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Suppression of Behavior by Food Pellet-Lithium Chloride Pairings in Squirrel Monkeys[1]

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BERGMAN, J. AND J. R. GLOWA. *Suppression of behavior by food pellet-lithium chloride pairings in squirrel monkeys.* PHARMACOL BIOCHEM BEHAV **25**(5) 973–978, 1986.—Responding by squirrel monkeys was maintained under a 30-response fixed-ratio schedule of food presentation; during different sessions responding produced either sucrose-flavored or banana-flavored food pellets. Pre-session administration of doses of lithium chloride (LiCl) less than 3.0 mEq/kg did not alter rates of responding whereas pairing either type of pellet with post-session injections of 1.8 mEq/kg LiCl suppressed both lever pressing and consumption during subsequent sessions in which that pellet type was available. When post-session injections of LiCl were discontinued, responding recovered within 14 sessions. The suppression of responding, but not pellet consumption, was then reliably reproduced in each monkey by pairing post-session LiCl with the previously non-paired type of pellet. Pre-session administration of chlordiazepoxide (CDAP, 3.0–17.0 mg/kg) increased rates of suppressed responding in a dose-related manner, but did not increase pellet consumption. These data indicate that different mechanisms may be involved in the suppression of responding and the suppression of consumption of food by post-session injections of drugs. The suppression of responding by post-session injections of drugs in primates appears to be qualitatively similar to the suppression of responding by other noxious stimuli such as electric shock in that it is reversible, it can be reinstated by re-exposure to post-session drug injections, and it can be attenuated by pre-session administration of CDAP.

Conditioned aversions Punishment Drug-paired stimuli Lithium chloride Chlordiazepoxide Fixed-ratio Lever press Squirrel monkeys

THE suppressing effects of drugs often have been studied in experiments in which consumption of a novel food is paired with a post-session drug injection [11]. With many drugs, as few as two or three post-session injections are sufficient to suppress consummatory behavior (cf. [20,21] for reviews). Previous research, conducted primarily in rodents, has stressed that the development of suppression depends upon the novelty of both the food and drug and upon the temporal relationship between the delivery of food and the injection of drug. With some drugs, for example, the same dose can either suppress food consumption when injected following the session or increase food consumption when administered before the session [4,16].

Presentations of food or water that maintain schedule-controlled behavior also may suppress responding after being paired with post-session drug injections. For example, when injections of *d*-amphetamine followed sessions in which a distinctively flavored liquid maintained responding by rats, the delivery of the flavored liquid alone subsequently decreased rates of responding [7,24]. In other

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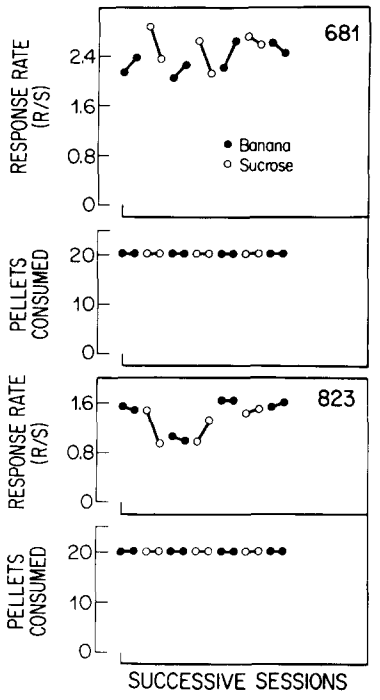

FIG. 1. Rates of responding under the FR 30-response schedule of food presentation and the numbers of food pellets consumed by squirrel monkeys S-681 (top) and S-823 (bottom) when post-session saline injections were paired with banana-flavored or sucrose food pellets. A maximum of 20 pellets could be consumed in each session. Abscissae: consecutive sessions. Ordinates: mean response rate and number of pellets consumed.

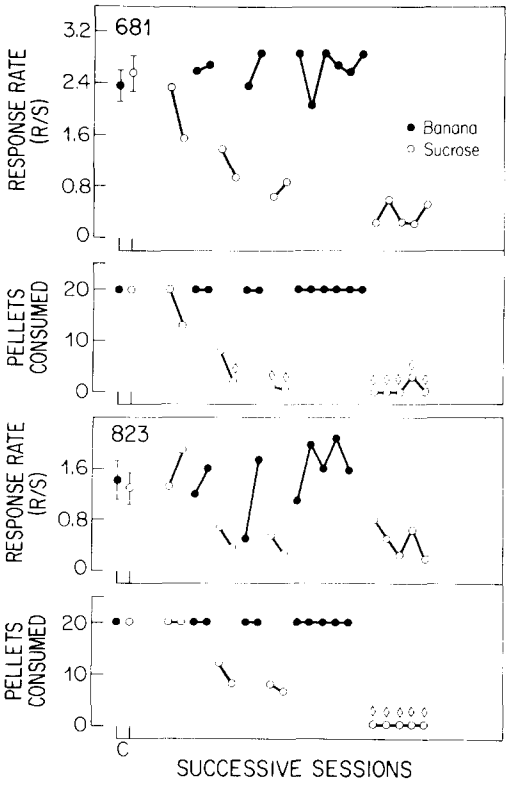

FIG. 2. Rates of responding under the FR 30-response schedule of food delivery and the numbers of food pellets consumed when post-session LiCl injections (1.8 mEq/kg) were paired with sucrose pellet availability and post-session saline injections were paired with banana-flavored pellet availability. Abscissae: successive sessions. Ordinates: mean response rate and number of pellets consumed. Points at C show mean control values based on the preceding eight sessions for response rate and consumption for each pellet type; brackets show S.D. ◇ Indicates occasions on which salivation by the monkey was noted when post-session injections were administered.

studies, responding by pigeons was suppressed by distinctively colored lights accompanying food or water presentation after the colors were paired with injections of either lithium chloride [17] or *d*-amphetamine [8]. Experiments such as these have permitted direct comparisons to be made between the suppression of operant and of consummatory behavior by post-session injections of drugs in the same subjects and, in addition, between the effects of drugs that are administered before and, separately, after the behavioral session.

Although a large body of information has accumulated to date regarding many of the effects of drugs on schedule-controlled behavior in the squirrel monkey [1], their suppressing effects only have been studied using IV drug injections that were consequent to responding [9,10]. Those experiments showed that the immediate suppression of responding produced by drug injections was comparable to that of other noxious stimuli such as electric shock. Of interest, recent studies also have shown that the presentation of distinctive stimuli associated with occasional electric shock also can effectively suppress schedule-controlled responding [25]. Despite procedural differences among these studies, such findings raise the possibility that the suppression of responding by distinctive stimuli associated with electric shock and by stimuli associated with post-session drug injections are qualitatively similar. If similar mechansims are involved in both types of suppression, the suppression of responding by post-session drug injections at least should be reproducible in the same subject and should be attenuated by the pre-session injection of drugs with known antisuppressant effects such as chlordiazepoxide [23,25]. The present experiments were conducted to evaluate this possibility by studying the development, reproducibility, and attenuation of the suppressing effects of distinctively flavored food pellets paired with post-session injections of lithium chloride in squirrel monkeys responding under a schedule of food pellet presentation. In the course of these experiments, the effects of post-session lithium chloride also were compared to its effects in the same monkeys when administered before the behavioral session.

METHOD

Subjects

Two adult male squirrel monkeys (*Saimiri sciureus*), weighing 570 g (S-823) and 800 g (S-681) were used. Monkey S-681 had been studied previously under a fixed-ratio schedule of food presentation and had received *d*-amphetamine; monkey S-823 was experimentally naive at the beginning of the study. Between experimental sessions, subjects were housed individually and had continuous access to water; weights were maintained at approximately 80% of

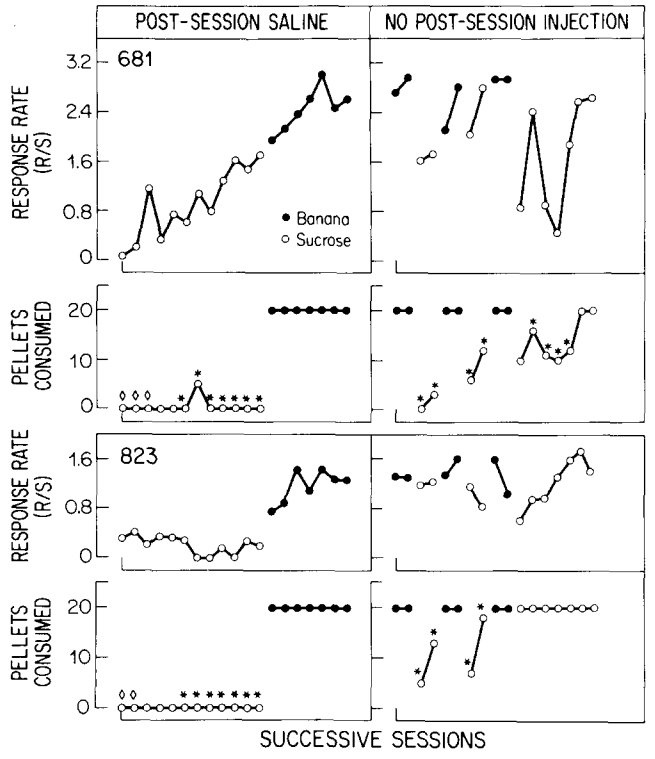

FIG. 3. Response rate and pellet consumption recovery when sucrose pellet availability was no longer paired with post-session LiCl injections. Abscissae: successive sessions. Ordinates: mean response rate and number of pellets consumed. Saline injections followed sessions denoted in the left panels and no injections followed sessions in the right panels. *Indicates consumption of sucrose pellets in home cage.

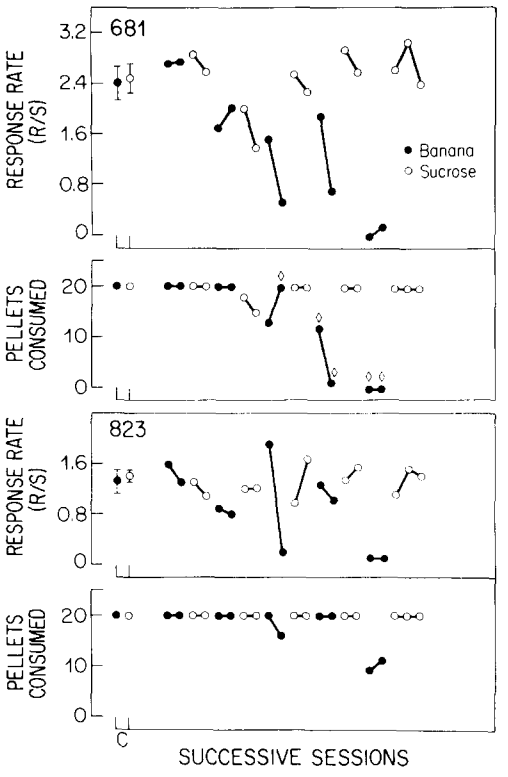

FIG. 4. Rates of responding under the FR 30-response schedule of food delivery and the numbers of food pellets consumed when post-session LiCl injections (1.8 mEq/kg) were paired with banana pellet availability and post-session saline injections were paired with sucrose pellet availability. Abscissae: successive sessions. Ordinates: mean response rate and number of pellets consumed. Points at C show mean control values based on the preceding eight sessions for response rate and consumption for each pellet type; brackets show S.D. ◇ Indicates occasions on which salivation by the monkey was noted when post-session injections were administered.

their free-feeding weights by restricting access to food (Purina Monkey Chow) in the home cages.

Apparatus

During experimental sessions, monkeys were seated in a Plexiglas chair similar to the one described by Herd [11]. The chair was placed in a ventilated, sound-attenuating chamber (Industrial Acoustics, model AC-5) provided with white noise to mask extraneous sounds. A response lever (BRS/LVE, model 121-05) was mounted on the transparent front wall of the chair. Each press on the lever with a minimum downward force of 0.20 N produced an audible click of a relay within the chamber and was recorded as a response. Green and amber lamps, mounted at eye level behind the front wall, could be illuminated to serve as visual stimuli. Two food pellet dispensers (Gerbrands, Model D-1) were mounted on the chair; 300 mg food pellets (Noyes type F, sucrose-flavored or banana-flavored) could be delivered to a tray accessible to the monkey through an opening in the front wall of the chair. The tray was illuminated by white light for 1 sec during food delivery.

Schedule

Responding was maintained under a 30-response fixed-ratio (FR 30) schedule of food presentation. In the presence of a green light, every 30th response produced a banana-flavored pellet and was followed by a 60-sec timeout period. During the timeout, the chamber was dark and responding had no scheduled consequences. Sessions ended after the completion of 20 FR 30 components or 60 min, whichever occurred first.

Procedure

Initially, responding by each monkey was developed under the FR 30 schedule by presentation of banana-flavored pellets. Subsequently, except where noted, the type of pellet (banana-flavored and sucrose-flavored) alternated every two sessions. After several weeks during which similar rates of responding were maintained by the presentation of the two types of pellet, a regimen of daily post-session IM injections of saline was begun. Two weeks later, injections of lithium chloride (1.8 mEq/kg LiCl) were substituted for injections of saline following each of the two and, subsequently, 5 or 6 consecutive sessions in which sucrose-flavored pellets were available; saline injections continued to follow sessions in which banana-flavored pellets were available.

After responding maintained by sucrose-flavored pellets was consistently suppressed, LiCl injections were discontinued. During the next twelve sessions responding produced

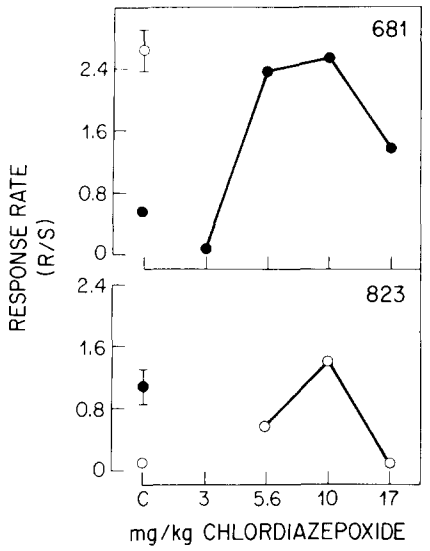

FIG. 5. Effects of doses of IM chlordiazepoxide administered 30 min pre-session on rates of responding suppressed by post-session LiCl (1.8 mEq/kg) pairings with banana-flavored (S-681) or sucrose (S-823) food pellet availability. Abscissae: dose, log scale. Ordinates: mean response rate for squirrel monkeys S-681 (top) and S-823 (bottom). Points at C show mean control values based on 8 (S-681) or 6 (S-823) sessions for each pellet type during chlordiazepoxide dose-effect determinations; brackets show S.D.

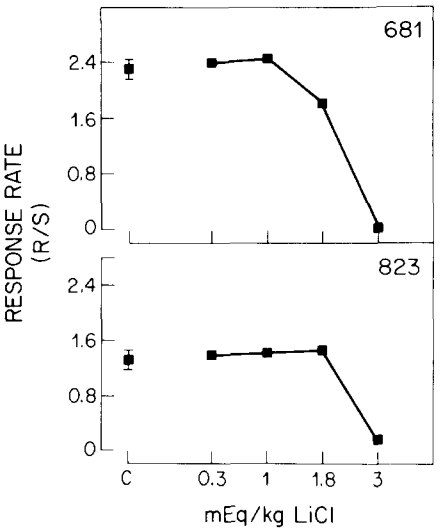

FIG. 6. Effects of doses of IM LiCl administered 10 min pre-session on rates of responding maintained under the FR 30 schedule of banana pellet delivery. Abscissae: dose, log scale. Ordinates: mean response rate. Points at C show mean control values based on 8 control sessions during LiCl dose-effect determinations; brackets show S.D.

only sucrose-flavored pellets paired with post-session injections of saline. Any sucrose-flavored pellets that were not consumed during the session were placed in the monkey's home cage later in the day. Subsequently, responding produced only banana-flavored pellets for seven consecutive sessions. Double alternation of sucrose-flavored and banana-flavored food pellet presentation then was resumed and all post-session injections were discontinued until responding and food consumption were at or near previous control values for both types of pellet.

The effects of pairing post-session LiCl injections with banana-flavored pellets then were studied in both monkeys. Injections of saline followed sessions in which sucrose-flavored pellets were available whereas injections of LiCl (1.8 mEq/kg) followed sessions in which banana-flavored pellets were available. After responding maintained by banana-flavored pellets was consistently suppressed, all injections were discontinued for monkey S-823 until control rates of responding recovered. Subsequently, post-session LiCl injections again were paired with sucrose-flavored pellets for this monkey and the effects of chlordiazepoxide (3–17 mg/kg) were assessed on suppressed responding in both monkeys. The effects of different doses of chlordiazepoxide were determined in an irregular order and no more than twice weekly. LiCl was not administered following sessions in which the effects of pre-session chlordiazepoxide were studied. After experiments with chlordiazepoxide, all post-session injections were discontinued. When responding maintained by banana-flavored pellets recovered to previous non-suppressed values for monkey S-681, the effects of pre-session LiCl administration were determined in both monkeys on responding maintained by banana-flavored pellets. Doses of LiCl were studied in an ascending order, no more often than twice weekly.

Drugs

Lithium chloride and chlordiazepoxide HCl were dissolved in a 0.9% saline solution and administered in volumes of 0.5 ml/kg. Post-session LiCl injections were given immediately after the session ended. Pre-session injections of LiCl and of chlordiazepoxide were given 10 min and 30 min, respectively, before the session. All injections were made in the thigh muscle (IM).

RESULTS

The FR 30 schedule of food presentation maintained rates of responding from 1.6–2.4 responses per second in S-681 and S-823. Each type of food pellet maintained typical FR patterns of responding in which all 30 responses occurred in rapid succession. Despite an initial perturbation in responding for S-823 when post-session saline injections were first introduced, neither the type of pellet nor post-session saline injections greatly altered response rates or pellet consumption (Fig. 1).

Figure 2 shows the effects of injecting LiCl after sessions in which sucrose-flavored pellets were available. After only two pairings, the rate of responding and consumption of sucrose-flavored pellets began to decrease in both monkeys, and salivation was evident each time the chamber door was opened to administer LiCl at the end of the session. By the sixth pairing with LiCl, both responding and consumption of sucrose pellets were suppressed to low levels; banana-flavored pellets however, maintained responding and pellet consumption at control levels throughout this period. After 5 additional sessions in which only banana-flavored pellets were available, subsequent presentations of sucrose-flavored pellets still suppressed rates of responding and pellet consumption. Vomiting occasionally was observed after the session during this time.

Figure 3 shows the effects of substituting post-session injections of saline for LiCl and, subsequently, of discontinuing all injections. By the fourth session after LiCl injections were discontinued, salivation and vomiting no longer were evident for either monkey, although response rate and pellet consumption were still suppressed. However, uneaten sucrose-flavored pellets that were placed in the monkey's home cage were always consumed immediately. In subsequent sessions, responding gradually recovered for S-681 but remained nearly completely suppressed for S-823. When responding subsequently led to the presentation of banana-flavored pellets, pellet consumption was restored immediately in each subject and rates of responding returned to control levels within several sessions. When post-session injections were discontinued, responding maintained by sucrose-flavored pellets eventually recovered to previous non-suppressed control rates for both monkeys.

Figure 4 shows the effects of subsequent pairings of banana-flavored pellets with post-session injections of LiCl. Rates of responding decreased over 8–10 pairings for both monkeys; pellet consumption, however, was completely suppressed only in S-681. The suppression of responding by pairings of banana-flavored pellets with post-session injections of LiCl developed somewhat more slowly than the previous suppression of responding by pairings of sucrose-flavored pellets and LiCl (compare Figs. 2 and 4).

When post-session injections were discontinued for S-823, rates of responding returned to previous control levels within 14 days. Subsequently, the renewed pairings of post-session LiCl injections with sucrose-flavored pellets suppressed responding, but did not fully suppress pellet consumption, over the course of 4 sessions in this monkey (not shown).

Figure 5 shows the effects of pre-session injections of chlordiazepoxide on responding suppressed by pairing of LiCl and banana-flavored pellets in monkey S-681 and by pairings of LiCl and sucrose-flavored pellets in monkey S-823. Rates of suppressed responding were restored to non-suppressed levels by intermediate doses of chlordiazepoxide (5.6 and 10 mg/kg) and either increased less or decreased by the highest dose in both monkeys. Doses of chlordiazepoxide which increased rates of suppressed responding, however, did not restore pellet consumption fully or in a dose-related manner for either monkey; no more than 10 pellets were consumed during the session after any dose of chlordiazepoxide. Remaining pellets were readily consumed in the home cage after the session.

The effects of pre-session injections of LiCl administration on responding maintained by banana-flavored pellets are shown for both monkeys in Fig. 6. Doses of LiCl below 3 mEq/kg had little or no effect on responding whereas 3 mEq/kg markedly decreased rates of responding in each subject. Rates of responding and pellet consumption were not affected differentially by pre-session injections of LiCl.

DISCUSSION

The present experiments show that schedule-controlled responding and food consumption by squirrel monkeys can be suppressed by distinctively flavored food pellets paired with post-session injections of LiCl. These results are consistent with earlier findings that foods paired with post-session injections of LiCl can suppress consumption in different species [19,20] and extend to primates findings in other species that schedule-controlled responding also can be suppressed by distinctive stimuli that are paired with post-session injections of drugs [8, 18, 24]. Moreover, the suppression of behavior by a dose of LiCl that did not markedly affect responding when administered before the session indicates that, as with other drugs, the effects of selected doses of LiCl may differ when studied in dissimilar experimental contexts [21].

A novel feature of these experiments was the repeated suppression and restoration of responding using familiar types of food pellets and a constant dose of LiCl. Findings in previous studies have indicated that familiarity with the paired stimuli or the post-session drug may retard greatly the development of suppression [2, 5, 14]. Extensive exposure to each type of food pellet prior to pairing with post-session injections of LiCl also may have retarded development of suppression in the present study. For instance, D'Mello and Stolerman [7] reported that schedule-controlled responding and fluid consumption were nearly completely suppressed in the course of only 3 pairings of a distinctively-flavored liquid with post-session injections of *d*-amphetamine whereas 6–8 pairings of sucrose-flavored pellets with post-session injections of LiCl were initially required to develop comparable suppression in both squirrel monkeys. However, the development of suppression is also known to be related to the dose of the post-session drug [8]. It is likely that suppression would have developed more rapidly in the present experiments with a higher dose of LiCl despite familiarity with the paired food pellets.

Continued exposure to either the type of food pellets or injections of LiCl did not retard the rate at which schedule-controlled responding was suppressed for either monkey in subsequent sets of pairings. In contrast, food consumption during behavioral sessions was affected more erratically during subsequent pairings and, for S-823, was never fully suppressed after the initial pairings of sucrose-flavored pellets with LiCl injections. These findings suggest that pairing distinctive foods with post-session injections of drugs has separable effects on consumption and on schedule-controlled behavior. They also indicate that changes in schedule-controlled behavior can provide an index of the suppressing effects of post-session injection of drugs that is reproducible and relatively independent of pre-exposure to the paired stimuli. In this regard, the suppression of responding by post-session injections of drugs and by other stimuli such as electric shock may be qualitatively similar.

The initial suppression of schedule-controlled responding and of food consumption by pairing sucrose-flavored pellets with LiCl usually was accompanied by salivation during experimental sessions for both monkeys and by occasional episodes of vomiting. These reactions may have reflected gastrointestinal disturbances that contributed to the suppression of behavior during pairings of food pellets with LiCl. However, the disappearance of salivation and vomiting before the recovery of responding and of food consumption after injections of LiCl were discontinued suggests that other factors also were involved in the suppression of behavior. It is interesting to note that Hasegawa and Matsuzawa [11] recently have reported that the pairing of injections of LiCl with the availability of soybeans in the home cages of Japanese macaques suppressed the consumption of soybeans in the home cage but did not suppress either FR responding maintained by soybeans or their consumption during sessions of operant performance. The present observation that uneaten pellets were readily consumed in the home cage after experimental sessions is consistent with such find-

ings and suggests that conditioning factors releated to the experimental session played an important role in retarding the recovery of suppressed behavior.

Responding was restored to control values in the present experiments either by administering chlordiazepoxide or by discontinuing the pellet-drug pairings. In contrast to its effects on rates of responding, no dose of chlordiazepoxide completely restored the consumption of food pellets. Previous studies have shown that the suppression of consummatory responding can be attenuated by pre-session administration of benzodiazepines [3, 6, 22]. Although the factors responsible for the difference between those findings and the present results are unknown, the dissimilar effects of the benzodiazepine on suppressed schedule-controlled responding and on pellet consumption in the present experiments further suggest that different mechanisms may underlie the suppression of these behaviors by post-session injections of drugs.

The slow recovery of behavior after pairings with LiCl were discontinued is consistent with findings in previous studies involving behavior suppressed by post-session injections of drugs [17] and in studies in which the delivery of intermittent electric shocks is used to suppress schedule-controlled responding [15]. The gradual restoration of responding which followed the discontinuation of post-session LiCl injections should be distinguished from the immediate increases in responding produced by injections of chlordiazepoxide. In addition to attenuating the suppression of consummatory responding by stimuli paired with post-session drug injections, benzodiazepines have been shown to restore responding suppressed by the presentation of stimuli such as electric shock [19,23] or visual stimuli paired with shock [25]. The immediate nature of such increases in those experiments and in the present experiment generally contrasts with the more protracted response recovery following the removal of the suppressing condition. These similar findings, in conjunction with the reproducibility of the suppression of responding in the present experiments, suggest some common functional properties of the suppression of schedule-controlled behavior, regardless of the stimuli or procedure used to produce suppression.

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