*EFFECTS OF CHLORDIAZEPOXIDE AND COCAINE ON
CONCURRENT FOOD AND AVOIDANCE-OF-TIMEOUT SCHEDULES*

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Five rats were trained on a concurrent schedule in which responses on one lever produced a food pellet on a random-interval 30-s schedule during 10 s of food availability associated with distinctive exteroceptive stimuli. Responses on another lever postponed for 20 s the presentation of a 50-s timeout, during which all stimuli were extinguished and the schedule contingencies on the food lever were suspended. The response rates maintained by the random-interval schedule exceeded those maintained by the avoidance contingency, but both provided a stable baseline to assess the behavioral effects of different drugs. Low doses of cocaine hydrochloride (1 and 3 mg/kg) did not affect food-reinforced responding or avoidance response rates. Intermediate doses (5.6, 10, and 13 mg/kg) produced a dose-dependent decrease in food-maintained and avoidance response rates, and both types of responding were virtually eliminated after administration of the highest doses (17 and 30 mg/kg) of cocaine. Low doses of chlordiazepoxide (1 and 3 mg/kg) increased food-maintained and avoidance response rates, and both rates decreased systematically after 10 and 30 mg/kg of this drug. The effects of cocaine and chlordiazepoxide on response rates maintained by avoidance of timeout from food presentation were unlike those reported when subjects responded to avoid shock presentation. The results of this experiment thus provide evidence to suggest that the effects of drug administration on avoidance behavior may be a function of the nature of the consequent event to be avoided.

Key words: random-interval schedule, negative reinforcement, avoidance of timeout from food presentation, timeout-timeout interval, response-timeout interval, lever press, rats

The behavioral effects of drugs have been shown to depend upon a number of nonpharmacological factors, including the schedule of reinforcement (e.g., Branch, 1990; Hoffman, Branch, & Sizemore, 1987; McAuley & Leslie, 1986), the degree of external stimulus control (e.g., Rees, Wood, & Laties, 1985), the species of the experimental subject (e.g., Picker & Dykstra, 1988; Picker, Heise, & Dykstra, 1987), its gender (van Haaren, Heinsbroek, Louwerse, & van de Poll, 1986), its experimental history (Urbain, Poling, Millam, & Thompson, 1978), and the nature of the event that maintains the behavior.

The observation that the behavioral effects of drugs can also depend on the nature of the consequent event is central to the present experiment. For example, it has frequently been shown that benzodiazepines can increase food-maintained responding but decrease behavior maintained by shock presentation (for review, see Barrett & Katz, 1981; Barrett, Valentine,

& Katz, 1981). In contrast to these observations, morphine at intermediate doses decreased food-maintained behavior but increased behavior maintained by shock presentation (e.g., Katz & Goldberg, 1986). On the other hand, intermediate doses of *d*-amphetamine have been shown to increase responding maintained by fixed-interval schedules of food and shock presentation, but high doses of this drug decreased response rates under both schedules (McKearney, 1974). It is important to note that it is not at all unlikely that the assessment of drug effects on behavior maintained by shock presentation or shock avoidance may be compromised by unconditioned reactions to the shock itself (for review, see Dworkin, Galizio, & Pitts, 1993).

The present experiment was designed to examine the effects of drug administration on behavior maintained by avoidance of timeout from food presentation. This schedule arrangement does not involve presentation of a noxious event (such as electric shock) but maintains a relation between behavior and its consequences similar to that arranged in conventional unsignaled shock-avoidance schedules. The reinforcing functions of avoidance of timeout from food have been investigated in only a few experiments. In the first report of the effects of this procedure, pigeons pecked a

This research was supported by a grant from the National Institute on Drug Abuse (R01-DA06463), which also provided the cocaine hydrochloride. The authors thank Karen Anderson for her help in conducting this experiment. Reprints may be obtained by writing Frans van Haaren, Department of Psychology, University of Florida, Gainesville, Florida 32611 (E-mail: haaren@webb.psych.ufl.edu).

key when pecking postponed the removal of a stimulus associated with a schedule of food reinforcement on another key. The rate of avoidance responding varied with the duration of the response-timeout interval (Morse & Herrnstein, 1956). Others have shown that the rate of avoidance responding was functionally related to the schedule of food reinforcement (Thomas, 1964) and the duration of the response-timeout interval (Thomas, 1965).

More recently, van Haaren and Zarcone (in press) exposed rats to a concurrent random-interval (RI) 15-s fixed-ratio (FR) 1 (avoidance of timeout from food presentation) schedule and observed avoidance behavior to be a function of the consequences that followed the avoidance response. In that experiment, subjects responded on one (food) lever on an RI 15-s schedule of reinforcement; responses on another (avoidance) lever postponed the presentation of a 50-s timeout, during which all stimuli were extinguished and responding on the food lever did not have any scheduled consequences. The timeout-timeout interval was 10 s, and the response-timeout interval was 20 s. These contingencies produced consistent responding on the food lever and the avoidance lever that, in turn, resulted in subjects spending most of the session in the presence of the stimuli associated with food availability. In different conditions of that experiment, avoidance response rates decreased when avoidance responses no longer resulted in postponement of timeout presentation and increased again when the contingencies associated with the avoidance lever were reinstated.

It has been previously shown that antianxiety drugs (such as chlordiazepoxide) decrease response rates maintained by a schedule of shock avoidance (Ator, 1979). The behavioral effects of psychomotor stimulant drugs (such as cocaine and *d*-amphetamine) are generally dose dependent: Low to moderate doses increase avoidance responding and decrease shock rates, whereas high doses eliminate responding altogether (for review, see Houser, 1978; Huang & Wilson, 1984). Low doses of antianxiety drugs tend to increase response rates maintained by different schedules of food presentation (e.g., Brocco & McMillan, 1983; Jeffery & Barrett, 1979). Low to intermediate doses of psychomotor stimulant drugs generally increase low response rates (e.g., McAuley & Lesley, 1986) and decrease or do not affect

high response rates maintained by different schedules of food reinforcement (Branch, 1990; but see van Haaren, 1992a).

The present experiment was designed to investigate the effects of chlordiazepoxide and cocaine on food-reinforced behavior and behavior maintained by avoidance of timeout from food presentation.

METHOD

Subjects

Three male (1104, 1105, and 1106) and 2 female (1204 and 1206) Wistar rats, who had previously participated in other experiments (van Haaren, 1992b; van Haaren & Zarcone, in press), served as subjects. They were housed in same-sex groups under a reversed 12-hr light/dark cycle (lights on at 7:00 p.m.) and constant temperature and humidity conditions. All subjects were approximately 18 months old at the start of experimentation and were food deprived for 22 hr before each experimental session (cf. Hurwitz & Davis, 1983).

Apparatus

Experiments were conducted in three identical Coulbourn Instruments modular rodent operant conditioning chambers (25 cm wide, 30 cm long, and 29 cm high). The side walls of each chamber, except for the intelligence panel, were made of translucent Plexiglas. The floors consisted of 16 rods, spaced 2 cm apart (center to center). Two nonretractable rodent levers were located symmetrically to the side of the pellet tray, 7 cm from the floor of each chamber. The levers protruded 2 cm from the intelligence panel and required a force in excess of 0.20 N to be operated. Three stimulus lights were located directly above each lever. A Sonalert® was mounted above each lever, approximately 6 cm from the ceiling of the chamber. A houselight was located 2 cm from the ceiling in the middle of the intelligence panel. A press on the left lever activated the Sonalert® directly above the lever for 0.10 s. A press on the right lever activated a clicker for 0.10 s. The pellet tray could be illuminated by a white light bulb. Experimental chambers were housed in individual sound-attenuating ventilated cabinets. The chambers were connected to a PDP® 11-23 microcomputer located in the experimental room itself. The experimental contingencies and data acquisition

procedures were programmed using SKED-11® (Snapper & Inglis, 1985).

Procedure

All subjects had previously participated in an experiment in which the functional characteristics of avoidance of timeout from food were first established (van Haaren & Zarcone, in press). In the present experiment, subjects could obtain a 45-mg BioServe food pellet by pressing the left (food) lever after the expiration of an RI 30-s schedule. The specific duration of the RI interval was determined by sampling a probability gate every 1 s with a probability of .033. Gating of food availability continued during changeover delays (see below), but the gated availability of food was canceled by timeout periods. The opportunity to complete the schedule requirements on the food lever was available for 10 s, during which the houselight and the stimulus lights above the left and right levers were illuminated (timeout-timeout interval, 10 s). If the subjects failed to press the right (avoidance) lever in the interval between timeout presentations, a timeout of 50 s was presented, during which the houselight and the stimuli above the levers were extinguished and all experimental contingencies were suspended. Subjects could avoid timeout presentation by pressing the right lever during the timeout-timeout interval. Each press on the avoidance lever during this interval immediately delayed the onset of the next timeout for 20 s (response-timeout interval, 20 s). Each press on the avoidance lever also initiated a changeover delay of 2 s, during which responses on the other (food) lever could not be followed by food presentation. If subjects responded consistently on the avoidance lever, it was possible to spend the total session in the presence of the stimuli associated with food availability. Sessions were conducted 5 days a week (Monday through Friday) and were terminated after 30 min had elapsed.

Drug administration. Once RI response rates and avoidance rates had stabilized, subjects were occasionally injected with different doses of cocaine hydrochloride (vehicle, 1, 3, 5.6, 10, 13, 17, and 30 mg/kg) and chlordiazepoxide (vehicle, 1, 3, 10, and 30 mg/kg), intraperitoneally (i.p.) in a volume of 1 mL/kg, 10 min prior to the start of the experimental session. Chlordiazepoxide hydrochloride was dissolved in an isotonic sodium-chloride solution that

was stored for a maximum of 7 days at 5 °C. Cocaine hydrochloride was dissolved in the same vehicle, and solutions were stored indefinitely. Both cocaine and chlordiazepoxide were allowed to attain room temperature prior to injection. Cocaine was tested first. All doses were tested at least twice (range, two to five times) in irregular order on Tuesdays and Fridays of each week, provided that baseline control values on Mondays and Thursdays were within the stable range. Subject 1204 did not complete the series of chlordiazepoxide doses, and its data are not included in the present report.

RESULTS

The left panels of Figure 1 show response rates maintained by the RI 30-s schedule of food reinforcement, avoidance response rates, and the total session time spent in the presence of the stimuli associated with the availability of food delivery for individual subjects after administration of the different doses of cocaine. The right panels show the same data expressed as a percentage of baseline control values. The response rates maintained by the RI schedule varied considerably among subjects (range, 50 to 130 responses per minute) as did the avoidance response rates (range, 10 to 50 responses per minute). The highest food-reinforced rates and avoidance rates were observed in the same subject (1206). The lowest doses of cocaine (1 and 3 mg/kg) did not systematically affect food-reinforced or avoidance responding. Response rates maintained by the RI schedule of reinforcement and response rates maintained by avoidance of timeout from food presentation decreased dose dependently after administration of the other doses of cocaine. The highest doses of cocaine (17 and 30 mg/kg) virtually eliminated all food-reinforced and avoidance responding.

The time that individual subjects spent in the presence of the stimuli associated with food availability was less affected by cocaine administration than were avoidance response rates. For most subjects avoidance response rates decreased after 5.6 mg/kg cocaine, whereas the time spent in the presence of the stimuli associated with food availability was seriously affected for only 1 of the 5 subjects (1106).

The left panels of Figure 2 show response

Fig. 1. Mean random-interval response rates, avoidance response rates (responses per minute), and total time spent in the presence of the stimuli associated with the availability of food (minutes) are shown in the top, middle, and bottom left panels, respectively, as a function of the different doses of cocaine. One standard error around the mean (SEM) is indicated unless encompassed by the data point itself. The points above C and S represent observations during control sessions and after vehicle administration, respectively. Control data are from those sessions that immediately preceded sessions in which drug or vehicle was administered. The dashed line in the bottom left panel indicates the amount of time spent in the presence of the stimuli associated with the availability of food in the absence of any avoidance responses. The right panels show the same data expressed as a percentage of control values. The dashed lines indicate no change from control values.

rates maintained by the RI 30-s schedule of food reinforcement, avoidance response rates, and the total session time spent in the presence of the stimuli associated with food availability for individual subjects after administration of the different doses of chlordiazepoxide. Low doses of chlordiazepoxide (1 and 3 mg/kg) consistently increased food-maintained re-

Fig. 2. Mean random-interval response rates, avoidance response rates (responses per minute), and total time spent in the presence of the stimuli associated with the availability of food (minutes) are shown in the top, middle, and bottom left panels, respectively, as a function of the different doses of chlordiazepoxide. One standard error around the mean (*SEM*) is indicated unless encompassed by the data point itself. The points above C and S represent observations during control sessions and after vehicle administration, respectively. Control data are from those sessions that immediately preceded sessions in which drug or vehicle was administered. The dashed line in the bottom left panel indicates the amount of time spent in the presence of the stimuli associated with the availability of food in the absence of any avoidance responses. The right panels show the same data expressed as a percentage of control values. The dashed lines indicate no change from control values.

sponding and avoidance response rates. Interestingly, the increase in avoidance response rates after 3 mg/kg chlordiazepoxide did not result in subjects spending more time in the

presence of the stimuli associated with food availability. Both food-reinforced response rates and avoidance rates decreased after 10 mg/kg chlordiazepoxide; for 3 of the 4 sub-

jects, avoidance rates decreased proportionally more than did food-reinforced responding. RI response rates and avoidance rates were completely suppressed for all subjects after administration of 30 mg/kg chlordiazepoxide, and therefore subjects spent only the minimum scheduled time in the presence of the stimuli associated with food availability after this dose, as did 2 of the 4 subjects (1104 and 1106) after 10 mg/kg.

DISCUSSION

The present experiment showed that cocaine hydrochloride did not affect food-reinforced responding or behavior maintained by the avoidance of timeout from food at low doses, but that intermediate and high doses produced a dose-dependent decrease in food-maintained and avoidance response rates. Chlordiazepoxide increased food-maintained and avoidance response rates at low doses, whereas both rates decreased after higher doses of this drug.

The effects of different doses of cocaine and chlordiazepoxide on response rates maintained by avoidance of timeout from food presentation were thus unlike those previously reported when subjects responded to avoid shock presentation. In those studies, cocaine dose dependently increased avoidance response rates and intertrial-interval responding while decreasing avoidance latencies (Huang & Wilson, 1984). When the effects of different doses of chlordiazepoxide were assessed under a multiple variable-interval schedule of food reinforcement and a continuous shock-avoidance schedule, chlordiazepoxide decreased avoidance rates at doses that increased food-maintained responding (Ator, 1979).

Other experiments in which rats were trained to avoid shock presentation on one lever and to produce timeout from shock avoidance on another lever have recently yielded results similar to those of the present experiment in terms of drug effects on behavior maintained by the presentation of timeout. In those studies, timeout from avoidance was reliably produced when it was available on variable-interval (Galizio, Journey, Royal, & Welker, 1990; Galizio & Perone, 1987; Galizio, Perone, & Spencer, 1986; Perone & Galizio, 1987) or variable-ratio schedules (Galizio & Allen, 1991). Drug effects on behavior maintained by timeout from avoidance were also similar

to drug effects on food-maintained behavior and were unlike those observed when behavior was maintained by negative reinforcement involving shock presentation. For instance, Galizio and Perone (1987) and Galizio et al. (1990) showed that chlordiazepoxide increased response rates maintained by the presentation of timeout from avoidance, whereas the same doses decreased or did not affect shock-avoidance response rates.

RI response rates that varied considerably among individual subjects were affected similarly by cocaine. Interestingly, different doses of cocaine also had the same effect on RI response rates and behavior maintained by the avoidance of timeout from food presentation, despite the fact that RI responding was maintained at much higher rates than avoidance responding. Psychomotor stimulant drugs (such as cocaine) usually increase low response rates at doses that decrease high response rates (e.g., Dews & Wenger, 1977; van Haaren, 1992b). These observations have been the basis for the well-known "rate-dependency" hypothesis of drug effects on schedule-controlled behavior (but see Branch, 1984). That rate-dependent drug effects were not observed in the present experiment may be due to any number of variables. When considering RI rates only, the absence of rate-dependent drug effects after different doses of cocaine may have been due to the presence of the avoidance contingency and/or the limited access to the RI schedule. The absence of rate-dependent drug effects after different doses of cocaine in RI and avoidance response rates may have been due to the fact that high and low response rates were maintained by different contingencies on separate response manipulanda.

Traditionally, negative reinforcement has been viewed in terms of postponement or prevention of primary aversive stimulation (such as shock, loud noise, or extreme cold) or situations that include primary aversive stimulation (see Hinson, 1984). The results of the present experiment suggest that postponement of a transition between situations in which access to primary reinforcement is available to one in which access to primary reinforcement is not available may also serve as negative reinforcement. The results presented in this report also suggest that the effects of different doses of a drug on behavior maintained by negative reinforcement involving avoidance of

timeout from food presentation may be unlike those observed when behavior is maintained by negative reinforcement involving shock avoidance.

The results of this experiment are obviously limited inasmuch as parametric manipulations of the schedule of food presentation, the avoidance schedule, or the schedule on which avoidance of timeout from food presentation was available were not attempted. Such studies should be conducted in the future to fully identify the variables that control the effects of different drug doses on positively reinforced behavior and behavior maintained by negative reinforcement not involving shock escape or shock avoidance.

Aversive control is a prevalent means of behavioral control in society today. Yet, it does not very often involve the threat of harmful stimulation. Instead, the threat of losing the opportunity to earn (conditioned) positive reinforcers permeates behavioral control (see Sidman, 1989). Therefore, the experimental analysis of behavior and behavioral pharmacology may be well served if the experimental analysis of avoidance of timeout from food presentation is seriously pursued in the future.

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Received February 16, 1993

Final acceptance January 2, 1994