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Avoidance of Time-Out From Response-Independent Food Presentation: Effects of Chlordiazepoxide and Buspirone

FRANS VAN HAAREN AND KAREN G. ANDERSON

University of Florida, Gainesville, FL 32611-2250

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VAN HAAREN, F. AND K. G. ANDERSON. *Avoidance of time-out from response- independent food presentation: Effects of chlordiazepoxide and buspirone.* PHARMACOL BIOCHEM BEHAV **61**(2) 207–214, 1998.—Five male Wistar rats were exposed to a two- component multiple schedule. In one component, signaled by a tone, food pellets were presented on a random-time 120-s schedule. In the other component, food pellets were presented on a random-time 30-s schedule. Pellets were only presented during a 10-s time-in period that alternated with a 50-s time-out period, unless the subject pressed a lever to postpone time-out presentation by 20 s. Response-independent food pellets were never presented within 2 s of this avoidance response. For most subjects avoidance rates were consistently higher when response-independent food pellets were delivered infrequently than when they were delivered more often. The amount of time spent in time-in varied considerably between subjects but was not consistently related to the frequency of response-independent pellet presentation. Once stable response rates were established subjects were intraperitoneally injected with different doses of chlordiazepoxide (1, 3, 10, 17, or 30 mg/kg) or buspirone (0.1, 0.3, 1.0, 1.7, 3.0, or 4.2 mg/kg). Low doses of chlordiazepoxide either did not affect or slightly increased avoidance response rates, whereas higher doses (10 mg/kg and up) produced a dose-dependent decrease in avoidance responding. The time subjects spent in the presence of stimuli associated with the availability of response-independent food either did not change or increased slightly after the lower doses of chlordiazepoxide, while it decreased dose dependently following the higher doses. Low doses of buspirone increased avoidance rates in subjects first exposed to chlordiazepoxide, but did not alter rates in the remaining subjects. Intermediate doses of buspirone decreased avoidance rates more in the component with the lower frequency of pellet presentation, higher doses further decreased response rates. The amount of time spent in the presence of stimuli associated with pellet presentation was minimally affected by the lower doses of buspirone, but decreased dose dependently following the higher doses. The results of this experiment add further credence to the notion that the behavioral effects of drug administration may depend on nonpharmacological variables including, but not limited to, the nature of the consequent event. © 1998 Elsevier Science Inc.

Random-time schedule Negative reinforcement—Avoidance of time-out Chlordiazepoxide Buspirone
Time- out Time-in Avoidance response Lever press Rat

THE behavioral effects of drugs may depend upon nonpharmacological factors such as the nature of the event that maintains behavior [for reviews, see (2,7)]. Low to intermediate doses of chlordiazepoxide (CDP), for instance, increase food-maintained responding but decrease the frequency of behavior maintained by the presentation of a mild electric shock (3). Others have observed that CDP administration decreases response rates maintained by a schedule of shock avoidance (1), but that it increases responding maintained by presentation of time-out from avoidance (9,10) or by avoidance of time-out from response-dependent food (27). In some of these same experiments CDP administration increased response rates maintained by response-dependent food presentation (1,27).

The present experiment was designed to examine the effects of CDP and buspirone (BUSP) on responding maintained by negative reinforcement involving avoidance of time-out from response-independent food presentation. The frequency of response-independent food presentation was manipulated in different components of a multiple (MULT) schedule because previously it has been shown that avoidance response rates vary as a function of the frequency of food presentation. More

Requests for reprints should be addressed to Frans van Haaren, Department of Psychology, University of Florida, Gainesville, FL 32611-2250.

frequent response-independent food presentation was accompanied by higher avoidance rates in one experiment (6), but others have shown the opposite, i.e., lower avoidance rates when (response-dependent or response-independent) food presentation occurred more frequently (21,22). The behavioral effects of CDP (an antianxiety agent) were evaluated in the present experiment to further our understanding of its interaction with behavior maintained by a schedule of avoidance of time-out from response-independent food (27). BUSP was included to extend the analysis of its behavioral effects to a situation in which rats respond to avoid time-out of response-independent food presentation. Like CDP, BUSP has been shown to result in a dose-dependent decrease in shock-avoidance responding (18), but despite its clinical effectiveness as an antianxiety agent, the behavioral effects of BUSP have been unlike those of CDP when response rates were suppressed by the presentation of a mild, but effective electric shock (5), or by the presentation of time-out from response-dependent food presentation (25).

METHOD

Subjects

Six, experimentally naive, male Wistar rats were obtained from Harlan Sprague–Dawley when they were approximately 60 days old. They were housed in groups of three under a reversed 12 L:12 D cycle (lights on 1900 h). One of the subjects died of natural causes before the experiment was completed, and its data are not included in the current analysis. All subjects were allowed only limited access to food such that they were without food for approximately 22 h prior to the start of each experimental session [cf. (13)], but tap water was always available in the home cage.

Apparatus

Experiments were conducted in six identical Coulbourn Instruments modular rodent operant-conditioning chambers, which were 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 floor 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. The houselight was located 2 cm from the ceiling in the middle of the intelligence panel. A press on the right (avoidance) 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 and connected to a PDP 11-23 microcomputer (Digital Equipment Corporation) located in the experimental room itself. The experimental contingencies and data acquisition procedures were programmed using SKED-11 (20), obtained from State Systems, Inc. (Kalamazoo, MI).

Procedure

Response-independent food pellets were presented according to a random-time 120-s (RT 120-s) schedule in the first component of the multiple (MULT) schedule (correlated with the presence of a tone) and according to a random-time 30-s (RT 30-s) schedule in the second component. Each component was in effect for 10 min and they were presented twice during a session in simple alternation. The schedule components were separated by 30 s, during which the houselight and stimulus lights above the right lever flickered (0.20 s on/off cycle) and food pellets were not presented. The specific duration of each RT interval was determined by sampling a probability gate every 1 s, with a probability of 0.008 (RT 120-s) or 0.033 (RT 30-s). Gating of food availability continued during thet 2 s following each avoidance response when food pellets could not be delivered (see below). Response-independent food pellets could be delivered for 10 s, during which the houselight and the stimulus lights above the right lever were illuminated (time-out–time-out (TO-TO) interval 10 s). If the subjects did not press the avoidance lever during the time interval between TO presentations (time-in, TI), a TO of 50 s was presented, during which the houselight and the stimuli above the lever were extinguished and all experimental contingencies were suspended. Subjects could avoid TO presentation by pressing the right lever during TI. Each press on the avoidance lever immediately delayed the onset of the next TO for 20 s [response-time-out (R-TO) interval 20 s] and also initiated a 2-s delay during which response-independent food pellets could not be presented. To initiate responding on the avoidance lever, subjects were first exposed to an experimental condition in which the lights over the avoidance lever remained illuminated during TO and in which a response during TO immediately reinstated the conditions associated with food availability (TO escape condition). Once subjects reliably pressed the lever, the escape contingency was no longer

TABLE 1

AVOIDANCE RESPONSE RATES (AVERAGE NUMBER OF RESPONSES/MINUTE AND SEM) DURING THE HIGH AND LOW REINFORCEMENT FREQUENCY COMPONENTS PRIOR TO CHLORDIAZEPOXIDE OR BUSPIRONE ADMINISTRATION

	Chlordiazepoxide		Buspirone	
	High	Low	High	Low
5302	10.87 (0.71)	15.34 (1.08)	15.39 (0.90)	16.54 (0.91)
5303	7.32 (0.53)	14.63 (0.82)	6.62 (0.49)	10.22 (0.84)
5304	4.96 (0.24)	5.36 (0.38)	5.38 (0.19)	7.16 (0.23)
5305	4.43 (0.29)	6.85 (0.40)	4.67 (0.20)	8.93 (0.36)
5306	28.24 (0.40)	23.16 (0.91)	27.34 (0.76)	25.04 (0.72)

TABLE 2

AVERAGE PERCENTAGE OF TOTAL SESSION TIME SPENT IN TIME-IN (AND SEM) DURING THE HIGH AND LOW REINFORCEMENT FREQUENCY COMPONENTS PRIOR TO CHLORDIAZEPOXIDE OR BUSPIRONE ADMINISTRATION

	Chlordiazepoxide		Buspirone	
	High	Low	High	Low
5302	65.97 (3.88)	64.89 (3.03)	77.87 (2.68)	61.63 (2.39)
5303	61.08 (2.45)	64.53 (2.34)	52.78 (2.06)	48.83 (2.77)
5304	46.97 (2.06)	45.93 (1.94)	56.21 (1.99)	62.31 (1.49)
5305	44.43 (2.14)	45.63 (2.33)	48.21 (1.64)	59.00 (1.88)
5306	88.94 (1.52)	75.38 (2.12)	86.33 (1.80)	80.27 (1.90)

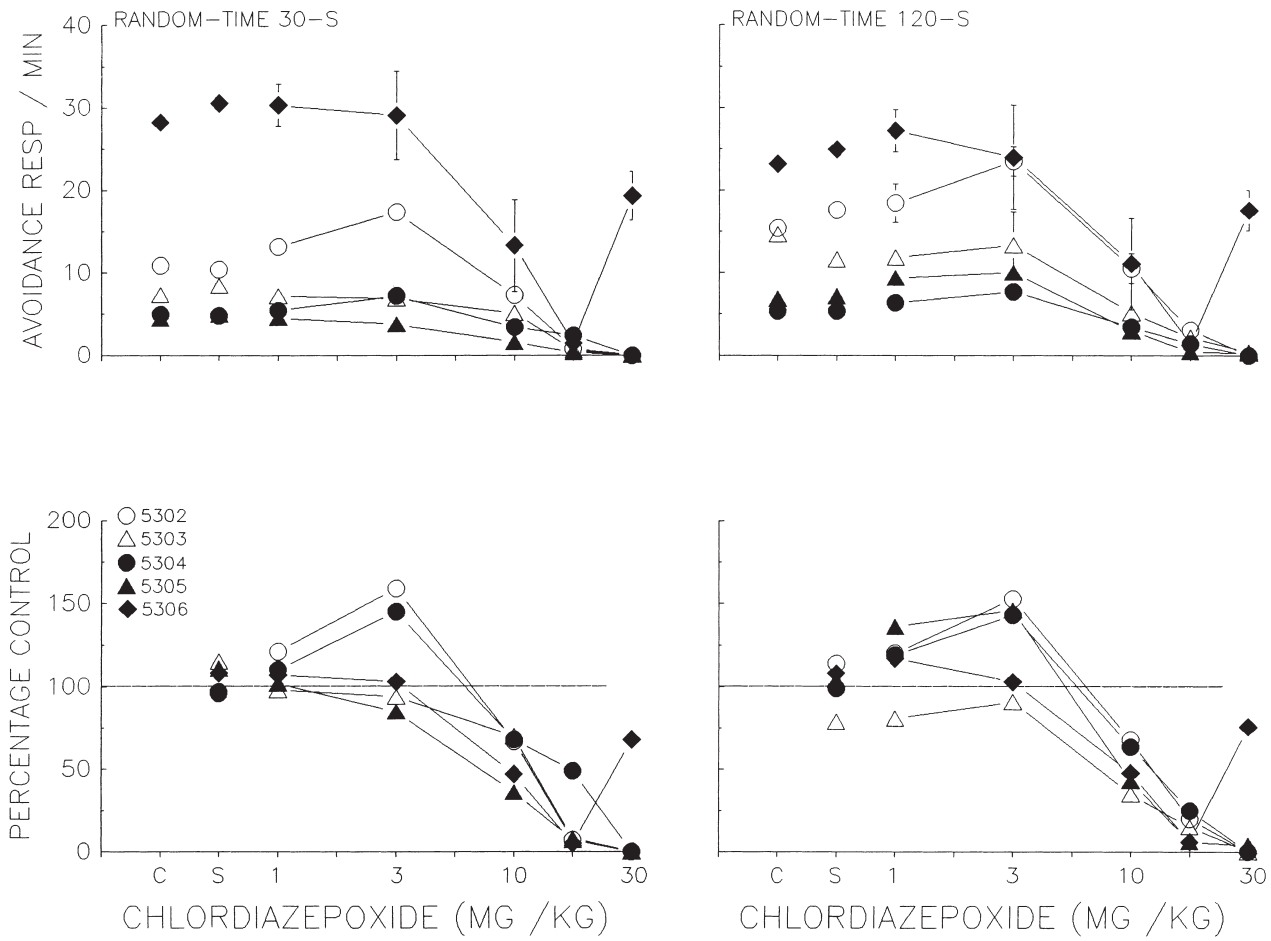

FIG. 1. Average avoidance response rates (responses/min) and one standard error around the mean during the random-time 30-s component and the random-time 120-s component of the multiple schedule are shown in the top left-hand and right-hand panels of the figure as a function of the different doses of chlordiazepoxide. When standard errors are not shown they are included in the data point. The data points above "C" and "S" represent observations during control sessions and after vehicle administration. The bottom panels of the figure show the same data expressed as a percentage of control values. The horizontal line indicates no change from control values.

available, and subjects were exposed to the experimental conditions described above for the remainder of the experiment. Experimental sessions were conducted 5 days a week (Monday through Friday).

Drug Administration

Once response rates on the avoidance lever had stabilized, subjects were injected with different doses of chlordiazepoxide hydrochloride (CDP, Sigma, St. Louis, MO: vehicle, 1, 3, 10, 17, and 30 mg/kg) or buspirone (BUSP, Sigma, St. Louis, MO: vehicle, 0.1, 0.3, 1.0, 1.7, 3.0, and 4.2 mg/kg). Subjects 5302 and 5303 were first injected with the different doses of CDP, while subjects 5304, 5305, and 5306 first received the different doses of BUSP. Injections were given intraperitoneally (IP) in a volume of 1 ml/kg, 15 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. Buspirone was dissolved in the same vehicle, divided in aliquots, and frozen until immediately before use. All drugs were allowed to attain room temperature prior to injection. All drug doses (and saline) were tested at least twice (range 2–5) in irregular order on Tuesdays and Fridays of each week. The intermediate doses of any given drug were administered more frequently because their behavioral effects were more variable than those of doses at either end of the dose–effect curves.

RESULTS

Tables 1 and 2 show average response rates (responses/min) and the average percentage of total session time spent in the presence of stimuli associated with the presentation of response-independent food in the absence of drug administration. Standard errors are also shown. These data reflect observations from all control sessions preceding sessions in which drugs or vehicle were administered. Table 1 shows that avoidance response rates varied considerably between subjects. Within subjects, avoidance rates were mostly higher during the component with the low frequency of response-independent food presentation (RT 120-s) than during the high-frequency component (RT 30-s) (not for subject 5306). The percentage of total session time spent in time-in ranged from a high of 88.94 to a low of 44.43 in different components, varied

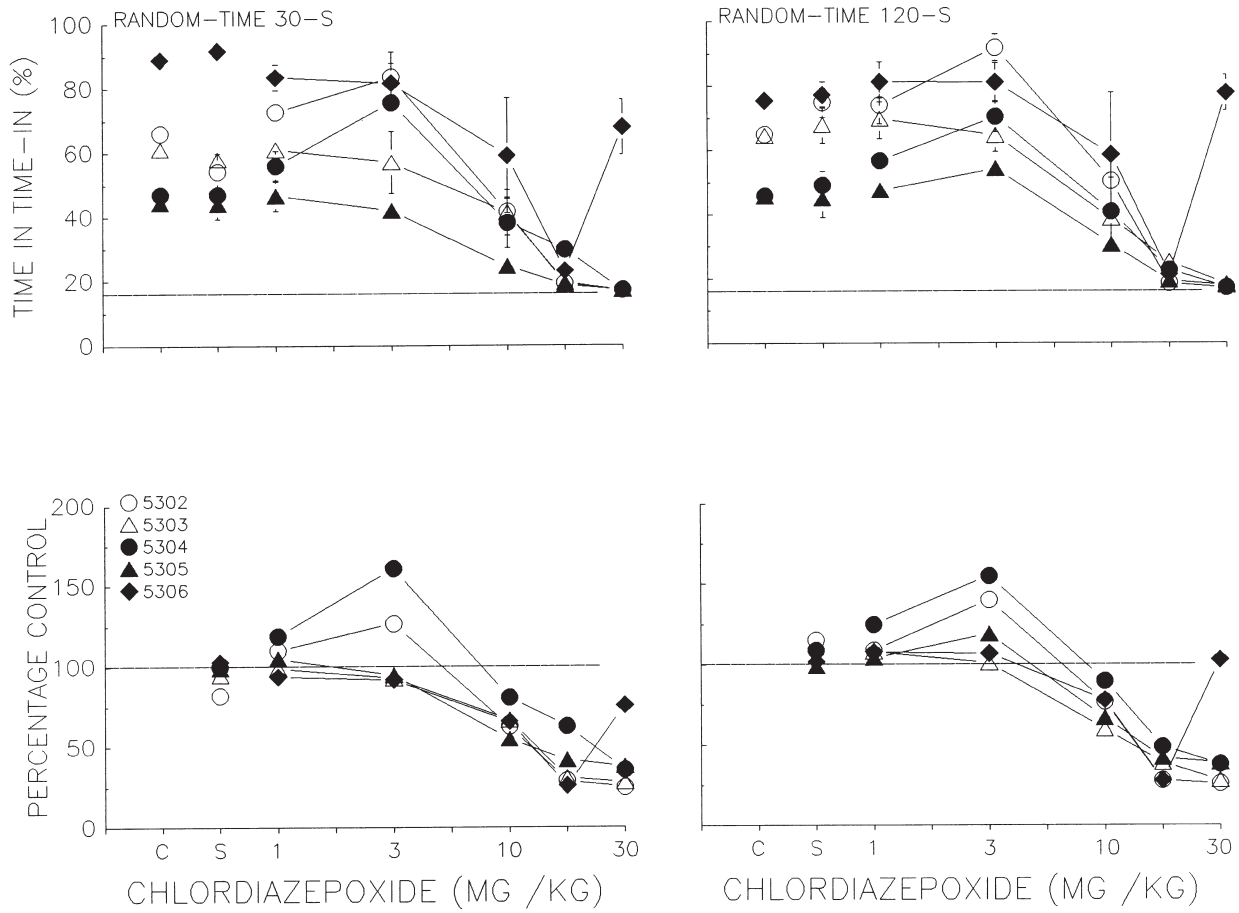

FIG. 2. Average amount of time spent in the presence of stimuli associated with response-independent food pellet presentation during the random-time 30-s component and the random-time 120-s component is shown in the top left-hand and top right-hand panels of the figure, respectively, as a function of the different doses of chlordiazepoxide. One standard error around the mean (SEM) is indicated unless encompassed by the data point itself. The data points above "C" and "S" represent observations during control sessions and after vehicle administration. Control data are from those sessions that preceded sessions in which drugs or vehicle were administered. The horizontal line 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 bottom panels of the figure show the same data expressed as a percentage of control values; the horizontal lines indicate no change from control values.

considerably between subjects and was not consistently related to the frequency of response-independent food presentation.

The top panels of Fig. 1 show avoidance response rates (responses/min) during the RT 30-s (left-hand panel) and the RT 120-s (right-hand panel) of the MULT schedule after administration of the different doses of CDP. The data points above "C" and "S" represent observations during control sessions in the absence of drug administration (C) and after vehicle administration (S), respectively. The bottom panels of Fig. 1 show these same data expressed as a percentage of baseline control values.

A dose-dependent increase in response rates was observed for subjects 5302 and 5304 in the component with the higher frequency of response-independent food presentation following the lower doses of CDP (1 and 3 mg/kg). These doses did not affect, or slightly decreased response rates in the other three subjects (5303, 5305, and 5306). The higher doses of CDP (10, 17, and 30 mg/kg) resulted in a dose-dependent decrease in avoidance response rates, with one exception. For unknown reasons, avoidance rates increased again after 30 mg/kg CDP for subject 5306, both in this and the other low reinforcement-frequency component of the schedule. The effects of CDP on avoidance rates in the low-frequency component were a bit more variable, as the lowest dose (1 mg/kg) increased response rates in four of five subjects, but decreased response rates in the fifth subject (5303). The administration of 3 mg/kg CDP further increased avoidance response rates in three of five subjects, but decreased rates in the other two subjects (5303 and 5306) compared to control values. The higher doses of CDP (10, 17, and 30 mg/kg) resulted in a dose-dependent decrease in avoidance response rates, with the exception noted above.

Figure 2 shows the percentage of total session time spent in the presence of the stimuli associated with food availability (time-in, TI) following CDP administration. The horizontal line in the top two panels indicates the amount of time that would have been spent in the presence of these stimuli in the absence of any avoidance responding. Other details are as in Fig. 1. Low doses of CDP (1 and 3 mg/kg) either did not affect

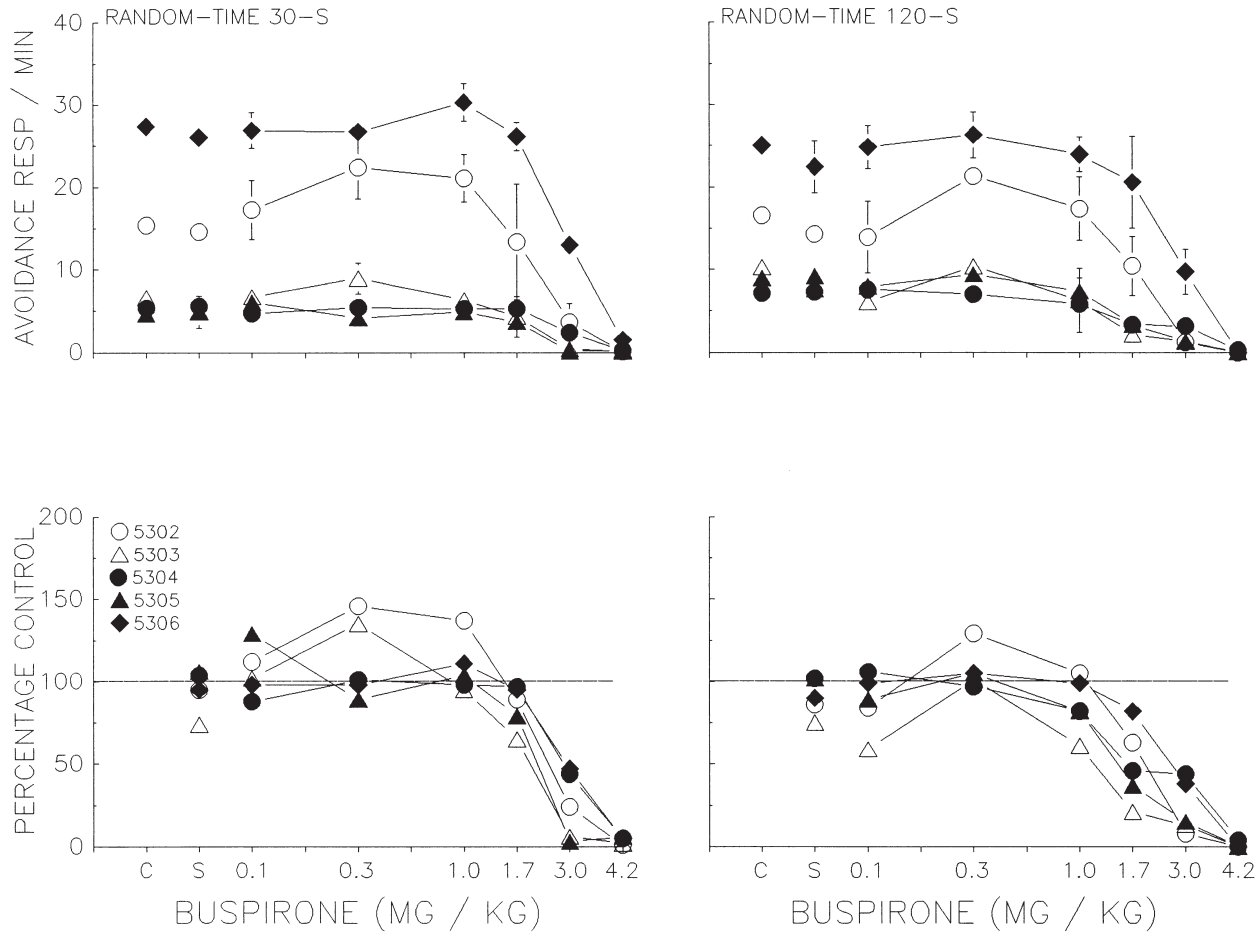

FIG. 3. Average avoidance response rates (responses/min) and one standard error around the mean during the random-time 30-s component and the random-time 120-s component of the multiple schedule are shown in the top left-hand and right-hand panels of the figure as a function of the different doses of buspirone. When the standard error is not shown it is encompassed by the data point itself. The data points above "C" and "S" represent observations during control sessions and after vehicle administration. The bottom panels of the figure show the same data expressed as a percentage of control values. The horizontal line indicates no change from control values.

(5303, 5305, and 5306) or increased the amount of time that subjects spent in TI during the component with the high frequency of response-independent food presentation (left-hand panels). Similar observations were made in the low-frequency component where low doses of CDP did not affect the amount of time in TI for subjects 5303 and 5306, but increased the percentage of session time in TI for the other three subjects, especially after 3 mg/kg CDP. The higher doses of CDP (10, 17, and 30 mg/kg) dose-dependently decreased the amount of time spent in TI in both components of the MULT schedule, with an exception—again, for subject 5306 after 30 mg/kg CDP.

Figures 3 and 4 show avoidance response rates and the amount of time spent in TI following exposure to different doses of BUSP. Figure 3 shows that low doses of BUSP (0.1 and 0.3 mg/kg) either did not affect or increased avoidance response rates. Increased response rates were specifically observed in subjects 5302 and 5303, who had been exposed to CDP prior to being tested with BUSP. The behavioral effects of the intermediate doses of BUSP (1.0 and 1.7 mg/kg) appeared to depend on the frequency of response-independent pellet presentation, as response rates decreased more in the component with the lower frequency of response-independent food presentation. The highest doses of BUSP effectively reduced response rates in both components of the MULT schedule. Figure 4 shows that the percentage of time that subjects spent in TI was hardly affected at all by the lower doses of BUSP (0.1 and 0.3 mg/kg). The higher doses of BUSP (1.0 mg/kg and up) generally decreased the amount of time that subjects spent in the presence of stimuli associated with response-independent food presentation, irrespective of the frequency of response-independent food presentation.

DISCUSSION

The present experiment produced a number of important observations to confirm and extend those of other studies. Avoidance response rates in the absence of drug administration varied considerably between subjects as a result of the free-operant acquisition of avoidance responding, but they were generally higher when response-independent food pellets were delivered infrequently than when they were delivered more often. As such, these results both confirm and con-

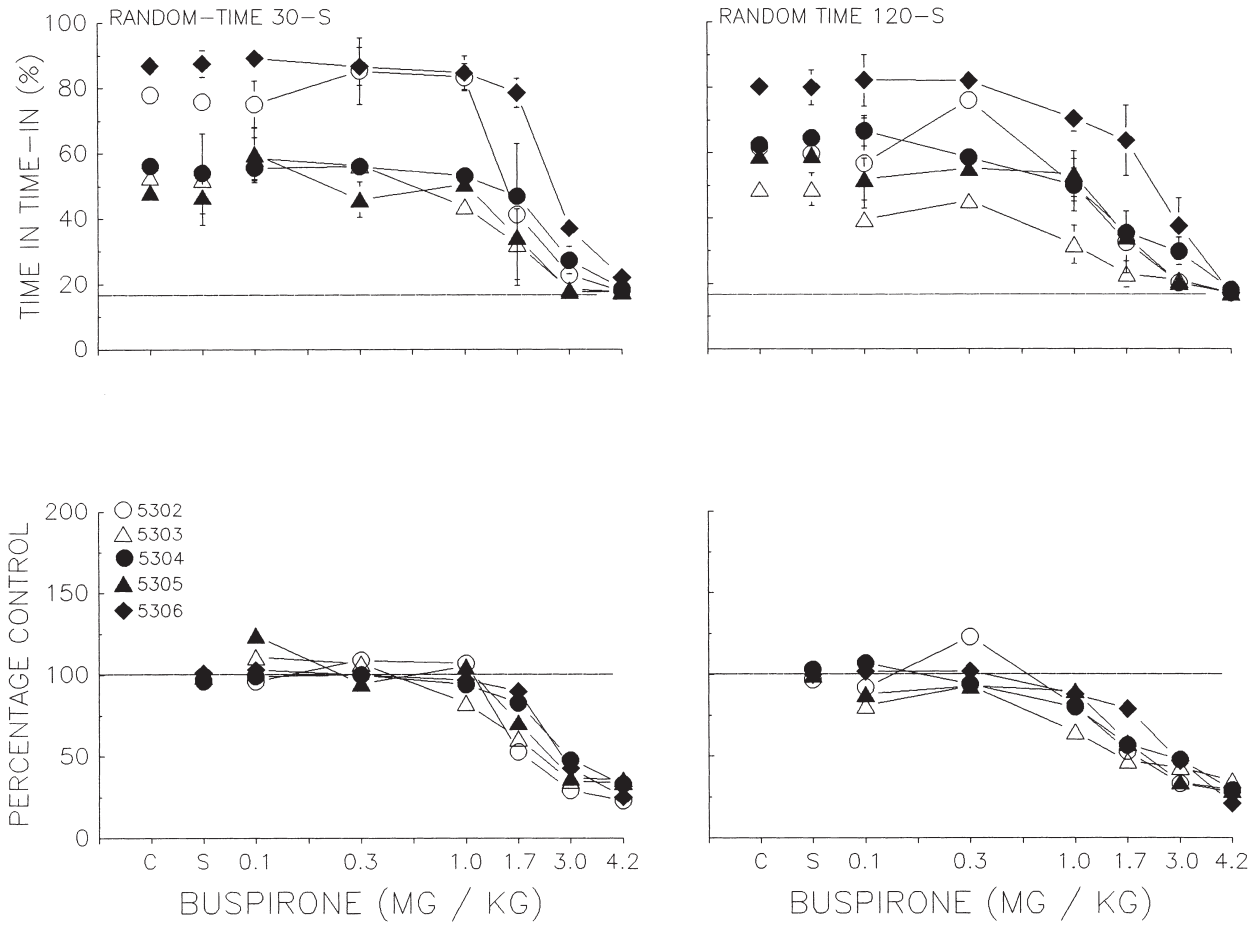

FIG. 4. Average amount of time spent in the presence of stimuli associated with response-independent food pellet presentation during the random-time 30-s component and the random-time 120-s component is shown in the top left-hand and top right-hand panels of the figure, respectively, as a function of the different doses of buspirone. One standard error around the mean (SEM) is indicated unless encompassed by the data point itself. The data points above "C" and "S" represent observations during control sessions and after vehicle administration. Control data are from those sessions that preceded sessions in which drugs or vehicle were administered. The horizontal line 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 bottom panels of the figure show the same data expressed as a percentage of control values; the horizontal lines indicate no change from control values.

tradict those previously observed by others (6,21,22). The paucity of experimental data prevents an in-depth analysis of the variables that might be responsible for one or the other experimental outcome. Early accounts emphasized that presentation of time-out from the schedule with the higher frequency of food presentation would be more aversive and, therefore, maintain higher avoidance response rates (8). An argument could also be couched, however, in terms of competing activities to suggest that subjects might be less likely to engage in avoidance responding when other activities occur at higher frequencies. These could include lever pressing for response-dependent food presentation (27) or behavior directed towards the site of response-independent pellet presentation, as may have been the case in the present study. Under such circumstances avoidance response rates would be lower when food presentation occurs at higher frequencies. It should be noted, however, that there appeared to be no direct relationship between avoidance response rates and time spent in time-in in the different components of the schedule. This suggests that response rates may not have been a direct function of the frequency of response-independent food presentation, but in addition may have been affected by the 2-s delay following each avoidance response during which response independent food was not presented. These considerations only further underscore the need for additional research to identify variables that might affect response rates when responding results in postponement of avoidance of time-out from response-dependent or response-independent food presentation.

Low doses of CDP either did not change or slightly increased avoidance response rates, while the higher doses (10 mg/kg and up) dose dependently decreased avoidance response rates. The time that subjects spent in the presence of stimuli associated with the availability of response-independent food presentation either did not change or increased slightly after the lower doses of CDP, while it decreased dose dependently following the administration of the higher doses. These results partially confirm and extend those observed by van Haaren and Zarcone (27), who reported that CDP administration increased responding that resulted in postponement of the presentation of time-out from response-dependent

food. These effects of CDP were similar to its effects on behavior maintained by presentation of time-out from an avoidance schedule and unlike those observed when behavior is maintained by negative reinforcement involving shock avoidance. CDP has been shown to decrease responding maintained by shock avoidance (1) and to increase response rates maintained by the presentation of time-out from avoidance, while the same doses decreased or did not affect shock avoidance response rates (9,10).

Low doses of BUSP increased response rates in subjects first exposed to chlordiazepoxide, but did not alter response rates in the remaining subjects. Intermediate doses of BUSP decreased avoidance response rates but they decreased more in the component with the lower frequency of pellet presentation. The higher doses of BUSP further decreased response rates dose dependently. The amount of time spent in the presence of stimuli associated with pellet presentation was little affected by the lower doses of BUSP, but decreased dose dependently following the higher doses. Thus, the effects of BUSP on avoidance of time-out from response-independent food were similar to those observed when behavior was maintained by the contingent presentation of time-out from an avoidance procedure (9,10).

The results of this and other experiments (6,27) 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 function as negative reinforcement. The results also suggest that the effects of different doses of a drug on behavior maintained by negative reinforcement involving avoidance of time-out from food presentation may be unlike those observed when behavior is maintained by negative reinforcement involving shock avoidance (11,12). As such, they add important information to the observations of others who have shown that drug effects may be influenced by any number of behavioral parameters such as the schedule of reinforcement (4,19,24), the degree of external stimulus control [e.g., (17)], the species of the experimental subject [e.g., (14,15,16)], its gender (26), or its experimental history (23). The results of this experiment are obviously limited inasmuch as parametric manipulations of the avoidance schedule or the schedule on which avoidance of time-out from food presentation was available were not attempted. Such studies will need to be conducted to fully identify the variables that control the effects of different doses of a drug on behavior maintained by negative reinforcement not involving shock escape or shock avoidance.

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