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Modeling Drug Dependence Behaviors for Animal and Human Studies

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HUGHES, J. R. AND W. K. BICKEL. *Modeling drug dependence behaviors for animal and human studies.* PHARMACOL BIOCHEM BEHAV **57**(3) 413–417, 1997.—Laboratory models are available to study drug reinforcement in animals and humans, but few are available to study other drug dependence phenomena, e.g., difficulty stopping or use despite harm. The present paper is a first attempt to illustrate the feasibility of developing such models for use in both nonhuman and human research and discusses their possible utility in research to understand and treat stimulant and other drug dependencies. © 1997 Elsevier Science Inc.

Drug abuse Drug dependence Drug self-administration Methods Drug withdrawal

UNLIKE many behavioral disorders, the central behavior in drug dependence (i.e., the drug serves as a strong reinforcer) has been elegantly modeled in studies of both animals and humans (7). Drug reinforcement has most often been operationalized as drug self-administration, although choice, brain stimulation, place preference, and other models have also been used (7). These models have been fruitful both in understanding the genesis, maintenance, and cessation of stimulant and other drug use and in developing behavioral and pharmacological therapies for drug dependence (19).

Although many drug abuse researchers believe that drug reinforcement is what they should focus on, many clinicians note that it is the clinical phenomena (Table 1) associated with drug reinforcement that bring patients into treatment and have to be dealt with. In fact, these phenomena, not strong drug reinforcement per se, constitute the diagnostic description of drug dependence (1,43). Whether these clinical phenomena are simply sociocultural manifestations of strong drug reinforcement or are the result of pharmacological processes not accounted for by drug reinforcement is unclear.

The present paper suggests laboratory models for studying these clinical phenomena in both humans and nonhumans. We see several assets to developing such models. First, drug self-administration is a necessary but not sufficient condition for drug dependence. Very reliable drug self-administration can occur without drug dependence; for example, most daily alcohol (22) and caffeine (29) users are not dependent. Thus, one requirement of an adequate model of drug dependence is that it more closely mimic the topography and function of the human condition of drug dependence. In doing so, such models may help us understand the pharmacological and behavioral mechanisms that are causal in changing drug self-administration into drug dependence.

Second, one of the most common exercises in the drug dependence area is to compare drugs. Although comparisons of how "reinforcing" different drugs are are most common, the various drug dependencies vary as much, if not more, in terms of clinical phenomena (9,21,23,32). Some of this variance is likely due to pharmacological factors and some to environmental factors. For example, giving up important activities to use the drug and spending large amounts of time to obtain the drug are much more common in opioid dependence than in nicotine dependence (12). How much of this is due to pharmacological differences in the reinforcing effects of these drugs vs. the availability of the drugs is unclear. By operationalizing the constructs of "giving up activities" and "spending large amounts of time obtaining the drug," one can bring this question into the laboratory and not only compare drugs but look at the factors that might influence these outcomes (e.g., drug dose, degree of deprivation).

Third, modeling these phenomena can provide laboratory measures useful in medication development. At present, medications are usually screened by their ability to decrease the rate of drug self-administration (42). However, consideration of clinical phenomena suggests other, perhaps equally relevant, target behaviors. For example, targets for drug development could include the amount of nondrug reinforcement or punishment necessary to produce extinction of drug taking (difficulty stopping the drug), or how much drug operants can replace nondrug operants in concurrent schedules (giving up

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activities to use). Also, if a medication was found to decrease the probability of reacquisition of self-administration in an animal model, then that medication might be particularly useful given after an abstinence attempt. Similarly, if a medication was found to increase the ability of alternate reinforcers and punishers to extinguish self-administration, that medication might be particularly useful to those who are not presently making an attempt to stop drug use.

Animal and human laboratory models have been developed to study several components of drug dependence, i.e., drug discrimination, drug self-administration, tolerance, and withdrawal. This paper suggests models of other drug dependence phenomena using DSM (1) and ICD (43) definitions of these phenomena. The purpose of this exercise is not so much to suggest definitive models as to illustrate the feasibility of developing such models.

TOLERANCE

Models to study tolerance are already well developed for both animals and humans (31). The issue is how these models map onto clinical observations of tolerance in drug abusers.

The first definition of tolerance in DSM-IV (1) is "a need for markedly increased amounts of the substance to achieve intoxication or desired effect." This definition suggests animal and human models of tolerance should focus on presumed reinforcing effects (e.g., performance enhancement) and not on aversive effects (e.g., nausea, lethality) or nonbehavioral effects (e.g., cardiovascular effects).

The second definition in DSM-IV is "markedly diminished effect with continued use of the same amount of the substance." This definition maps very well onto existing models of tolerance, with one possible exception. The term "continued use" suggests that models of tolerance should examine effects after self-administered rather than experimenter-administered drug. This is important as self- and experimenter-administered drugs can produce very different effects (14,36).

TABLE 1

DSM-IV DIAGNOSTIC CRITERIA FOR SUBSTANCE DEPENDENCE

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  (b) markedly diminished effect with continued use of the same amount of the substance
(2) Withdrawal, as manifested by either of the following:
  (a) the characteristic withdrawal syndrome for the substance
  (b) the substance taken to relieve or avoid withdrawal symptoms
(3) The substance is often taken in larger amounts or over a longer period than was intended
(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
(5) A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects
(6) Important social, occupational or recreational activities are given up or reduced because of substance use
(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

WITHDRAWAL

Again, elegant models of withdrawal for both animals and humans have been developed (16,34). More recently, these models have focused not only on observable signs but also on how much withdrawal disrupts ongoing functional (i.e., operant) behavior (16).

A major issue with modeling withdrawal is the definition of "withdrawal." Withdrawal is defined in DSM-IV (1) as "a substance-specific maladaptive behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use." In reality, the DSM-IV definition fails to distinguish what most basic scientists term withdrawal from other types of abstinence effects. We have proposed four types of abstinence effects: a) indefinite effects when only a single on-drug and a single off-drug data point are available, b) offset effects when several off-drug points are available and a uniphasic change occurs after drug cessation, c) transient effects, when a biphasic time course (i.e., a finite period of withdrawal) is observed after drug cessation, and d) rebound effects, when a predrug baseline is known and the transient effect can be documented as "overshooting" the predrug baseline (28). Almost all investigators would label rebound and most would label transient effects as withdrawal effects, but note that the DSM-IV definition would also include indefinite and offset effects.

Also important in the DSM-IV definition is that behavioral change is primary and physiological changes secondary. This definition reinforces the recent interest in using operant baselines (e.g., responding for food) as dependent variables in studies of withdrawal (16). This is further emphasized by clinical observations that behavioral, not physiological, withdrawal changes are the basis for drug-dependent persons relapsing or seeking treatment for drug withdrawal (27).

A correlated phenomenon in the DSM-IV definition is use of the drug to avoid withdrawal (1). To demonstrate this, one has to first demonstrate that withdrawal is an aversive stimulus or punisher. Studies have illustrated this by showing cross-generalization of drug withdrawal to anxiogenic stimuli in a drug discrimination paradigm (16). The other step is to show that severe withdrawal causes relapse. In animals, stimuli paired with antagonist-induced withdrawal will increase the probably of drug self-administration (20). However, other experimental evidence in animals or humans that withdrawal precipitates relapse is sparse (10,26,41), and this is an area in need of further study.

DRUG USE IN LARGER AMOUNTS OR LONGER THAN INTENDED

This is one of several phenomena listed in the DSM-IV definition that are taken as evidence of "loss of control" or "compulsive use" (15). One could argue that this phenomenon can only be modeled in humans because verbal behavior is central to the phenomenon. That is, the essence of this phenomenon is a verbal statement about how much or how long one intends to use a drug and then use of more drug or for a longer period than stated. However, there may be creative ways to train animals to use only a prescribed amount of drug or for a prescribed time and to signal when they "intend" to do this (13).

Usually, the phrase "using more or longer than intended" refers to drug use during a single episode and thus refers to "binging" in contrast to "controlled" drug use. One "model"

of binging has already been observed in self-administration studies of alcohol in animals and humans: i.e., free access to a drug leads to periods of self-administration followed by periods of abstinence or light use (6,35). Both regularly spaced (i.e., controlled-use-like) patterns and use to the point of toxicity (i.e., bingelike) patterns have been observed with cocaine in animals (30). Unfortunately, few studies have examined factors that might control binging vs. controlled drug use (13). For example, perhaps a history of controlled use in the presence of available drug prevents later binging. Or, perhaps the magnitude of the dose of the initial self-administration is important? Or, perhaps the time delay between onset of "rewarding effects" vs. onset of aversive effects is crucial. Also, perhaps there are medications whose main effect is in preventing initial use from eventuating in a binge. Finally, clinical issues such as controlled drinking could be modeled: i.e., can one take an organism exhibiting binge use and train the organism to controlled use?

DESIRE OR UNSUCCESSFUL EFFORTS TO STOP, CUT DOWN, OR CONTROL USE

Again, efforts to stop, cut down, or control use are usually signalled by verbal behaviors in humans. However, one could model such attempts without including measures of verbal behavior. For example, verbal statements that one wants to stop drug could be thought of (and modeled) as an operant that serves as discriminative stimuli for later behavior that leads to reinforcement (e.g., social reinforcement from a spouse).

Modeling these phenomena would appear to be quite feasible. In fact, several studies have examined "extinction" and subsequent reacquisition of drug self-administration (38). However, the extinction procedure often used does not closely mimic the clinical situation. Extinction can be arranged by allowing responding for drug to occur but not delivering drug. This would be like having one's drug source begin providing blank doses of cocaine. Extinction has also been arranged by removing the opportunity to respond. This would be like imprisonment for drug use. Thus, neither of these two extinction paradigms mimics the conditions that lead most drug users to attempt to stop or control their drug use. In reality, most attempts to stop drug use occur in an environment in which drug is highly available; thus, extinction models of drug cessation should show suppression of drug intake for long periods of time when the drug and drug-paired stimuli are readily observable to the subject.

Attempts to stop drug use are often due to an aversive stimulus occurring contingent upon continuing drug use (8). The aversive stimulus may be a direct effect of the drug (e.g., a cocaine-induced heart pain) or socially mediated (e.g., losing a spouse due to cocaine use). Attempts to stop drug use can also be due to competition from alternate or incompatible nondrug reinforcers (e.g., social reinforcement from non-drug-using friends) (8). Sometimes it is the threat of an aversive stimulus or the promise of an alternative reinforcer that prompts an attempt.

Thus, one could more closely model real world cessation attempts by first establishing a baseline of drug self-administration and then programming aversive stimuli contingent on drug use or programming nondrug reinforcers contingent on periods of nondrug use or programming reinforcement for behaviors other than drug intake [i.e., a DRO (differential reinforcement of other behavior) schedule]. The magnitude of the aversive stimuli or the nondrug reinforcer necessary to produce abstinence could be used as an index of difficulty stopping a drug. In fact, this has been done with nondrug reinforcers in a paradigm called "resistance to extinction" (37), but to our knowledge has not been done with drug reinforcers.

A GREAT DEAL OF TIME SPENT OBTAINING, USING, OR RECOVERING FROM THE DRUG

These three phenomena could be quantified using complex schedules that have different components for working to obtain access to the drug, working to consume the drug, and a postconsumption period during which nondrug reinforcers are less potent. Similar complex schedules have been used successfully to study foraging behavior in animals (11) but have rarely been applied to drugs (33). Studying these three phenomena as separate but intertwined is important, because different drugs might produce different effects on the three different phenomena.

The first phenomenon (great deal of time spent obtaining drug) could be quantified in the first component of a complex schedule (e.g., a second-order schedule) as a large amount of responding to obtain access to the drug (18). In fact, behavioral economic studies indicate the amount of time spent obtaining a reinforcer may be as accurate a measure of response cost as the amount of responding for the reinforcer (3,4).

The second phenomenon (large amount of time spent using the drug) could be measured by allowing the subject to determine how much time he/she would stay in the component where he/she is working to consume the drug. The amount of time spent working to consume the drug could be compared with similar schedules using other drug or nondrug reinforcers.

The third phenomenon (time spent recovering from the drug) could be measured by establishing a nondrug operant, allowing drug self-administration, and seeing how long after the subject terminates drug self-administration it takes to recover baseline levels of responding on the nondrug operant.

IMPORTANT ACTIVITIES GIVEN UP TO USE DRUG

If life can be conceptualized as a series of choices, then this phenomenon can be conceptualized as drug use becoming preeminent over other activities (3,39). In fact, some see this as central to conceptualizations of drug dependence (3,4,39). Thus, one model of this phenomenon is that, in a concurrent schedule, as responding for the drug reinforcer increases, responding for nondrug reinforcers decreases. Thus, the metric here is *not* the rate of drug self-administration, but the degree to which drug self-administration suppresses responding for potent nondrug reinforcers. In behavioral economics, this can be quantified with a term called the cross-price elasticity (4). Choice of the nondrug reinforcer can be crucial to this paradigm, because some nondrug reinforcers will decrease with increased drug use (i.e., substitutes) and some will increase with increased drug use (i.e., complements) (4).

Interestingly, this model could also be used to study the effects of nondrug reinforcers on drug reinforcement: e.g., how much drug self-administration will be suppressed by programming nondrug reinforcers into a concurrent schedule (3–5,24). This is an especially intriguing use of this paradigm, given that much of the efficacy of our existing drug counseling and behavior therapy procedures is probably due to their ability to substitute nondrug for drug reinforcers (2,3,25).

USE OF THE DRUG DESPITE HARM

Harm can be defined as an aversive stimulus; thus, one operationalization of this phenomenon would be to make an aversive stimulus contingent on drug self-administration, i.e.,

similar to a "punished responding" paradigm (17). To best mimic the human condition, the schedule should program an aversive event that is very delayed and of low probability but still conditional on the amount of drug self-administration. Thus, an aversive stimulus could be delivered on a very large variable ratio schedule and with a long delay between self-administration and delivery of the aversive stimulus. The metric here could be the degree to which the self-administration baseline is suppressed by the aversive stimulus, the point at which self-administration is terminated, the magnitude of the aversive stimulus necessary to terminate self-administration, etc. Because there are often ethical problems with delivering noxious or painful stimuli to humans, reinforcement loss (e.g., loss of money) could be used as an aversive stimulus (40).

CLOSING REMARKS

The drug reinforcement paradigm has been immensely useful in understanding stimulant and other forms of drug dependence and in developing and testing behavioral and pharmacological treatments (7,19). The thesis of this paper is that developing behavioral models of the clinical phenomena associated with strong drug reinforcement might also enhance our understanding of how dependence develops and lead to new treatment approaches. For example, the models described herein could be used to ask many important questions about stimulant and other drug dependencies: does programming non-drug reinforcers decrease the degree to which a subject will work for stimulants, does programming punishment vs. programming alternate reinforcers produce suppression of self-administration of stimulants that is equally resistant to reinitiation, and under what conditions is drug self-administration especially resistant or sensitive to contingent aversive stimuli?

The present paper is a first step in suggesting such models. Again, the purpose of the paper was not so much to provide definitive models but to illustrate the feasibility of such models and encourage others to consider developing such models. One would hope that the models developed could be used with both humans and nonhumans and could be varied to more closely mimic the specific clinical features of a group of persons with a specific drug dependence. The models also could produce continuous measures that would be sensitive to pharmacological and behavioral analysis and would be helpful in developing new target behaviors for developing pharmacological and behavioral treatments for drug dependence.

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