in

the presence of distinctive cues, this tolerance is attenuated by subsequent unpaired presentation of these cues and the drug (Faneslow & German, 1982). Extinction of morphine tolerance is seen with a variety of routes of administration, including subcutaneous (Siegel et al., 1980) and directly into the ventricles of the brain (MacRae & Siegel, 1987). Furthermore, tolerance to a variety of effects of ethanol, amphetamine, midazolam (a short-acting benzodiazepine), and the synthetic polynucleotide, Poly I:C, can also be extinguished (see reviews by Siegel, 1989, 1991).

External inhibition of tolerance. Pavlov (1927) noted that presentation of a novel, extraneous stimulus disrupts the elicitation of established CRs. Such *external inhibition* of conditional responding has also been shown to eliminate tolerance to the analgesic effect of morphine (Poulos, Hunt, & Cappell, 1988) and the hypothermic (Siegel & Sdao-Jarvie, 1986) and ataxic (Siegel & Larson, 1996; Larson & Siegel, 1998) effects of ethanol. That is, drug-experienced rats that normally display tolerance fail to do so when, following drug administration, they are presented with an arbitrary novel stimulus. This novel stimulus can consist of the unexpected presentation of a light and noise compound (e.g., see Siegel & Sdao-Jarvie, 1986; Siegel & Larson, 1996), the administration of a drug (e.g., Poulos et al., 1988), or the unexpected omission of such exteroceptive or interoceptive stimuli (Larson & Siegel, 1998, and Poulos et al., 1988, respectively).

Some instances of overdose may result because an extraneous stimulus intrudes into the usual drug administration ritual thus disrupting the expression of tolerance. Siegel (1989) described such a scenario occurring in the case of an enigmatic overdose suffered by a heroin addict. Poulos et al. (1988) suggested that their finding that a pharmacological cue may serve as an external inhibitor is also relevant to understanding overdoses:

> People who have acquired tolerance to a substantial dose of a drug for either medical or nonmedical purposes sometimes incorporate a new drug into their regime . . . the added drug may make such an individual vulnerable to drug overdose reactions because the previously established tolerance could be disrupted by the cue effects of the added drug. (p. 415)

Retardation of the development of tolerance. One technique for attenuating the development of a CS–US association is to present the CS alone repeatedly prior to pairing it with the US (the CS preexposure or latent inhibition effect, see Lubow, 1973). If Pavlovian conditioning contributes to tolerance, it would be expected that subjects with extensive experience with drug administration cues prior to the time that these cues are paired with the drug effect should be relatively retarded in the acquisition of tolerance (compared with subjects with minimal preexposure to these cues), despite the fact that the groups do not differ with respect to their histories of drug administration. Such an effect of CS preexposure has been demonstrated with respect to tolerance to the analgesic effect of morphine, the immunostimulatory effect of Poly:IC, and the anorectic effect of CCK (see Goodison & Siegel, 1995a; Siegel, 1989).

Another procedure for attenuating the development of a CS–US association is intermittent (rather than continuous) pairings of a CS and US. That is, if only a portion of the presentations of the CS are paired with the US, then CR acquisition is retarded (compared with the situation in which all presentations of the CS are paired with the US; see Mackintosh, 1974). On the basis of a conditioning analysis of tolerance, it would be expected that a group in which only a portion of the presentation of drug administration cues are followed by the drug should be slower to acquire tolerance than a group that never has exposure to drug-paired cues without actually receiving the drug, even when the two groups are equated with respect to all pharmacological parameters. Such findings have been reported with respect to tolerance to several effects of morphine (see Siegel, 1989, 1991).

Other manipulations of predrug cues. In addition to the parallels between conditioning and tolerance summarized thus far, the two phenomena are similar in other respects. Like other CRs, drug tolerance displays inhibitory learning (Faneslow & German, 1982; Hinson & Siegel, 1986; Siegel, Hinson, & Krank, 1981), stimulus generalization (e.g., Caggiula et al., 1991), and a flattening of the generalization gradient as a result of extending the interval between acquisition and assessment (Feinberg & Riccio, 1990). Tolerance also displays sensory preconditioning (Dafters, Hetherington, & McCartney, 1983) and a variety of compound-conditioning effects, such as overshadowing (e.g., see Dafters & Bach, 1985; Walter & Riccio, 1983) and blocking (Dafters et al., 1983).

Glucose administration and cholinergic manipulations. In recent years there has been increasing evidence that simple glycemic manipulations applied immediately after a CS–US pairing modulate learning. For example, injection of glucose after a trial facilitates learning in mice and rats, and oral consumption of glucose facilitates learning in humans. The posttraining treatments presumably modulate memory storage processes because the effect of glucose on memory is time-dependent. That is, the effects are maximal if the glycemic manipulations occur immediately after a trial, and they are minimal to nonexistent if the manipulations are delayed (e.g., for 1 hr; for reviews of glycemic manipulations and conditioning, see Manning, Parsons, Cotter, & Gold, 1997; Okaichi & Okaichi, 1997).

If drug tolerance is due in part to associations between drug administration cues and the systemic effects of the drug, then the formation of these associations and, hence, the development of tolerance should be enhanced in subjects receiving glucose shortly after each drug administration. Consistent with this prediction, Siegel (1999b) recently demonstrated that, in rats, the development of tolerance to both the analgesic effect of morphine and to the ataxic effect of ethanol is enhanced if each administration of the drug is followed by an injection of 120 mg/kg glucose. However, if the injection of glucose is delayed, the glucose does not enhance the development of tolerance.

Glucose facilitates release or synthesis of acetylcholine, and it has been hypothesized that this enhancement of central cholinergic function is the mechanism by which glucose enhances learning (e.g., see Kopf & Baratti, 1996). Indeed, various anticholinesterase inhibitors, in common

with glucose, facilitate learning (e.g., see Alvarez et al., 1997). Recently, it has been demonstrated that tacrine, an anticholinesterase inhibitor that enhances learning, similarly enhances the development of tolerance to the ataxic effect of ethanol in rats (Siegel, 1998).

The design of the experiment evaluating the effect of tacrine on ethanol tolerance was very similar to the design of the experiment evaluating the effect of glucose on ethanol tolerance (Siegel, 1999b, Experiment 2), except that rats received the anticholinesterase inhibitor, rather than glucose, following each ethanol administration. Ethanol-group rats were injected with ethanol (1.5 g/kg) in a distinctive room on 10 occasions—once every other day for 20 days. Ataxia was measured with a tilting plane following each ethanol injection. The tilting plane consists of an alley that is hinged at one end. The rat was placed in the alley, and the free end was gradually elevated. The angle of inclination at which the rat started to slip was noted. Greater levels of ataxia result in slippage at smaller angles of inclination. Ethanol-induced ataxia was compared with baseline levels, and an "impairment score" was derived. Increasing ataxia is denoted by increasingly negative impairment scores (see Siegel, 1999b; Siegel & Larson, 1996).

Rats assigned to the ethanol immediate tacrine group (EIT) were injected with tacrine (1 mg/kg) immediately after each ethanol injection (and ataxia assessment) and were injected with saline on the alternate days when they were not injected with ethanol (all injections were intraperotoneal). Rats in another group (ethanol delayed tacrine, EDT) were injected with saline immediately after each ethanol administration and ataxia assessment and were injected with tacrine on the alternate days when they were not injected with ethanol. Thus, rats in both EIT and EDT groups were injected with ethanol and tacrine at 48-hr intervals. However, the tacrine injection occurred very shortly after an ethanol injection for EIT rats, and 24 hr after each ethanol injection for EDT rats. In addition, the design of the experiment included two additional groups of rats that were treated like the ethanol groups except that they were injected with physiological saline rather than ethanol. Thus, rats assigned to the saline immediate tacrine group (SIT) were injected with tacrine immediately after each saline injection and ataxia assessment, and rats assigned to the saline delayed tacrine group (SDT) group were injected with tacrine 24 hr after each saline injection and ataxia assessment.

Figure 1 displays the mean (± 1 *SEM*) impairment scores for each group over the course of the tolerance acquisition (presented in blocks of two sessions). As is apparent in Figure 1, ethanol-injected rats were more impaired than saline-injected rats (as indicated by the negative impairment scores displayed by ethanol-injected rats). However, over the course of repeated injections the ataxic effect of ethanol decreased, that is, tolerance developed. This tolerance was more pronounced in EIT rats than in EDT rats. Although administration of tacrine shortly after ethanol facilitated the development of ataxic tolerance in ethanol-injected rats, there is no evidence that tacrine modulated ataxia in saline-injected rats. In summary, tacrine, an anticholinesterase inhibitor, administered after the injection of ethanol in a distinctive environment, facilitates the acquisition of ethanol tolerance. Inasmuch as tacrine facilitates learning, the finding is expected on the basis of the conditioning interpretation of tolerance, according to which tolerance results from an association between predrug cues and the drug.

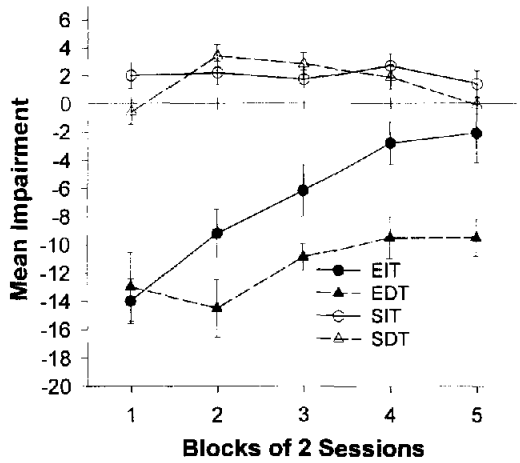

Figure 1. Mean (± 1 *SEM*) impairment scores following injection of ethanol (E) or saline (S) in groups administered tacrine (T) immediately (I) after impairment assessment (groups EIT and SIT, respectively) or following a 24-hr delay (D) after assessment (groups EDT and SDT, respectively). Greater ataxia is denoted by increasingly negative impairment scores. Results are presented in consecutive blocks of two sessions (one session every other day).

Just as an increase in cholinergic functioning may facilitate tolerance acquisition, a decrease in cholinergic function may retard tolerance acquisition. H. Zhou, Ge, Wang, Ma, and Pei (1999) recently reported that scopolamine, known to retard the many types of learning, reduces tolerance and withdrawal symptoms in rats, "suggesting the involvement of learning and memory in the development of morphine tolerance and dependence" (H. Zhou et al., 1999, p. 2010). Although, as discussed by H. Zhou et al., there are several potential mechanisms by which scopolamine may retard learning, a primary one is a decrease in cholinergic functioning.

Cues for Drugs

Although experimental studies of the associative basis of drug effects have typically manipulated environmental cues (e.g., the room where the drug is administered), there is evidence that a variety of stimuli may become associated with a drug and control the display of tolerance. For example, distinctive flavors (McNally & Westbrook, 1998), ambient temperatures (Kavaliers & Hirst, 1986), or magnetic fields (Kavaliers & Ossenkopp, 1985) may, after being paired with morphine administration, influence the display of morphine tolerance. Two types of cues that have recently been studied in our laboratory are cues incidental to self-administration (SA) and pharmacological cues.

Effect of Self-Administration

Self-administration and tolerance. Typically, humans self-administer the drugs that they use. Such SA is a characteristic of both illicit (e.g., cocaine and heroin) and licit (e.g., nicotine and ethanol) drug use. Although some psychopharmacology researchers investigate effects of drugs that are self-administered (especially the rewarding effects), most researchers administer the drug to subjects. Thus, much of what we know about the effects of drugs, such as the development of drug tolerance, is based on results of studies in which the experimenter—not the subject—administered the drug. However, there are findings indicating that the SA contingency modulates the acquisition of tolerance, the expression of tolerance, or both; organisms that self-administer a drug generally are more tolerant than organisms that passively receive the drug. For example, Ehrman, Ternes, O'Brien, and McLellan (1992) evaluated the effects of 4-mg hydromorphone in detoxified opiate abusers under two conditions: When they intravenously self-administered the drug and when the drug was infused by the experimenter. Ehrman et al. (1992) reported that several effects of hydromorphone were greater when the drug was passively received than when it was self-administered and concluded that "tolerance was observed when the subjects injected the opiate, but not when the same dose was received by unsignaled intravenous infusion" (p. 218).

An especially elegant procedure for evaluating the role of SA in drug effects is the yoked-control design. With this design, each time a subject assigned to an SA group makes a particular response (e.g., presses a lever in an operant chamber), the same amount of drug is administered to that subject and to another yoked (Y) subject. Thus, both SA and Y subjects receive the same dose of the drug, equally often, and at the same intervals. Several investigators have reported that, after some drug experience, the effects of the drug are greater in Y than in SA animals (i.e., tolerance is less pronounced in Y animals). For example, nicotine does not affect plasma epinephrine and norepinephrine levels in SA rats, but nicotine markedly elevates the levels of these adrenal hormones in Y rats (Donny, Caggiula, Knopf, & Brown, 1995).

Reports that self-administered drugs are less toxic than passively received drugs provide especially dramatic evidence for the importance of the self-administration contingency in drug tolerance. Johanson and Schuster (1981) reported that experimenter-programmed administration of phencyclidine in monkeys is frequently lethal "at dose levels at or below those self-administered, which animals survived" (p. 280). They suggested that the role of self-administration in drug lethality should be assessed in species more readily available than primates, such as rats. S. I. Dworkin and colleagues (S. I. Dworkin, Mirkis, & Smith, 1995; S. M. Dworkin, Volkmer, & Dworkin, 1988) did just that. They evaluated the lethal effects of cocaine in rats using the yoked-control design; mortality was significantly lower in SA than in Y rats.

Mello and Mendelson (1970) provided perhaps the first demonstration of the importance of the self-administration contingency in a drug effect. Alcoholic men were allowed to ingest alcohol in each of two conditions: When they wished (spontaneous condition) or only during experimenter-determined intervals (programmed condition). Tolerance was greater in the same individuals following the spontaneous condition than following the programmed condition.

The effect of the self-administration contingency on the ataxic effect of orally consumed ethanol was recently evaluated (Weise-Kelly & Siegel, 1999). Rats were prepared with chronic intragastric cannulae and participated in the experiment in simultaneously run groups of three. Within each triad, one rat was assigned to a self-administration-of-ethanol (SA-E) group. Rats in the SA-E group drank a highly palatable, sweetened water solution during each of 20 daily 30-min tolerance acquisition sessions. Licking the solution operated a lickometer circuit. The circuit operated an infusion pump that delivered ethanol intragastrically to the SA-E rat. Thus, each SA-E rat in effect "drank" an ethanol solution (although the drug was directly infused into its stomach as it drank the sweet solution, thus avoiding complications of spillage). The same amount of ethanol self-administered by the SA-E subject was delivered intragastrically (in an equivalent amount of sweet solution) to a yoked-ethanol (Y-E) rat (which had no drinking solution available). The third member of the triad, a yoked-control (Y-C) rat, received an intragastric infusion of nonalcoholic sweet solution whenever the SA-E rat consumed its solution.

Following each session, ataxia was measured with the tilting plane described previously. Despite the fact that the SA-E and Y-E subjects received the same doses of ethanol at the same times, the ataxic effect of the drug was much greater in Y-E than in SA-E rats. The mean ($\pm$ 1 *SEM*) impairment scores for each group (in blocks of four daily sessions) are summarized in Figure 2 (increasing ataxia is indicated by increasingly negative impairment scores). As is apparent in Figure 2, although both groups of ethanol rats were initially impaired by the drug, only SA-E rats acquired some tolerance—they became less impaired over the course of tolerance acquisition sessions.

Why does a drug have a greater effect for Y-E than for SA-E subjects? It has been suggested that self-administration may provide internal cues for a drug that function like external cues; that is, interoceptive cues accompanying self-administration, in common with external signals, may elicit CCRs. Thus, each drug delivery is functionally signaled for SA-E rats, but not for Y-E rats.

As discussed previously, an implication of the conditioning analysis of tolerance is that tolerance is situationally specific, thus it would be expected that an alteration in predrug cues should attenuate tolerance. That is, tolerance seen in SA-E rats should be decreased (i.e., they should display greater ataxia in response to IG ethanol) if ethanol were administered without regard to their drinking (thus removing the postulated relevant predrug cue). The effect of self-administration cues on ethanol tolerance in SA-E rats was evaluated on a test session conducted following tolerance acquisition. For this role-reversal test, formerly Y-E rats (now designated Y-E $\rightarrow$ SA-E) received the drug con-

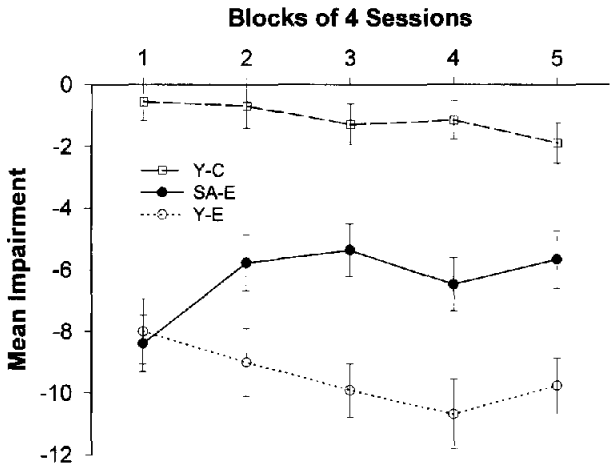

Figure 2. Mean (± 1 *SEM*) impairment scores in self-administering rats receiving intragastric (IG) ethanol contingent on their drinking (SA-E), in yoked rats (Y-E) receiving the same doses of IG ethanol at the same times as SA-E rats but not contingent on drinking, and in control rats, also yoked to SA-E rats, but receiving nonalcoholic IG infusions (Y-C). Greater ataxia is denoted by increasingly negative impairment scores. Results are presented in consecutive blocks of four daily sessions.

tingent on their consumption of the sweetened solution. Formerly SA-E (now designated SA-E → Y-E) rats were yoked to the Y-E → SA-E member of the triad. On the last pretest session (prior to the role-reversal test), the mean (± 1 *SEM*) impairment score of SA-E rats was −7.70 (± 1.80), and the mean dose of ethanol administered to each these rats was about 2 g/kg. On the role-reversal test session, although again receiving about 2 g/kg ethanol, the mean impairment score of these SA-E → Y-E rats was −12.6 (± 2.44)—a statistically significant difference. Thus, the same rats were more impaired by the same amount of ethanol when they received the drug as Y-E rats than as SA-E rats.

The results of the role-reversal test suggest that internal self-administration cues function like external cues in controlling the display of tolerance. Some rats in Weise-Kelly and Siegel's (1999) experiment received CCR test sessions in order to evaluate whether cues inherent to self-administration elicit CCRs. On these CCR tests, all rats were permitted to consume the sweetened water solution, but no ethanol was administered. The mean (± 1 *SEM*) impairment scores obtained on this test were as follows: Group SA-E, 5.7 (± 0 .96); Group Y-E, 1.76 (± 1.15); Group Y-C, −1.35 (± 1.04). Recall that increasing impairment (inability to maintain balance on a tilted floor) is indexed by increasingly negative impairment scores. Thus, the positive impairment scores on this test indicate an extraordinary ability to maintain balance on a tilted floor—*hypertaxia*. On the CCR test, SA-E rats demonstrated hypertaxia, compared with both Y-E rats and Y-C rats with no history of ethanol administration. It has previously been demonstrated that such hypertaxia is a CCR elicited by ethanol-associated cues (Larson & Siegel, 1998).

Self-administration and withdrawal symptoms. Weise-Kelly and Siegel's (1999) finding that SA-E rats are more tolerant to the ataxic effect of ethanol than Y-E rats is similar to Mello and Mendelson's (1970) results with alcoholic men. In Mello and Mendelson's study withdrawal symptoms as well as tolerance were evaluated. Mello and Mendelson reported that withdrawal effects also were greater in the spontaneous condition (when participants could ingest alcohol when they wished) than in the programmed condition (when participants could ingest alcohol only during experimenter-determined intervals).

The conditioning analysis of tolerance is relevant to withdrawal symptoms. Conditional compensatory responses, which mediate tolerance when the drug is administered in the presence of the usual predrug cues, may be expressed as withdrawal symptoms when the usual predrug cues are not followed by the drug (see Siegel, 1999a); that is, "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, 1991, p. 412). Thus, 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. This prediction is consistent with Mello and Mendelson's finding concerning the alcohol withdrawal in humans and also with results recently reported concerning morphine withdrawal in rats (MacRae & Siegel, 1997). In MacRae and Siegel's experiment, rats assigned to a self-administration-of-morphine group (SA-M) could press a lever in an operant chamber to deliver an intravenous infusion of morphine to themselves and to a yoked-morphine (Y-M) rat and an infusion of an inert substance (Ringer's solution) to another yoked rat (Y-R). On subsequent test sessions, no infusions were delivered. Although rats assigned to SA-M and Y-M groups received the same drug doses at the same time, withdrawal symptoms were much more pronounced in SA-M rats. These results would be expected if, as we have suggested, withdrawal symptoms in response to drug-associated cues are another manifestation of the CCRs that mediate tolerance.

Pharmacological Cues for Drugs

There is considerable evidence that through Pavlovian conditioning, organisms can learn that a stimulus, normally considered to be a US, can signal the delivery of another US (Goddard, 1999); thus, it is not surprising that organisms can associate two drug effects. There have been various types of experiments concerning pharmacological cues for drugs. In some experiments (*interdrug* conditioning), a given drug (Drug A) is administered before a second drug (Drug B). Other experiments have evaluated the ability of a drug to serve as a cue for itself. In such *intradrug* conditioning studies, a small dose of Drug A is administered prior to a larger dose of Drug A. Finally, results of some research suggest that even in the absence of explicit pairings of a pharmacological CS with a pharmacological US, an associ-

ation may nevertheless develop within each administration. Because a drug effect may be protracted, the early, small drug-onset cues may become associated with the later, larger drug effect. That is, there is a possibility for *intraadministration* associations (Kim, Siegel, & Patenall, 1999).

Interdrug associations. There is evidence that interdrug associations may make an important contribution to tolerance (see Krank & Bennett, 1987). For example, Taukulis (1986) described the results of an experiment in which atropine sulfate was routinely injected prior to pentobarbital. Tolerance to the hypothermic effect of the barbiturate was much more pronounced when it was preceded by atropine than when it was presented without the signal provided by the anticholinergic.

As discussed by Siegel (1988b), such pharmacological associations may be manifest as state-dependent learning of tolerance. As elaborated by MacQueen and Siegel (1989), interdrug associations and the contribution of such associations to the display of tolerance may be important considerations in treatment schedules that routinely involve sequential presentations of different drugs (e.g., chemotherapy for cancer).

Intradrug associations. There are reports that a small dose of a drug may serve as a CS, signaling a subsequent, larger dose of the same drug (see Greeley & Ryan, 1995). Greeley, Lê, Poulos, and Cappell (1984) used a paired–unpaired design to provide the first demonstration of such an intradrug association. In Greeley et al.'s (1984) study, rats in the paired group consistently received a low dose of ethanol (0.8 g/kg) 60 min prior to a high dose of ethanol (2.5 g/kg). Rats in the unpaired group 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 subjects, but not unpaired subjects, displayed tolerance. Moreover, if the high dose of ethanol was not preceded by the low dose, paired rats failed to display their usual tolerance. This tolerance, dependent on an ethanol–ethanol pairing, was apparently mediated by an ethanol-compensatory thermic CR; paired rats, but not unpaired rats, displayed a hyperthermic CR (opposite to the hypothermic effect of the high dose of ethanol) in response to the low dose of ethanol.

There is also 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. Although Cepeda-Benito and Tiffany (1993) reported an inability to demonstrate such an intradrug association with morphine, results of more recent research provide clear evidence of such an association (Cepeda-Benito & Short, 1997).

Intra-administration associations. Several investigators have proposed that intradrug-conditioning findings have important implications for understanding the contribution of conditioning to tolerance. Within each drug administration, drug-onset cues reliably precede the later and larger drug effect, thus there is the potential for the formation of intradrug associations whenever a drug is administered (e.g., Greeley et al., 1984; King et al., 1987; Mackintosh, 1987; Tiffany, Petrie, Baker, & Dahl, 1983). Such associations, formed within a single administration, have been termed *intra-administration associations* (Kim, Siegel, & Patenall, 1999).

Intra-Administration Associations, Drug Tolerance, and Drug Withdrawal

It has been suggested that the potential for intra-administration associations to develop within each drug administration has profound implications for understanding the contribution of conditioning to drug tolerance and withdrawal (Kim, Siegel, & Patenall, 1999; McDonald & Siegel, 1999).

Intra-Administration Associations and Drug Tolerance

According to the conditioning analysis of tolerance, signals for the drug effect elicit CCRs. If signaling is inherent within an administration, injection of a smaller dose of the drug to subjects with a history of injections of a larger dose of the drug might be expected to elicit such a CCR; the smaller dose should reproduce the early effect of the larger doses previously administered. Such a finding was reported by Krank (1987). Following 10 daily injections of 5 mg/kg morphine, 1 mg/kg elicited hyperalgesia.

More recently, Mucha, Kalant, and Birbaumer (1996) also provided evidence that intra-administration associations contribute to tolerance. They evaluated the analgesic effect of morphine administered either intravenously or intraperitoneally on a final test session. Prior to the test, rats had extensive experience with the drug administered by one or the other of the two parenteral routes. Tolerance was maximal when the route on the test corresponded with the route used for pretest administrations. Mucha et al. (1996) suggested that their findings were "analogous to the specificity of environmental factors of a tolerance treatment situation reported in the literature on classically conditioned tolerance" (p. 371); that is, "interoceptive stimuli produced by morphine acting through a particular route" (p. 371), in common with environmental stimuli, may act as CSs in the control of tolerance.

Kim, Siegel, and Patenall (1999) developed a technique to assess directly the contribution of intra-administration associations to tolerance. With this procedure, rats receive infusions via chronically implanted jugular cannulae. Three types of morphine infusions are used in these experiments (see Figure 3). *Long morphine* infusions are accomplished by a gradual (0.0167 ml/min) infusion of a morphine solution (5 mg/ml) for a duration sufficient to administer a dose of 5 mg/kg. The exact duration of the infusion depends on the weight of the rat but is approximately 30 min. We reasoned that if intra-administration associations form with such gradual onset administration conditions, the long morphine condition would promote such associations relatively readily compared with the typical, more rapid intravenous administration.

The more rapid intravenous administration is accomplished in the *short morphine* condition. In this short mor-

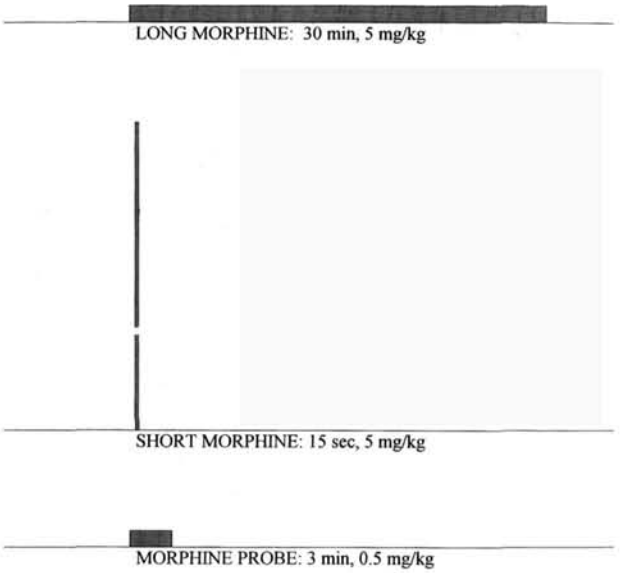

Figure 3. Schematic representation of infusion parameters used in experiments investigating intra-administration associations (Kim, Siegel, & Patenall, 1999). Long morphine infusions are accomplished by a gradual (0.0167 ml/min) intravenous infusion of a morphine solution (5 mg/ml) for a duration sufficient to administer a dose of 5 mg/kg (approximately 30 min). Short morphine infusions are accomplished by infusing the same dose of morphine in the same solution but at a much higher rate (1.7 ml/min), thus the 5 mg/kg dose is administered in approximately 15 s. A subanalgesic dose of morphine designed to mimic the early drug effect is delivered as a morphine probe infusion. The morphine probe consists of approximately one tenth of the long morphine infusion (0.5 mg/kg morphine is administered in 3 min).

phine condition the same dose of the drug is administered as in the long morphine condition (5 mg/kg), but the infusion occurs at a rate of over 100 times the rate of the long morphine infusion (i.e., the short morphine infusion rate is 1.7 ml/min). The short morphine infusion requires about 15 s. We reasoned that the short morphine condition would not promote the development of intra-administration associations.

The direct assessment of the intra-administration association involves the presentation of the usual pharmacological signal without the usual drug effect. This is accomplished with the *morphine probe* infusion. The morphine probe consists of the first one-tenth of the long morphine infusion; 0.5 mg/kg morphine is administered in about 3 min (at the slower infusion rate of .0167 ml/min). We reasoned that if long morphine subjects have acquired an intra-administration association, they would display conditional compensatory responding to this initial drug effect.

In one experiment reported by Kim, Siegel, and Patenall (1999), one group of rats received six daily long morphine infusions (each infusion followed by analgesia assessment). These rats developed tolerance to the analgesic effect of the drug over these sessions. If this long infusion promoted the development of an intra-administration association between the initial (small) and subsequent (large) effect of the drug, these rats should fail to display tolerance if the drug is administered without the usual pharmacological cue. That is, these rats, although tolerant to the analgesic effect of 5 mg/kg morphine administered as a long infusion, should fail to display this tolerance following administration of this dose as a short infusion. This prediction was confirmed.

If an intra-administration association contributed to the analgesic tolerance seen in long-morphine-infused subjects, it should be possible to observe the CCR by presenting the putative CS (the early effect of the drug) alone. Thus, on a further test session, rats tolerant to the analgesic effect of morphine induced by long morphine infusions were administered the morphine probe infusion. These rats displayed hyperalgesia in response to this small initial drug effect, thus providing direct evidence of the CCR resulting from an intra-administration association.

Intra-Administration Associations and Interpretation of Discrepant Findings

Since it was first elucidated over 25 years ago, the conditioning analysis of tolerance has generated considerable research. Although much of this research has supported the model, there are apparently conflicting findings. For example, some investigators have reported that sometimes tolerance is not situationally specific, and sometimes a CCR is not apparent (especially a hyperalgesic CCR following a series of morphine injections) when the usual predrug cues are presented without the drug (e.g., see Goudie, 1990; Kesner & Cook, 1983; Sherman, 1979; Tiffany, 1995). The exceptions have been characterized as "clearly embarrassing for Siegel's account of tolerance" (Goudie & Griffiths, 1986, p. 193) and indicate "that compensatory responses are not integral components of associational tolerance phenomena" (Baker & Tiffany, 1985, p. 95). Some investigators have concluded that there are two types of tolerance that may result from chronic drug administration: *associative* and *pharmacological* (see review by Grisel et al., 1994). The former is dependent on the availability of drug-associated cues (and thus is situationally specific), but the latter is nonassociative (and thus is transsituational).

Although some investigators have suggested that such failures to find results expected on the basis of the conditioning interpretation of tolerance compromise the generality of the theory, others have indicated that the apparently contrary findings may be explicable by recognition that intra-administration associations may form within each administration:

> It is possible that an integral part of the stimulus complex acting as the CS in studies involving opponent CRs is the drug itself. To the extent that when any drug is administered, a reliable predictor of the presence of any specific dose will be [the] lower "functional" dose of the drug, as the drug gradually increases in body tissue after administration, it follows that drug-onset may be a critical part of the CS complex controlling the compensatory CR. (Goudie, 1990, p. 679)

If a particular administration procedure promotes such an intra-administration association, it may be expected that the

pharmacological cue would be especially effective. Unlike typical exteroceptive CSs (which likely generalize to stimuli encountered outside the conditioning situation), this putative interoceptive CS is both novel and presented in a perfectly positively contingent manner with the subsequent drug effect. Also, there is evidence that CSs that are physically similar to the USs with which they are paired are especially salient (see review by Mackintosh, 1983, pp. 213–214), and the CS and US that are paired to form an intra-administration association are very similar indeed. This very effective pharmacological cue, then, may overshadow (Kamin, 1969; Pavlov, 1927, pp. 142–143 and 269–270) simultaneously presented environmental cues. In such circumstances, the display of tolerance would not be influenced by environmental cues, and thus the tolerance would appear transsituational, or nonassociative (e.g., Greeley et al., 1984; Grisel et al., 1994; King et al., 1987; Mackintosh, 1987; Walter & Riccio, 1983).

Kim, Siegel, and Patenall (1999) provided direct evidence supporting the overshadowing interpretation of transsituational tolerance. They demonstrated that rats that acquired tolerance with long morphine infusions (a condition that promotes the development of an intra-administration association) demonstrated transsituational tolerance; that is, they were equally tolerant in the presence of drug-paired and non-drug-paired environmental cues. In contrast, rats that acquired similar tolerance but with short morphine infusions (a condition that does not promote the development of an intra-administration association) demonstrated situationally specific tolerance; they were more tolerant in the presence of drug-paired than non-drug-paired environmental cues. Similarly, Grisel et al. (1994) demonstrated that there is greater situational specificity of tolerance induced with intravenous morphine administrations than with subcutaneous administrations. They reasoned that the relatively more gradual onset of the subcutaneous opiate effect (compared with the intravenous opiate effect) resulted in an association between drug-onset cues and the later, larger drug effect, and these pharmacological cues overshadowed simultaneously present environmental cues.

Intra-Administration Associations and Drug Withdrawal

On the basis of the conditioning analysis of drug effects, withdrawal symptoms—a manifestation of a pharmacological CR—should be elicited not only by drug-associated environmental cues but also by drug-associated pharmacological cues. Thus, a small dose of the drug might be expected to elicit withdrawal symptoms in subjects experienced with large doses.

There is some evidence that a small dose of nicotine elicits nicotine-withdrawal symptoms in human smokers who regularly consume high-nicotine cigarettes. Schachter (1977) reported that some heavy smokers given low-nicotine cigarettes failed to regulate their nicotine intake (i.e., increase the number of cigarettes smoked). These smokers, who repeatedly self-administered lower than normal doses of nicotine, reported extreme withdrawal distress. Other heavy smokers, who increased consumption when given low-nicotine cigarettes, effectively maintaining their normal nicotine intake, reported no withdrawal distress.

McDonald & Siegel (1999) demonstrated that a small dose of morphine elicited withdrawal symptoms in rats previously administered large doses of the opiate. During each of 10 daily tolerance acquisition sessions, two groups of rats were injected intraperitoneally with morphine—either a large dose (i.e., 50 mg/kg) or a small dose (i.e., 5 mg/kg). Rats in a third group were injected with physiological saline during tolerance acquisition. On the test day, following the final tolerance development session, half the rats in each of the three tolerance acquisition conditions were injected with 5 mg/kg morphine, and the remaining rats were injected with saline. A number of behaviors indicative of opiate withdrawal were tabulated during the test session (see MacRae & Siegel, 1997; McDonald & Siegel, 1998). The frequency of withdrawal behaviors was computed as the sum of all withdrawal behaviors, and the mean withdrawal behavior frequency (± 1 *SEM*) for each of the six groups is summarized in Table 1 .

As can be seen in Table 1, the small dose of morphine suppressed all behaviors in subjects receiving the drug for the first time on this test session (the group that received saline during tolerance acquisition). However, this same small dose elicited considerable withdrawal behaviors in rats with pretest experience with the large dose of morphine. In fact, as is apparent in Table 1, rats tested with the small dose of morphine following tolerance acquisition with the large dose displayed the greatest frequency of withdrawal behaviors at test. Nonparametric statistical analyses of the data summarized in Table 1 indicated that rats in this group displayed significantly more withdrawal behaviors than did rats in each of the other groups. This demonstration that a small dose of morphine can actually elicit withdrawal symptoms, although counterintuitive, is consistent with the conditioning analysis of drug effects.

Conditioning and the Physiological Mechanisms of Tolerance

Although there is substantial evidence that conditioning contributes to tolerance, there has been little research concerning the physiological events that mediate this contribution. Some researchers have noted conditional metabolic or drug-dispositional changes that may function as CCRs (Melchior & Tabakoff, 1985; Roffman & Lal, 1974). More recent research has concerned conditional pharmacodynamic alterations—what happens in the brain in response to predrug cues?

Table 1
Mean Frequencies (±1 SEM) of Withdrawal Behavior

Tolerance acquisition phase	Test	
	5 mg/kg morphine	Saline
50 mg/kg morphine	24.18 (±2.44)	11.41 (±2.41)
5 mg/kg morphine	2.75 (±1.95)	5.86 (±1.79)
Saline	0.00 (±0.00)	4.94 (±0.83)

Conditional Neurochemical Alterations

Conditional release of taurine and ethanol tolerance. The amygdala has been implicated in both learning and drug effects (see Quertemont, de Neuville, & De Witte, 1998). Quertemont, de Neuville, and De Witte used microdialysis to evaluate neurochemical changes in the amygdala during repeated ethanol administrations and during presentation of a distinctive olfactory cue that had been paired with ethanol. They reported that ethanol elicited an increase in extracellular taurine. Taurine is a neuromodulator believed to attenuate ionic and osmotic changes that occur after ethanol administration. Furthermore, taurine decreases the aversive effects of ethanol, as measured by aversion to the side of a two-choice chamber that contains an ethanol-paired odor (Quertemont, Goffaux, Vlaminck, Wolf, & De Witte, 1998). In rats with a history of ethanol administration in the presence of a vinegar odor CS, administration of saline in the presence of the olfactory CS elicited an increase in taurine microdialysate content. Quertemont, de Nueville, and De Witte (1998) suggested that such conditional release of taurine is a CCR in rats presented with a CS for ethanol, and this CCR contributes to tolerance.

Conditional antiopioid peptide activity. Some evaluations of neurochemical alterations that mediate opiate tolerance have focused on antiopioid peptides (AOPs). There is evidence that AOPs are released by the central nervous system in response to opiate stimulation and that they contribute to tolerance by attenuating the effect of the drug (Rothman, 1992). Although several putative AOPs have been proposed, one that has received considerable attention is CCK. There is evidence that CCK attenuates the effect of morphine. For example, if CCK is administered exogenously, it blocks morphine-induced analgesia in a dose-dependent manner (e.g., see Han, 1995; Mitchell, Lowe, & Fields, 1998). Conversely, blocking CCK receptors potentiates morphine analgesia in rats (e.g., see Y. Zhou, Sun, Zhang, & Han, 1992) and humans (e.g., see McCleane, 1998). Moreover, morphine administration accelerates the release of CCK from the central nervous system in a dose-dependent manner (Y. Zhou et al., 1992). Treatment with CCK receptor antagonists has been shown to prevent the development of morphine tolerance (e.g., see Kellstein & Mayer, 1991) and to attenuate the expression of established morphine tolerance (e.g., see Hoffmann & Weisenfeld-Hallin, 1994; Siegel, Kim, & Sokolowska, 1999).

Recently, the contribution of CCK to the expression of the CCRs that mediate tolerance to the analgesic effect of morphine was evaluated. As previously discussed, rats with a history of long morphine infusions form an intra-administration association. This association is seen if a morphine probe (the first 10% of the long morphine infusion) is delivered; the probe elicits a CCR of hyperalgesia (Kim, Siegel, & Patenall, 1999). Recently, researchers evaluated whether the expression of this CCR resulting from an intra-administration association was mediated by CCK (Kim, Sokolowska, & Siegel, 1999; Siegel et al, 1999). During the initial tolerance acquisition phase of the experiment, two groups of rats received a series of eight long morphine infusions (5 mg/kg, infused over a period of approximately 30 min; see Figure 3) and displayed tolerance to the analgesic effect of the drug (M rats). Two other groups of rats received physiological saline infusions during this phase of the experiment (S rats). All rats received morphine probe (0.5 mg/kg, 3 min in duration; see Figure 3) on the compensatory response test. Fifteen min prior to the probe test, half the rats that received each substance during tolerance acquisition were pretreated with an intrathecal administration of PD135,158, a CCK_B receptor antagonist (Groups M-PD and S-PD), and the remaining rats were pretreated with intrathecal saline (Groups M-SAL and S-SAL). Analgesia was assessed with the tail flick test (latency for the rat to flick its tail out of 48 °C water). The mean tail-flick latencies (+ 1 *SEM*) seen in each group 30 min following morphine probe infusion are shown in Figure 4 .

As can be seen in Figure 4, morphine-trained rats that did not receive CCK antagonist pretreatment (M-SAL) displayed the shortest response latency—shorter than both saline-trained control groups that received the probe for the first time on the test session and shorter than morphine-trained rats pretreated with the CCK receptor antagonist prior to the test. Group M-SAL rats displayed significantly shorter response latencies than did rats in any of the other three groups (with the response latencies of the other groups not differing significantly). Thus, it would appear that the

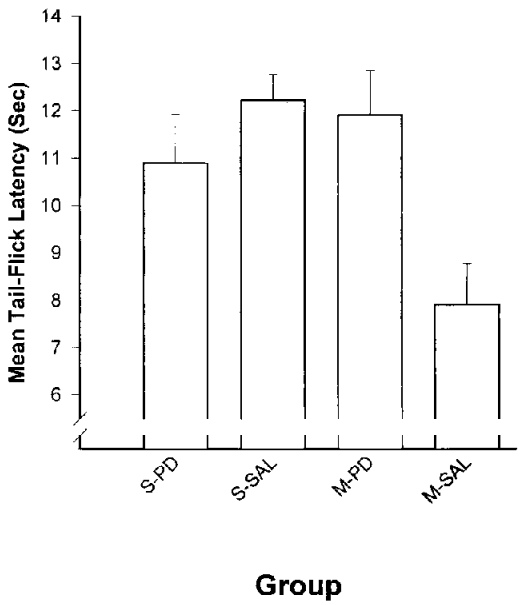

Figure 4. Mean (+ 1 *SEM*) tail-flick latencies following a morphine probe infusion (3 min, 0.5 mg/kg) in rats with a prior history of either long morphine (M) infusions (approximately 30 min, 5 mg/kg) or saline (S) infusions. Some rats with prior exposure to M and S were intrathecally administered a cholecystokinin receptor antagonist (PD 135,158) 15 min prior to the probe morphine assessment (Groups M-PD and S-PD, respectively). The remaining rats with prior exposure to M and S were intrathecally administered saline 15 min prior to the probe morphine assessment (Groups M-SAL and S-SAL, respectively).

hyperalgesic CCR elicited by drug-onset cues is eliminated by a CCK receptor antagonist, consistent with suggestions that this CCR is a manifestation of increased CCK activity.

In summary, there is evidence that (at least with respect to ethanol and morphine) cues that signal drug delivery not only modulate the expression of tolerance but also modulate the activity of neurotransmitter systems that mediate tolerance. Moreover, these conditional alterations of neurotransmitter activity may provide a mechanism for the CCRs that mediate the behavioral expression of tolerance.

Conditional Intracellular Alterations

In addition to studying learned modifications of neurotransmitter activity, researchers interested in the biological bases of associative contributions to tolerance have also studied learned modifications in intracellular events that mediate tolerance. The structural changes in the central nervous system that are responsible for learning and drug effects require gene activation.

The gene that encodes a transcription factor, c-Fos, has been implicated in learning and drug tolerance (Nye & Nestler, 1996; Sotty, Sandner, & Gosselin, 1996). That is, there is considerable evidence that c-Fos (especially striatal c-Fos) mediates the action of many common drugs of abuse (Graybiel, Moratalla, & Robertson, 1990; Hope, Kosofsky, Hyman, & Nestler, 1992; Liu, Nickolenko, & Sharp, 1994) and that c-Fos is also important for memory consolidation (Sotty et al., 1996). Recently, Thiele, Roitman, and Bernstein (1998) reported that tolerance to ethanol-induced induction of c-Fos (in common with tolerance to other effects of ethanol) is situationally specific.

Nye and Nestler (1996) reported that chronic morphine induces striatal c-Fos expression, but they did not evaluate the role of learning in this effect. More recently, Baptista et al. (1998) evaluated the contribution of conditioning to such c-Fos expression. Baptista et al. used the paired–unpaired situational specificity design of Siegel et al. (1978), described previously, to simultaneously evaluate both tolerance to the analgesic effect of morphine and striatal c-Fos levels. They found that rats not only showed behavioral evidence of situational specificity of tolerance (i.e., paired morphine rats were more tolerant to the analgesic effect of morphine than unpaired morphine rats) but also demonstrated situational specificity of c-Fos expression (i.e., paired morphine rats displayed higher striatal c-Fos levels than unpaired morphine rats).

The c-Fos protein combines with other proteins to form an activator protein 1 complex—AP-1 (Angel et al., 1988; Bohmann et al., 1987). This AP-1 complex binds to and activates genes. Baptista et al. (1998) demonstrated that AP-1 binding was increased more in the striatum of paired morphine rats than in the striatum of unpaired morphine rats. In summary, environmental stimuli modulate not only the expression of tolerance but also the intracellular changes hypothesized to mediate tolerance.

Conditional Noncompensatory Responses

On the basis of the conditioning analysis of tolerance, the compensatory responses unconditionally elicited by a drug come to be elicited conditionally by a variety of cues paired with the drug. It is not always the case, however, that pharmacological stimulation initiates compensatory responses. Sometimes, drug URs consist of responses that augment (rather than attenuate) the pharmacological US (see Ramsay & Woods, 1997). Such URs result in CRs that similarly augment the drug effect. Such CRs would be expected to progressively enhance the drug effect over the course of repeated administrations—a phenomenon termed *reverse tolerance,* or *sensitization.*

There is substantial evidence supporting the conditioning analysis of sensitization. For example, in many instances sensitization displays situational specificity and is subject to extinction (see Ramsay & Woods, 1997; Siegel, 1989). There is also evidence that CRs resulting from intra-administration associations contribute to sensitization. For example, if rats have experience with large doses of cocaine, a small (usually ineffective) dose of the stimulant will (like the large dose) suppress operant responding (Walker & Branch, 1998). A full discussion of factors contributing to the topography of pharmacological URs and CRs and the contribution of CRs to sensitization is beyond the scope of this article (but see Eikelboom & Stewart, 1982; Ramsay & Woods, 1997).

Discussion

We have summarized research conducted over a period of about 25 years indicating that Pavlovian conditioning plays an important role in the acquisition and expression of tolerance (and withdrawal symptoms). For example, there are many demonstrations that, following a series of drug administrations, drug-paired stimuli elicit CCRs. Furthermore, tolerance often is situationally specific; that is, tolerance is more pronounced when assessed in the presence of drug-paired cues than when assessed in the presence of alternative cues. In addition, there are many parallels between tolerance and other conditional responses: Nonpharmacological manipulations that attenuate conditioning (e.g., latent inhibition and extinction) as well as pharmacological manipulations that facilitate conditioning (e.g., glucose and anticholinergic drugs) similarly modulate the acquisition of tolerance. Researchers are starting to discover the conditional neurochemical and molecular-biological events that are elicited by drug-paired cues and mediate the associative contribution to tolerance. Many of these findings are very well-established, having been demonstrated with many drugs, drug effects, and species. Others have only recently been obtained, sometimes using novel procedures, and have not yet been subject to the scrutiny and replication tests that characterize long-established findings.

We do not mean to suggest that a Pavlovian conditioning analysis of tolerance addresses all phenomena of chronic drug tolerance ever reported. There are some findings not readily consistent with the conditioning interpretation of

tolerance (Carter & Tiffany, 1996; Ramsay et al., 1999). In addition, some results require that we add complexity to the initial description of the conditioning model (Siegel, 1975) by recognizing that there are a variety of potential predrug stimuli. That is, we have summarized recently reported evidence that many types of cues present at the time of drug administration come to elicit the CCRs that contribute to tolerance. Since the 1960s, learning theorists have been concerned with cue interactions in compound conditioning, that is, conditioning that occurs when a variety of potential CSs signal a US. This very rich literature is applicable not only to basic phenomena of associative learning, but also to understanding findings in many other areas (Siegel & Allan, 1996). It is now apparent that the compound-conditioning effects studied by learning researchers are relevant to understanding drug tolerance. Effective CSs may be public (such as the environment of drug administration or distinctive audio or visual cues) or private (such as interoceptive cues incidental to self-administration or pharmacological drug-onset cues), and several CSs may be simultaneously present at the time the drug effect occurs. Kim, Siegel, and Patenall (1999) and others (e.g., Grisel et al., 1994) have presented evidence that some findings apparently contrary to the conditioning analysis of tolerance (lack of situational specificity and inability to detect CCRs) may be explicable by appreciation of the several potential signals for a drug. For example, environmental control of tolerance and environmentally elicited CCRs may not be detectable because environmental stimuli are overshadowed by more salient, simultaneously present stimuli (intra-administration, pharmacological drug-onset cues).

Of course, an apparent problem with a compound-conditioning analysis of tolerance is that it is not readily disconfirmed. As Kim, Siegel, and Patenall (1999) discussed, a demonstration of tolerance that appears nonassociative (e.g., it is not situationally specific) may be reinterpreted as associative by appealing to hypothesized private cues, such as cues incidental to self-administration or intra-administration pharmacological cues, which may overshadow experimenter-manipulated public cues. However, techniques have been developed to isolate such private cues (e.g., Kim, Siegel, & Patenall, 1999; Weise-Kelly & Siegel, 1999), and recognition that they may contribute to tolerance does lead to novel predictions, many of which have been confirmed. For example, the effects of the self-administration cue may be seen by nonreinforcement of a response that previously resulted in pharmacological reinforcement. Such a presentation of the putative CS in the absence of the US results in CCRs (Weise-Kelly & Siegel, 1999). Similarly, if drug-onset cues have reliably signaled a later, larger drug effect, presentation of only the drug-onset cues results in CCRs (Cepeda-Benito & Short, 1997; Greeley et al., 1984; Kim, Siegel, & Patenall, 1999). Procedures that favor the development of an association between self-administration cues and drug effects lead to greater tolerance (e.g., see S. I. Dworkin et al., 1995; Mello & Mendelson, 1970; Weise-Kelly & Siegel, 1999) and withdrawal symptoms (MacRae & Siegel, 1997; McDonald & Siegel, 1999; Mello & Mendelson, 1970) than do administration procedures that do not favor this association. Administration procedures that would be expected to favor the development of intra-administration associations lead to transsituational tolerance with respect to environmental cues (Grisel et al., 1994; Kim, Siegel, & Patenall, 1999).

Further research can evaluate other predictions of a conditioning analysis of tolerance that incorporates the contribution of compound CSs. For example, it would be expected that if transsituational tolerance is the result of private cues overshadowing simultaneously present environmental cues, procedures that reverse overshadowing (e.g., repeated presentation of the overshadowing CS) should similarly restore environmental control of tolerance (e.g., see Matzel, Schachtman, & Miller, 1985; Matzel, Shuster, & Miller, 1987).

Even at this early stage of research concerning self-administration and intra-administration CSs, it is clear that such private cues should be of considerable interest to psychopharmacologists and clinicians. For example, as already indicated, CCRs elicited by private cues incidental to self-administration influence tolerance to several effects of drugs, including lethality (S. I. Dworkin et al., 1995; Johanson & Schuster, 1981): "Although the response-dependent administration of a pharmacological agent can be reinforcing, the response-independent administration of the same or similar dosage pattern can be lethal" (S. I. Dworkin et al., 1995, p. 265). Because the CCRs elicited by self-administration cues may be seen as withdrawal symptoms, the amount of prior drug history necessary before these symptoms are seen is less in rats that self-administer morphine than in yoked rats: "It is possible that the amount of morphine necessary to induce dependence (as evidenced by the spontaneous occurrence of withdrawal symptoms following termination of drug administration) has been overestimated because of the typical, passive administration procedures" (MacRae & Siegel, 1997, p. 81).

Intra-administration cues, too, have dramatic effects on drug tolerance and withdrawal. Patients receiving drugs for pain relief may be at risk of overdose when the route of administration is changed, thus effectively altering the pharmacological drug-onset CS (Kim, Siegel, & Patenall, 1999; Siegel & Kim, 2000). Such intra-administration associations may also contribute to the effect of a priming dose on relapse to drug use. For example, it has frequently been reported that a small dose of alcohol will augment the craving for additional alcohol and enhance subsequent alcohol consumption (see Goddard, 1999; Siegel, 1986a). This loss of control initiated by a priming dose is incorporated in the dogma of Alcoholics Anonymous:

> Once he takes any alcohol into his system, something happens, both in the bodily and mental sense, which makes it virtually impossible for him to stop. The experience of any alcoholic will confirm that . . . we are without defense against the first drink. (Anonymous, 1939, pp. 34–35)

The insalubrious effect of the first drink may be due to the alcoholic's association of that initial effect of alcohol with subsequent larger amounts of the drug: "The signal value of

a small drug dose may make a contribution to 'binge' drinking and drug 'priming' effects in humans" (Goddard, 1999, p. 418).

Recognition that intra-administration associations contribute to drug effects may have important treatment implications. Some addiction treatment strategies are designed to extinguish the association between drug-predictive cues and the systemic effect of the drug (see Kim, Siegel, & Patenall, 1999; Siegel, 1988a). Such treatments consist of presenting predrug cues in the absence of the drug. There are conflicting reports of the efficacy of such cue-exposure treatments; some clinicians are enthusiastic, but others have obtained mixed results (see Kim, Siegel, & Patenall, 1999). As indicated by Cepeda-Benito and Short (1997), if the early effect of a drug is one cue that elicits compensatory CRs, it is possible that mere exposure to predrug environmental cues may not effectively extinguish the association between predrug cues and the drug effect. Rather, "the inclusion of small drug doses during cue-exposure treatments may better reproduce the CSs responsible for craving" (Cepeda-Benito & Short, 1997, p. 239).

In summary, evidence indicating that a variety of private cues (in addition to public cues) may become associated with a drug both complicates and enriches the conditioning analysis of tolerance.

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