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### PAVLOVIAN CONDITIONING AND DRUG OVERDOSE: WHEN TOLERANCE FAILS

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There is a considerable amount of evidence that Pavlovian conditioning contributes to tolerance; Organisms learn to make responses that attenuate the effect of the drug in the presence of cues previously paired with the drug. The conditioning analysis is relevant to understanding seemingly enigmatic "failures" of tolerance that occur when a drugexperienced (and presumably drug-tolerant) individual suffers an "overdose." There are several demonstrations that Pavlovian conditioning is relevant to understanding opiate (as well as barbiturate and alcohol) "overdose" deaths in laboratory studies with rats. There also are case-reports of human opiate "overdoses," both in illicit users and in patients receiving medically prescribed morphine, that are consistent with the conditioning interpretation of drug overdose.

Keywords: Conditioning; overdose; Pavlovian conditioning; tolerance; learning

Many heroin addicts die shortly after injecting the opiate. Although it has been conventional to attribute such deaths to "heroin overdose," it is has been clear, since the pioneering work of Brecher (1972), that "overdose" is a misnomer in describing the cause of death in heroin addicts. Most of the deaths are not due to a pharmacological overdose, as the term is usually understood. Brecher summarized the extensive literature that existed 30 years ago indicating that "(1) the deaths cannot be due to overdose. (2) there has never has been any evidence that they are due to overdose. (3) There has long been a plethora of evidence demonstrating they are not due to overdose" (p. 102). Results

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of subsequent research confirmed Brecher's conclusions, and it has been suggested that "the term 'overdose' has served to indicate lack of understanding of the true mechanism of deaths in fatalities directly related to opiate use" (Greene, Luke and DuPont, 1974, p. 175), and "continued utilization of the term 'overdose' to cover all heroin-related fatalities may be counterproductive in developing strategies to reduce the morbidity and mortality associated with heroin" (Darke and Zador, 1996, p. 1770). Despite the likely misuse of the word, we will continue to use the generally-accepted term "heroin overdose," rather than more cumbersome alternatives, when referring to these enigmatic fatalities.

#### HEROIN OVERDOSE AND HEROIN TOLERANCE

The heroin overdose victim typically dies of respiratory depression, and it has been suggested that the death is a failure of the expected level of tolerance to occur (e.g. Siegel et al., 1982; White and Irvine, 1999). Tolerance refers to the decreasing effect of a drug over the course of repeated administrations. Tolerance develops to many effects of many drugs, and pronounced tolerance develops to the lethal effects of heroin. That is, it requires a much larger dose of heroin to induce fatal respiratory depression in the drug-experienced individual than in the drug-naïve individual (see Brecher, 1972).

The victims of overdose typically are not novice users. Rather, they are users with a long history of addiction (e.g., Darke and Zador, 1996), and it would be expected that they are very tolerant to heroin. However, post-mortem examination of heroin overdose victims often do not reveal very high levels of opiate in their system. For example, Monforte (1977) found that about three-quarters of the victims of heroin overdose had blood levels of morphine no higher than those seen in a control group of heroin addicts who were died as a result of homicide (rather than heroin overdose): "one must conclude that in the great majority of cases death was not a result of a toxic quantity of morphine in the blood" (p. 720).

An implication of such findings is that many heroin addicts suffer an overdose because they do not display the level of tolerance that would be expected in such drug-experienced individuals. Why might tolerance sometimes not occur? To answer the question, we must first

summarize evidence that drug tolerance depends not only upon experience with the drug but also experience with drug-paired cues.

### LEARNING AND DRUG TOLERANCE

As early as the 1960s, some investigators proposed that a complete analysis of tolerance requires an appreciation of learning principles. For example, in 1965, Cohen, Keats, Krivoy and Ungar 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 (see Siegel, 1983, for a historical summary of research concerning the relationship between learning and tolerance). In addition, some researchers proposed that learning contributed to tolerance because tolerance often was 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 and Kornetsky, 1964; Kornetsky and Bain, 1968). Since learned responses typically display very substantial retention (e.g. Kimble, 1961, p. 281), some investigators 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, is incorporated in an analysis of tolerance that emphasizes Pavlovian conditioning principles.

### Pavlovian conditioning and tolerance

In the Pavlovian conditioning situation (Pavlov, 1927), a contingency is arranged between two stimuli; typically, one stimulus reliably predicts the occurrence of the second stimulus. Using the usual terminology, the second of these paired stimuli is termed the "unconditional stimulus" (UCS). The UCS, as the name implies, is selected because it elicits some response from the outset (i.e. unconditionally), prior to any pairings. This response unconditionally elicited by the UCS is

termed the "unconditional response" (UCR). The stimulus signaling the presentation of the UCS is "neutral" (i.e. it elicits little relevant activity prior to its pairing with the UCS), and is termed the "conditional stimulus" (CS). The CS, as the name implies, becomes capable of eliciting new responses as a function of (i.e. conditional upon) its pairing with the UCS. Such responses elicited by the CS are termed "conditional responses" (CRs).

Events occurring during drug administration correspond to a Pavlovian conditioning trial. Cues accompanying the drug effect function as CSs, and the direct drug effect constitutes the UCS. Prior to any learning, this UCS elicits responses – UCRs – that compensate for drug-induced disturbances. After some pairings of the predrug CS and pharmacological UCS, the drug-compensatory responses are elicited by drug-paired stimuli as CRs. For example, about 60 years ago Subkov and Zilov reported that after injecting dogs with epinephrine (adrenaline) on a number of occasions, merely placing the dog in the injection stand and administering an inert substance produced bradycardia (compensatory to the tachycardiac effect of the hormone): "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 and Zilov, 1937, p. 295).

Subsequent research has demonstrated conditional compensatory responses with respect to many effects of a variety of drugs, including commonly abused drugs such as opiates, ethanol, and caffeine (see review by Siegel *et al.*, 2000). These conditional compensatory responses, elicited by cues that have been paired with the drug in the past, attenuate the drug effect and contribute to tolerance.

There is a considerable amount of evidence indicating that Pavlovian conditioning contributes to tolerance (Siegel *et al.*, 2000). On finding that is especially relevant to understanding the contribution of conditioning to overdose has been termed the "situation-specificity of tolerance."

### Pavlovian conditioning and the situational-specificity of tolerance

The results of over a dozen experiments by Clifford Mitchell and colleagues (published between 1969 and 1973) demonstrated that, fol-

lowing a series of drug administrations, tolerance is more pronounced in the presence of the usual drug-associated cues than in the presence of alternative cues (see review by Siegel, 1978). The phenomenon has been termed the "situational-specificity of tolerance" (Siegel, 1976). Situational-specificity has been demonstrated with respect to tolerance to many effects of a variety of drugs (see Baptista et al., 1998; Kim, Siegel and Patenall, 1999; Siegel et al., 2000): opiates, naloxone, ethanol, nicotine, pentobarbital, phencyclidine, immunoenhancing drugs, cholecystokinin, carisoprodol, haloperidol and several benzodiazepines. It is seen in many species, from snails to humans, and is manifest both by behavioral and neurochemical measures of drug effects. Situational-specificity typically also is 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.

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

## PAVLOVIAN CONDITIONING AND TOLERANCE TO THE LETHAL EFFECT 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. However, altering the context of drug administration increases the lethality of several drugs.

# Pavlovian conditioning and tolerance to the lethal effect of drugs – experiments with non-human animals

Obviously, experiments to determine if altering the context of drug administration is a factor contributing to drug overdose can be performed only with non-human animals. The results of first such experiment did indeed indicate that altering the context of drug administration increased heroin-induced mortality in rats (Siegel et al., 1982). In this experiment, a total of 107 rats, prepared with chronic intravenous cannulae, received an intravenous infusion of 15 mg/kg heroin on a test session. Prior to this test, some of the rats received intravenous infusions of lower doses of heroin, and received the test infusion in the same environment where they received the prior infusions (Same-Tested). Other rats had the same pretest history of heroin infusions as Same-Tested rats, but received the test infusion in a different environment than that previously paired with heroin (Different-Tested). Finally, rats in a Control group received heroin for the first time on the test session. Heroin induced mortality was 96% in the Control group, 64% in the Different-Tested group, and 32% in the Same-Tested group. Statistical analyses  $(\chi^2)$  indicated that although both groups with experienced with sublethal doses of heroin were more likely to survive the highest dose than were Control rats, mortality was significantly higher in Different-Tested than in Same-Tested rats (p < .001). Because of the large number of rats that were used, this experiment was conducted in six replications. In every replication, a greater proportion of Different-Tested than Same-Tested rats died (p < .02, binomial test):

"In conclusion, groups of rats with the same pharmacological history of heroin administration can differ in mortality following administration of a high dose of the drug: rats that received the potentially lethal dose in the context of cues previously associated with sublethal doses were more likely to survive than animals that received the dose in the context of cues not previously associated with the drug" (Siegel *et al.*, 1982, p. 437).

Subsequent experiments demonstrated the contribution of environmental cues to overdose death to other drugs. Despite similar pretest histories of pentobarbital administration, Different-Tested rats are more likely than Same-Tested rats to die from a high dose of the barbiturate (Vila, 1989). Similarly, despite similar pretest histories of

ethanol administration, Different-Tested mice display a lower LD<sub>50</sub> for ethanol than do Same-Tested mice (Melchior, 1990; but see Tsibulsky and Amit, 1993).

Results of correlational studies of human drug addicts and patients that receive medically prescribed opiates for pain relief are consistent with the results obtained from experiments with non-human animals – altering the context of drug administration increases the risk of overdose.

### Studies with drug addicts

There are some clinical reports suggesting that addicts may, when they suffered a fatal overdose, have injected in unusual circumstances. For example, Winek, Wagdy and Wahba (1999) reported a fatality resulting from heroin injection into the penis. Siegel (1984) reported the results of interviews with 10 heroin overdose survivors. For seven of the overdoses, the drug was administered in an environment not previously associated with drug use. That is, the relative frequency of overdose appears higher following injection in unusual circumstances than following administration in the usual circumstances. Although such a finding is suggestive, it also raises questions. What is the relative frequency with which addicts inject themselves in drug-associated and non-associated environments and do not suffer an overdose?

A study by Gutiérrez-Cebollada et al. (1994) was designed to address such questions. These investigators interviewed 76 heroin addicts admitted consecutively to the emergency room of a university hospital in Barcelona, Spain; 54 subjects because of heroin overdose, and 22 seeking urgent medical cares for unrelated conditions for whom the interview revealed intravenous heroin self-administration one hour or less before admission. Of the patients that had recently used heroin but did not suffer an overdose, all had injected in an environment where they had previously used the drug before. In contrast with this 100% of the subjects that injected in the usual place and did not overdose, only 48% of the overdose victims administered heroin in the usual environment, i.e., 52% injected "in an unusual setting" (Gutiérrez-Cebollada et al., 1994, p. 171). The different frequencies of overdoses in usual and unusual settings by these subjects who had recently injected themselves with heroin resulted in a highly significant

 $\chi^2$  (p < .0001). As summarized by Gutiérrez-Cebollada *et al.* (1994), "The association between heroin overdose and unusual drug administration setting confirms the influence of non-pharmacological factors in heroin overdosing. Further studies should be considered to address the role played by self-administration of heroin in an unusual setting in conditioned tolerance" (p. 173).

### Studies with patients that receive medically prescribed opiates

There are case reports of patients that were receiving medically prescribed opiates and, for seemingly inexplicable reasons, suffered an apparent overdose following a particular administration. These reports are consistent with the conditioning analysis of tolerance, and the failure of tolerance that occurs when the environment of drug administration is altered.

Siegel and Ellsworth (1986) described a case report of a patient, suffering with pancreatic cancer, who was receiving about four morphine injections in his home every day for pain relief. The patient stayed in his bedroom (which was dimly lit and contained apparatus necessary for his care), and received his injections in this environment. For some reason, after staying in this bedroom for about a month, the patient left his bed and went to the living room (which was brightly lit and different in many ways from the bedroom/sickroom). He was in considerable pain in the living room, and, as it was time for his next scheduled morphine administration, he was administered his usual dose of the drug. The patient quickly displayed signs of opiate overdose (constricted pupils, shallow breathing), and died a few hours later.

More recently, Johnson and Faull (1996) described the case of a patient who demonstrated tolerance to morphine but no cross-tolerance to fentanyl. The patient had been treated for pain with a regimen that included oral morphine for about three months; however, tolerance to the analgesic effect of the drug developed. The patient opted to change to transdermal fentanyl, and cross-tolerance was expected. Fortuitously, the morphine-fentanyl conversion dose was incorrectly calculated and the patient received one-quarter of the manufacturer's recommended conversion dose. Nevertheless, the patient suffered an opioid overdose. Johnson and Faull concluded that, despite the

patient's tolerance to oral morphine, there was apparently no cross-tolerance to fentanyl: "If this man had received the 'correct' dose [of fentanyl] as calculated from the manufacturer's data sheet he would have experienced severe toxicity" (Johnson and Faull, 1996, p. 74).

Siegel and Kim (2000) suggested that this disruption of tolerance seen following a change in route of administration is a further demonstration of the situational-specificity of tolerance. Among the stimuli that comprise the "drug-associated cues" are those cues inherent within the administration procedure (such as route of administration and early, weak drug effects experienced immediately after administration). There are several experimental demonstrations of the role of such interoceptive stimuli in the display of tolerance to opiates (see Kim et al., 1999). Additionally, Mucha, Kalant and Birbaumer (1996) recently reported that alteration of the route of administration of morphine in rats (from intraperitoneal to intravenous) attenuated the display of analgesic tolerance, and they suggested that "interoceptive stimuli produced by morphine acting through a particular route" functions similarly to exteroceptive stimuli in modulating the display of tolerance. As summarized by Siegel and Kim (2000), "Johnson and Faull's observations concerning a failure of cross-tolerance to occur between two  $\mu$ -opioid receptor agonists in conjunction with an alteration in administration procedure may represent another demonstration of the situational-specificity of tolerance. The phenomenon has been implicated in unexpected overdose deaths resulting from opiates, alcohol, and pentobarbital, and may also (as Johnson and Faull's observations suggest) be relevant to understanding and preventing enigmatic overdoses in clinical practice" (p. 76).

### **CONCLUSIONS**

Undoubtedly there are many factors that contribute to heroin overdose. There is evidence that some cases may indeed be due to a pharmacological overdose, as the term is usually used (Tagliaro and De Battisti, 1999). Others may result from a synergism between the opiate and other drugs concomitantly administered, or from adulterants in the heroin (see Brecher, 1972; Darke and Zador, 1996; Gutiérrez-Cebollada *et al.*, 1994; White and Irvine, 1999). However, some

overdoses occur because "the opiate addict, who can usually tolerate extraordinarily high doses...is not tolerant on the occasion of the overdose" (Siegel et al., 1982, p. 436). On the basis of a Pavlovian conditioning analysis of tolerance, this failure of tolerance would result if the drug is administered in the presence of cues that have not, in the past, been extensively associated with the drug effect. There are considerable data, from experimental research with animals, and studies of human overdose victims (both heroin addicts and medical patients), supporting this interpretation of some heroin overdose.

Zador (1999) recently noted that "ingesting heroin in an unusual or unfamiliar setting is not currently publicized as a risk" (p. 976). Based on the available evidence, such behavior should be considered dangerous.

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