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Drug Injections as Negative Reinforcers

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IN a review of the literature in 1969, Schuster and Thompson examined experimental results of drug self-injection "within the framework of operant conditioning principles" (22, p. 483). Their premise was that drugs functioned as positive reinforcers and maintained behavior according to basic operant principles. Conditioning, extinction, stimulus control, effects of deprivation, and control by basic schedules of reinforcement were essentially the same as had been found with other reinforcers.

However positive reinforcement is only one of two major processes that modulate behavior. Negative reinforcers act in concert with positive reinforcers to mold ultimate patterns. Yet, in 1969 there were virtually no examples of drug injections acting as negative reinforcers. Subsequently, experiments began to suggest that self-injected drugs might indeed function in this way. The developments in this area are represented by the papers in this section on responding maintained by termination of a drug infusion or a stimulus associated with such infusions. Our purpose here is to examine experiments on drugs as negative reinforcers within the framework of operant conditioning principles.

Drugs as Negative Reinforcers

By definition, negative reinforcers (aversive stimuli) are those events that share a capacity to 1) support responses that eliminate or prevent them, and/or 2) suppress responses that produce them (punishment) (6). Many noxious stimuli have this capacity, *e.g.*, electric shock, bright light, loud noise, intense heat. However, beside the capacity to act as negative reinforcers, these stimuli have other properties that must be evaluated in analyzing their effects in behavioral experiments. Electric shock has become the stimulus of choice because its extraneous features do not seriously interfere with its use as a negative reinforcer. (It affects behavior over a wide range of intensities that do not produce irreversible tissue damage, and it can be finely graded to produce effects in reproducible degrees. Its duration, locus and intensity can be controlled with precision.) Other events that act as negative reinforcers are more difficult to control and thereby introduce other features that complicate an evaluation of their effects on behavior.

In the case of drugs as negative reinforcers, an analysis must consider their times of onset and their durations of action. These depend not only on the specific drug being studied, but also on the dose and the rate at which it is infused. Thus, the effects of drugs may be delayed and prolonged, and consequently these effects may not be precisely related to the responses that produce or terminate them.

Experimenters who work with drugs as reinforcers have found methods to minimize problems of onset and duration. Intravenous administration of a drug usually produces a rapid effect. An exteroceptive stimulus correlated with drug infusion can, through conditioning, become associated with a drug's effects, and can be controlled with temporal precision. Such techniques at least minimize the problems of delayed and prolonged effects.

As Schuster and Thompson (22) emphasize, the operant control exerted by positive reinforcers must be judged by their

effect on *future* emission of responses. That is, eliciting functions of the reinforcer must be ruled out. Similarly, eliciting functions must also be excluded in an analysis of negative reinforcers. Chlorpromazine administered before experimental sessions suppresses operant behavior in many situations. Such drug-induced suppression could be mistaken for a punishing effect if it occurred during a punishment procedure. Similarly, if infusions of chlorpromazine suppressed behavior before escape responses were emitted, one might wrongly conclude that the infusion could not act as a negative reinforcer.

Additionally, a drug with side effects that we might subjectively conisder unpleasant will not necessarily be a negative reinforcer. In an operant analysis, "negative reinforcement" is defined strictly in terms of its effect on the future emission of a response. While unpleasant side effects may be induced by a drug that is a negative reinforcer, severe side effects can also accompany a drug which continues to be self-administered and thus acts as a positive reinforcer (23).

To summarize, in operant conditioning a negative reinforcer is defined by its effects on the future probability of a response that produces or terminates it. A variety of stimuli can be negative reinforcers, but possibly have other, confounding effects. With drugs as negative reinforcers, the relatively slow onset and extended duration of effects as well as direct suppressant or stimulant actions can complicate an analysis of their effects as response consequences.

Punishment

In punishment procedures, a response-contingent negative reinforcer (aversive stimulus) reduces the future probability of a response (3). Several reports suggest that injections of some drugs may function in this way.

For the most part, the reports have stemmed from observations in standard substitution tests that some substituted drugs not only fail to maintain responding, but lead to a more rapid decrease in responding than occurs when saline is substituted. Hoffmeister and Schlichting (18) found that substitution of nalorphine (0.5 mg/kg per injection) for cocaine or codeine in rhesus monkeys resulted in response levels that were below the confidence limits of response levels found when saline was substituted. Further, subsequent recovery of performance with the standard maintenance drugs (cocaine or codeine) was delayed when compared to recovery after saline injection. Woods and Tessel (28) observed that fenfluramine would not maintain responding when substituted for cocaine, and at doses of 0.1 to 3.0 mg/kg per injection the number of injections self-administered was well below saline levels.

Hoffmeister and Goldberg (17) compared chlorpromazine, saline, and other psychoactive drugs as substitutes for cocaine in rhesus monkeys. Chlorpromazine (0.05, 0.1 and 0.5 mg/kg/injection) reduced responses below saline levels in a dose related fashion, while imipramine at these same doses was comparable to saline.

In all of these experiments (17, 18, 28) the punishing effect of drugs was studied as responding was undergoing extinction. That is, the positive reinforcing drug had been removed (extinction), and responding was decreasing due to the absence of reinforcement. Therefore a punishing effect had to be determined as a more rapid decline in response rate than would be found when only saline was substituted.

During the course of substitution experiments of our own, we had opportunity to investigate the punishment of non-reinforced responding in another way. Our experiments involved squirrel monkeys, which were restrained at the waist in a chair, inside a sound attenuating compartment during 100-min sessions. They had indwelling venous catheters and responded under fixed-ratio schedules of cocaine injections. Each 6-sec infusion of cocaine was

accompanied by a change in illumination and was followed by a 1-min time-out, during which the chamber was dark. Stable levels of responding for cocaine were determined and contrasted with sessions in which saline alone was substituted. When saline was substituted, responding typically dropped to low levels within 5 days. However, we have found that with low fixed ratios about half the monkeys studied eventually continued to respond over an extended number of sessions (10 or more).

Illustrated in figure 1 (upper) is the usual decline in responding on two occasions when saline was substituted for cocaine. The middle part of the figure shows sustained responding in the third series. Responding continued through several experimental manipulations over a period of 2½ months of daily sessions. We do not know how long it might have continued had there been no change in the experimental situation. The lower part of the figure shows the operation that ultimately resulted in cessation of responding. The number of responses required to produce the injection and associated stimuli was raised over successive sessions from 10 to 30. At FR-30, responding was not maintained with saline but could be reinstated with cocaine or other reinforcing drugs.

We observed responding maintained by saline and associated stimuli over several months in two other monkeys. However, we are unsure how many might behave similarly, because we now increase the fixed-ratio response requirement when responding does not decline within 5 days. Raising

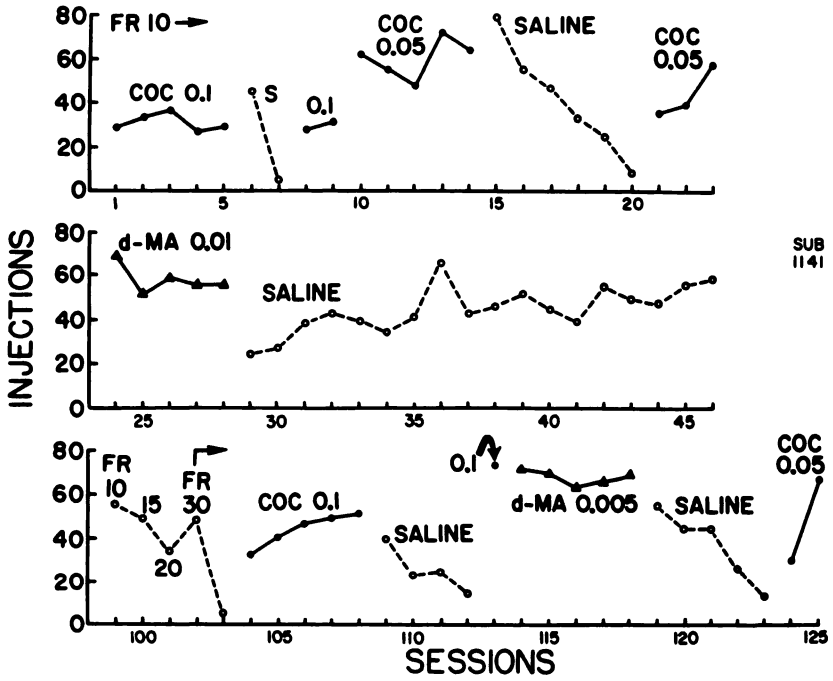

FIG. 1. Injections of cocaine (COC), *d*-methylamphetamine (*d*-MA) or saline self-administered by monkey 1141 in daily 100-min sessions. Sessions 1 to 5 show a stable intake of cocaine (0.1 mg/kg per injection) under a 10-response fixed-ratio (FR) schedule. (This followed a training period that is not shown.) Responding rapidly decreased when saline was substituted for cocaine in sessions 6 and 7, but returned to previous levels when cocaine was reinstated (session 8 and 9). When saline was substituted (session 15–20) for cocaine (0.05 mg/kg per injection) responding decreased over 6 days; but after *d*-methylamphetamine, self-administration of saline continued at a high level (session 29–46, and sessions 47–98, which are not shown). When the fixed-ratio response requirement was increased to 30, responding decreased by the 2nd day (session 103). Subsequently, responding was maintained at high levels only by drug (sessions 104–125).

the ratio to 20, 30, or 50 has been successful in decreasing responding during saline substitution without decreasing levels of responding subsequently maintained by cocaine.

Although we do not know why responding should fail to extinguish, we think it is significant that raising the ratio normalizes performance. This and also the continuing consistency of the fixed-ratio pattern of response (*i.e.*, well defined pauses preceeding continued responding until the infusion stimuli and time-out result) indicate that responding is not simply out of control or random in occurrence. In speculating about a possible basis for responding, we note that with low doses of a reinforcing drug, several injections and some elapsed time must occur before enough drug is available to act as a reinforcer. And, in the typical substitution procedure the reinforcing drug standard is reinstated after a series of saline sessions. Perhaps these factors shape extended responding (in anticipation of an ultimate effect), such that only by enlarging the work requirement per injection is there insufficient basis for response.

We experimented with drugs that might act as negative reinforcers in two of the monkeys that showed extended responding during saline substitution. That the substitution of chlorpromazine, at a dose of 0.1 or 0.2 mg/kg per injection, clearly reduced responding of subject 1270 and a dose of 0.05 reduced responding of subject 1141 is shown in figure 2. Saline response levels could be consistently recovered when chlorpromazine was removed. The inset in the lower right of the figures, which shows the final performance at each dose level relative to saline, describes a dose-dependent decrease.

The pattern of responding within sessions is illustrated in figure 3. In saline sessions, responding was negatively accel-

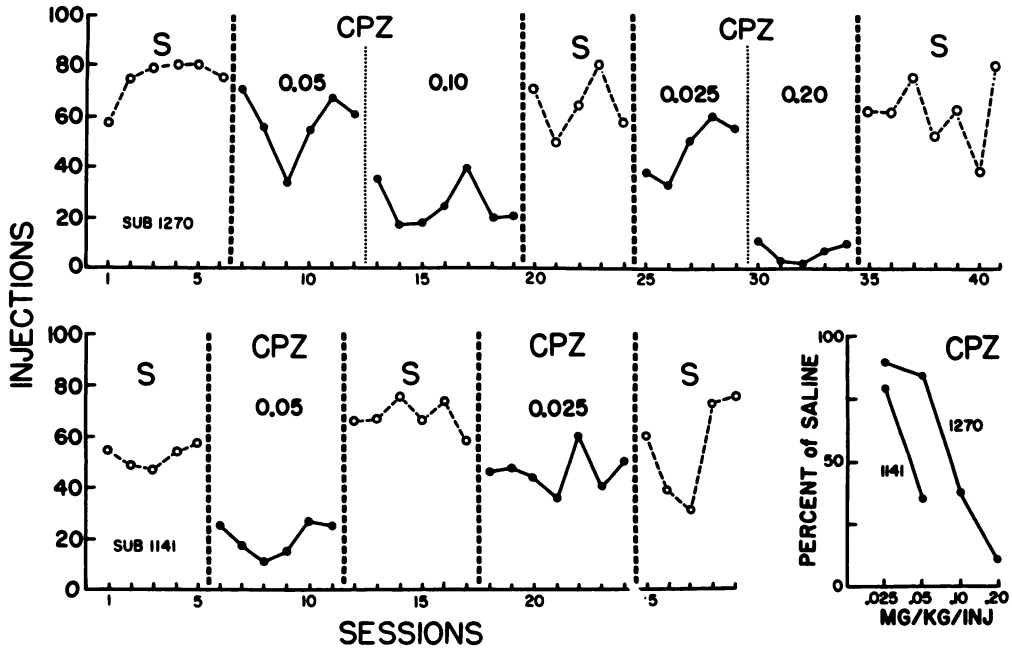

FIG. 2. Substitution of chlorpromazine (CPZ) in two monkeys self-administering saline (S) at high levels under a 10-response fixed-ratio schedule. Sessions were conducted daily for 100 min. Self-administration of CPZ (0.10 or 0.20 mg/kg per injection) by monkey 1270 (top plot) suppressed responding well below the saline level (sessions 13–19 and 30–34). CPZ (0.05 mg/kg per injection) suppressed responding in monkey 1141 (bottom plot). Results are summarized in the lower right: Each point is an average of the last 3 days of CPZ self-administration taken as a percent of the saline sessions before and after it.

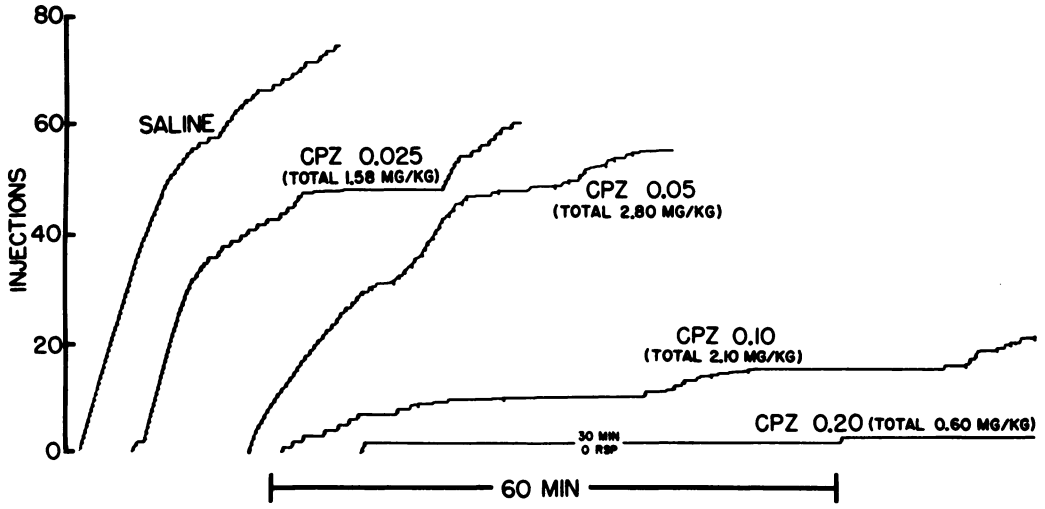

FIG. 3. Representative effects of substituting various doses of chlorpromazine (CPZ) for saline in monkey 1270, which consistently self-administered saline at high levels (see fig. 2). All sessions were 100 min. The paper drive (abscissae) stopped during 1-min time outs which followed each injection. Injections are indicated by downward deflections of the recording pen.

erated over the session. The performance appeared as an exaggeration of the spontaneous recovery typically observed in successive sessions of experimental extinction. At low doses of chlorpormazine, the deceleration in rate tended to occur earlier than with saline; at the higher doses (0.1 and 0.2 mg/kg per injection), responding was greatly suppressed, yet remained highest in the beginning of sessions with occasional injections occurring later.

The pattern of responding with the suppressive doses is atypical of that seen in other procedures where responses produce punishing electric shocks. The common pattern is for maximal suppression to occur in the beginning of sessions (1, 15). Because of the opposite type of effect seen with chlorpromazine, its effects are not clearly equivalent to those obtained with a noxious stimulus like electric shock. A direct suppressive effect of the drug seems unlikely, because we saw no signs of depression at the end of the sessions, and relatively low total doses (see fig. 3) were delivered.

Hoffmeister and Goldberg (17) discussed the possibility that the low levels of responding that they observed when chlorpromazine (0.5 mg/kg per injection) was substituted for cocaine might have been due to a general depressant action. They argued that this was unlikely because: 1) over a 6-day substitution, two of the three monkeys failed to administer any injections on the last 2 days, and they were slow to resume responding when cocaine was reinstated; 2) imipramine, which also has a general depressant action on operant behavior, was self-injected at levels comparable to saline. Although these are important arguments, we do not feel the issue of whether chlorpromazine suppresses responding because of a true punishment effect can be definitively settled by the data now available. Responding that is decreasing during extinction experiments is a notoriously variable base line against which to study small effects. Further, a drug that simply has a novel physiological effect might disrupt responding because of its abrupt alteration of the stimulus conditions. Even a different type of reinforcing drug (*e.g.*, cocaine *vs.* codeine) is less readily accepted than a reinforcer within the same class (18). In addition, the slow recovery of responding Hoffmeister and Goldberg saw when cocaine was resub-

stituted may only reflect the degree to which the response had been extinguished.

Only one earlier experiment considered the punishing effect of self-administered drugs under conditions in which responding was stably maintained (27). Rhesus monkeys self-administered codeine (0.1 mg/kg per injection) as a reinforcer. When the narcotic antagonist naloxone (0.001 to 0.1 mg/kg per injection) was *added* to the codeine solutions, responding was reduced in a dose related fashion. A problem in evaluating these data, however, is that naloxone administered before sessions (and thus not as a response consequence) also eliminated or greatly reduced responding.

One experiment, which appears at first to be anomalous, failed to find a suppressive effect of nalorphine when it was substituted for morphine in morphine-dependent rhesus monkeys (11). Nalorphine sessions were interspersed among morphine sessions without correlated stimuli. Hence, before responding began there was no basis for distinguishing the consequence that would follow. Once abstinence symptoms began to appear, it is plausible that the monkey would continue to perform the response that had in the past alleviated the symptoms (*i.e.*, because it has produced morphine).

We conclude from the experiments with substituted drugs that as yet experiments have established only the possibility that self-administered drugs can function as typical punishers. The obvious type of experiment to resolve several problems in the analysis of drugs as punishers would be to maintain responding with an explicit reinforcer other than drug, and make a drug with negative reinforcing properties contingent on it. To our knowledge such an experiment has not been reported.

Conditioned Suppression

Estes and Skinner (9) in 1941 designed a procedure in which an electric shock was paired with an otherwise neutral light. When these pairings occurred during sessions in which rats were lever pressing for food, responding became suppressed in the presence of the light. This conditioned suppression procedure has been widely studied as a paradigm for evaluating effects of noxious stimuli (16). However, its utility for defining a negative reinforcer has been called to question by the findings of Azrin and Hake (2) that responding will also be suppressed during a stimulus which has been correlated with a positive reinforcer.

Several studies of drugs have used the conditioned suppression procedure. Two by Goldberg and Schuster examined the effect of nalorphine in morphine-dependent (12, 13) and postdependent (13) rhesus monkeys. Both experiments used food-deprived monkeys responding under a 10 response fixed-ratio schedule of food presentation. In some sessions an originally neutral red light appeared from 5 min before to 5 min after an intravenous injection of nalorphine ($\simeq$ 0.2 mg/kg). In both dependent monkeys and in monkeys withdrawn from morphine 3 months before, the results were the same. When nalorphine was first injected, responding was eliminated for the remainder of the experimental session. After several sessions in which nalorphine injections were paired with the light, responding stopped when the light first appeared. But besides suppressing responding, the light elicited a conditioned withdrawal syndrome (including vomiting). As a result the authors interpreted the response suppression as not necessarily evidence of nalorphine being a negative reinforcer *per se*, but as "probably due to a more general effect of disrupting ongoing behavior" (13, p. 45).

A related experiment by Goldberg *et al.* (14) was a study of the pairing of nalorphine with an orginally neutral red light while morphine-dependent rhesus monkeys were pressing a lever to self-administer *morphine* (0.1 mg/kg per injection). Once a day the light appeared 10 min before to 30 min after an injection of 0.1 mg

of nalorphine per kg. After 10 pairings, responding was not affected during the critical 10 min before the nalorphine injection even though responding for morphine increased after the injection. Thus, no conditioned suppression occurred. The findings of these three experiments (12–14) do not provide clear evidence for a negative reinforcing effect of nalorphine, even in morphine-dependent subjects.

Cameron and Appel (5) studied chlorpromazine (8 or 10 mg/kg) and LSD-25 (0.2 mg/kg) in a conditioned suppression procedure in rats. Lever pressing was maintained by water reinforcement on a 30-sec variable-interval schedule. A white stimulus light preceeded by 3 min an intraperitoneal injection of drug. (Subjects were taken from the chamber, injected with drug—or saline for control sessions—and returned within 25 sec.) After a few pairings of drug and light, responding was reduced during the light preceding drug injections.

Whitney and Trost (25) found a suppressive effect of a high dose of *d*-amphetamine (0.75 mg/kg, i.v.) in a Java monkey (*Macaca iris*). Key pressing was maintained by a 45-sec variable-interval schedule of food presentations, and a 3.5-min tone started 1 min before the drug infusion which lasted for 1 min. Only one stimulus was presented in a session, and sessions without a stimulus presentation or drug infusion randomly alternated. The first time *d*-amphetamine was injected it eliminated responding for the remainder of the session. By the fifth conditioning session responding had ceased during the tone before the drug infusion.

The Whitney and Trost result is of interest because others (26) have suggested that drugs which act as positive reinforcers at low doses may act as negative reinforcers at high doses. The result with *d*-amphetamine, which can act as a positive reinforcer, lends support to this. However, the previously noted findings by Azrin and Hake (2) that the presentation of a stimulus previously correlated with positive reinforcers can also suppress responding clouds the interpretation of drug results with this procedure.

Termination of Stimuli Associated with Drug Infusion

The first experimental demonstration that drugs would support responding which terminated stimuli associated with drug infusions was reported by Goldberg *et al.* (11) in 1971. They found that morphine-dependent rhesus monkeys would respond under fixed-ratio schedules to terminate infusions of nalorphine or naloxone and associated stimuli. Subsequent experiments have expanded the number of drugs that can function as negative reinforcers under these conditions. These are listed in table 1. Included are the results from the experiments presented in the present session. The eight experiments all used rhesus monkeys and intravenous drug administration. In these experiments, periodic or continuous infusions of a drug were scheduled to occur in the presence of a stimulus light. Responding terminated the light and any associated infusions for a 1-min time out, during which the stimulus-infusion complex was absent and responses had no consequence. In the study by Hoffmeister and Wuttke (20), for example, at 30-sec intervals the drug was infused for 10 sec; a single response terminated the light-infusion complex. In other studies periodic brief infusions (24) or continuous infusions (7, 8, 27) in the presence of the stimulus and 3- to 30-response fixed-ratio schedules were used.

Inspection of the table reveals that drugs of several classes have been shown to support responding maintained by termination of a stimulus associated with drug infusions. Early work concentrated on the narcotic antagonists in morphine-dependent subjects. Many of these drugs were later shown to be effective with non-dependent subjects as well. The report by Downs and Woods (8) that high doses of naloxone maintained responding in non-dependent subjects raises the question of

TABLE 1

Drugs studied in procedures in which responding terminated drug infusions and associated stimuli

All studies used intravenous drug administration and rhesus monkeys. Italicized references are to papers presented at this conference.

Compounds	Effect[a]	Mg/Kg per Injection[b]	Subjects	Reference
Narcotic antagonists				
Nalorphine	+	0.005-0.01	Morphine dependent	10, 11, *24*
	+	0.01-0.5	Nondependent	19, *20*
Naloxone	+	0.0001-0.02	Morphine dependent	7, *8*, 10, 11, 27
	+	[0.0003-0.002][c]	Morphine dependent	*8*, 27
	+	[0.3-1.0][c]	Nondependent	*8*
	–	0.005-0.1	Nondependent	19
Pentazocine	+	0.05-1.0	Morphine dependent	10
	– (–)	0.05	Nondependent	19
Propiram fumarate	+	0.05-1.0	Morphine dependent	10
	– (–)	0.05	Nondependent	19
Cyclazocine	+	0.0001-0.01	Nondependent (not studied in morphine dependent)	19
Hallucinogens				
LSD	+	0.0005-0.0025	Nondependent	*20*
STP	+	0.001-0.005	Nondependent	*20*
Other				
Chlorpromazine	+	0.005-0.05	Nondependent	*20*
Imipramine	–	0.005-0.1	Nondependent	*20*
Pentobarbital	– (–)	0.01-0.1	Nondependent	*20*
Codeine	– (–)	0.05	Nondependent	19
Cocaine	– (–)	0.05	Nondependent	19

[a] Effects: + = supports responding; – = fails to support responding above saline levels; – (–) = responding below saline levels.

[b] Listed are doses of compounds infused over 10-sec periods at 30-sec intervals when no response occurs [except in (24) where doses were infused in 0.25 sec at 20-sec intervals]. For compounds supporting responding, the range of effective doses is given; for compounds not supporting responding, the range of doses studied is given.

[c] Continuous infusions (mg/kg per min).

whether higher doses of pentazocine and propiram fumarate might not be similarly effective.

The current work by Hoffmeister and Wuttke (20) extends the range of drug classes studied and shows that two of the hallucinogens can also act as negative reinforcers. Their results with chlorpromazine confirm the suggested effects in the punishment and conditioned suppression experiments. The extended exposure that they found necessary to establish avoidance possibly shows that depressive actions of drugs may have to be overcome before their reinforcing effect will be apparent.

The stimulus-infusion termination paradigm is better suited than the punishment and conditioned suppression paradigms for demonstrating the effects of drugs as negative reinforcers. The stimulus characteristics which are problems for these latter procedures are less troublesome here. As previous studies have shown, once a correlation is established between an electric shock and a stimulus, termination of the stimulus can maintain responding even when electric shocks rarely occur (4, 21). When a drug is used as the noxious event associated with a stimulus, the stimulus can bridge the delays of onset and termination, and the infrequent delivery of the drug reduces interfering side effects. Also, general response depression is the most troublesome side-effect in evaluating the action of a drug in a punishment or conditioned suppression paradigm, but is much

less a problem with the stimulus-infusion termination paradigm. In this case generalized depression would act against the demonstration of the drug infusion having negative reinforcing properties.

Conclusion

The problems found in an analysis of drugs as negative reinforcers do not differ fundamentally from those found in other areas of operant analysis. Extraneous characteristics of stimuli influence the ability of these stimuli to control behavior and must be taken into consideration. Through experience, methods are generally found for contending with the complications they present.

The problems of drug onset and duration, as well as eliciting effects, which complicate an analysis of the control by drugs as negative reinforcers, were all confronted earlier in experiments with drugs as positive reinforcers. In these earlier experiments intravenous administration was used to minimize drug onset time and a stimulus was used to bridge the delay between response and drug onset. Such techniques were taken directly from experiments with food reinforcement, where such stimuli are important even during the short intervals between a response and activation of a food delivery mechanism.

In the early stages of research on self-administration of drugs, before the problems were fully recognized and a suitable technology developed for managing them, experimenters had difficulty in demonstrating that drugs could function as positive reinforcers. In studying psychomotor stimulants, for example, they also had to contend with the direct behavioral effects of the drugs. That increased lever pressing was not simply part of a general pattern of stimulated motor behavior could not be immediately excluded. Only through continued experimentation (particularly the demonstration of control by reinforcement schedules), was it conclusively demonstrated that these drugs could act as positive reinforcers.

Similarly, the clear demonstration that drugs can act as negative reinforcers has evolved through experimentation. Early substitution experiments suggested that some drugs were doing more than simply not supporting responding. Studies of drugs as punishers and as unconditioned stimuli in conditioned suppression strengthened this belief. But, the convincing experiments are those that have used procedures in which responding terminates stimuli associated with drug infusions. The complicating effects of drugs are less troublesome here. Stimulus onset and duration are not as critical in these procedures, and because responding is maintained, depressant actions do not complicate the analysis.

Many of the principles of operant conditioning that Schuster and Thompson (22) could show for drugs as positive reinforcers can now be demonstrated with drugs as negative reinforcers (8, 20, 24). The list of effective drugs includes examples from several classes. The basic processes of response conditioning and elimination are shown to hold to the same form found in comparable procedures with electric shock. Control of responding by fixed-ratio schedules of terminating the stimulus associated with infusions have been demonstrated. Here responses are patterned in the same manner as is found with a stimulus associated with shock. And, the dose-response relationships seem functionally equivalent to the stimulus-intensity-response relationships found with other noxious stimuli.

REFERENCES

1. Azrin, N. H.: Sequential effects of punishment. Science 131: 605–606, 1960.
2. Azrin, N. H. and Hake, D. F.: Positive conditioned suppression: Conditioned suppression using positive reinforcers as the unconditioned stimuli. J. Exp. Anal. Behav. 12: 167–173, 1969.
3. Azrin, N. H. and Holz, W. C.: Punishment. *In* Operant Behavior: Areas of Research and Application, ed. by W. K. Honig, Appleton-Century-Crofts, New York, 1966.
4. Azrin, N. H., Holz, W. C., Hake, D. R. and Ayllon, T.: Fixed-ratio escape reinforcement. J. Exp. Anal. Behav. 6: 449–456, 1963.
5. Cameron, O. G. and Appel, J. B.: Conditioned suppression of bar-pressing behavior by stimuli associated with drugs. J. Exp. Anal. Behav. 17: 127–137, 1972.

6. Catania, A. C.: Contemporary Research in Operant Behavior, Scott, Foresman and Co., Glenview, Ill. 1968.
7. Downs, D. A. and Woods, J. H.: Fixed-ratio escape and avoidance-escape from naloxone in morphine-dependent monkeys: Effects of naloxone dose and morphine pretreatment. J. Exp. Anal. Behav. **23:** 415–427, 1975.
8. Downs, D. A. and Woods, J. H.: Naloxone as a negative reinforcer in rhesus monkeys: Effects of dose, schedule, and narcotic regimen. Pharmacol. Rev. **27:** 397–406, 1976.
9. Estes, W. K. and Skinner, B. F.: Some quantitative properties of anxiety. J. Exp. Psychol. **29:** 390–400, 1941.
10. Goldberg, S. R., Hoffmeister, F. and Schlichting, U.: Morphine antagonists: Modification of behavioral effects by morphine dependence. *In:* Drug Addiction: I. Experimental Pharmacology, ed. by J. M. Singh, L. Miller and H. Lal, Futura Publishing Co., Mount Kisco, N. Y., 1972.
11. Goldberg, S. R., Hoffmeister, F., Schlichting, U. and Wuttke, W.: Aversive properties of nalorphine and naloxone in morphine-dependent rhesus monkeys. J. Pharmacol. Exp. Ther. **179:** 268–276, 1971.
12. Goldberg, S. R. and Schuster, C. R.: Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. J. Exp. Anal. Behav. **10:** 235–242, 1967.
13. Goldberg, S. R. and Schuster, C. R.: Conditioned nalorphine-induced abstinence changes: Persistence in post morphine-dependent monkeys. J. Exp. Anal. Behav. **14:** 33–46, 1970.
14. Goldberg, S. R., Woods, J. H. and Schuster, C. R.: Morphine: Conditioned increases in self-administration in rhesus monkeys. Science **166:** 1306–1307, 1969.
15. Hake, D. F., Azrin, N. H. and Oxford, R.: The effects of punishment intensity on squirrel monkeys. J. Exp. Anal. Behav. **10:** 95–108, 1967.
16. Hoffman, H. S.: Stimulus factors in conditioned suppression. *In:* Punishment and Aversive Behavior, ed. by B. A. Campbell and R. F. Church, Appleton-Century-Crofts, New York, 1969.
17. Hoffmeister, F. and Goldberg, S. R.: A comparison of chlorpromazine, imipramine, morphine and *d*-amphetamine self-administration in cocaine-dependent rhesus monkeys. J. Pharmacol. Exp. Ther. **187:** 8–14, 1973.
18. Hoffmeister, F. and Schlichting, U.: Reinforcing properties of some opiates and opioids in rhesus monkeys with histories of cocaine and codeine self-administration. Psychopharmacologia **23:** 55–74, 1972.
19. Hoffmeister, F. and Wuttke, W.: Negative reinforcing properties of morphine antagonists in naive rhesus monkeys. Psychopharmacologia **33:** 247–258, 1973.
20. Hoffmeister, F. and Wuttke, W.: Psychotropic drugs as negative reinforcers. Pharmacol. Rev. **27:** 419–428, 1976.
21. Morse, W. H. and Kelleher, R. T.: Schedules using noxious stimuli: I. Multiple fixed-ratio and fixed-interval termination of schedule complexes. J. Exp. Anal. Behav. **9:** 267–290, 1966.
22. Schuster, C. R. and Thompson, T.: Self-administration of and behavioral dependence on drugs. Annu. Rev. Pharmacol. **9:** 483–502, 1969.
23. Talley, W. H. and Rosenblum, I.: Self-administration of dextropropoxyphene by rhesus monkeys to the point of toxicity. Psychopharmacologia **27:** 179–182, 1972.
24. Tang, A. H. and Morse, W. H.: Termination of a schedule complex associated with intravenous injections of nalorphine in morphine-dependent rhesus monkeys. Pharmacol. Rev. **27:** 407–417, 1976.
25. Whitney, G. D. and Trost, J. G.: Response disruption following amphetamine self- and programed administration. *In* Drug Dependence, ed. by R. T. Harris, W. M. McIsaac and C. R. Schuster. Univ. Texas, Austin, 1970.
26. Wilson, M. C., Hitomi, M. and Schuster, C. R.: Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. Psychopharmacologia **22:** 271–281, 1971.
27. Woods, J. H., Downs, D. A. and Carney, T: Behavioral functions of narcotic antagonists: Response-drug contingencies. Fed. Proc. **34:** 1777–1784, 1975.
28. Woods, J. H. and Tessel, R. E.: Fenfluramine: Amphetamine congener that fails to maintain drug-taking behavior in the rhesus monkey. Science **185:** 1067–1069, 1974.