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VARIABLE-INTERVAL SCHEDULES OF TIMEOUT FROM AVOIDANCE: EFFECTS OF CHLORDIAZEPOXIDE, CGS 8216, MORPHINE, AND NALTREXONE

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Rats were trained on concurrent schedules in which pressing one lever postponed shock and pressing the other occasionally (variable-interval schedule) produced a 2-min timeout during which the shock-postponement schedule was suspended and its correlated stimuli were removed. These procedures provided a baseline for studying the effects of drugs on behavior maintained by different sources of negative reinforcement (shock avoidance and timeout from avoidance). Experiment 1 studied a benzodiazepine agonist, chlordiazepoxide, and antagonist, CGS 8216. Chlordiazepoxide (2.5–30 mg/kg) had little effect on avoidance responding except at higher doses, when it reduced responding. By comparison, responding on the timeout lever was increased in 5 of 6 rats. These effects were reversed by CGS 8216 (2.5–5 mg/kg) in the 2 rats tested, but CGS 8216 had no effect by itself. Experiment 2 studied an opiate agonist, morphine, and antagonist, naltrexone, with 3 rats. Morphine's (2.5–20 mg/kg) effects were opposite those of chlordiazepoxide: At doses that either increased or had no effect on avoidance responding, morphine depressed timeout responding. Naltrexone (5 mg/kg) reversed these actions but had no effect by itself.

Key words: negative reinforcement, avoidance, timeout from avoidance, chlordiazepoxide, CGS 8216, morphine, naltrexone, lever press, rats

Pharmacological analysis of operant behavior under aversive control is less frequent than analysis of behavior under appetitive control. One possible explanation is the limited number of aversive-control procedures. Most studies have analyzed behavior maintained under avoidance procedures, using the shock-postponement schedule devised by Sidman (1953). However, several problems are associated with interpretation of drug effects on avoidance (Houser, 1978; Seiden & Dykstra, 1977). For example, there may be difficulties in differentiating among effects involving unconditioned reactions to shock, conditioned responses, and simple motor reactions. A drug that depresses response rate might act by any of several mechanisms—for example, by producing analgesia, reducing the conditioned aversiveness of the situation, or inducing motor ataxia. Another problem is that avoidance-schedule parameters are not directly comparable to those of appetitive schedules, making it difficult to compare drug effects on positively versus negatively reinforced behavior. In studies of positive reinforcement, the motivating or establishing operations—usually defined in terms of hours of food deprivation—can be manipulated independently of the rate or magnitude of reinforcement. By comparsion, avoidance procedures confound these variables: Both motivation and reinforcement are directly related to the rate or intensity of scheduled shocks. Similar problems exist with procedures that study behavior maintained by termination of stimuli paired with unavoidable shock or by shock presentation (Barrett & Katz, 1981; Kelleher & Morse, 1964).

Other procedures are available for research on aversive control. As Hineline (1984) has noted, one way to expand the analysis of negative reinforcement beyond conventional avoidance procedures is to study the aversiveness of "behavioral situations" as a whole (cf.

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Baum, 1973; DeWaard, Galizio, & Baron, 1979). Negative reinforcement can be viewed not only in terms of the postponement of primary aversive stimuli within the avoidance situation, but also in terms of the removal of the avoidance situation itself. Accordingly, several studies have investigated the reinforcing properties of "timeout from avoidance." Verhave's (1962) early research suggested that, by comparison with appetitive stimuli, timeout is a relatively weak reinforcer, at least with rats. Perhaps as a consequence, few published experiments have attempted to maintain responding solely by timeout, opting instead for conjoint procedures in which responding both postpones shock and produces timeout (Baron, DeWaard, & Lipson, 1977; Baron & Trenholme, 1971; DeWaard et al., 1979; Mellitz, Hineline, Whitehouse, & Laurence, 1983; Schrot, Boren, & Moerschbaecher, 1976; Schrot, Boren, Moerschbaecher, & Simoes Fontes, 1978). A limitation of such conjoint schedules is that the reinforcing properties of timeout are not easily distinguished from those arising in the avoidance schedule. An alternative strategy, incorporated in the present research, is to use concurrent schedules in which avoidance and timeout contingencies are associated with independent responses. Despite Verhave's reservations about the reinforcing potency of timeout, recent research in our laboratory has demonstrated that it is capable of maintaining stable responding on variable-interval schedules over extended numbers of sessions (Perone & Galizio, 1987).

A two-lever procedure involving concurrent schedules of avoidance and timeout may have promise as a technique for behavioral pharmacology because it allows simultaneous assessment of drug effects on two forms of negatively reinforced behavior. Of interest is whether drugs have different effects on behavior related directly to the primary aversive events within the avoidance situation (pressing the avoidance lever) versus behavior maintained solely by suspension of the avoidance situation (pressing the timeout lever). In addition, because timeout can be scheduled in basically the same ways as appetitive stimuli, it is possible to directly compare drug effects on negatively and positively reinforced behavior.

In the present study rats were trained on concurrent schedules with shock postponement contingent upon responses on one lever and timeouts arranged on a variable-interval schedule contingent upon responses on the other lever. After performances stabilized, the effects of a benzodiazepine agonist, chlordiazepoxide (CDZ), and a benzodiazepine antagonist, CGS 8216, were evaluated alone and in combination; a second experiment evaluated the effects of an opiate agonist, morphine, and an opiate antagonist, naltrexone. Chlordiazepoxide and morphine were selected for study because in previous research their behavioral effects depended on the nature of the event maintaining the behavior, with different effects observed on food- and shock-maintained responding (Barrett, 1985; Barrett & Katz, 1981).

EXPERIMENT 1

The effects of benzodiazepine agonists such as CDZ and diazepam on free-operant avoidance are usually characterized by a dose-dependent decrease in response rate with an accompanying increase in shocks received (e.g., Heise & Boff, 1962). However, some studies have noted that the effects of benzodiazepine agonists may depend upon baseline avoidance proficiency, with CDZ or diazepam impairing performance of animals that are proficient avoiders, and enhancing performance in animals whose baseline avoidance is poor (Bignami, de Acetis, & Gatti, 1971; Kuribara & Tadokoro, 1979; 1984). Moreover, there is reason to argue that benzodiazepine impairment is specific to behavior maintained by aversive stimuli. Barrett, Dworkin, and Zuccarelli (1977) studied squirrel monkeys on multiple fixed-interval schedules maintained by different consequent events and found that CDZ increased responding maintained by food presentation, but decreased responding maintained by termination of a stimulus paired with shock. Similar results have been obtained in studies with squirrel monkeys on multiple and concurrent schedules of food and shock presentation, where CDZ increased food-maintained behavior but decreased shock-maintained behavior (Barrett, 1976; Barrett, Valentine, & Katz, 1981), and in studies with rats where CDZ increased food-maintained behavior but decreased or had no effect on shock avoidance (Ator, 1979).

In the first phase of Experiment 1, concurrent schedules were used to compare the effects of CDZ on behavior maintained by shock postponement versus behavior maintained by timeout from the shock-postponement schedule. Because reinforcement for both responses is based on aversive stimuli, it might be predicted that CDZ would decrease rates of both. Alternatively, because CDZ is widely labeled as possessing potent anxiolytic properties, it might be expected to decrease timeout responding that is maintained by reduction in conditioned aversive stimulation. At the same time, because CDZ is thought to have little or no analgesic functions at low doses, it might be expected to have minimal effects on avoidance responding, which is more closely related to shock stimuli. A third possibility is suggested by a recent study from our laboratory where ethanol, also a putative anxiolytic drug, impaired avoidance but had relatively little effect on timeout rates (Galizio, Perone, & Spencer, 1986). Timeout responding may have been maintained because, as impaired avoidance responding led to increased shock rates, the overall aversiveness of the avoidance situation was increased. The second phase of Experiment 1 tested the ability of a newly developed benzodiazepine-receptor antagonist, CGS 8216 (Boast, Bernard, Barbaz, & Bergen, 1983) to reverse the effects of CDZ.

METHOD

Subjects

Six male Sprague-Dawley rats (Holtzman Co.), 100 to 120 days old at the outset, were housed in individual cages under continuous lighting, with free access to food and water.

Apparatus

Training took place in commercially constructed chambers, approximately 28 cm long, 26 cm wide, and 28 cm high, enclosed in sound-attenuating, ventilated chests (Gerbands, G7452 or G7211). The side walls and ceiling were constructed of Plexiglas, the end walls of stainless steel, and the floor of 0.2-cm diameter stainless steel rods spaced 1.3 cm apart. Illumination was provided by a 28-V houselight mounted at the top of the chamber. A constant-current shock generator and scrambler (Lafayette, 82400-SS and 58020) delivered 1-mA, 0.5-s shocks to the floor. White noise (80 dB) was supplied through a speaker mounted behind the front wall. Two retractable levers were centered 12 cm apart on the front wall, 7.5 cm above the floor; the right lever (shock-postponement) remained fixed in place throughout the experiment. A force of approximately 0.3 N was required to operate each lever. Response feedback was provided by turning off the white noise for 0.5 s after presses on the right lever (avoidance lever), and by turning off the houselight for 0.2 s after presses on the left (timeout lever). Control and recording operations were accomplished with a microcomputer (Tandy, TRS-80® Model 4) connected to the chambers by a commercial interface (Alpha, Interfacer 80) and electromechanical components, using software described elsewhere (Perone, 1985).

Drug Preparation

Chlordiazepoxide hydrochloride (Sigma) was dissolved in isotonic (0.9%) sodium chloride solution, and intraperitoneal injections were administered in a volume of 1 mL/kg. Solutions were stored for a maximum of 10 days and were kept at 5 °C. Doses are expressed in terms of the total salt. Injections of CGS 8216 were prepared by adding 40 mg of the drug to a vehicle of 20 drops of Tween 20 and 20 mL isotonic sodium chloride solution, and placing it in suspension via ultrasonic mixing.

Procedure

Preliminary training. With the left lever retracted, the rats were trained with a shaping procedure to avoid shock by pressing the right lever. Control was then transferred to a schedule in which each response postponed shock for 30 s (response–shock interval), but in the absence of responding, shocks were presented every 5 s (shock–shock interval). White noise and chamber illumination accompanied the start of the session, and these stimuli were removed at the end. The rats were given daily 2-hr training sessions until they consistently avoided at least 90% of the shocks scheduled by the response–shock interval. This required 10 to 23 sessions.

Multiple-schedule training. To establish a discrimination between periods of avoidance and timeout from avoidance, 10-min avoidance components (houselight and white noise

on, shock-postponement schedule operative) alternated with 10-min timeout components (light and noise off, schedule suspended). A "correction" procedure ensured that timeout components could not end within 1 min of a press on the avoidance lever. Training on the multiple schedule continued until virtually no responding was observed during timeout components (2–15 sessions).

Concurrent-schedule training. The left lever was inserted for the first time, and presses on it resulted in immediate retraction of the lever, suspension of the shock-postponement schedule, and removal of the white noise and chamber illumination for 5 min. All of the rats acquired the timeout response within three sessions. When responding was consistent, the timeout duration was gradually reduced to the terminal value of 2 min. Thereafter, the timeouts were produced according to a variable-interval (VI) schedule, with the mean interval gradually increased to the terminal value of 45 s. Subjects were trained daily on the concurrent schedules of avoidance and timeout from avoidance until responding stabilized on both levers. The stability criterion was based upon the most recent 10 sessions; it required that the difference between the means of the first five and last five sessions be within 10% of the grand mean. After reaching stable performance levels (18–41 sessions), with all 6 rats avoiding shocks effectively and producing timeouts reliably, the drug probes were introduced.

Drug probes. Drugs were administered twice per week (Wednesday and Friday), and sessions were conducted under baseline conditions 3 days per week (Monday, Tuesday, and Thursday). On drug days, subjects received intraperitoneal injections of CDZ (2.5, 5.0, 10.0, 20.0, or 30.0 mg/kg) or saline 10 min prior to session onset. Rats I5, I2, and J2 were studied at every dose; Rat R12 received all but the 20-mg/kg dose; and Rats S15 and T10 received all but 20- and 2.5-mg/kg. Three sessions were conducted at each dose. The schedule of drug conditions was randomly generated for each rat with the constraints that no dose was repeated on successive sessions, and that the end of each cycle (one exposure to each dose) of the drug regimen was completed before beginning the next cycle. Following the completion of the CDZ study, the effects of CGS 8216, both alone and in combination with CDZ, were studied in 2 of the rats (S15 and I5). An injection of CGS 8216 (2.5 or 5.0 mg/kg) or Tween vehicle (in volume equal to that for the 5.0-mg/kg dose) was administered, followed 5 min later by an injection of CDZ (30 mg/kg) or saline. The session began 10 min after the second injection. Three sessions were conducted at each dose combination for I5, whereas S15 had three under the 5.0-mg/kg CGS 8216 conditions, but only two under the Tween and 2.5-mg/kg CGS 8216 conditions. All data analyses were based on the final 100 min of the 2-hr sessions.

Results

To summarize the effects of CDZ with a single measure, relative rate of responding on the timeout lever was computed by dividing timeout response rates by the sum of timeout and avoidance rates. The results are summarized in Figure 1. Five of the 6 rats showed increases in relative timeout responding produced by CDZ (I2 was the exception). In 2 rats (R12 and I5) the increase appeared at relatively low doses of CDZ (2.5–5.0 mg/kg). For I5 the effect was sustained throughout the dose range studied, whereas R12 showed a decline in relative rate at the highest dose (30 mg/kg). For the other 3 rats that showed the effect (S15, T10, and J2), there were trends toward increased relative rates at the lower doses of CDZ, but the increase was greatest at the highest CDZ dose. This facilitation of relative timeout responding was similar to the effect of ethanol noted by Galizio, Perone, and Spencer (1986), but the effect of CDZ was more robust. Whereas the ethanol effect was limited to the early part of the session and appeared only at high doses, the effect of CDZ was maintained throughout the entire session and appeared across a fairly broad range of doses.

The basis of the increased relative timeout rates can be seen in Table 1, which shows the absolute rates of responding on the avoidance and timeout levers as well as shock rates. In general, absolute timeout rates were increased by CDZ, but avoidance rates remained relatively constant or declined only slightly. In Rats I5 and R12, elevated timeout rates were observed even at the lowest doses of CDZ, and they remained elevated throughout the dose range for I5 and until the highest dose for R12. At the same time, avoidance rates were

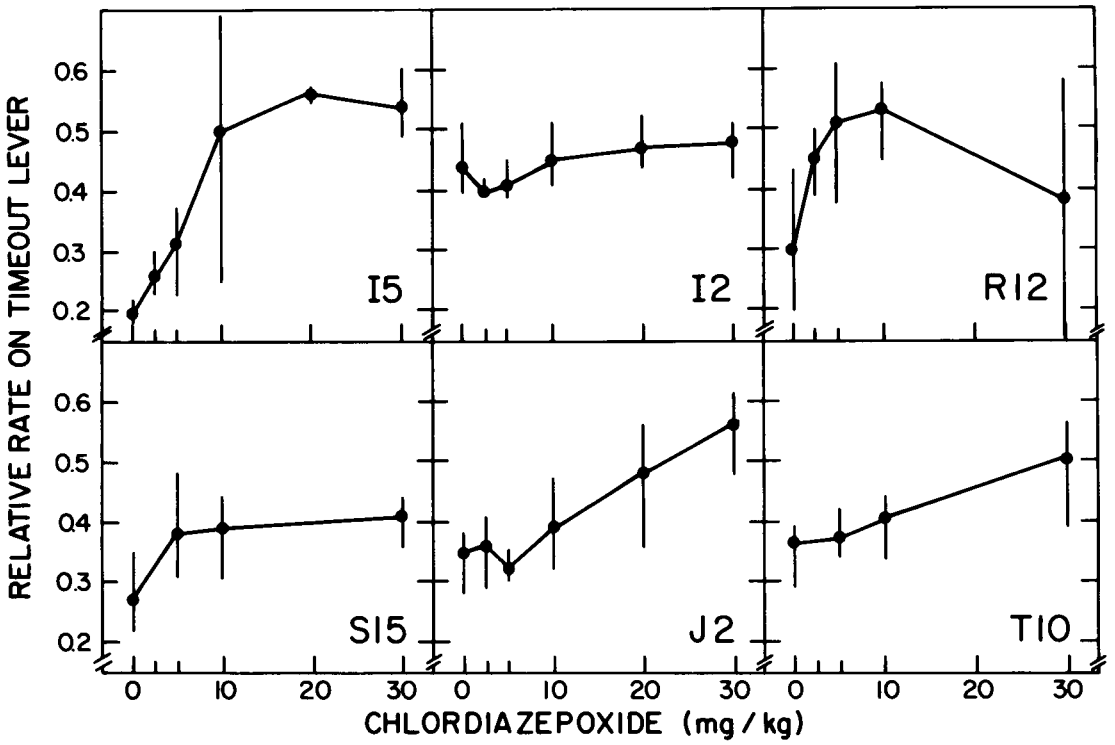

Fig. 1. Experiment 1: Mean relative rate on the timeout lever (timeout responses/timeout response + avoidance responses) for each of the 6 rats is plotted as a function of chlordiazepoxide dose. Vertical lines indicate ranges.

relatively constant for both animals until the 30-mg/kg dose, which depressed rates. Rat J2 did not show increased timeout rates until the 20-mg/kg dose, but avoidance rates were somewhat increased at the 5-mg/kg dose and then declined at the 30-mg/kg dose. Rat T10 showed suppression of avoidance at the 10-mg/kg dose of CDZ, but this rat did not show clear facilitation of timeout responding until the 30-mg/kg dose was reached. No clear suppression of avoidance responding was observed in S15 at any dose, but timeout rates were increased at the 5- and 30-mg/kg doses of CDZ. Thus, the increase in relative timeout responding was primarily due to increased rates on the timeout lever, whereas responding on the avoidance lever declined slightly or remained unchanged. Finally, for Rat I2, the animal that did not show CDZ-enhancement of relative timeout rate, responding on both levers was relatively unaffected until the 20-mg/kg dose was reached, and then declines were observed. It may be relevant that this rat had the highest baseline timeout rate.

Table 1 also presents shock rates as a function of CDZ dose. As indicated by shock rates, avoidance proficiency generally declined somewhat as a function of CDZ dose, particularly at 30 mg/kg. Rat S15 was an interesting exception to this generalization because this animal actually showed improved avoidance at some CDZ doses. This rat was by far the worst avoider under baseline and placebo conditions, and thus the outcome was supportive of previous studies that have shown that baseline shock rates are an important determinant of the effects of benzodiazepines on avoidance (Bignami et al., 1971; Kuribara & Tadokoro, 1979). Finally, the shock-rate data show that impaired avoidance was not necessary in order to produce the enhancement of timeout rates, because response rates of 3 of the 5 rats showing the effect were enhanced at doses lower than those necessary to increase shock rates (R12, I5, S15).

The results of the second phase of Experiment 1, during which we sought to determine whether the effects of CDZ could be reversed by CGS 8216, are presented in Figure 2 and Table 2. Figure 2 shows relative timeout rates

Table 1

Experiment 1: Summary of mean avoidance and timeout responses per minute and shocks per minute as a function of CDZ dose. Ranges are in parentheses.

Condition	Avoidance rate	Timeout rate	Shock rate
	Rat I5		
Saline	9.7 (8.6–10.5)	2.4 (2.1–2.9)	0.0 (None)
2.5 CDZ mg/kg	12.0 (10.1–13.1)	4.2 (3.9–4.4)	0.0 (0–0.0)
5.0 CDZ mg/kg	10.2 (8.5–11.5)	4.6 (3.1–5.5)	0.0 (0–0.0)
10.0 CDZ mg/kg	9.1 (6.8–11.7)	10.2 (3.9–15.3)	0.0 (0–0.1)
20.0 CDZ mg/kg	8.0 (7.6–8.6)	10.3 (10.0–10.5)	0.1 (0.1–0.2)
30.0 CDZ mg/kg	6.2 (5.6–6.5)	7.6 (5.4–9.8)	0.2 (0–0.3)
	Rat I2		
Saline	5.8 (4.7–7.6)	4.6 (3.5–5.4)	0.1 (0–0.2)
2.5 CDZ mg/kg	5.8 (5.0–6.3)	3.9 (3.1–4.6)	0.1 (0–0.1)
5.0 CDZ mg/kg	5.6 (4.8–6.6)	4.0 (3.1–4.6)	0.2 (0–0.3)
10.0 CDZ mg/kg	4.9 (4.0–6.2)	4.0 (3.0–4.7)	0.3 (0–0.7)
20.0 CDZ mg/kg	3.7 (3.4–3.8)	3.3 (3.0–3.8)	0.5 (0.3–0.7)
30.0 CDZ mg/kg	3.2 (2.5–4.4)	2.8 (2.7–2.8)	0.9 (0.1–1.3)
	Rat R12		
Saline	5.1 (3.7–6.5)	2.1 (1.6–2.7)	0.6 (0.3–0.8)
2.5 CDZ mg/kg	6.4 (4.2–8.1)	5.1 (4.2–5.7)	0.3 (0.1–0.7)
5.0 CDZ mg/kg	5.0 (3.8–6.3)	5.3 (3.9–7.6)	0.5 (0.3–1.0)
10.0 CDZ mg/kg	5.3 (4.4–6.1)	6.1 (5.0–7.4)	0.5 (0.1–0.7)
20.0 CDZ mg/kg	—	—	—
30.0 CDZ mg/kg	3.1 (2.0–3.7)	2.4 (0.1–4.4)	2.2 (0.9–3.2)
	Rat S15		
Saline	5.2 (4.0–5.9)	2.2 (1.4–2.8)	2.2 (1.4–2.8)
2.5 CDZ mg/kg	—	—	—
5.0 CDZ mg/kg	5.6 (4.4–6.7)	3.5 (2.6–4.2)	0.8 (0.4–1.2)
10.0 CDZ mg/kg	4.3 (3.4–5.4)	2.7 (2.5–3.1)	1.1 (0.8–1.3)
20.0 CDZ mg/kg	—	—	—
30.0 CDZ mg/kg	4.6 (3.9–5.7)	3.3 (2.3–4.5)	0.9 (0.8–1.3)
	Rat J2		
Saline	6.5 (6.0–6.9)	3.4 (2.8–3.9)	0.0 (0–0.1)
2.5 CDZ mg/kg	7.6 (6.5–8.9)	4.3 (3.7–4.6)	0.0 (0–0.1)
5.0 CDZ mg/kg	8.3 (7.6–8.8)	3.9 (3.3–4.7)	0.1 (0.1–0.2)
10.0 CDZ mg/kg	7.3 (6.4–9.0)	4.6 (4.0–5.6)	0.2 (0–0.4)
20.0 CDZ mg/kg	6.9 (5.8–8.9)	6.3 (5.0–7.3)	0.2 (0.1–0.4)
30.0 CDZ mg/kg	4.8 (4.2–5.6)	6.1 (5.1–7.1)	0.4 (0.3–0.6)
	Rat T10		
Saline	5.9 (5.4–6.4)	3.4 (2.7–3.7)	0.2 (0.1–0.2)
2.5 CDZ mg/kg	—	—	—
5.0 CDZ mg/kg	5.4 (4.8–5.7)	3.2 (2.7–4.0)	0.3 (0.2–0.3)
10.0 CDZ mg/kg	4.5 (4.3–4.7)	3.1 (2.2–3.6)	0.2 (0–0.6)
20.0 CDZ mg/kg	—	—	—
30.0 CDZ mg/kg	4.5 (3.7–5.3)	4.5 (3.5–5.7)	0.7 (0.3–1.1)

as a function of the dose of CGS 8216 given as the first injection, with the contents of the second injection represented by filled circles (30 mg/kg CDZ) or unfilled circles (saline). When CDZ was the only drug given (zero CGS 8216), it clearly facilitated relative timeout rates by comparison with the saline control, as it did in the previous phase of the study. This effect was markedly reduced by a dose of 2.5 mg/kg CGS 8216 in both rats, and was completely abolished by 5.0 mg/kg CGS 8216. Alone, CGS 8216 did not appear to affect relative timeout responding. Absolute rates presented in Table 2 parallel the relative rate measures. By itself, CDZ enhanced timeout rates without clear effects on avoidance

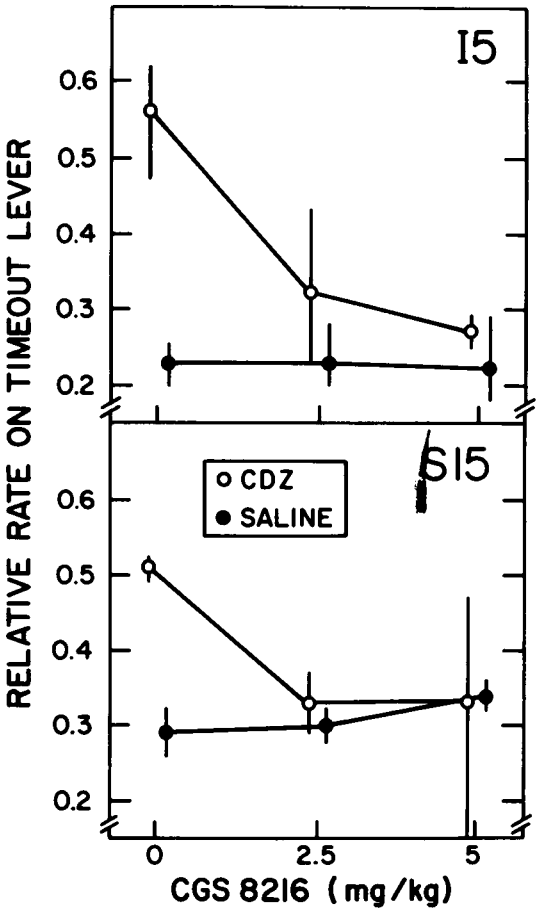

Fig. 2. Experiment 1: Mean relative rate on the timeout lever (timeout responses/timeout responses + avoidance responses) for each of the 2 rats exposed to CGS 8216. Open circles indicate data obtained after chlordiazepoxide (30 mg/kg)–CGS 8216 combinations; filled circles indicate data obtained after saline–CGS 8216 combinations. Vertical lines indicate ranges.

responding or shock rates. Alone, CGS 8216 did not affect performances in either rat. When the drugs were combined, CGS 8216 clearly antagonized the CDZ effect.

Discussion

There are a number of possible interpretations of these data. The finding that baseline avoidance rates were higher than baseline timeout rates suggests the possibility that the enhanced timeout responding by CDZ might involve rate-dependency. Similarly, inspection of Table 1 reveals that as CDZ dose was increased, there was a convergence of avoidance and timeout rates. This convergence could have been due to a loss of differential control by the two levers, which could account for the enhancement of timeout responding.

An alternative account that cannot be ruled out would emphasize the different schedules maintaining avoidance and timeout responding. Finally, the similarity between the present results and previous studies that have shown CDZ increasing food-maintained and decreasing shock avoidance or shock-maintained behavior (see Barrett & Katz, 1981) suggests that the effect may be related to the event maintaining the behavior. One difference between previous studies and our results is that the behavior increased by CDZ in our experiment was based on negative reinforcement (timeout) rather than positive reinforcement (food).

The absence of a solitary CGS 8216 effect contrasts with previous research using the present procedure, in which that drug impaired avoidance proficiency (Galizio, Perone, & Spencer, 1986). One difference is that the rats in that study had received extensive exposure to ethanol prior to CGS 8216 exposure. In view of studies that have noted effects of long-term ethanol exposure on the GABA-benzodiazepine receptor complex (Freund, 1980), it may be that chronic exposure to ethanol is necessary for intrinsic actions of CGS 8216 to be observed. In any case, the main outcome of this phase was the demonstration that the effects of CDZ on timeout responding are reversed by the benzodiazepine receptor antagonist, CGS 8216, which suggests that the effect is related to activity at the benzodiazepine receptor site.

EXPERIMENT 2

In view of the findings that relative rates of timeout responding were increased by CDZ (Experiment 1) and ethanol (Galizio, Perone, & Spencer, 1986), Experiment 2 studied the effects of opioid drugs with the concurrent procedure. Opioid agonists like morphine have many pharmacological properties in common with ethanol and benzodiazepines (Blum, Briggs, Elston, Hirst, Hamilton, & Vereby, 1980). However, there are both similarities and differences in the effects of these drugs on behavior maintained under aversive control. For example, benzodiazepines are noted for their "anti-punishment" effects, but mor-

Table 2

Summary of mean avoidance and timeout responses per minute and shocks per minute for the second (CGS 8216) phase of Experiment 1. Ranges are in parentheses.

Condition	Avoidance rate	Timeout rate	Shock rate
	Rat I5		
Tween	10.7 (9.2–11.9)	3.2 (2.7–4.0)	0 (None)
2.5 CGS	9.1 (7.0–10.4)	2.7 (2.6–2.7)	0.1 (0–0.1)
5.0 CGS	11.6 (10.3–12.3)	3.3 (2.6–4.2)	0 (0–0.1)
30 CDZ–Tween	9.2 (8.1–11.1)	11.7 (9.7–13.4)	0 (0–0.3)
30 CDZ–2.5 CGS	9.5 (8.3–10.6)	4.4 (3.2–6.2)	0.1 (0–0.2)
30 CDZ–5.0 CGS	10.2 (9.2–11.5)	3.8 (3.2–4.6)	0.1 (0–0.1)
	Rat S15		
Tween	5.3 (4.3–6.2)	2.1 (2.0–2.2)	2.0 (1.9–2.2)
2.5 CGS	5.5 (5.1–5.9)	2.4 (2.3–2.4)	1.5 (1.4–1.6)
5.0 CGS	4.7 (4.5–5.0)	2.4 (2.3–2.5)	2.3 (1.8–2.7)
30 CDZ–Tween	4.0 (3.3–4.6)	4.1 (3.1–5.0)	1.5 (0.6–2.4)
30 CDZ–2.5 CGS	4.7 (4.7–4.8)	2.4 (1.9–2.9)	2.1 (1.9–2.2)
30 CDZ–5.0 CGS	4.3 (2.6–5.8)	2.2 (0.8–4.2)	2.6 (2.0–3.4)

phine does not increase punished behavior unless animals are exposed to special environmental conditions in conjunction with the drug (Brady & Barrett, 1986). Although most studies have found morphine to impair free-operant avoidance proficiency (Curley, Walsh, & Burch, 1980; Dworkin & Branch, 1982; Heise & Boff, 1962), under some conditions morphine increases avoidance responding (Holtzman & Jewett, 1972) or responding maintained by stimulus–shock termination procedures (McKearney, 1975). Another apparent difference between the behavioral effects of morphine and those of benzodiazepines was reported by McKearney (1974). In that study, morphine increased behavior maintained under fixed-interval schedules of shock presentation but decreased or had no effect on food-maintained behavior. The event-dependency of this effect resembles that of CDZ, but the outcome was in the opposite direction: In most studies, CDZ decreased shock-related behavior and increased food-maintained behavior. Thus, in Experiment 2 we sought to determine whether morphine would produce effects similar to those of CDZ and ethanol under the same concurrent schedules of avoidance and timeout from avoidance studied in Experiment 1. In addition, the effects of an opiate antagonist, naltrexone, were assessed alone and in combination with morphine.

Method

Subjects and Apparatus

Three male Sprague-Dawley derived rats served. One (T10) had been studied in Experiment 1; a drug-free week of sessions with the concurrent schedules of avoidance and timeout intervened between the two experiments. The other 2 rats were given the same preliminary training as described for Experiment 1. Rat V1 was given 20 sessions on the avoidance schedule, 9 on the multiple schedule of avoidance and timeout, and 29 on the concurrent avoidance and VI timeout schedules, before stability was attained. Rat U10 was given 10 avoidance sessions, 5 multiple-schedule sessions, and 18 concurrent-schedules sessions. The apparatus was the same as in Experiment 1.

Procedure

Except for differences in drug preparation and doses, the procedures were the same as in Experiment 1. Morphine sulfate and naltrexone hydrochloride solutions were prepared in isotonic saline solution, and intraperitoneal injections were given in a volume of 1 mL/kg. Morphine injections or equal volumes of saline were administered 10 min prior to session onset and were followed immediately by an injection of 5 mg/kg naltrexone or an equal volume of saline. Rat T10 received doses of

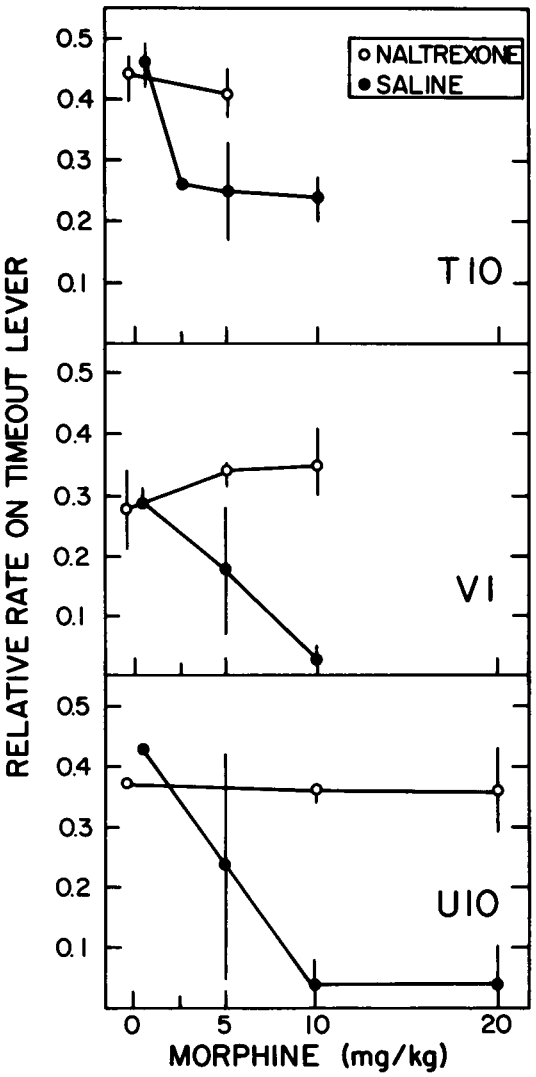

Fig. 3. Experiment 2: Mean relative rate on the timeout lever (timeout response/timeout responses + avoidance responses) for each of the 3 rats. Open circles indicate data obtained after morphine–naltrexone combinations; filled circles indicate morphine–saline combinations. Vertical lines indicate ranges.

2.5, 5.0, and 10 mg/kg of morphine, Rat V1 received 5 and 10 mg/kg, and Rat U10 received 5, 10, and 20 mg/kg. Doses are expressed in terms of the total salt. Naltrexone (5 mg/kg) was studied without morphine in all rats and in combination with effective doses of morphine. All conditions were studied with two or three replications and the order was random, with two exceptions: (a) naltrexone–morphine combinations were administered toward the end of the cycle after an effective morphine dose had been determined; and (b) for Rat U10, the 20 mg/kg dose of morphine was added to the regimen after the second cycle of lower doses.

Results

Figure 3 shows relative rates of timeout responding with dose of morphine on the abscissa; presence of naltrexone (5 mg/kg) is indicated by open circles and absence of naltrexone (saline) by filled circles. The top panel of Figure 3 shows results from Rat T10. Morphine produced a clear decrease in relative timeout responding beginning with the 2.5-mg/kg dose and the effect was maintained at both higher doses. Similar results were apparent in Rat V1; 5 mg/kg produced a large decline in relative timeout responding, and 10 mg/kg resulted in near-zero relative rates. Rat U10 showed only slightly reduced relative timeout rates at 5 mg/kg of morphine, but the rates were near zero at both higher doses. In all 3 rats, the effect of morphine was completely reversed by naltrexone, but naltrexone had little or no effect of its own.

Details of morphine's effect on relative timeout responding are presented in Table 3, which shows absolute response and shock rates. In all 3 rats, morphine suppressed absolute timeout rates; for Rats V1 and U10, morphine virtually abolished timeout responding at doses of 10 mg/kg and higher. The major suppressive effect of morphine was restricted to timeout responding: As Table 3 shows, the same dose of morphine that reduced or eliminated timeout responding either had no effect on avoidance responding (Rat V1), or actually *increased* it (T10 and U10). All animals' shock rates were slightly increased at the higher doses.

Discussion

The effects of morphine could depend on the maintaining event (timeout vs. shock avoidance), the nature of the baseline schedule (VI vs. shock-postponement), or the baseline response rates engendered by the schedules (timeout rates were generally lower than avoidance rates). Morphine-induced analgesia does not seem a likely explanation for the effect, because avoidance responses, which

Table 3

Experiment 2: Summary of mean avoidance and timeout responses per minute. Ranges are in parentheses.

Condition	Avoidance rate	Timeout rate	Shock rate
	Rat T10		
Saline	4.4 (4.1–4.6)	3.7 (3.4–3.9)	0.0 (None)
2.5 Morphine	9.5 (8.3–10.7)	3.3 (3.1–3.5)	0.1 (0–0.1)
5.0 Morphine	7.2 (6.4–7.9)	2.6 (1.3–3.9)	0.2 (0.1–0.3)
10.0 Morphine	5.4 (4.2–6.6)	1.2 (1.1–2.4)	0.5 (0.1–1.1)
20.0 Morphine	—	—	—
5 NALT	4.6 (3.9–5.2)	3.5 (3.4–3.5)	0.1 (0–0.1)
5 M/5 NALT	5.2 (4.7–5.6)	3.6 (3.3–3.9)	0.1 (0–0.1)
10 M/5 NALT	—	—	—
20 M/5 NALT	—	—	—
	Rat V1		
Saline	4.5 (4.1–5.2)	1.9 (1.7–2.1)	0.3 (0–0.7)
2.5 Morphine	—	—	—
5.0 Morphine	5.8 (5.2–6.8)	1.5 (.4–2.7)	0.5 (0.2–0.7)
10.0 Morphine	5.1 (4.6–5.7)	.2 (0–.3)	0.5 (0.3–0.7)
20.0 Morphine	—	—	—
5 NALT	5.3 (4.8–5.8)	2.0 (1.6–2.5)	0.2 (0.1–0.3)
5 M/5 NALT	5.8 (4.7–6.8)	2.9 (2.6–3.2)	0.2 (0.1–0.3)
10 M/5 NALT	4.7 (4.2–5.1)	2.6 (2.2–2.9)	0.3 (0.1–0.4)
20 M/5 NALT	—	—	—
	Rat U10		
Saline	7.3 (6.5–8.0)	5.3 (4.9–5.7)	0 (None)
2.5 Morphine	—	—	—
5.0 Morphine	10.9 (7.5–14.8)	3.2 (.8–5.4)	0 (None)
10.0 Morphine	11.4 (8.2–14.9)	.4 (.2–.6)	0.3 (0–0.5)
20.0 Morphine	15.0 (5.7–26.1)	.3 (.1–.7)	1.0 (0.5–1.5)
5 NALT	9.1 (8.5–9.6)	5.3 (5.1–5.5)	0 (None)
5 M/5 NALT	—	—	—
10 M/5 NALT	8.1 (6.3–9.9)	4.5 (4.1–4.8)	0 (None)
20 M/5 NALT	6.6 (6.0–7.1)	3.7 (3.2–4.2)	0 (None)

were more closely linked to primary aversive stimuli, were unaffected or increased by morphine. The most plausible conclusion is that morphine's effects depend on the event maintaining the behavior (timeout vs. shock avoidance), and that the nature of the relationship between the drug effect and the event is opposite that of CDZ. Because the effect was naltrexone-reversible, it would appear that the effect is related to activity at the opiate receptor.

GENERAL DISCUSSION

A major finding of the present studies was that drugs differentially affected responding maintained by concurrent schedules of avoidance and timeout from avoidance. Chlordiazepoxide increased response rates on the timeout lever at doses that depressed or had no effect on avoidance responding. Morphine depressed timeout responding at doses that stimulated or had no effect on avoidance rates. The effects of CDZ were reversed by the benzodiazepine antagonist CGS 8216, whereas those of morphine were reversed by the opiate antagonist naltrexone.

The selective nature of the drug effects with this procedure indicates its utility for behavioral pharmacology. Concurrent schedules with different events maintaining different responses permit analyses that would not be possible with simpler baseline procedures, although it must be recognized that the possibility of concurrent-schedule interactions may complicate the interpretation of drug effects. Further support for use of the present procedure stems from the observation that in many subjects timeout responding was more sensitive to drug effects than was avoidance re-

sponding. The fact that drugs differentially affected timeout and avoidance responding may be of general significance in the analysis of behavior under aversive control, because it is consistent with the proposition that there is a functional difference between behavior maintained by suspension of an avoidance situation and behavior maintained by avoidance contingencies within the situation (cf. DeWaard et al., 1979; Hineline, 1984). As previously shown (Perone & Galizio, 1987), the reinforcing properties of timeout derive from suspension of the avoidance schedule and do not merely reflect sensory reinforcement. Therefore, it would appear that both timeout and avoidance responding are maintained by negative reinforcement, and that the nature of drug effects on responding depends on the source of the negative reinforcement. Such an outcome raises questions about the traditional view of negative reinforcement as a unitary concept.

The finding that the effects of the benzodiazepine agonist, CDZ, were radically different from those of the opiate agonist, morphine, may be of particular significance. At doses that depressed or had no effect on avoidance responding, CDZ stimulated timeout responding, whereas morphine depressed or eliminated timeout responding at doses that stimulated or had no effect on avoidance rates. These results parallel those of several studies that have shown selective effects of CDZ and morphine on food- versus shock-related behavior (Ator, 1979; Barrett, 1976; Barrett et al., 1977, 1981; McKearney, 1974). An important difference, however, is that the present results showed selectivity with two different types of negative reinforcement. In our studies, the effects of CDZ and morphine on avoidance paralleled effects of these drugs on behavior maintained by the presentation or deletion of aversive stimuli (see Barrett & Katz' 1981 review). However, the effects of CDZ and morphine on timeout responding in our research were identical to the outcomes previous studies have reported for the effects of these drugs on food-maintained behavior (Barrett & Katz, 1981). Thus, there appears to be a functional similarity between the effects of drugs on behavior maintained by food and by timeout from avoidance. However, it is important to recognize the presence of several confounds that limit conclusions from the present studies. In addition to different events, responding on the two levers was maintained by different schedules (variable interval vs. Sidman avoidance), and at different rates. Accounts of the data in terms of schedule- or rate-dependency cannot be ruled out. Thus, although it is tempting to speculate about the processes involved in these differential drug effects, further research is needed to allow definite conclusions. The procedures we have described are novel, and additional information about the behavior they engender is required. Appropriate extensions, involving various concurrent schedules of avoidance and timeout, would allow interactions among drugs, negative reinforcers, schedules, and response rates to be investigated systematically within a single analytic framework.

REFERENCES

Ator, N. A. (1979). Differential effects of chlordiazepoxide on comparable rates of responding maintained by food and shock avoidance. *Psychopharmacology,* **66,** 227–231.

Baron, A., DeWaard, R. J., & Lipson, J. (1977). Increased reinforcement when timeout from avoidance includes access to a safe place. *Journal of the Experimental Analysis of Behavior,* **27,** 479–494.

Baron, A., & Trenholme, I. A. (1971). Response-dependent and response-independent timeout from an avoidance schedule. *Journal of the Experimental Analysis of Behavior,* **16,** 123–131.

Barrett, J. E. (1976). Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. *Journal of Pharmacology and Experimental Therapeutics,* **196,** 605–615.

Barrett, J. E. (1985). Modification of the behavioral effects of drugs by environmental variables. In L. S. Seiden & R. L. Balster (Eds.), *Neurology and neurobiology: Vol. 13. Behavioral pharmacology: The current status* (pp. 7–22). New York: Lisse.

Barrett, J. E., Dworkin, S. I., & Zuccarelli, R. R. (1977). Effects of *d*-amphetamine, chlordiazepoxide and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination. *Pharmacology Biochemistry and Behavior,* **7,** 529–535.

Barrett, J. E., & Katz, J. L. (1981). Drug effects on behaviors maintained by different events. In T. Thompson, P. B. Dews, & W. A. McKim (Eds.), *Advances in behavioral pharmacology* (Vol. 3, pp. 119–168). New York: Academic Press.

Barrett, J. E., Valentine, J. O., & Katz, J. L. (1981). Effects of chlordiazepoxide and *d*-amphetamine on responding of squirrel monkeys maintained under concurrent or second-order schedules of response-produced food or electric shock presentation. *Journal of Pharmacology and Experimental Therapeutics,* **219,** 199–206.

Baum, W. M. (1973). The correlation-based law of effect. *Journal of the Experimental Analysis of Behavior,* **20,** 137–153.

Bignami, G., de Acetis, L., & Gatti, G. L. (1971). Facilitation and impairment of avoidance responding by phenobarbital sodium, chlordiazepoxide, and diazepam—the role of performance base lines. *Journal of Pharmacology and Experimental Therapeutics,* **176,** 725–732.

Blum, K., Briggs, A. H., Elston, S. F. A., Hirst, M., Hamilton, M. G., & Vereby, K. (1980). A common denominator theory of alcohol and opiate dependence: Review of similarities and differences. In H. Rigter & J. C. Crabbe, Jr. (Eds.), *Alcohol tolerance and dependence* (pp. 371–391). Amsterdam: Elsevier/North-Holland Biomedical Press.

Boast, C. A., Bernard, P. S., Barbaz, B. S., & Bergen, K. M. (1983). The neuropharmacology of various diazepam antagonists. *Neuropharmacology,* **22,** 1511–1521.

Brady, L. S., & Barrett, J. E. (1986). Drug–behavior interaction history: Modification of the effects of morphine on punished behavior. *Journal of the Experimental Analysis of Behavior,* **45,** 221–228.

Curley, M. D., Walsh, J. M., & Burch, L. S. (1980). Behavioral effects of morphine on free-operant avoidance under hyperbaric pressure. *Pharmacology Biochemistry and Behavior,* **12,** 413–417.

DeWaard, R. J., Galizio, M., & Baron, A. (1979). Chained schedules of avoidance: Reinforcement within and by avoidance situations. *Journal of the Experimental Analysis of Behavior,* **32,** 399–407.

Dworkin, S. I., & Branch, M. N. (1982). Behavioral effects of morphine and naloxone following chronic morphine administration. *Psychopharmacology,* **77,** 322–326.

Freund, G. (1980). Benzodiazephine receptor loss in brains of mice after chronic alcohol consumption. *Life Sciences,* **27,** 987–992.

Galizio, M., Perone, M., & Spencer, B. A. (1986). Variable interval schedules of timeout from avoidance: Effects of ethanol, naltrexone, and CGS 8216. *Pharmacology Biochemistry and Behavior,* **25,** 439–448.

Heise, G. A., & Boff, E. (1962). Continuous avoidance as a base-line for measuring behavioral effects of drugs. *Psychopharmacologia,* **3,** 264–282.

Hineline, P. N. (1984). Aversive control: A separate domain? *Journal of the Experimental Analysis of Behavior,* **42,** 495–509.

Holtzman, S. G., & Jewett, R. E. (1972). Shock intensity as a determinant of the behavioral effects of morphine in the rat. *Life Sciences,* **11,** Pt. 1, 1085–1091.

Houser, V. P. (1978). The effects of drugs on behavior controlled by aversive stimuli. In D. E. Blackman & D. J. Sanger (Eds.), *Contemporary research in behavioral pharmacology* (pp. 69–158). New York: Plenum Press.

Kelleher, R. T., & Morse, W. H. (1964). Escape behavior and punished behavior. *Federation Proceedings,* **23,** 808–817.

Kuribara, H., & Tadokoro, S. (1979). Effects of psychotropic drugs on avoidance response in rats: Role of baseline performances. *Pharmacology Biochemistry and Behavior,* **11,** 203–209.

Kuribara, H., & Tadokoro, S. (1984). Conditioned lever-press avoidance response in mice: Acquisition processes and effects of diazepam. *Psychopharmacology,* **82,** 36–40.

McKearney, J. W. (1974). Effects of *d*-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. *Journal of Pharmacology and Experimental Therepeutics,* **190,** 141–153.

McKearney, J. W. (1975). Effects of morphine, methadone, nalorphine, and naloxone on responding under fixed-interval (F1) schedules in the squirrel monkey. *Federation Proceedings,* **34,** 766. (Abstract)

Mellitz, M., Hineline, P. N., Whitehouse, W. G., & Laurence, M. T. (1983). Duration-reduction of avoidance sessions as negative reinforcement. *Journal of the Experimental Analysis of Behavior,* **40,** 57–67.

Perone, M. (1985). A software system for real-time laboratory use of TRS-80 microcomputers. *Behavior Research Methods, Instruments, & Computers,* **17,** 119–121.

Perone, M., & Galizio, M. (1987). Variable-interval schedules of timeout from avoidance. *Journal of the Experimental Analysis of Behavior,* **47,** 97–113.

Schrot, J., Boren, J. J., & Moerschbaecher, J. M. (1976). Sequential reacquisition as a function of timeout from avoidance. *Journal of the Experimental Analysis of Behavior,* **25,** 303–310.

Schrot, J., Boren, J. J., Moerschbaecher, J. M., & Simoes Fontes, J. C. (1978). Effects of *d*-amphetamine and cocaine on repeated acquisition with timeout from avoidance. *Pharmacology Biochemistry and Behavior,* **9,** 659–663.

Seiden, L., & Dykstra, L. A. (1977). *Psychopharmacology: A biochemical and behavioral approach.* New York: Van Nostrand Reinhold.

Sidman, M. (1953). Avoidance conditioning with brief shock and no exteroceptive warning signal. *Science,* **118,** 157–158.

Verhave, T. (1962). The functional properties of a time out from an avoidance schedule. *Journal of the Experimental Analysis of Behavior,* **5,** 391–422.

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