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Librium Prevents the Analgesia and Shuttlebox Escape Deficit Typically Observed Following Inescapable Shock[1]

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DRUGAN, R. C., S. M. RYAN, T. R. MINOR AND S. F. MAIER. *Librium prevents the analgesia and shuttlebox escape deficit typically observed following inescapable shock.* PHARMACOL BIOCHEM BEHAV 21(5) 749–754, 1984.—Administration of a benzodiazepine, chlordiazepoxide (CDP), prior to exposure to inescapable shock prevented both the long-term analgesia and the shuttle-escape deficit typically observed following inescapable shock. If given only prior to testing, CDP had little effect. The protective effects of CDP were determined not to be a result of state dependency or a general facilitatory effect of the drug on escape performance. It is suggested that the induction of anxiety or fear by inescapable shock is critical in mobilizing endogenous changes such as transmitter depletion which are thought to be responsible for the deficits observed.

Librium Inescapable shock Anxiety Fear Analgesia Shuttle-escape deficit Learned helplessness

MANY of the consequences of exposure to a stressor are modulated by the degree of control (ability to alter the onset, termination, duration, intensity or temporal pattern) that the organism can exert over the stressor. Thus, organisms exposed to inescapable and unavoidable electric shocks later fail to learn to escape shock in a different situation in which escape is possible [28,41], become inactive in the presence of shock [1, 11, 12, 23], show reduced aggressiveness and dominance in a variety of situations [25, 35, 37, 38], become analgesic when reexposed to small amounts of shock 24 hours later [22,27], and show enhanced growth of implanted tumors [44,50]. On a neurochemical level, inescapable shock also produces a variety of changes not seen after exposure to escapable shock [2, 53, 54, 55]. These effects typically do not follow experience with equal amounts and distributions of escapable (controllable) shock and have been referred to as "learned helplessness" effects [28].

The most extensively investigated of these learned helplessness effects is the poor learning in tasks such as the shuttlebox escape deficit that follows exposure to inescapable shock [24, 28, 41]. Considerable research has been directed at an explanation of this phenomenon, and the role of a number of behavioral and physiological processes has been explored. For example, associative interference resulting from the learning of act-outcome independence [28] and catecholamine depletion [2,53] have received support as factors. However, two sets of recent findings suggest that anxiety or fear might be a more important mediational factor than has previously been supposed. First, inescapable shock seems to condition more fear to environmental cues present during shock than does escapable shock. Thus, a cue paired with shock produces more suppression of appetitive behavior if the shock is inescapable than if it is escapable [8]. Similarly, environmental contexts in which inescapable shocks occur produce more fear related behavior than do contexts in which escapable shocks occur [30]. It is reasonable to assume that inescapable shock produces more fear than escapable shock if inescapable shock leads to the conditioning of more fear than does escapable shock. Second, there is preliminary evidence indicating that the provision of a feedback stimulus following the termination of each of the inescapable shocks reduces the subsequent shuttlebox escape learning deficit [51], and this procedure seems to reduce the amount of fear produced by the shock [46].

If inescapable shock produces the learned helplessness effect in part because it induces more fear or anxiety than does escapable shock, then pharmacological agents that reduce fear or anxiety should reduce or eliminate the effect. The benzodiazepines are a particularly interesting group of compounds in this regard. Their anxiolytic action is produced by action on specific benzodiazepine recognition sites [34]. The benzodiazepine receptor appears to be functionally coupled to both a gamma-aminobutyric acid (GABA) receptor and an associated chloride ionophore [48], with a variety of interactions occurring between these elements. For example, GABA-mimetic compounds increase benzodiazepine binding, while GABA antagonists decrease benzodiazepine binding [18]. Conversely, benzodiazepines increase GABA binding and can facilitate GABAergic transmission [4]. It is believed that benzodiazepines do not mimic

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GABA but instead facilitate GABAergic transmission by sensitizing GABA receptors to the natural agonist [6]. Moreover, it has been proposed that it is the GABA system that mediates the anxiolytic action of the benzodiazepines [6], with increased GABAergic activity being responsible for anxiety reduction.

This relationship between benzodiazepine action and GABAergic processes is of special importance because several recent studies have implicated alterations in GABAergic processes in the production of learned helplessness. Petty and Sherman [36] found inescapably shocked animals to show a decrease in depolarization-induced release of GABA in hippocampal slices. Moreover, injection of bicuculline, an active GABA antagonist, into the hippocampus produced an escape learning deficit similar to that which results from inescapable shock, and an injection of GABA prevented the inescapable shock-produced escape deficit. Thus, benzodiazepines might be expected to prevent learned helplessness, both because they facilitate GABAergic processes as well as because they reduce fear or anxiety.

Sherman, Allers, Petty, and Henn [42] administered lorazepam 4 hours before exposure to inescapable shock. Escape learning was tested 2 hours later, and the lorazepam appeared to have a protective effect. Although encouraging, these findings are somewhat difficult to interpret. The experimental procedure involved only a 6 hour 40 minute interval between lorazepam administration and testing. Lorazepam has a long half-life [15] and it is quite possible that it was still effective at the time of escape testing. It is thus not possible to know whether the protective effect of lorazepam resulted from action during the exposure to inescapable shock, during testing, or both. Indeed, if the lorazepam was still effective during testing it might have facilitated escape performance directly rather than blocking learned helplessness. A group which receives the drug but no inescapable shock is required, but was not provided. In fact, if the lorazepam had cleared the system by the time of testing, the results could be attributed to a state dependency rather than to a specific anxiolytic action. This becomes a particularly troublesome possibility when it is recognized that what an organism learns during inescapable shock is critical in producing the learned helplessness effect. Thus, the prevention of a learned helplessness effect could have been due to a state dependent absence of the learning that had transpired during the inescapable shock. The absence of a group injected both before testing as well as before inescapable shock precludes an evaluation of a state dependency argument. Finally, the initial few injections of a benzodiazepine sometimes has sedative as well as anxiolytic effects, and these could have been responsible for the obtained outcome.

EXPERIMENTS 1A AND 1B

The purpose of the present experiment was to more systematically explore the effect of a benzodiazepine on the development of learned helplessness. A 24 hour interval between inescapable shock and testing was employed, so that effects produced during inescapable shock and testing could be separated. In addition, the experimental design was such as to allow evaluation of the possibilities of state dependence and direct drug action on shuttlebox escape performance. Thus, subjects were given a benzodiazepine either before inescapable shock, before escape acquisition testing, before both, or before neither. Finally, the possibility of sedative effects was reduced by providing a number of benzodiazepine administrations before the experimental treatment. There are numerous reports that tolerance to the sedative effects of benzodiazepines develop after only two or three treatments, while the anxiolytic action does not [13].

METHOD

Subjects

The subjects were 68 Holtzman-derived male albino rats bred at the University of Colorado. The subjects were 300–350 grams, maintained on a 12 hour light/dark cycle, and had food and water continuously available.

Apparatus

Inescapable shock or restraint occurred in Plexiglas restraining tubes which were 23.4 cm in length and 7.0 cm in diameter. The rat's tail extended from the rear of the tube and was taped to a Plexiglas rod. Unscrambled shock was delivered by shock sources modeled after the Grason-Stadler Model 700 through electrodes attached to the tail with adhesive tape and augmented with electrode paste. Rats were tested for escape performance in one of 4 two-way shuttleboxes 34.5×20.5×19.5 cm. The floors consisted of stainless steel grids 0.35 cm in diameter and spaced 1 cm apart. The shuttleboxes were divided into two compartments of equal size by a metal sheet which spanned the width of the box from floor to ceiling. A 5.2×5.5 cm archway was cut from the center of the metal sheet, allowing the rat access to the compartments. During the escape task, scrambled 0.6 mA shocks were delivered across the grid floors to each side of the shuttlebox by independent constant current shockers.

Procedure 1A

Thirty-six rats were randomly divided into 4 groups (N=9). All subjects first received 4 daily IP injections of chlordiazepoxide hydrochloride (CDP) dissolved in distilled water. The injections were 10 mg/kg at 2 ml/kg volume. This high dose was chosen because the purpose of these injections was to tolerate the sedative effects of the CDP. Such tolerance develops more rapidly with larger doses. On these days the subjects were weighed, injected, and returned to their home cages. On day 5 two of the groups were again injected with CDP but at a dose of only 5 mg/kg. This lower dose was used here in order to minimize the possibility of residual drug effects 24 hours later. Five mg/kg has been shown to be an effective anxiolytic dose in a variety of situations [7]. Thirty minutes following the injection, the animals were observed for any evident ataxia and then transported to another room and restrained in the restraining tubes. Here they received 80-5 second, 1 mA tailshocks delivered on a variable time schedule averaging 60 seconds (range 5–200 seconds). The remaining two groups received an equivolume injection of vehicle, followed by inescapable shock. On day 6, one of the groups which had received CDP on day 5 received only vehicle, while the other again received CDP. Similarly, one of the groups which had received vehicle now received CDP while the other again received vehicle. Thirty minutes later all subjects were placed in a shuttlebox in order to assess escape performance. A 5 minute adaptation period preceded the first trial. Trials were presented on a variable time 60 second schedule. A 2000 Hz tone which raised the background noise level from 70 dB to 75 dB began each trial. If no response occurred during the first 5 seconds of the tone, a 0.6 mA gridshock was applied and terminated upon

the execution of the required response. The shock automatically terminated if a response had not occurred after 35 seconds from tone onset. During the first 5 trials the rat was required to cross the shuttlebox once (FR-1) in order to terminate shock, while 2 crossings (FR-2) were required during the next 25 trials. It should be noted that responses during the 5 second warning stimulus are extremely rare, and so this task should be viewed as an escape task rather than an avoidance task. This task in which the rat has to cross back and forth to escape shock is a standard test for learned helplessness [24].

Thus, the design of this experiment was a 2×2 factorial with rats getting either CDP or vehicle before inescapable shock and either CDP or vehicle before escape testing 24 hours later. The CDP was at only half of the dose received during habituation, and so sedative effects should have been minimal.

Procedure 1B

The apparatus and general procedures were the same as in 1A. Thirty-two rats were assigned to one of 4 groups (N=8) in the same 2×2 factorial arrangement as in 1A. Thus, subjects received 4 daily injections of CDP at a 10 mg/kg dose and either a 5 mg/kg dose of CDP or only vehicle on day 5. The rats were again placed in the restraining tubes 30 minutes after injection, but no shock was delivered. Twenty-four hours later these rats received shuttlebox training as above, and training was preceded by either CDP or vehicle. So, experiment 1B differed from 1A only in that inescapable shocks were not presented on day 5. Experiment 1B thus allows an evaluation of the direct effects of CDP on shuttlebox performance, both when administered 24 hours and 30 minutes before testing. Experiment 1B is presented here as a separate experiment because it was conducted after 1A rather than concurrently.

RESULTS AND DISCUSSION

Figure 1 shows the mean latency to escape shock in the shuttlebox for each of the groups. The left panel of Fig. 1 depicts the results of Experiment 1A (the inescapably shocked groups) while the right panel shows the results of Experiment 1B (the restrained control subjects). The data points at the left of each panel represent the FR-1 trials and as is typical [24] there were no group differences. Focusing first on Experiment 1A, animals given saline injections before both inescapable shock and shuttlebox testing revealed the typical escape deficit on the FR-2 trials. However, CDP administered before the inescapable shock session markedly attenuated the escape deficit. CDP administered before the shuttlebox test session had an initial protective effect which dissipated across the 30 minute test session. Importantly, these effects appeared to be additive in that CDP administered before both inescapable shock and test sessions had a larger protective effect than at either time separately, and seemed to completely block the learned helplessness effect when compared to the non shocked controls. These impressions are confirmed by a repeated measures analysis of variance. The analysis revealed a reliable effect of CDP administered before inescapable shock, $F(1,32)=7.32$, $p<0.01$, and a reliable drug treatment × trials interaction, $F(4,128)=3.12$, $p<0.02$. Newman-Keuls individual group comparisons (α 0.05) found both the group given CDP before the inescapable shock session and the group given CDP before the inescapable shock and test session to differ from the saline control. The group given CDP before only the shuttlebox test session differed reliably from the saline control only on trial block 3.

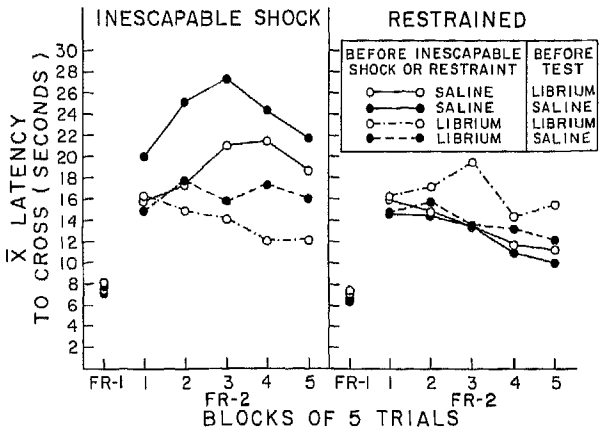

FIG. 1. Mean latency to escape across blocks of five shuttlebox test trials for subjects receiving either inescapable shock (left panel) or restraint (right panel) 24 hours prior to testing.

With regard to Experiment 1B, CDP had little if any effect on shuttlebox responding in non-inescapably shocked subjects. A repeated measures analysis of variance revealed a significant effect of only trials, $F(4,112)=6.84$, $p<0.001$.

The results of this experiment were quite clear. CDP administered before inescapable shock strongly attenuated the interference with escape responding that is normally produced by inescapable shock. The fact that Experiments 1A and 1B were conducted at different times makes it difficult to determine whether this blockade was complete. However, a comparison of the two inescapably shocked groups given librium before shock and before shock plus testing, with the restrained controls from Experiment 1B, does not yield a reliable difference ($F<1$). CDP administered before the test session rather than before inescapable shock did not have as clear an effect, but did tend to reduce the escape deficit somewhat, at least on early trials. Importantly, the present results cannot be attributed to sedation, state dependency, or a direct effect of CDP on shuttlebox behavior. The animals were observed, and the 4 prior CDP injections did eliminate ataxia. CDP did not have a detectable direct effect on escape performance when given either 24 hours or 30 minutes before the test session. State dependency would be indicated by a failure of CDP to block the learned helplessness effect when given before testing as well as before inescapable shock, and the opposite results were observed.

EXPERIMENT 2

Exposure to inescapable shock produces a variety of outcomes other than poor escape performance. Shifts in pain sensitivity/reactivity have been of particular recent interest [22,27]. Jackson, Maier, and Coon [22] reported that 5 mild footshocks resulted in an analgesic reaction on tail-flick and hot plate measures in rats that had received inescapable shock 24 hours earlier. In contrast, the 5 shocks did not produce analgesia in subjects that had received either escapable shock or no shock 24 hours earlier. This long-term

reinstated analgesia proved to have a number of interesting properties including complete reversibility by opiate antagonists [26], and cross tolerance with morphine [9]. Moreover, exposure to inescapable but not escapable shock led to exaggerated analgesic reactivity to morphine 24 hours later. In this context it can be noted that benzodiazepines have sometimes been found to antagonize systemically-induced morphine analgesia [52], and to produce an attenuation of morphine analgesia when administered directly into the ventricles or the periacqueductal gray [29]. The purpose of the present experiment was to determine whether CDP would prevent the long-term reinstated analgesia which follows 24 hours after inescapable shock exposure.

METHOD

Subjects

The subjects were 32 rats of the same age, sex, and strain as in the previous experiment. The weights of the subjects ranged from 300–350 grams.

Apparatus

The apparatus used to deliver inescapable shock was identical to that used in Experiment 1. Pain sensitivity/reactivity was assessed by measuring tail-flick latencies to radiant heat. The tail-flick apparatus consisted of a 43.0×17.7×8.0 cm metal box supporting a 7.4×3.0 cm aluminum plate. On each trial the rat's tail was placed in a shallow groove cut in the plate. A photocell receiver was located in this groove and automatically recorded a response when the rat flicked its tail out of the groove. A 5–7 mm deflection of the tail was required. A General Electric 150W projector spotlight was mounted above the tail and a light beam was focused on the rat's tail by a condenser lens. Voltage to the heat source was adjusted so that control latencies were in the 4–6 second range.

Procedure

All rats first received 4 days of CDP pretreatment as in the previous experiment. On day 5, two groups of 8 subjects each received CDP (5 mg/kg) and two groups received equivolume vehicle. Thirty minutes later all subjects were placed in the restraining tubes and given inescapable shocks exactly as described in Experiment 1. On day 6, one of the groups which had received CDP on day 5 was then again given CDP while the other group was given vehicle. Similarly, one of the groups which had received vehicle on day 5 was then again given CDP while the other group received vehicle. Thirty minutes following the injection, all subjects were given a baseline tail-flick test. The rat's tail was placed in the groove of the plate and the radiant heat was initiated. A trial terminated automatically if a flick had not occurred after 10 seconds. Immediately following the baseline tail-flick test all subjects were given five-5 second 0.6 mA reinstating gridshocks in a shuttlebox. This is the standard procedure used to produce long-term analgesia [22]. Prior work has shown that 5 shocks of this sort are insufficient to, by themselves, produce analgesia with this measure; the prior inescapable shocks are required [27]. All subjects were then given 7 tail-flick tests at 2 minute intervals. The experimenter was unaware of group membership during tail-flick testing.

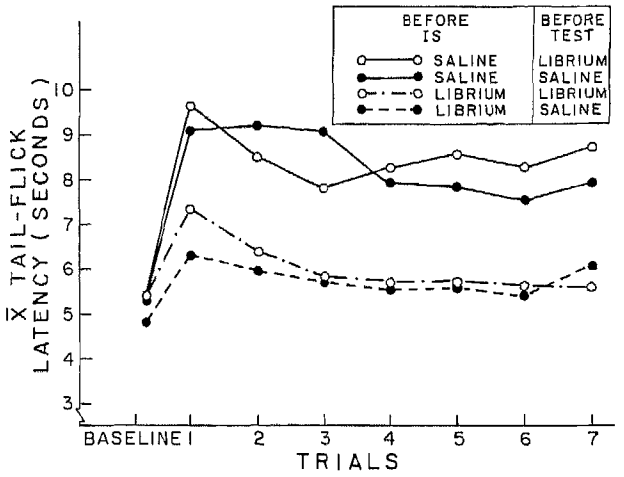

FIG. 2. Mean tail-flick latencies for all groups before 5 reinstating grid shocks (baseline) and after. Tail-flick trials were separated by a 2 minute interval.

RESULTS AND DISCUSSION

Figure 2 shows the mean tail-flick latencies for each of the groups. As usual, the 5 footshocks produced an analgesic reaction. The mean tail-flick latencies for saline controls rose from 5.2 to 9.5 seconds. Recall that the tail-flick trials are automatically terminated after 10 seconds, and a mean latency of 9.5 seconds is thus very close to the ceiling. Seven of the eight subjects in the saline group failed to flick by the 10 second cutoff on the initial trial. However, subjects which had received CDP before the inescapable shock session 24 hours earlier revealed only a very small increase in tail-flick latency following the reinstating gridshock. Thus, CDP given before inescapable shock was sufficient to strongly attenuate the long-term analgesia. In contrast, CDP given before the reinstating shocks and tail-flick testing had no effect. A repeated measures analysis of variance revealed a reliable effect of CDP administered before inescapable shock, $F(1,28)=41.72$, $p<0.001$, a significant trials effect, $F(7,196)=6.90$, $p<0.001$, and a significant drug treatment × trials interaction, $F(7,196)=3.96$, $p<0.01$. Newman-Keuls comparisons (α 0.05) yielded reliable differences between the two groups given CDP before the inescapable shock and the other two groups across the entire testing session.

GENERAL DISCUSSION

Administration of a benzodiazepine immediately prior to pretreatment with inescapable shock eliminated the deficit in shuttle-escape learning [24] and the long-term analgesia [22] that are typically observed upon reexposure to shock 24 hours later. These findings confirm and extend the report of Sherman *et al.* [42], but are not subject to interpretation in terms of state dependency or a direct action of the drug on escape performance. If elimination of helplessness effects was due to a change in drug-induced state from pretreatment to testing, shuttle-escape deficits and analgesia should have been greatest when CDP was administered in both experimental phases. As this outcome did not occur, the elimination of these deficits can not be attributed to a change in

state. Moreover, a direct action of CDP on shuttle-escape performance was evaluated directly, but was not found.

Shuttle-escape performance and long-term analgesia were influenced differentially when CDP was administered only prior to testing. Whereas the deficit in escape performance was attenuated under this condition, the analgesia was unaffected. Of course, it is possible that a different dose might have had a more dramatic effect, but these results stand in contrast to the complete blockade produced by the same dose when administered before the inescapable shock.

The present results support the notion that the production of anxiety or fear by inescapable shock might play a role in the generation of learned helplessness effects [3, 10, 31, 32, 53]. Inescapable shock is known to produce more fear than does equal amounts and distributions of escapable shock, and here administration of an anxiolytic before inescapable shock prevented the behavioral consequences that normally follow. The most obvious possibility is that the heightened fear in the inescapable shock subjects transfers to the test situation, either through a conditioning or sensitization process. That is, fear might become conditioned to cues present during inescapable shock that are also present during testing such as odor and handling cues [32,53], or some part of the fear production system might be sufficiently activated during inescapable shock so that it remains in a sensitized state for 24 hours [3]. In either case, the inescapably shocked subjects would be expected to be more fearful during testing than are control animals. Thus, excessive fear might be important in producing the behavioral effects observed.

However, the observation that CDP had only a small effect when administered before testing rather than before inescapable shock suggests that any potential role for anxiety or fear will not be this simple. If inescapably shocked subjects perform poorly in shuttlebox escape tasks and/or become analgesic because they are more fearful or anxious during testing, then benzodiazepine administration should have been equally effective before inescapable shock and testing. The present data suggest that anxiety or fear activation during the inescapable shock rather than the anxiety or fear level during testing might be the critical factor. That is, anxiety or fear might be important not because it transfers to the test situation and there exerts a direct effect, but rather because it sets into motion some other process (i.e., transmitter depletion) that is directly involved in the production of the behavioral outcomes here measured, and which is not restored by subsequent benzodiazepine treatment. CDP might have exerted its protective effect when given before inescapable shock by preventing this process.

GABA appears to be important in mediating the actions of the benzodiazepines [18,33]. As previously noted, the benzodiazepines bind to a specific receptor site that is coupled to a GABA receptor site and a chloride ionophore. The binding of a benzodiazepine to its site facilitates GABA binding and GABAergic transmission [19]. The augmentation of the response to GABA appears to be essential to the anxiolytic action of the benzodiazepines. For example, GABA receptor antagonists will eliminate the anxiolytic action of the benzodiazepines [5, 45, 49].

As noted earlier, a number of recent findings suggest that alterations in GABA might be important in generating the poor escape learning following inescapable shock. The present data support this possibility. However, GABA interacts with many other neurotransmitter and neuroendocrine systems, and the important function of GABA and the benzodiazepines in learned helplessness effects might be in its interactions with one or more of these systems. For example, it has been shown that inescapable shock depletes locus coeruleus norepinephrine, and it has been proposed that this depletion is critical in producing some of the behavioral outcomes which follow [53]. It is thus interesting to note that benzodiazepines are known to lower norepinephrine turnover and inhibit locus coeruleus activity, with GABA being the probable intermediate neurotransmitter [20,39]. Moreover, noradrenergic neurons of the locus coeruleus contain benzodiazepine/GABA receptors [16,21] thus suggesting direct GABA regulation of noradrenergic activity.

In sum, the present experiments support an involvement of anxiety, fear, and/or GABA in the production of analgesic and shuttle-escape learning deficits produced by inescapable shock. Due to the fact that GABA is involved in the regulation of many other systems, and is itself affected by many of these same systems (e.g., dorsal bundle norepinephrine inhibits GABA interneurons in the hippocampus), a cascade of events is suggested with the "rate limiting" step being as yet undetermined.

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