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Pentobarbital Facilitated Extinction: Effects of Different Schedules of Drug Withdrawal[1]

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GRIFFITHS, R. R. AND T. THOMPSON. *Pentobarbital facilitated extinction: Effects of different schedules of drug withdrawal.* PHARMAC. BIOCHEM. BEHAV. 2(3) 331–338, 1974. – Bar pressing by rats was trained on a fixed-ratio food reinforcement schedule and subsequently extinguished under different schedules of drug withdrawal. Reduced total extinction responding was obtained with 20–25 sessions of 15 min duration or 3 sessions of 5 hr duration. Both the gradual discontinuation dose schedule (fading) and the abrupt discontinuation dose schedule were equally effective in reducing extinction responding. However, the absolute number of sessions of drug treatment by the graded dose schedule or the abrupt discontinuation schedule had no effect on total responding. Although there was no difference on total extinction responding under the 2 dose schedules, the pattern of extinction responding was markedly different. The graded dose procedure produced little or no responding on the first extinction session with intermittent response bursting thereafter. However, the abrupt discontinuation procedure produced complete response suppression during initial drug sessions followed by substantial responding on the first saline session with progressively fewer responses over the next few sessions. Except for the initial response suppression, the pattern of extinction responding for the abrupt discontinuation procedure was identical to that observed when saline alone was administered in extinction.

Pentobarbital Extinction Fading

PREVIOUS research [2] suggests that the extinction procedure of behavior elimination can be facilitated by combining it with pentobarbital treatment. Rats were trained to emit a bar-press response on a fixed-ratio schedule and subsequently extinguished. During extinction, a gradual decreasing dose regimen was employed in which high doses of pentobarbital were administered on the first extinction session and progressively reduced over successive sessions. Responding by pentobarbital-treated animals differed from that of saline-treated animals in two ways: (1) Total extinction responding: the pentobarbital groups had significantly fewer cumulative responses in extinction than saline groups, and (2) The pattern of responding in extinction: the pattern for saline-treated animals was characterized by substantial responding on the first session with progressively fewer responses over succeeding sessions; whereas pentobarbital-treated animals had little responding during the first extinction session and response bursting during both early and later sessions.

The rationale behind this previous research was that extinction could be facilitated by initially giving immobilizing doses of drug, and then gradually reducing the drug dose over successive sessions. Although initial extinction responding could be decreased by administering high doses of drug on early extinction sessions, the goal was to develop a procedure to reduce the over-all extinction responding. Since research suggests that behavior learned under the interoceptive stimulus conditions of the drug state will not necessarily generalize to those of a nondrug state [3,4], a fading procedure was employed with the expectation that it

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would facilitate transfer between drug states. Research has demonstrated that a fading procedure is effective in eliminating incorrect responding in a visual discrimination task [6]. The significant feature of a fading procedure is that behavior present during one set of stimulus conditions can generalize with minimal errors to a different set of stimulus conditions if the initial stimulus dimension is gradually removed (faded) rather than abruptly removed. Therefore, the rationale for using graded doses of drug is that a drug fading procedure could be employed to reduce extinction responding. In this case, the drug state would be treated as the relevant stimulus dimension. Initial extinction responding would be reduced by administering high doses of drug on early extinction sessions. A fading procedure would then be used to transfer behavior present during one set of stimulus conditions (no responding-drug state) to another set of stimulus conditions (no responding-nondrug state) with minimal errors. Fading would be controlled by gradually reducing the drug dosage over successive sessions.

Although previous research [2] demonstrated and replicated drug effects on pattern and number of extinction responses, no attempt was made to determine whether the graded dose schedule (fading procedure) was relevant to the experimental findings as was initially believed. Therefore, a series of studies (Experiments 1, 2 and 3) was designed to investigate the effect of different dose schedules on the total number and pattern of responses in extinction. Experiment 1 was undertaken to determine the effects of administering high, constant doses of sodium pentobarbital prior to the initial 1, 4, or 12 extinction sessions.

EXPERIMENT 1: EXTINCTION WITH ABRUPT DRUG DISCONTINUATION

METHOD

Animals

Thirty experimentally naive male Sprague-Dawley rats approximately 90 days old at the beginning of the experiment were used. They were maintained at 80% of their free feeding weights by post-session rations of Purina rat chow.

Apparatus

Six Gerbrands, two-lever rat operant-conditioning chambers were enclosed in sound-attenuating boxes. Experimental procedures were scheduled by relay-timer circuitry located in another room. The houselight and magazine light provided continuous illumination. Noyes pellets (45 mg) served as reinforcers.

Procedure

Training. Since the experimental design included individual and group comparisons, uniform training and subsequent performance among animals was essential. Accordingly, the FR (fixed-ratio) training procedure was made as uniform as possible for all animals. Data from a previous study [2] indicated that when a group of animals was subjected to the uniform FR training procedure, most animals developed typical FR performance [1], while some exhibited erratic performance. The performance of these latter animals was characterized by a low running rate (i.e., 0.5 responses per sec), long between-ratio pausing, and some mid-ratio pausing. Because similar response rates were desirable, it was decided that in this experiment and following experiments more animals would be trained than actually used. The animals with the lowest and most erratic response rates would be discarded prior to extinction.

On the first session food was presented independently of responding at variable times (a VT 1-min schedule) while a response-contingent FR 1 schedule was concurrently in effect. Any animal which had not acquired the bar-press response (rate greater than 0.2 responses per sec) on the second session was shaped by hand on the third session. During the following session, the total number of reinforcements that each animal had received on the FR 1 schedule was equalized (170 FR 1). During subsequent sessions, animals received identical training on increasing fixed-ratio values (100 FR 2; 100 FR 4; 100 FR 8; 100 FR 12; 200 FR 20). All sessions were started when the animal was placed in the box and terminated when removed. Therefore, animals had no experience with extinction during training. Initial training required 18 sessions.

Extinction. The animals were rank-ordered according to rates of responding during the last 4 training sessions and members of successive triads were randomly assigned to 3 groups of 6 animals. Fifteen-min extinction sessions were scheduled at 24 hr intervals. Extinction sessions began when the animal was placed in the box and terminated when removed. The feeder was disconnected during extinction and there were no programmed consequences other than the usual click from the lever each time it was depressed. Ten min prior to each extinction session, animals received an intraperitoneal (I.P.) injection of either saline or 24 mg/kg sodium pentobarbital. Group I received sodium pentobarbital prior to the first session only. Groups II and III received sodium pentobarbital prior to the initial 4 sessions and the initial 12 sessions respectively.

RESULTS

Responding in all animals was completely suppressed on the initial extinction session(s) during which high doses of pentobarbital were administered. However, during subsequent saline sessions extinction responding by all animals was characterized by periodic high rate performance alternating with periods of no responding. After 20 extinction sessions, the mean cumulative number of responses in extinction was similar for the 3 groups and the standard error of the means showed considerable overlap ($\bar{X}$ of G I = 838 ± 219; $\bar{X}$ of G II = 906 ± 241; $\bar{X}$ of G III = 742 ± 83).

EXPERIMENT 2: EXTINCTION WITH GRADUAL DRUG DISCONTINUATION

The data from Experiment 1 suggest that the absolute number of sessions over which responding has been suppressed by high, constant doses of pentobarbital has no effect on the total number of extinction responses. The purpose of Experiment 2 was to determine whether a regimen involving gradually decreasing dose schedules rather than constant dose schedules would differentially effect extinction responding. Extinction responding was examined as a function of experimental groups which differed with respect to the number of sessions over which the drug was decreased.

METHOD

The animals, apparatus, and details of training were

similar to Experiment 1. Thirty animals were used.

Extinction. Except for scheduling drug administration, details of extinction were similar to Experiment 1. Six animals were assigned to each group. Ten min prior to each extinction session, animals received an I.P. injection of either saline or sodium pentobarbital. A dose of 20 mg/kg sodium pentobarbital was given to all animals on the first session, and was decreased over successive sessions. Group I received 20 mg/kg on the first session, 10 mg/kg on the second, and saline thereafter. For Group II, the dose was decreased by 4 mg/kg on each succeeding session (i.e., 20 mg/kg; 16 mg/kg . . . 4 mg/kg). The dose for the Group III was decreased by 1.67 mg/kg on each succeeding session (i.e., 20 mg/kg; 18.33 mg/kg; 16.67 mg/kg . . . 1.67 mg/kg). Therefore, the 3 groups differed with respect to the rate at which the drug dose decreased over successive sessions. The experiment was discontinued after 22 extinction sessions.

RESULTS AND DISCUSSION

As in earlier experiments, extinction responding by all animals was characterized by periodic high rate performance typical of behavior generated by ratio schedules alternating with periods of no responding. After 22 extinction sessions, the mean cumulative responses in extinction was similar for the 3 groups and the standard error of the means showed considerable overlap ($\bar{X}$ of G I = 928 ± 181; $\bar{X}$ of G II = 753 ± 115; $\bar{X}$ of G III = 781 ± 224).

These data indicate that the absolute number of extinction sessions over which the drug dosage is decreased has no effect on the total number responses emitted in extinction. There was no significant difference in total extinction responding between the group in which the drug was progressively decreased over two sessions and the group in which the drug was progressively decreased over 12 sessions. This result was unexpected because it implies that the gradually decreasing dose schedule (fading) may not be important in reducing extinction responding. The effectiveness of any fading procedure should vary as a function of the size of the successive steps. If the successive steps become very large (the dimension is faded very rapidly), the fading procedure becomes similar to an abrupt change procedure, and it becomes less effective. In the current study, even when the successive steps became quite large, there was no apparent decrement in the effectiveness of the drug treatment. These data suggest that other drug schedules may be as effective as the fading porcedure in reducing total extinction responding.

EXPERIMENT 3: COMPARISON OF ABRUPT AND GRADUAL DRUG DISCONTINUATION

The results of Experiment 2 suggest that other drug schedules may be as effective as the graded dose procedure in reducing total extinction responding. However, since Experiment 1 did not include a saline control group, there is no information about the effectiveness of the abrupt discontinuation of drug treatment in decreasing total extinction responding. Experiment 3 was undertaken: (1) to determine whether the abrupt discontinuation schedule was effective in reducing total extinction responding, and (2) to compare the effect of the abrupt and graded dose schedules on pattern and number of responses in extinction.

METHOD

The animals, apparatus, and details of training were similar to Experiment 1. Thirty-six animals were used.

Extinction. Except for scheduling drug administration, details of extinction were similar to Experiment 1. Ten min prior to extinction sessions 1–15, animals received an I.P. injection of either saline or sodium pentobarbital. Group I (saline) received only saline injections. Group II (abrupt decrease) received 24 mg/kg sodium pentobarbital on Sessions 1–6 and saline injections on Sessions 6–15. Group III (graded decrease) received a dose of 24 mg/kg on the first session, which was decreased by 2.18 mg/kg on each succeeding session (i.e., 24 mg/kg; 21.82 mg/kg. . .2.18 mg/kg). Groups II and III received the same total amount of drug during extinction. No pre-session injections were given on session 15–20. The experiment was discontinued after 20 extinction sessions.

To minimize the possibility that physical dependence on pentobarbital and subsequent withdrawal would affect the extinction performance on Group II (abrupt decrease), post-session injections of pentobarbital were administered to the drug-treated groups (Groups II and III). Both groups received a dose of 20 mg/kg after the seventh extinction session, which was decreased by 2 mg/kg on each succeeding session. Therefore, the total amount of drug administered to these animals was gradually reduced over successive days. Group I (saline) received similar post-session injections of saline. Because of equipment failures during extinction 2 animals were discarded, 1 animal each from Groups I and II.

RESULTS

Figure 1 shows the number of responses during each extinction session for Group I (saline). Without exception, all Group I animals responded more on the first extinction session than on any subsequent session. The records of the saline animals typically show substantial responding during the first session with progressively fewer responses over the next few sessions and near zero responding thereafter. Little responding occurred on later extinction sessions.

Figure 2 shows the number of responses during each extinction session for Group III (graded decrease). These data show little or no responding during the first extinction session. Instead of the steep slope of the extinction function seen with the saline animals during initial extinction sessions, the records of Group III show response bursting during both early and later extinction sessions.

Figure 3 shows the number of responses during each extinction session for Group II (abrupt decrease). Responding was completely suppressed on the initial 6 extinction sessions during which high doses of pentobarbital were administered. On subsequent sessions, saline was administered prior to the session. Without exception, all Group II animals responded more on the first saline session than any subsequent session. The data from these animals typically show substantial responding during the first saline session with progressively fewer responses over the next few sessions and near zero responding thereafter. Little responding occurred in later extinction sessions. This pattern of responding in extinction is similar to that observed in Group I (saline).

As in earlier experiments, extinction responding by all animals was characterized by periodic high rate performance alternating with periods of no responding. The total mean

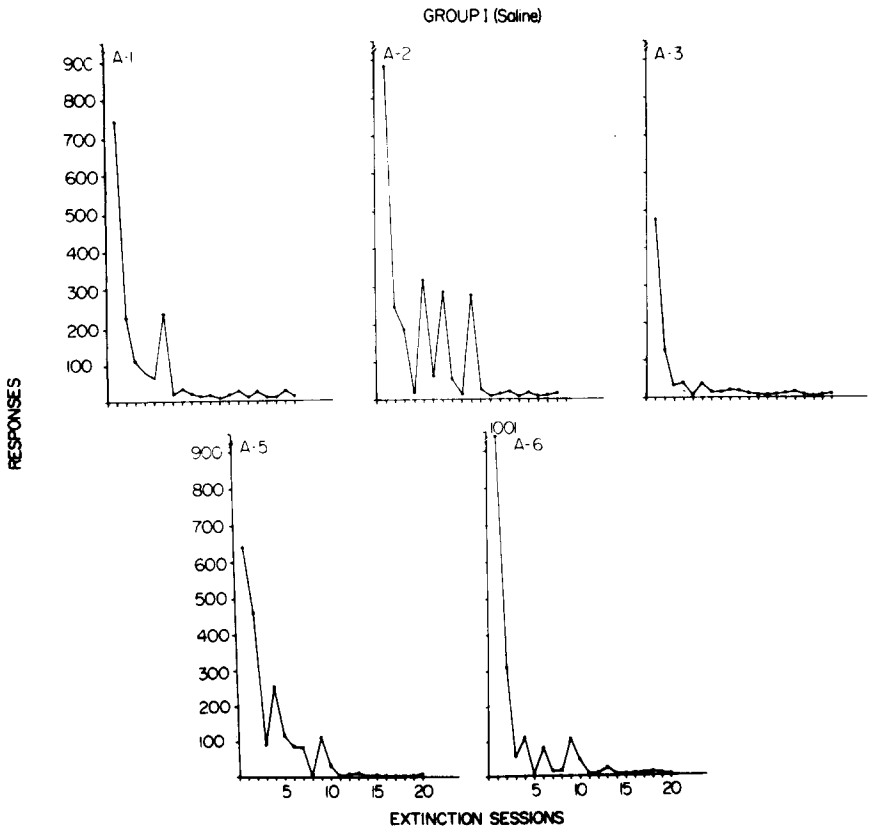

FIG. 1. Experiment 3. Responses for all Group I (saline) animals during each extinction session.

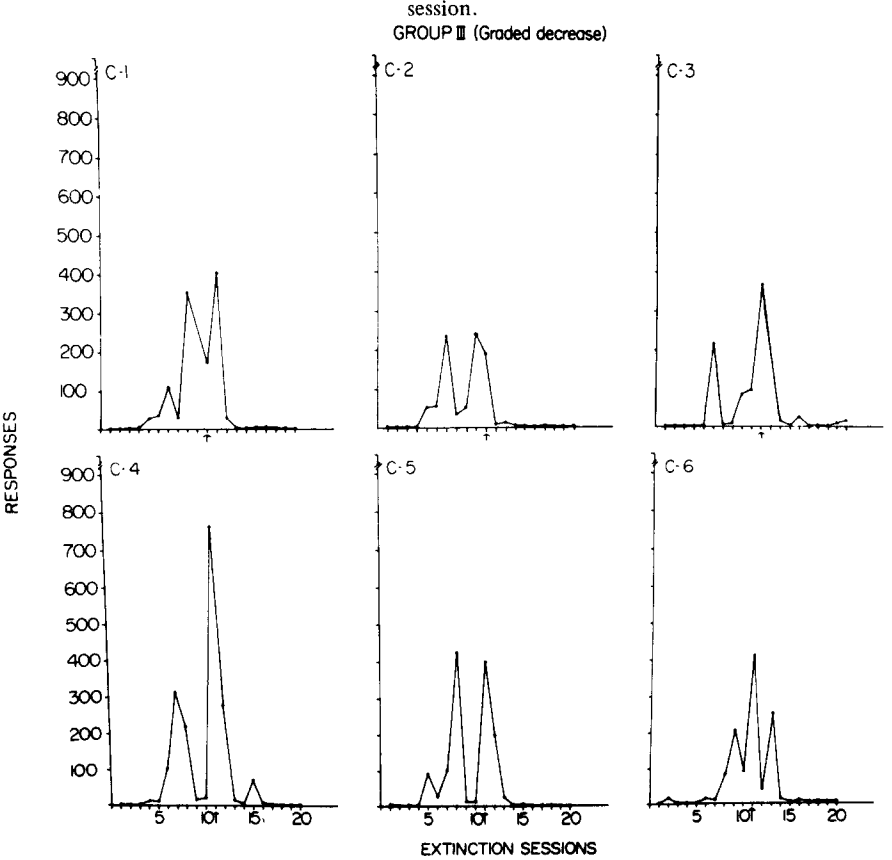

FIG. 2. Experiment 3. Responses for all Group III (graded decrease) animals during each extinction session. Arrows indicate last day that drug was administered.

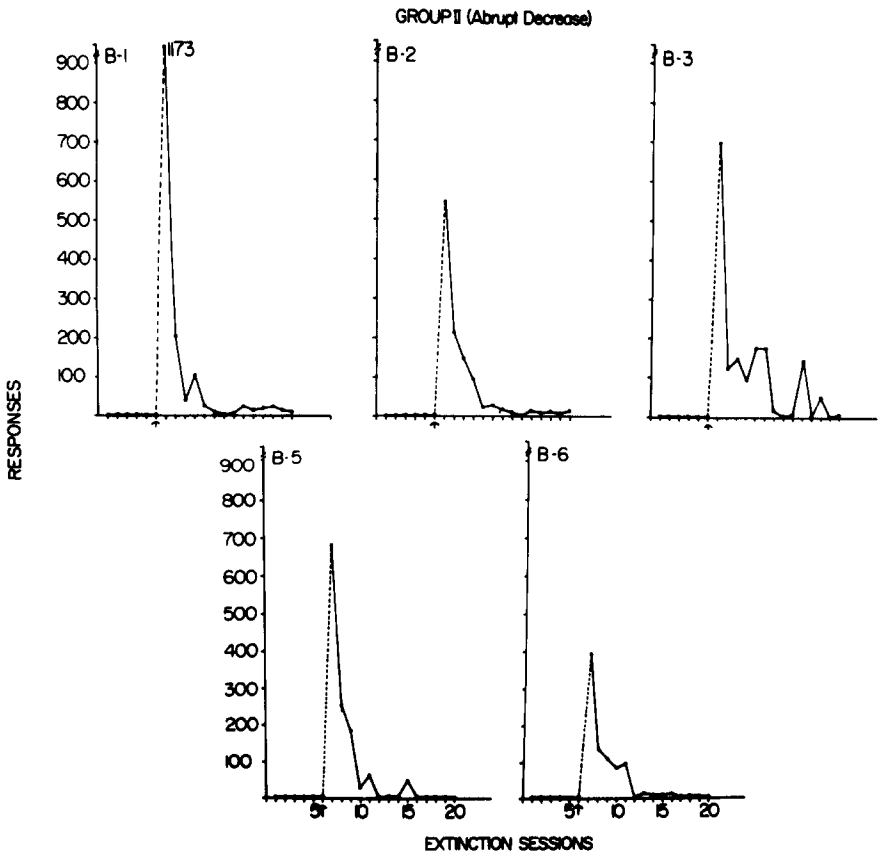

FIG. 3. Experiment 3. Responses for all Group II (abrupt decrease) animals during each extinction session. Arrows indicate last day that drug was administered.

cumulative responses in extinction for the drug-treated groups (Group II [abrupt decrease $\bar{X}$ = 1333] and Group III [graded decrease $\bar{X}$ = 1272]) was significantly lower than Group I (saline $\bar{X}$ = 1785) (t-test $p<0.05$). There was no significant difference in total responding between Group II (abrupt decrease) and Group III (graded decrease).

DISCUSSION

In Experiment 3 it was found that a schedule of abrupt drug withdrawal was as effective in reducing extinction responding as a gradually decreasing dose procedure. Although there was no difference in total extinction responding, the 2 drug schedules did produce different patterns of responding in extinction. As in previous experiments [2] animals treated with a pentobarbital graded dose procedure show little or no responding during the first extinction session and response bursting during later extinction sessions. Sessions with little or no responding alternated in an erratic fashion with sessions with much extinction responding. In contrast, the abrupt withdrawal dose schedule completely suppressed responding during the initial 6 drug sessions. On the first session of drug withdrawal (saline treatment) all animals responded more than on any other extinction session. Records of responding during this latter saline treatment typically show substantial responding during the first session with progressively fewer responses over the next few sessions and near zero responding thereafter. Except for the initial response suppression during drug treatment, this general pattern of responding is identical to that observed in animals which received only saline treatment.

In Experiments 1, 2 and 3 there is considerable variability in the grouped mean number of extinction responses between experiments. Such between-experiment variability was also apparent in three previously reported extinction experiments [2]. Although all 6 experiments utilized a similar training method, it is likely that between-experiment procedural variations accounted for the between-experiment differences. For instance, between the 6 experiments the number of training sessions varied from 17 to 24; the number of reinforcements received at FR 20 varied from 190 to 450; and the ratio of the number of animals retained to the number initially trained varied from 0.5 to 0.75.

EXPERIMENT 4: EFFECTS OF PENTOBARBITAL ON PROLONGED EXTINCTION SESSIONS

Since the absolute number of sessions of drug treatment had no effect on total extinction responding with an abrupt discontinuation schedule (Experiment 1) or a graded dose schedule (Experiment 2), this suggests that all abrupt and graded dose schedules will be equally effective in reducing total extinction responding. Thus, it is possible that a single session of drug-suppressed responding will be as effective in reducing total extinction responding as many drug sessions.

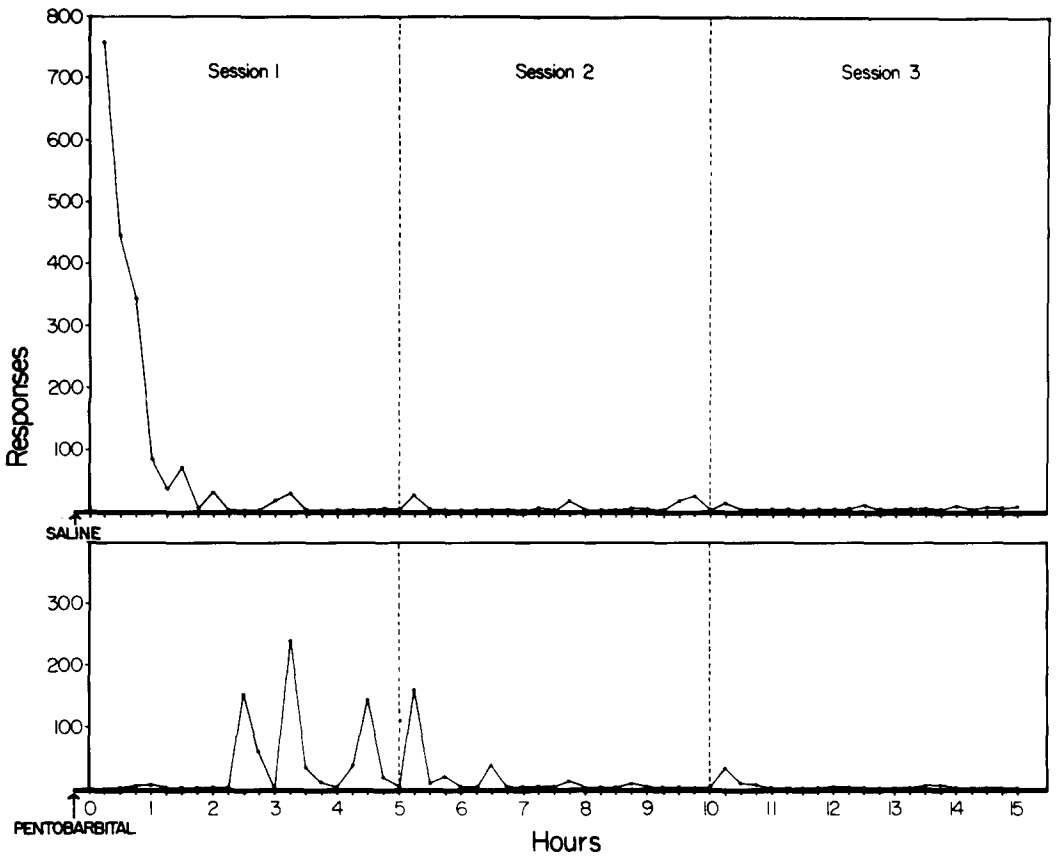

FIG. 4. Experiment 4. Pattern of extinction responding for a typical saline animal (upper record) and a typical pentobarbital animal (lower record). Arrows indicate injection of either saline or pentobarbital. Data are plotted for successive 15-min blocks of extinction.

Experiment 4 investigated the possibility that total extinction responding can be reduced if responding is suppressed only in the beginning of one extinction session.

METHOD

The animals and apparatus were similar to Experiment 1. Twenty-four animals were used.

Training. Initial training of the lever press response was similar to Experiment 1. During subsequent 55-min training sessions, animals were exposed to increasing fixed-ratio values (FR 2; FR 4; FR 8; FR 12; FR 16; FR 20). Animals remained on the FR 20 schedule for 7 sessions. This training procedure differed from previous training procedures in that the amount of training time at each FR value was held constant instead of the number of reinforcements. This change simplified the training procedure and therefore facilitated the training of large numbers of animals. The typical number of reinforcements received at each FR value was: (220 FR 1; 200 FR 2; 200 FR 4; 120 FR 8; 100 FR 12; 100 FR 16; 1000 FR 20). Initial training required 11 sessions.

Extinction. The animals were rank ordered according to rates of responding during the last 4 training sessions and members of successive pairs were randomly assigned to 2 groups of 9 animals each. Extinction sessions were of 5 hr duration. Ten min prior to the first extinction session, the pentobarbital group received 24 mg/kg, I.P. injection of sodium pentobarbital while the saline group received a similar injection of saline. No injections were given prior to the second or third extinction session.

RESULTS AND DISCUSSION

Extinction responding by all animals was chracterized by periodic high rate of performance typical of behavior generated by ratio schedules alternating with periods of no responding. Figure 4 shows the pattern of extinction responding during successive 15-min blocks for a typical saline animal and a typical pentobarbital animal. Without exception, all saline animals responded more during the first 15-min block of extinction than during any subsequent 15-min block of extinction. The records of saline animals typically show substantial responding during the first 15-min block with progressively fewer responses over the next few 15-min blocks and near zero responding thereafter. In contrast, records of the pentobarbital animals show little or no responding during the initial 15-min block of extinction. Instead of the steep slope of the extinction function seen with the saline animals, records of the pentobarbital animals show response bursting during later 15-min blocks of extinction.

The total mean cumulative responses in extinction for the pentobarbital group ($\bar{X}$ = 919) was significantly lower than that of the saline group ($\bar{X}$ = 1532) (t-test $p<0.001$).

Although the total mean responding for the saline group was considerably higher than that of the pentobarbital group, the pentobarbital animals responded significantly more than the saline animals during the second and third sessions (2 tail t-test $p<0.02$). This effect was particularly apparent during the first 15-min of Session 2. This effect may simply indicate that the drug had not been fully metabolized by the end of the first extinction session. Alternatively, this effect may be the result of an interaction of the state-dependent properties of pentobarbital with the stimulus control over responding.

GENERAL DISCUSSION

The set of studies indicate that total extinction responding can be reduced by drug treatment (Experiments 3 and 4; [2], Experiments 2 and 3). This effect has been obtained with 20–25 sessions of 15-min duration (Experiment 3; [2], Experiments 2 and 3) or 3 sessions of 5 hr duration (Experiment 4). Both the graded discontinuation dose schedule and the abrupt discontinuation dose schedule are equally effective in reducing extinction responding (Experiment 3). However, the absolute number of sessions of drug treatment by the graded dose schedule (Experiment 2) or the abrupt discontinuation schedule (Experiment 1) has no effect on total extinction responding. Drug state change may account for part of the reduced extinction responding since the effect is partially attenuated by administration of the drug in training ([2], Experiments 3 and 4). Although there is no difference on total extinction responding under the two dose schedules, the pattern of extinction responding is markedly different (Experiment 3). The graded dose procedure reliably produces little or no responding on the first extinction session with response bursting thereafter (Experiment 3; [2], Experiments 2, 3, 4). However, the abrupt discontinuation procedure produces complete response suppression during initial drug sessions followed by substantial responding on the first saline session with progressively fewer responses over the next few sessions (Experiment 3). Except for the initial response suppression, the pattern of extinction responding for the abrupt discontinuation procedure is identical to that observed when saline is administered in extinction (Experiment 3; [2], Experiments 1, 2, 3).

The current studies did not substantiate the initial rationale of using a drug fading procedure to reduce extinction responding. Previous work by Terrace [6] had demonstrated the efficacy of a stimulus fading procedure, and work by Sherman [5] had suggested that fading procedures may be used effectively with a drug as the relevant fading dimension. However, the current studies indicated that fading pentobarbital doses was no more effective in reducing extinction responding than abruptly discontinuing the dose (Experiment 3). Furthermore, the absolute number of sessions of drug treatment by the fading schedule had no effect on total extinction responding (Experiment 2). Finally, extinction responding was reduced by administration of pentobarbital before one 5 hr session (Experiment 4). Again, this does not support the contention that programmed drug fading is a relevant mechanism to the decreased extinction responding.

These findings have demonstrated that under a variety of experimental conditions pentobarbital can reduce extinction responding. One possible explanation of such results is that pentobarbital produces prolonged behavioral or pharmacological effects which affect extinction responding by some non-specific mechanism (i.e., alteration of sleep-wake cycle or metabolism). Data from previous research using similar training and extinction procedures argue against this interpretation [2], Experiment 3). In this experiment, 2 groups of rats were pretreated with injections of pentobarbital outside of the experimental situation for 4 days prior to extinction. Subsequently, 1 group received saline during extinction while the other received the graded dose schedule of pentobarbital during extinction. If pentobarbital affected extinction responding via prolonged effects on some non-specified mechanism, no difference would be observed between the groups. However, as in experiments without the pretreatment conditions (Experiments 3 and 4; [2], Experiment 2), subjects receiving pentobarbital in extinction responded significantly less than those receiving saline in extinction.

An interesting aspect of the current research is that it provides a comparison of extinction responding with and without drug treatment between extinction sessions of different durations. For instance, the effects of saline and drug treatment were examined on 15-min extinction sessions (Experiment 3; [2], Experiments 1, 2, 3); and on 5 hr extinction sessions (Experiment 4). Despite this 20-fold difference in parameter values, the pattern of extinction responding of the undrugged animals is very similar when plotted as a function of the amount of time in extinction. The greatest number of responses occur during the first 15 min of extinction with progressively fewer responses occurring during the next 2 hr and near zero responding thereafter (compare saline-treated animals in Figs. 1 and 4). Therefore, a major determinant of responding in extinction appears to be the absolute amount of time the animal has been exposed to the extinction contingency. Given this, it is informative to compare the effect of a single dose of drug on the 5 hr sessions with the graded dose schedule on the 15-min sessions. In both cases the effective drug level is decreasing with time. The drug dose is experimentally decreased over the shorter sessions and the drug is metabolized during the longer sessions. It is interesting that the pattern of extinction responding by these two schedules is remarkably similar. In both cases, the pattern is characterized by high rate performance alternating erratically with zero rates during successive 15-min periods (compare pentobarbital-treated animals in Figs. 2 and 4). The similarity of these data suggests that the effective drug level may interact with the absolute amount of time in extinction to produce a characteristic pattern of responding under pentobarbital.

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