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BRIEF COMMUNICATION

# Effects of Librium and Shock Controllability Upon Nociception and Contextual Fear[1]

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WARREN, D. A. AND R. A. ROSELLINI. *Effects of Librium and shock controllability upon nociception and contextual fear.* PHARMACOL BIOCHEM BEHAV 30(1) 209–214, 1988.—Controllable shock is known to exert less deleterious effects than does the equivalent exposure to inescapable shock. Recent findings have encouraged speculation that some of these effects may result from differences in the severity of fear produced by the shock experiences. In particular, mediation by gamma-aminobutyric acid has been implicated. In the present experiment, we examined the possibility that chlordiazepoxide (CDP) would attenuate the impact of shock in a manner similar to that of providing control over shock. As shown by others, CDP administered prior to shock treatment blocked the long-term analgesic response, as did the provision of control during shock. Furthermore, whereas animals given controllable shock subsequently exhibited less fear of the shock context than did yoked animals, CDP treatment prior to uncontrollable shock did not appreciably reduce the contextual fear subsequently shown. These results suggest that under some conditions, controllability attenuates the impact of stress by mechanisms other than those shared by benzodiazepine treatment.

Chlordiazepoxide Learned helplessness Analgesia Inescapable shock Benzodiazepines Stress

EXPOSURE to uncontrollable shock is known to have a variety of deleterious effects upon animals. Among these effects are deficits in the ability to acquire a novel response to escape or avoid shock [13, 18, 22], or to produce appetitive reinforcer delivery [3, 26–28, 39]. Further consequences include decreased activity [1, 15, 17], reduced aggressiveness [25, 41, 42], an antinociceptive response to subsequent shock [7,14], brain catecholamine changes [2, 35, 36, 40] and immune function impairment [16, 31, 37]. The degree to which the animal can exert control over shock is a critical factor, since exposure to the equivalent pattern and amount of escapable shock typically does not produce these effects. Because the uncontrollability of shock has been generally considered a necessary component, these deficits are collectively termed "learned helplessness" effects.

Manipulations which are believed to reduce the animal's level of fear during inescapable shock appear to protect the animal from some of the adverse effects otherwise observed [10, 20, 38]. Consequently, fear is implicated as an important factor in the production of learned helplessness. Animals for whom a signal predicts the onset of inescapable shock show greater fear of the signal than those for whom the signal predicts escapable shock [21,32], and inescapable shock supports greater contextual fear conditioning than does escapable shock [20,29]. These effects can be eliminated by the provision of a brief stimulus of which the onset occurs simultaneously with shock offset on each trial [20, 29, 32]. Thus, a "feedback" stimulus, marking the beginning of the intertrial interval during an inescapable shock session, can functionally resemble the escape response in its ability to attenuate fear. Importantly, the provision of a feedback stimulus during inescapable shock has also been shown to attenuate the learned helplessness effect as measured on a lever press escape test [38]. Indeed, Mineka, Cook and Miller [20] have argued that the factor of controllability may be important only insofar as it reduces fear via the pairing of shock offset with response-produced feedback.

Recent studies have shown that pharmacological treatments which affect fear or anxiety can enhance or attenuate learned helplessness effects in a manner consistent with the fear hypothesis. One such manipulation is the administration of benzodiazepines. Benzodiazepine agonists are believed to exert their anxiolytic effects by facilitating the action of gamma-aminobutyric acid (GABA) [4,12]. Drugan, Ryan,

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Minor and Maier [10] showed that administration of chlordiazepoxide (CDP, or Librium) 30 min prior to inescapable shock eliminated the learned helplessness effect 24 hr later as measured on tests for both shock-induced analgesia and shuttle escape performance. However, CDP was without appreciable effect if administered prior to the test only, suggesting that the helplessness effect does not depend upon the direct transfer of fear from training to test situations, but rather, that the level of fear reached at the time of shock treatment is the critical factor. Consistent with this, it was later reported that treatment with the anxiogenic benzodiazepine receptor ligand FG-7142 could mimic inescapable shock exposure in producing a shuttle escape deficit 24 hr later, and that this effect could be blocked by administration of the benzodiazepine competitive antagonist Ro15-1788 [8].

The results of Drugan and colleagues [8,10] are consistent with the findings of earlier investigations which also suggest an important role for GABA in learned helplessness [24,30]. Whereas this work begins to outline a relationship between GABA processes and the behavioral effects of inescapable shock, little is known about the mechanisms by which the ability to control shock antagonizes these effects. Presumably, however, if a reduction or inhibition of GABA activity underlies the learned helplessness effect, then one might expect that control over shock would in some manner enhance GABA action [9]. Consistent with this notion, the convulsant action of bicuculline is potentiated by prior inescapable shock, and antagonized by escapable shock [9]. Controllability over shock thus resembles treatment with benzodiazepine agonists in its ability to engender resistance to seizures induced by GABA blockade [12].

Given the suggestion that benzodiazepine agonist treatment and shock controllability share at least one common neural correlate (i.e., GABA enhancement), it is of interest to characterize behavioral tests which are more or less sensitive to differences between the treatments. Such information could uncover processes unique to controllability, over and above its role in suppressing fear at the time of shock training. The present experiment demonstrates such a dissociation in that both controllability and CDP treatment blocked the long-term analgesic response that is otherwise observed [10], yet only the provision of control over shock effectively inhibited the conditioning of fear to contextual cues.

## METHOD

### *Subjects*

The subjects were 60 experimentally naive male Holzman rats, weighing between 384 and 619 g on Day 1 of the experiment. Animals were housed individually under conditions of ad lib food and water. All procedures were conducted during the light phase of a 12 hr light/dark cycle.

### *Apparatus*

Four operant chambers were used for the placement, shock training, and fear test phases of the study. Each measured 21.0×30.5×27.9 cm, and was housed in a light- and sound-attenuating container equipped with a ventilation fan. The walls were constructed of aluminum, and the ceiling and door of clear Plexiglas. The floor consisted of stainless steel rods 3.0 mm in diameter and spaced by 1.2 cm. A response lever, measuring 3.0×1.0 cm, was centered on the front wall of the chamber, 3.8 cm above the grid floor and protruding 2.3 cm into the chamber. A 28 V DC houselight was located 29.0 cm above the grid floor and was centered on the front wall. White noise (78 dB, scale A) was delivered to each chamber by a speaker mounted behind the front wall. For the placement and fear test phases, a wooden platform (19.0×12.0×4.0 cm) was inserted into the rear of the chamber. A clear Plexiglas barrier was inserted between the platform and the remainder of the chamber in order to limit the animal's access when appropriate.

A tail-flick apparatus was used for the nociception test. This consisted of a 33.0×50.8 cm wooden platform into which a 1.0 cm diameter hole was cut. Two 2.5 cm long × 0.8 cm high strips of wood flanked the hole and provided a groove into which the animal's tail rested. A 150 W projector lamp, supplied with approximately 85 V AC through a variable transformer, was located 4.4 cm below the hole to provide radiant heat.

A shuttlebox was used to administer inescapable reinstatement shocks prior to the tail-flick test. This box measured 45.7×21.6×24.5 cm, with walls of aluminum, the ceiling of clear Plexiglas, and the floor of stainless steel rods 6.3 mm in diameter and spaced by 1.9 cm. The chamber was divided in half by an aluminum barrier providing a 10.8×6.3 cm opening at floor level.

Scrambled shock was delivered to the grid floor of the operant chambers and shuttlebox by solid-state shock sources (Coulbourn Instruments Model 13-16). Control of apparatus during shock exposure was implemented by a TRS-80 microcomputer.

### *Procedure*

This experiment consisted of five phases: (a) drug preexposure, (b) platform placement, (c) shock training, (d) nociception test and (e) fear test.

### *Drug Preexposure*

Procedures in this phase were modelled after those of Drugan *et al.* [10], and were included for the purpose of inducing tolerance to the sedative effects of CDP. For the first four days, all animals received daily intraperitoneal injections of 10 mg/kg chlordiazepoxide hydrochloride dissolved in isotonic saline solution, in a concentration of 5.0 mg/ml. On Day 5, all animals received a dose of only 5 mg/kg in order to minimize residual drug effects 24 hr later. This drug regimen is similar to that shown to result in tolerance to the sedative effects of CDP, but little or no tolerance to the anxiolytic effects [11].

### *Placement*

In this phase, animals were simply placed on the platform and retained there for 15 min. This session occurred on Day 5, prior to the final preexposure injection. Subjects were then assigned randomly to the five experimental groups (n=12).

### *Shock Training*

On Day 6, all animals received shock treatment. Group ES-S was given 80 trials of shock escape training (the first letter in the group designation refers to the type of shock, escapable or yoked; the second and third letters refer to saline or Librium treatment during shock and during the test phases). The initial 15 trials required a single barpress to terminate shock (FR-1), with the remaining 65 trials requiring two responses (FR-2). If an animal failed to meet the ratio criterion, shock was terminated 30 sec from onset. Trials were administered on a Random Time 90 sec schedule (range

60–120 sec). The remaining four groups received yoked inescapable shock such that each received the same pattern and duration of shock as animals in Group ES-S. Barpresses during shock in the yoked groups were recorded but had no programmed consequences. Shock intensity on all trials was 0.90 mA. Thirty min prior to the shock session, animals in two of the yoked groups (Groups YL-S and YL-L) received injections of 5 mg/kg CDP as on Day 5. Animals in the remaining yoked groups (YS-S and YS-L), as well as those in Group ES-S, received equivolume injections of saline vehicle.

*Nociception Test*

Procedures on Day 7 were also modelled after those of Drugan *et al.* [10]. To control for state dependency [23], animals in Groups YL-L and YS-L were given injections of 5 mg/kg CDP, whereas those in Groups YL-S, YS-S and ES-S were given equivolume injections of saline vehicle. Thirty min later, animals were placed into the shuttlebox and given five 5 sec, 0.6 mA inescapable shocks presented on a Fixed Time 60 sec schedule. It has been shown that these shocks are necessary to reinstate analgesia resulting from exposure to inescapable shock 24 hr earlier, but alone are insufficient to produce analgesia [19]. The tail-flick test was begun approximately 3 min following the fifth reinstatement shock. Each animal was restrained individually on the apparatus with its tail resting in the groove. Latency to deflect the tail following onset of the projector lamp was recorded for three trials separated by intervals of 1 min. If the animal failed to deflect the tail within 60 sec from lamp onset, the lamp was turned off and a latency of 60 sec was recorded for that trial. Latencies were averaged across trials to provide one unit of observation per animal.

*Fear Test*

The final phase commenced on Day 8 of the experiment and was conducted for four days. This test was identical to that which we have used previously [29] and was modelled after that employed by Mineka *et al.* [20]. It consisted of placing the animal on the platform for a 15 min period, then opening the door and allowing it 15 min of access to the chamber. As in the nociception test, Groups YL-L and YS-L received 5 mg/kg CDP 30 min prior to each fear test session for the purpose of controlling for state dependency, whereas the remaining groups received vehicle. Behavior was recorded on videotape and later scored to determine for each animal the total amount of time spent on the grid floor. Total grid time was defined as the sum of all grid episode durations during the session. An episode duration was defined as the elapsed time from the point at which the animal placed both rear paws onto the grid floor to the point at which the animal replaced both rear paws onto the platform. This measure is highly reliable and is believed to inversely reflect contextual fear [20,29]. A second observer, who was blind to each animal's group membership, scored one randomly chosen session for each of fifteen animals (three animals per treatment group) for the purpose of assessing inter-observer reliability. As expected, a high level of agreement was reached (r=.99).

## RESULTS

*Shock Training*

All animals in Group ES-S acquired the escape response as evidenced by the fact that no animal failed to escape more than twice during the last twenty trials. The mean escape latency per trial, and thus the mean duration of shock for yoked animals, was 4.96 sec. An analysis of variance (ANOVA) on the escape latencies in blocks of five FR-2 trials revealed a significant decrease across blocks, $F(12,11)=2.24$, $p=0.013$, indicative of a typical response acquisition function. The mean total number of responses given during shock by yoked animals was 75.3 for those given saline vehicle, and 48.8 for those given CDP (standard errors are 6.4 and 4.5, respectively). This difference is supported statistically, $F(1,46)=11.58$, $p=0.002$.

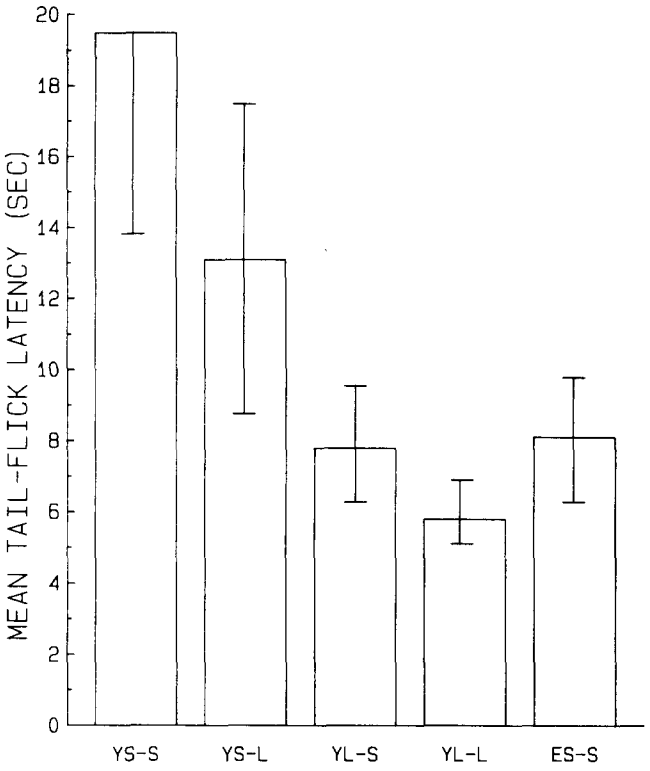


FIG. 1. Mean tail-flick latencies for the five groups (E=Escapable shock, Y=Yoked shock, S=Saline, L=Librium; vertical bars denote standard errors of the mean).

*Nociception Test*

Figure 1 depicts the mean tail-flick latencies for the five groups. As expected, animals given yoked shock with saline showed longer tail-flick latencies than animals given escapable shock or yoked shock with CDP. Animals receiving CDP on the test showed shorter latencies than those receiving saline vehicle, although this effect appears weak. An ANOVA performed on these data supported these observations, revealing significant differences among groups, $F(4,55)=2.67$, $p=0.041$. A set of four orthogonal contrasts was then conducted. The first compared Groups YL-S and YL-L to Group ES-S, because on the basis of the work of Drugan *et al.* [10] no significant difference was expected and indeed was not obtained, $F(1,55)<1.0$. The second contrast compared these three groups to Groups YS-S and YS-L in order to assess the effect of receiving yoked shock without benefit of CDP during shock training. This contrast proved significant, $F(1,55)=8.62$, $p=0.005$. To assess the effect of CDP given prior to the test, the third contrast compared Groups YS-S and YL-S to Groups YS-L and YL-L. This

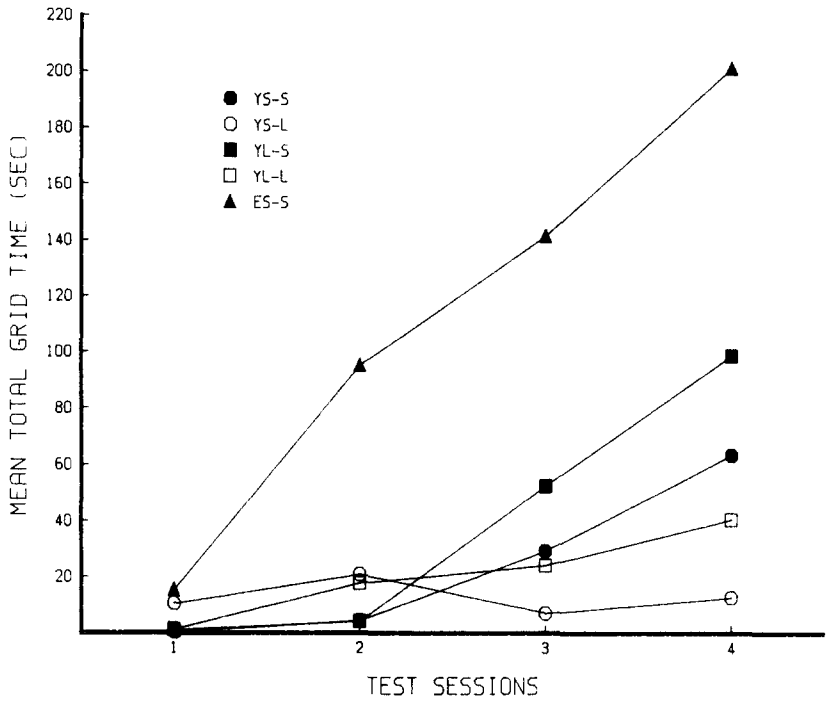


FIG. 2. Mean total grid time across fear test sessions for the five groups (E=Escapable shock, Y=Yoked shock, S=Saline, L=Librium).

contrast failed to reach significance, $F(1,55)=1.55$, $p=0.216$. The final contrast was conducted to assess the interaction of drug treatment prior to shock training with treatment prior to the test. Thus, Groups YS-S and YL-L were compared to Groups YS-L and YL-S. This contrast also was not significant, $F(1,55)<1.0$.

*Fear Test*

As shown in Fig. 2, all groups spent little time on the grid floor on the first day of the test. On subsequent sessions, Group ES-S dramatically increased grid time, reflecting the extinction of fear, whereas the increase was slight in the remaining groups. Among animals that received yoked shock, those treated with CDP prior to shock training had slightly higher grid time scores than vehicle-treated animals. Conversely, those treated with CDP prior to the test showed lower scores than their vehicle-treated counterparts. A group × sessions ANOVA supported these impressions, yielding significant effects of both sessions and groups, and the interaction between them, $F(3,165)=11.51$, $p<0.001$, $F(4,55)=3.81$, $p=0.008$, and $F(12,165)=2.07$, $p=0.022$, respectively. Simple main effect analyses of groups within each session were then conducted. This analysis showed significant effects at Sessions 3 and 4, $F(4,218)=3.55$, $p=0.008$, and $F(4,218)=6.68$, $p<0.001$. Four orthogonal group contrasts were conducted within these sessions. The first compared Groups YS-S and YS-L to Groups YL-S and YL-L in order to assess the effect of drug treatment prior to shock training. The second compared Groups YS-S and YL-S to Groups YS-L and YL-L to assess the effect of drug treatment prior to the test. The third contrast compared Groups YS-S and YL-L to Groups YS-L and YL-S to assess the interaction between the two drug factors. The final contrast compared Group ES-S to the remaining groups in order to assess the effect of providing control over shock during training. The effect of drug treatment during shock was not statistically significant on either Session 3 or 4, $F(1,218)<1.0$ and $F(1,218)=1.26$, $p=0.263$, respectively. The effect of drug treatment during the test was not significant on Session 3, but marginally significant on Session 4, $F(1,218)<1.0$ and $F(1,218)=3.72$, $p=0.052$, suggesting a possible sedative effect of the drug. The interaction between the two drug treatments did not approach significance on either session, $Fs(1,218)<1.0$. Finally, the effect of providing control over shock during training was statistically significant on both test sessions, $F(1,218)=12.86$, $p<0.001$ and $F(1,218)=21.74$, $p<0.001$, respectively.

## DISCUSSION

The results of the present experiment replicate those of Drugan *et al.* [10] in that animals that received either escapable shock, or inescapable shock with CDP, were less analgesic 24 hr later than were animals that received yoked inescapable shock without CDP. Furthermore, CDP administered prior to the tail-flick test did not significantly affect the analgesia otherwise evident in yoked animals. The lack of an interaction between drug treatment prior to shock training and treatment prior to the test discounts interpretations of the protective effect of CDP in terms of state dependent memory of the shock experience. The tail-flick data are thus amenable to the interpretation that fear during shock training is a necessary antecedent to the learned helplessness effect as measured in a test of pain sensitivity. The results of the fear test, however, appear initially to be at odds with the fear hypothesis. Whereas the present experiment replicated the finding that the provision of a means to affect shock offset attenuates contextual fear, as evidenced in the total amount of time the animals freely remained in contact with the grid

floor [20,29], there was only a faint trend to suggest that CDP administered prior to shock training had any effect upon the conditioning of fear to the context.

The failure to observe an anxiolytic effect of CDP may be viewed as consistent with several findings regarding the limits of benzodiazepines to suppress fear. Treit, Pinel and Fibiger [34], employing a conditioned defensive burying paradigm, showed that doses of diazepam which were effective in suppressing the burying response when a single 1.0 mA shock was given were ineffective when a 10.0 mA shock was used as the inducing stimulus. In a similar vein, Treit [33] reported that after chronic diazepam treatment, tolerance to the anxiolytic effect is not observed when a single 1.5 mA shock is used, but is evidenced when a 4.0 mA shock is employed. While differences in drug and test procedures preclude direct comparisons between the present experiment and those of Treit and coworkers [33,34], the possibility is raised that the dose of CDP administered in the present experiment is insufficient to suppress the fear generated by shock of the parameters employed. Assessment of the response over a range of doses would be required to address this issue. However, the possibility that a larger dose of CDP might have reduced fear conditioning does not weaken the present finding that the blockade of fear conditioning is unnecessary for the complete blockade of long-term analgesia.

There is a second possible reason for the present failure to observe an effect of CDP upon fear conditioning. Davis [6] administered either diazepam or vehicle prior to each of two sessions of signalled inescapable shock, and subsequently administered either diazepam or vehicle prior to a fear test. The test measured the potentiated startle response, which is defined as the increase in startle magnitude in response to a sudden novel stimulus as a function of the presence of the conditioned signal for shock. Drug treatment prior to the test attenuated the response, whereas drug treatment prior to the conditioning sessions was without detectable influence. It should be noted that the exact opposite result on a test for conditioned suppression of locomotor activity has also been reported [5]. Nevertheless, under some conditions benzodiazepines appear to suppress the performance of a fear response, without blocking the conditioning of fear.

The high level of fear displayed by Group YL-S in the present experiment is consistent with the suggested inability of benzodiazepines to inhibit fear conditioning under some circumstances. The suppression of fear in Groups YS-L and YL-L would thus appear to have been masked by the sedative effect of the drug. That sedation indeed occurred despite efforts to induce tolerance is suggested by the fact that CDP treatment prior to shock training decreased unconditioned barpress responding, and that treatment prior to the fear test decreased grid time.

Given that benzodiazepines may suppress the expression of fear while simultaneously allowing the conditioning of fear, the present results are not necessarily inconsistent with the fear hypothesis of learned helplessness. Indeed, the results of Drugan *et al.* [10] and of the nociception test in the present experiment suggest that it is not the transfer of fear to the test situation, but rather the experience of fear during shock training, that governs the learned helplessness effect on pain sensitivity. However, this conclusion, arrived at in large measure via the results of benzodiazepine treatments, must be tempered by the present finding that the effects of controllability are dissociable from those of benzodiazepine treatment on a test of conditioned contextual fear. While processes which may be common to controllability and benzodiazepine treatment, such as GABA enhancement, may well mediate the prophylactic effects of control in situations involving reexposure to shock (e.g., escape performance, reinstated analgesia), contextual fear conditioning appears to index distinct processes, not shared by benzodiazepine treatment, that are mobilized when control over stress is exerted.

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