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BRIEF COMMUNICATION

Stressor-Provoked Response Patterns in a Swim Task: Modification by Diazepam[1]

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PRINCE, C R C COLLINS AND H ANISMAN *Stressor-provoked response patterns in a swim task Modification by diazepam* PHARMACOL BIOCHEM BEHAV **24**(2) 323–328, 1986 —When placed in a water-filled arena in which one area is illuminated mice tend to remain in the illuminated region Moreover, in a forced-swim task mice initially exhibit vigorous responding followed by a rapid decay of active swimming, and the adoption of a characteristic floating posture Immediately following exposure to inescapable shock the response invigoration was appreciably enhanced, as was the tendency to remain in the illuminated region of the arena Administration of low doses of diazepam (0 5 and 1 0 mg/kg) prior to testing effectively eliminated the response invigoration, as well as the response of approaching the illuminated region of the arena It is proposed that the behavioral variations evident soon after uncontrollable shock are related to a transient increase of anxiety or vigilance Moreover it is suggested that several time-dependent behavioral variations associated with inescapable shock may be related to alterations of anxiety

Stress Response invigoration Perseveration Diazepam

A wide range of behavioral deficits may be engendered by uncontrollable aversive events including disturbances of shock- and water-escape performance [17,19], disruption of appetitively motivated behaviors [25], alterations of responding for electrical brain stimulation [35], decreased responsivity in a test of analgesia [18], as well as variations of exploratory style [8] and social dominance hierarchies [34] Further, it was recently reported that uncontrollable footshock may result in the provocation of a perseverative response style wherein animals persist in adopting response strategies that had previously proved successful in terminating stressors [5] Indeed, mice will maintain these behavioral styles even when the effectiveness of such responses are diminished and more appropriate defensive responses are available

In addition to the response perseveration elicited by shock, it was shown that in some situations mice may exhibit a stimulus perseveration tendency, such that the propensity to remain in the vicinity of particular environmental stimuli is greatly enhanced Specifically, when placed in a water-filled V- or Y-maze in which one area was illuminated, mice tended to remain in the vicinity of the light while avoiding the nonilluminated region [9, 30, 31] Immediately after exposure to shock the time spent in the illuminated area was increased, and the frequency of entries into the nonilluminated area was reduced Within 24 hr of shock termination the enhanced preference for the illuminated region of the maze was absent [31]

In a forced-swim task, inescapable shock was shown to provoke time-dependent variations of motor excitation Soon after exposure to uncontrollable shock mice exhibited response invigoration, while 24 hr after the shock treatment mice engaged in active swimming for only brief periods, before adopting a floating posture [24] Likewise, it was demonstrated that in a shuttle-escape task performance deficits were not evident soon after shock of moderate severity and long duration (5 sec trains), whereas marked escape disturbances were seen 24 hr afterward It has been argued that although many of the behavioral disturbances seen after inescapable shock are due to variations of norepinephrine (NE), dopamine (DA), acetylcholine (ACh) and serotonin (5-HT), the expression of these deficits at short intervals after inescapable shock may be obviated owing to heightened arousal engendered by the stressor [4, 15, 16] Indeed, it was proposed that the motor excitation and stimulus perseveration seen in the swim task shortly after exposure to shock may reflect the anxiety or arousal provoked by this treatment

In accordance with the view that arousal contributes to the expression of performance deficits induced by inescapable shock, treatment with a benzodiazepine prior to inescapable shock treatment was shown to prevent an escape inter-

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ference in rats tested 2 hr afterward [29] More recently, it was demonstrated [11] that chlordiazepoxide administered prior to inescapable shock prevented the appearance of an escape interference ordinarily evident 24 hr later Of particular interest was the finding that drug treatment administered prior to the shuttle escape session was without effect on performance Thus, it was concluded that anxiety or fear engendered by inescapable shock is a necessary condition for the provocation of the neurochemical changes that subserve the escape interference Reducing anxiety or fear during the inescapable session precluded the development of the subsequent behavioral deficits Taken together, the results of the Drugan *et al* [11] study, and those of Anisman *et al* [4] and Glazer and Weiss [15,16] suggest that the arousal necessary for the development of neurochemical changes that promote subsequent behavioral disturbances, may be instrumental in preventing the expression of short-term behavioral deficits Furthermore, the possibility exists that the response invigoration and stimulus perseveration evident shortly after exposure to inescapable shock may be a reflection of the arousal or anxiety provoked by the aversive stimulation The present experiments were undertaken to determine whether treatment with a benzodiazepine would influence the response invigoration and stimulus perseveration engendered by inescapable shock

EXPERIMENT 1

When placed in a water-filled arena where one region is illuminated, mice tend to remain in the illuminated area for longer periods of time relative to that spent in the dark region This tendency is further enhanced in animals that were exposed to inescapable shock Unlike the escape interference induced by inescapable shock of moderate severity and long duration, the stimulus perseveration tendency is a transient one, no longer being evident within 24 hr of stressor termination [31] Inasmuch as the stimulus perseveration could be induced by a relatively small number of shock presentations [30] and was augmented by reducing water temperature [9], it was suggested that the perseveration was a reflection of anxiety engendered by the aversive situation Thus, it might be expected that treatment with a benzodiazepine, such as diazepam, which has been shown to modify other anxiety related behaviors [26], would likewise minimize the stimulus perseveration tendency

METHOD

Subjects

Eighty naive, male, CD-1 mice were obtained from Charles River (Canada) Ltd , Laprairie, Que, at 55–60 days of age Mice were housed in groups of 5 in standard polypropylene cages, and were acclimatized to the laboratory for 10–14 days prior to being used as experimental subjects

Apparatus

Foot-shock was delivered in three black Plexiglas chambers that measured 30×14×15 cm The floor of each chamber consisted of 0 32 cm stainless-steel rods spaced 1 0 cm apart (center to center) and connected in series by neon bulbs The end walls of the chambers were lined with stainless steel plates and connected to the grid floor Shock could be delivered to the floor through a 3000-V source, thereby providing relatively constant current Illumination of the chambers was reduced through a 0 63 cm red Plexiglas roof

Stimulus perseveration was monitored in a circular black Plexiglas pool that measured 86 0 cm in diameter and 30 0 cm in height Two 14 watt bulbs were located on one side of the pool, spaced 30 0 cm apart, 6 5 cm from the side of the pool and 5 0 cm above the water The pool was filled with water (20°C) to a height of 13 5 cm

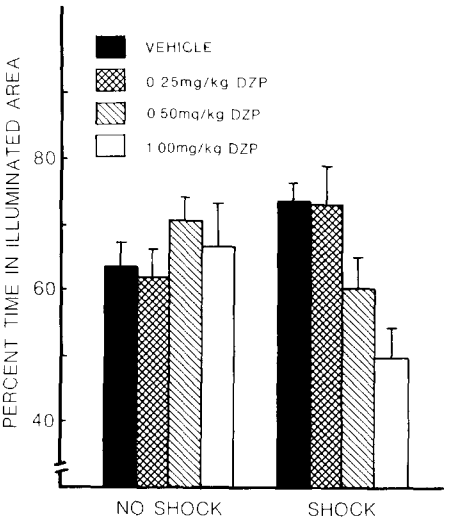

FIG 1 Percentage (±S E M) of time spent in the illuminated portion of a water-filled arena in mice that had been exposed to inescapable shock or no shock and treated with either diazepam (0 25, 0 5, or 1 0 mg/kg) or vehicle

Procedure

Mice received intraperitoneal injection of diazepam (0 25, 0 50 or 1 00 mg/kg) or vehicle on each of three consecutive days in order to permit adaptation to the sedative effects of the drug [14] On the fourth day mice were placed in the shock chambers and half the animals of each group were exposed to 180 shocks of 6 sec duration (150 μA, AC) at 16 sec intervals, while the remaining mice were not shocked Immediately thereafter mice (n=10/group) received intraperitoneal injection of diazepam (0 25, 0 50 or 1 00 mg/kg) or vehicle as they had on the 3 days prior to shock application Diazepam was dissolved in 40% propylene glycol, 10% alcohol and the final volume made up of saline Fifteen minutes after the drug treatment mice were placed individually in the center section of the pool, and the time spent in the illuminated and dark halves of the pool were recorded Mice received 3 trials of 1 min duration at intervals of 1 minute between trials

RESULTS

The analysis of the proportion of time spent in the illuminated portion of the arena revealed that performance was most affected during the first of the three test trials Analysis of variance of performance on this test revealed that time spent in the bright area varied as a function of the Shock Treatment × Drug interaction, $F(3,66)=5\ 74$, $p<0\ 01$ Consistent with earlier observations [31], Newman-Keuls multiple comparisons of the simple main effects revealed that in vehicle treated mice the shock treatment enhanced the propensity of mice to remain in the illuminated area (or con-

versely to avoid the dark area) Although the drug treatment did not influence the performance of nonshocked animals, in previously shocked animals the 0 5 and 1 0 mg/kg doses of diazepam significantly reduced the tendency to remain in the illuminated area relative to vehicle treated mice (see Fig 1) Indeed, at these doses the shocked animals spent less time in the illuminated area than did their nonshocked counterparts that received the same drug doses

In view of the finding that shuttle escape deficits are dependent on the duration of shock applied during the inescapable shock session [15,16], two additional experiments were undertaken to determine whether shock of brief duration (2 sec) would influence the preference for the illuminated area of the pool, and whether such an effect was modifiable by diazepam It was observed that 360 shocks of 2 sec duration (the procedure being otherwise identical to that of the previous experiment) significantly enhanced the preference for the illuminated area, $F(1,23)=8\ 76$, $p<0\ 01$, just as shock of long duration was effective in this respect Likewise, it was found that enhanced preference for the illuminated region of the arena was eliminated by treatment with an intermediate dose of diazepam (0 8 mg/kg) Thus, it appears that the consequence of inescapable shock and diazepam on the brightness preference are independent of the shock duration to which animals had been exposed, despite the fact that such procedures may be differentially effective in leading to learned motor response tendencies [4, 15, 16]

The effects of diazepam were not due to gross motor impairments engendered by the drug treatment An additional experiment was conducted (n=20) to assess whether repeated administration of diazepam over 4 consecutive days would influence the animals ability to grasp and hang from a 0 32 diameter bar Thus the procedure of Experiment 1 was repeated, but instead of testing mice in the swim task, the grasp response was assessed The analysis of variance confirmed that the Drug treatment reduced the grasping response, $F(3,16)=7\ 28$, $p<0\ 05$, and that performance varied over Test days, $F(3,16)=5\ 97$, $p<0\ 01$ Multiple comparisons confirmed that on the first test day a dose dependent reduction of the time mice could hang from the metal bar was observed (mean±S E M =10 20±2 43, 7 94±2 91, 5 68±1 51, 3 86±1 40 sec for vehicle, 0 25, 0 50 and 1 00 mg/kg groups, respectively) However, by the fourth test session performance of the 0 25 and 0 50 mg/kg doses (13 00±2 00, 11 30±1 89) did not differ from vehicle animals (13 80±0 73), while the 1 0 mg/kg dose (7 04±2 01) still influenced performance ($p<0\ 05$) Inasmuch as the 0 50 mg/kg dose did not impair gross motor ability, this factor clearly did not account for the effects seen in the swim task It will be noted as well that if mice were tested in the water task after only a single injection of diazepam, then several mice encountered difficulties in swimming, however, following repeated injection of the drug no such disturbances were evident even at the highest dose employed

EXPERIMENT 2

As indicated earlier, several minutes after exposure to inescapable shock mice display invigorated responding in a swim test Although this response style does not appear to be causally related to the stimulus perseveration, it was suggested that it may be reflective of the anxiety associated with the shock session [31] Accordingly, Experiment 2 assessed the effects of diazepam on the response invigoration provoked by inescapable shock

METHOD

Subjects and Apparatus

Seventy-four naive, male CD-1 mice, were employed The subject-characteristics were the same as those of Experiment 1 Likewise, the apparatus used to administer the footshock treatment was the same as that of Experiment 1 The swim test was conducted in three Pyrex beakers (height=25 cm, diameter=17 cm) filled with water (20°C) to a height of 17 cm The beakers were placed side by side, separated by nontransparent Plexiglas panels The swim performance in the three beakers was monitored simultaneously by a video recorder

Procedure

As in Experiment 1 mice received intraperitoneal injection of diazepam (0 25, 0 50 or 1 00 mg/kg) or vehicle on each of three consecutive days, and on the fourth day were exposed to either 180 shocks of 6 sec duration (150 μA, AC) at 16 sec intervals, or were placed in the apparatus without being shocked Immediately thereafter mice received intraperitoneal injection of diazepam (0 25, 0 5 or 1 0 mg/kg) or vehicle as they had on the 3 days prior to shock application Ten mice were represented in each of the groups, except the shocked and nonshocked mice in the 0 25 mg/kg dose, which had 8 and 6 mice, respectively Fifteen minutes after injection mice were individually placed in the water filled beakers for a 9 min period during which their behavior was monitored by videotape These recordings were subsequently used to determine the amount of time animals remained in a floating (immobile) posture Immobility was defined as floating without hind or fore-limb movement Occasionally mice displayed a single stroke of a hind limb, apparently to remain upright, a behavior which was still considered floating The animals were coded by numbers, and the experimenter who assessed the video recordings was unaware of the shock and drug treatment that mice had received It was previously observed [23] that within- and between-rater reliability in measuring the time floating varied less than 5 percent

RESULTS

The amount of time mice engaged in floating as a function of the treatment conditions is shown in Fig 2 Analysis of variance revealed that the time spent in a floating posture varied as a function of the Shock Treatment × Test period interaction, $F(2,144)=5\ 02$, $p<0\ 01$ Newman-Keuls multiple comparisons ($\alpha=0\ 05$) of the means comprising this interaction revealed that floating increased over time, but the magnitude of the increase was less pronounced in shocked than in non-shocked animals Accordingly, during the latter two periods the shocked animals exhibited significantly less floating than non-shocked mice In addition to the effect of shock, performance was influenced by the Drug treatment mice received, $F(3,72)=3\ 45$, $p<0\ 05$ Newman-Keuls multiple comparisons indicated that relative to vehicle treated mice, the amount of time engaged in floating was increased by the 0 5 and 1 0 doses of diazepam

Although the interaction between the Shock and Drug treatments did not reach statistical significance, multiple comparisons of the simple main effects were conducted since an *a priori* prediction had been made concerning this interaction These comparisons revealed that in nonshocked animals diazepam did not increase floating significantly, while in shocked animals a pronounced increase of floating

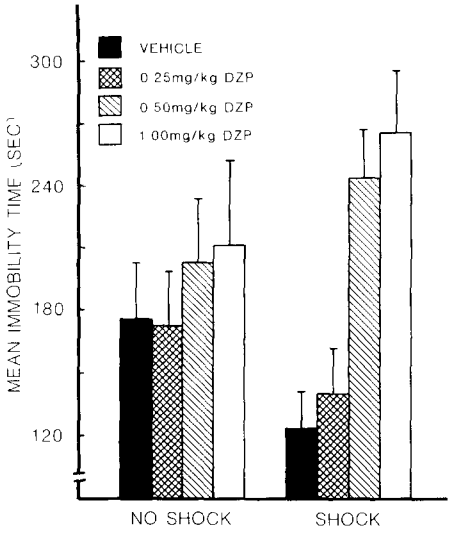

FIG 2 Mean (±S E M) immobility (floating) time in mice exposed to inescapable shock or no shock and treated with either diazepam (0 25, 0 50 or 1 0 mg/kg) or vehicle prior to testing in a forced swim task

was induced by the 0 5 and 1 0 mg/kg doses of the drug Indeed, as seen in Fig 1, the small excitation of performance seen in vehicle treated mice that had been exposed to shock was entirely absent after the 1 0 mg/kg dose of the drug In fact, at this dosage the shocked animals displayed somewhat more floating than their nonshocked counterparts Clearly, the behavioral excitation ordinarily observed shortly after exposure to inescapable shock was modifiable by treatment with diazepam

DISCUSSION

As previously observed [24], response invigoration was evident in mice that were tested in a swim task shortly after exposure to inescapable shock Moreover, the tendency of mice to remain in the illuminated portion of the arena and to avoid the dark region was intensified in mice that had been exposed to inescapable shock [31] The perseverative tendency, which we previously demonstrated does not occur in the absence of the water (i e , on land) may be a reflection of arousal (or hypervigilance) engendered by the stressor [5, 24, 31] Furthermore, it was proposed that the perseveration reflects a narrowing of the organisms defensive repertoire so that highly prepared responses predominate The perseveration is considered to be of adaptive significance when animals are tested in a task where escape can be accomplished through highly prepared responses or when the response requirements are relatively unambiguous, however, when the task requirements are fairly complex the perseverative response style may be counterproductive [5]

In accordance with the proposition that the motor invigoration and perseveration were a consequence of the anxiety engendered by the shock treatment, it was observed that diazepam reduced these response tendencies in animals that had been exposed to inescapable shock It will be noted that diazepam did not appreciably influence the time engaged in active swimming in naive animals, a finding commensurate with that of Porsolt, Pichon and Jalfre [22], which would suggest that the drug influenced responding by eliminating the anxiety associated with the previous shock treatment Further, since the tendency to remain in the illuminated area of the arena is unrelated to motor activity changes engendered by either shock or drug treatments [9,31], it is unlikely that alterations of the perseveration was secondary to motor changes (e g , freezing) engendered by the experimental manipulations It is noteworthy as well, that it is possible to dissociate the behavioral effects of diazepam from other pharmacological compounds in swim paradigms As observed by Crawley [10] in a test of locomotor activity and transitions between bright and dark areas of a field, the effects of anxiolytics were distinguishable from those of neuroleptics Contrary to the effects of diazepam in the present report, we previously observed that the DA receptor blocker, pimozide, reduced motor activity in a swim task, however, the tendency of mice to approach an illuminated area was not affected by this compound [9] These data not only divorce the perseveration from the motor effects of pharmacological treatments, but reveal some degree of behavioral specificity of the diazepam treatment

In assessing performance in a forced-swim task, catecholamine stimulants were previously shown to prevent the decay of active responding that is ordinarily evident [22,23] Likewise, the escape deficits introduced by inescapable shock were eliminated by catecholamine stimulants applied prior to either inescapable shock or the test session [6, 27, 28] In contrast, benzodiazepines were only effective in eliminating the escape interference if administered before the inescapable shock session [11,29] Together these findings suggest that independent mechanisms are responsible for the stressor related behavioral alterations, as well as time dependent performance variations associated with inescapable shock For instance, although inescapable shock reliably provokes deficits of shuttle-escape performance [6], such effects vary over time following shock application Immediately following shock of moderate severity the escape deficits are absent or minimal and become progressively more pronounced over time [4, 15, 16] It is conceivable that the heightened arousal or anxiety engendered by the stressor may prevent expression of the shuttle deficits that might otherwise be evident [24] The fact that benzodiazepines administered prior to inescapable shock prevented the long-term behavioral disturbances [11], suggests that the increased arousal (fear) may be fundamental in provoking neurochemical alterations which contribute to the subsequent behavioral disturbances Although the present investigation revealed that diazepam administered prior to testing influenced performance, it should be underscored that the initial shock and later test sessions were separated by only a brief period Thus, it is likely that the response invigoration and the perseveration were a reflection of the anxiety or vigilance associated with the preceding shock treatment

Several neurotransmitters have been implicated in subserving the behavioral effects of uncontrollable stressors Whereas Weiss *et al* [33] attributed the escape interference to norepinephrine alterations, Sherman and Petty [27] argued for a major role of 5-HT, while Anisman [1] suggested that DA, as well as NE, subserve the escape disturbances Additionally, it was suggested that DA variations contribute to motivational disturbances evident in uncontrollably shocked animals [35] In addition to these amines, there is reason to believe that GABAergic variations may contribute to stressor-provoked behavioral variations Indeed, it has been shown that aversive stimulation may influence GABA activity [21] and receptor binding [7], and GABA administration into the hippocampus altered behavioral disturbances

induced by inescapable shock [27,28] Inasmuch as the effects of benzodiazepines may be due to GABA variations [20], the possibility should be considered that the short-lived response invigoration and the tendency to approach light and avoid dark in the swim test, may be related to GABA activity Of course, this does not preclude a role for other transmitters in the mediation of the behavioral invigoration It has been reported that stressor-induced DA changes in frontal cortical areas were prevented by treatment with a benzodiazepine [12,13] Moreover, it was suggested that the actions of benzodiazepines on GABA neurotransmission may be influenced by DA activity [32] Thus, the possibility exists that the behavioral variations observed in the present investigation were DA mediated Nevertheless, the proposition should be entertained that the wide variety of behavioral changes associated with stressors probably involve alterations of several transmitter systems Moreover, the relative contributions of these transmitters may vary over time following stressor application Accordingly, in determining the behavioral changes associated with uncontrollable aversive events it may be essential to assess the conjoint effects of these different transmitters

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