

Prevention of “Learned Helplessness” in the Rat by Hydroxyzine

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ABSTRACT

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The effects of hydroxyzine (8, 16, and 32 mg/kg i.p.), administered either 30 min before exposing rats to a series of inescapable shocks (preventive treatment) or during the subsequent acquisition of a shuttle box avoidance response (curative treatment), were investigated. In these conditions untreated rats, previously exposed to inescapable shocks (“stress”), show a marked increase in escape failures in the shuttle box when compared with nonshocked control animals (“learned helplessness”). Control experiments examined the effects of hydroxyzine on memory (passive avoidance test) and on electric shock sensitivity. Diazepam (2 mg/kg i.p.) was used as a reference compound. Hydroxyzine, when administered before “stress,” clearly decreased at 8 and 32 mg/kg the number of escape failures observed but was without effect when administered after “stress” during the subsequent shuttle box avoidance learning. Similar results were observed with diazepam. Unlike diazepam, hydroxyzine at 32 mg/kg⁻¹ induced no amnesia in the passive avoidance test, whereas clear amnesia was observed with diazepam. Neither compound altered the rats’ sensitivity to shock. These results suggest that hydroxyzine decreases the effects of “stress” and that these effects cannot be attributed either to impaired memory for the aversive stimulation or to diminished shock sensitivity.

Key words: diazepam, atypical anxiolytics, stress, memory, shock sensitivity

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INTRODUCTION

"Learned helplessness" is a phenomenon first described by Seligman, who observed that some dogs exposed to a series of inescapable shocks were subsequently unable to learn to escape from shocks of similar intensity [Seligman and Maier, 1967]. Seligman suggested that the behavior deficits observed resulted from the animal having learned that it had no control over aversive environmental events [Maier and Seligman, 1976]. Although interpretations of this phenomenon have varied, there is a general consensus that exposure to inescapable shock represents a stress for the experimental animal [Anisman et al., 1979; Weiss et al., 1981].

Repeated administration of antidepressants both before [Sherman et al., 1979] and after [Sherman et al., 1982] exposure to inescapable shocks has been shown to decrease the escape deficits induced in rats in these conditions. In contrast to antidepressants, benzodiazepines are only active in attenuating "learned helplessness" when administered before the exposure to inescapable shocks (preventive treatment) but are ineffective when administered afterwards (curative treatment) during the learning test [Sherman et al., 1979; Sherman et al., 1982; Drugan et al., 1987]. This "anti-stress" effect of benzodiazepines in a "learned helplessness" model is shared by a more recent anxiolytic compound, buspirone [Drugan et al., 1987]. Buspirone, although clinically effective as an anxiolytic [Rickels et al., 1982], differs from the benzodiazepines in that it is virtually without releasing effects on behavior suppressed by punishment [McCloskey et al., 1987], the major behavioral sign of benzodiazepine-like activity.

The present experiments investigated the effects of another atypical anxiolytic, hydroxyzine, in a "learned helplessness" paradigm. Hydroxyzine has long been used for the control of anxiety [Shalowitz, 1961; Barranco and Bridger, 1977] and, in animals, decreases measures of spontaneous and fear-motivated active behavior [Olson and Whittaker, 1963; unpublished ITEM-Labo report to U.C.B., 1986] without inducing benzodiazepine-like release of punished behavior [unpublished ITEM-Labo report to U.C.B., 1986]. Hydroxyzine was administered either immediately before exposure to inescapable shock (preventive treatment) or after shock exposure during the learning of a shuttle box active avoidance task (curative treatment). Further experiments were then undertaken to determine whether hydroxyzine, in the dose range found effective in preventing "learned helplessness," affected memory in a passive avoidance task or modified the sensitivity of rats to electric foot shock. The supplementary experiments were aimed at evaluating alternative explanations that the antistress effects observed with hydroxyzine were due to drug-induced memory impairment for the shocks received or to decreased shock sensitivity.

MATERIALS AND METHODS

Animals

The subjects were male Wistar rats, weighing between 185 and 230 g on delivery, supplied by the Centre d'Élevage Roger Janvier (CERJ), 53940 Le Genest Saint Isle, France. They were delivered to the laboratory at least 3 days before the experiments and on arrival were housed in groups of five in transparent macrolon cages (41 × 25.5 × 14.5 cm) containing sawdust supplied by CERJ with free access to food (U.A.R. 113) and tap water throughout the experiments. They were kept in an ambient temperature of $21 \pm 1^\circ\text{C}$ under artificial lighting (12 hr) between 8:00 and 20:00.

Drugs

The following drugs were used: hydroxyzine hydrochloride (Union Chimique Belge), diazepam (Hoffmann-LaRoche), and morphine hydrochloride (Coopération Pharmaceutique Française). Hydroxyzine and morphine were dissolved in an aqueous solution of 0.9% NaCl (physiological saline), and diazepam was dispersed in an aqueous suspension of acacia gum

(5%). All drugs were injected in a volume of 0.5 ml/100 g body weight. Doses are expressed as salt or base where appropriate.

Learned Helplessness

The "learned helplessness" procedure was similar to that described by Martin et al. [1986].

Inescapable shock pretreatment. Electric foot shocks were delivered in $20 \times 10 \times 10$ cm chambers with Plexiglass walls and cover. The floors were stainless steel grids (1.5 cm mesh). A constant-current shocker was used to deliver 60 scrambled randomized inescapable shocks (15 sec duration, 0.8 mA intensity, every min \pm 15 sec) to the grid floor. Control rats were placed for 1 hr in identical chambers, but no shocks were administered. Inescapable shock pretreatment was performed in the morning on day 1.

Conditioned avoidance training. In order to evaluate interference effects, avoidance training was initiated 48 hr (day 3) after inescapable shock pretreatment in automated two-way Ugo Basile shuttle boxes ($60 \times 21 \times 30$ cm) with Plexiglass walls and a floor consisting of stainless steel rods spaced 1.0 cm apart. Each shuttle-box was divided into two equal-size chambers by a stainless steel partition with a gate providing access to the adjacent compartment through a 7×7 cm space.

Animals were placed singly in the shuttle box, were allowed to habituate to the test environment for 5 min (for the first session only), and were then subjected to 30 avoidance trials (intertrial intervals: 30 sec). During the first 3 sec of each trial, a light signal (used as a conditioned stimulus) was presented, allowing the animals to avoid shocks. If no response occurred within this period, a 0.8 mA shock was applied via the grid floor. If no escape response to the shock occurred within 3 sec, the shock and light CS were terminated, and an escape failure was recorded. The response (avoidance or escape) required of the rat was to cross the gate into the other compartment of the box. Only 3 sec was permitted for escape, since, although escape failure is defined as failure to escape within a 30–60 sec period in most procedures used for helplessness assessment, the very first seconds following shock onset seem to be critical for detecting interference effects in animals preexposed to inescapable shocks. Shuttle box sessions were performed for 3 consecutive days (days 3, 4, and 5) in the morning, and the number of escape failures was recorded.

Effects of hydroxyzine given after the stress induction (curative treatment). To assess the eventual antagonism by hydroxyzine of the deleterious effects of prior electric shocks on subsequent avoidance learning, different groups of rats were given repeated injections of hydroxyzine at the following daily doses: 8, 16, and 32 mg/kg i.p. The first injection (8, 16, and 32 mg/kg) was given 6 hr after stress induction on day 1 and then, at half the quantity per injection, twice a day in the morning (on days 3, 4, and 5, 30 min before the shuttle box session) and in the afternoon at 16:00 (except the 5th day, when 4, 8, and 16 mg/kg were given only in the morning). Each animal therefore received a total of eight injections. Diazepam (2 mg/kg per day, i.p.), administered in the same conditions, was used as a reference compound. The experiment included two control groups, a "helpless" control that received the same treatment as the drug groups except that instead of receiving a drug the animals received i.p. injections of physiological saline, and a "nonhelpless" control that received i.p. injections of physiological saline but was not exposed to inescapable shocks. Ten rats were studied per group, and the experiment was performed under blind conditions.

Effects of hydroxyzine given before the stress induction (preventive treatment). To assess the eventual prevention by hydroxyzine of the deleterious effects of stress on subsequent avoidance learning, different groups of ten rats were given a single i.p. injection of hydroxyzine 30 min before the inescapable shock session. The following doses of hydroxyzine were investigated: 8, 16, and 32 mg/kg. Diazepam (2 mg/kg) was used as a reference compound. Otherwise the procedure was identical to that described in the experiment above

with "helpless" and "nonhelpless" controls. Ten rats were studied per group, and the experiment was performed under blind conditions.

Passive Avoidance Test

The passive avoidance procedure was similar to that described in the mouse by Lenègre et al. [1988a].

During the afternoon of the day preceding the experiment, all animals were subjected to a preliminary handling consisting of weighing, marking, and an i.p. administration of physiological saline (0.9% NaCl).

On the first day of the experiment (learning session, S1) each rat was introduced into the smaller lighted compartment (17 × 17 × 34 cm) of a two-compartment box. When it crossed to the larger, darker compartment (49.5 × 31.5 × 34 cm), it received a continuous foot shock (0.75 mA) (Apelex, Bagneux-France; ref.: 01 1346) until it returned to the lighted compartment. The step-through and escape latencies were recorded. Twenty-four hours later, the rat was replaced in the lighted compartment, and the step-through latency was recorded with a cut-off at 180 sec (S2).

A longer latency at S2 would indicate that the rat remembered the shock received 24 hr previously. In animals that received an injection of an amnesic agent before S1, a shorter step-through latency at S2 would indicate reduced memory for the shock.

Hydroxyzine was investigated at the following doses: 8, 16, and 32 mg/kg administered i.p. 30 min before S1. Diazepam (2 mg/kg i.p.), administered in the same conditions, was used as a reference compound. These doses were the same as those used in the "learned helplessness" experiments described above. The experiment included one control group that was treated similarly to the drug groups except that the animals received an injection of physiological saline. Twenty animals were studied per group, and the experiment was performed under blind conditions.

Foot Shock Sensitivity Test

The technique is based on that described by Charpentier [1961].

Rats were placed individually into a transparent cage (49.5 × 31 × 34 cm) with a grid floor connected to an electric shock generator (Apelex, Bagneux-France; ref. 01 1346), which transmits a brief electric shock (0.5 sec) to the animal's paws. Four intensities (0.5, 1, 2, and 4 mA) were investigated. Three shocks were given at each intensity before proceeding to the next higher intensity. The shocks were spaced at 30 sec intervals.

Response to electric shock was quantified using a scale incorporating three parameters scored 0–3: jump, vocalization, and flight. The total score obtained for all three parameters at each intensity was taken as a measure of shock sensitivity.

Hydroxyzine was investigated at the following doses: 8, 16, and 32 mg/kg administered i.p. 30 min before the test and compared with diazepam (2 mg/kg). These doses were the same as those used in the "learned helplessness" experiments. Morphine (16 mg/kg i.p.), administered in the same conditions, was used as a reference compound. The experiment included one control group, which instead of receiving a drug was given i.p. injections of physiological saline. Ten animals were studied per group under blind testing conditions.

Statistical Tests

All data were analyzed for overall statistical significance using parametric analysis of variance followed by individual comparisons with the control groups using a two-tailed Dunnett's *t* test.

NUMBER OF ESCAPE FAILURES

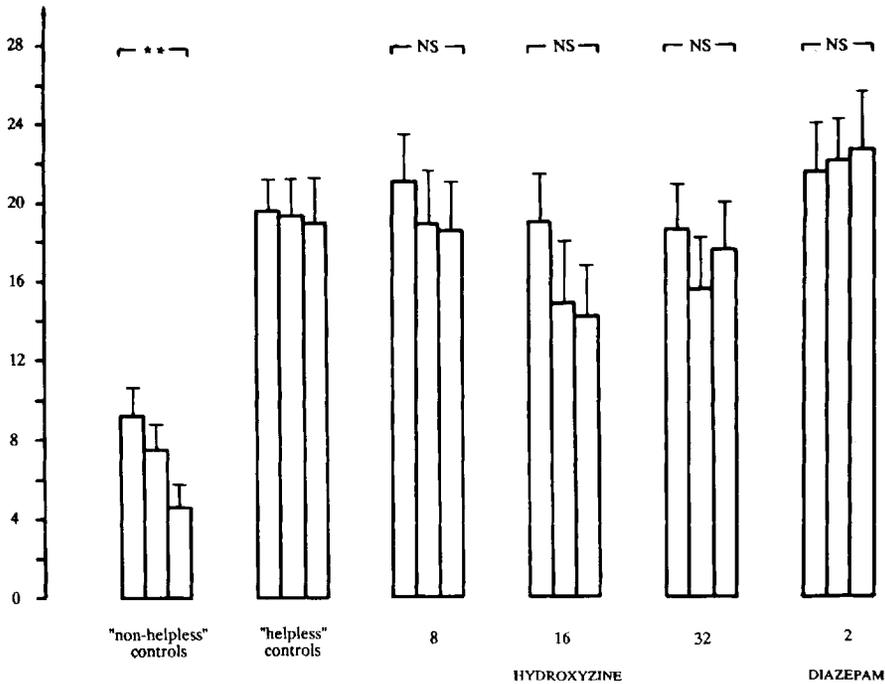


Fig. 1. "Learned helplessness"—curative treatment. The effects of repeated administration of hydroxyzine and diazepam given during avoidance learning on the mean (\pm SEM) number of escape failures during three consecutive acquisition sessions (columns 1, 2, and 3 per treatment). The maximum number of escape failures was 30 per session. The drugs were given i.p. twice daily 30 min before training in the morning and at 16:00 in the afternoon. Doses are expressed as mg/kg per day. The total escape failures for each group ($n = 10$) were compared with the "helpless" controls using Dunnett's t test. NS, not significant. **, $P < 0.01$ (two-tailed).

RESULTS

"Learned Helplessness": Effects of Hydroxyzine and Diazepam Given After Stress Induction (Curative Treatment)

The effects of hydroxyzine given during the acquisition of the active avoidance response are shown in Figure 1. The analysis of variance showed a highly significant overall difference between the treatments ($F = 7.33$; $df = 5,54$, $P < 0.001$). Individual comparisons showed that there was a highly significant difference between the "helpless" and "nonhelpless" controls (Dunnett's $t = 8.209$; $df = 6,54$, $P < 0.01$); "helpless" controls made considerably more escape failures than "nonhelpless" controls. Furthermore, "nonhelpless" controls decreased the number of escape failures over the three acquisition sessions, whereas "helpless" controls continued to make the same number of escape failures over the three sessions. These results indicate that clear and lasting behavioral deficits ("learned helplessness") were induced in control animals by exposure to inescapable electric shock.

Neither hydroxyzine at any of the doses tested (8, 16, and 32 mg/kg per day) nor diazepam (2 mg/kg per day), when administered repeatedly during the course of avoidance acquisition (curative treatment), significantly affected the total number of escape failures during three acquisition sessions in rats previously exposed to inescapable shock. These rats,

NUMBER OF ESCAPE FAILURES

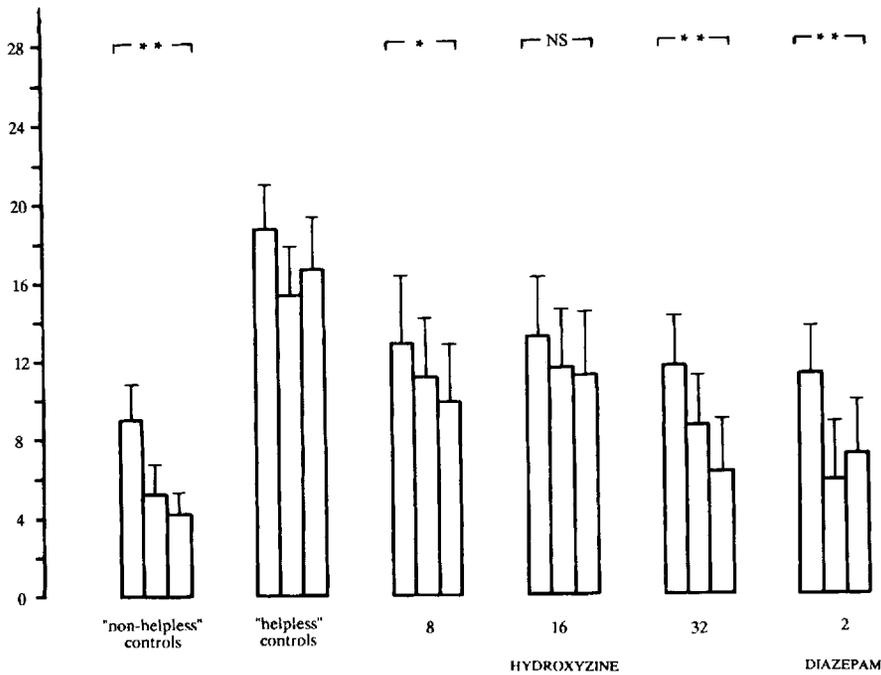


Fig. 2. "Learned helplessness"—preventive treatment. The effects of a single administration of hydroxyzine or diazepam given i.p. 30 min before exposure to prior inescapable shock on the mean (\pm SEM) number of escape failures during three consecutive acquisition sessions (columns 1, 2, and 3 per treatment). The maximum number of escape failures was 30 per session. Doses are expressed as mg/kg. The total escape failures for each group ($n=10$) were compared with the "helpless" controls using Dunnett's t test. NS, not significant. *, $P < 0.05$; **, $P < 0.01$ (two-tailed).

like the "helpless" controls, continued to make an important number of escape failures during the three acquisition sessions.

"Learned Helplessness": Effects of Hydroxyzine and Diazepam Given Before Stress Induction (Preventive Treatment)

The effects of hydroxyzine given once 30 min before exposure to inescapable shock (preventive treatment) are shown in Figure 2. Although the overall analysis of variance did not show a significant difference between the groups in the total number of escape failures over the three acquisition trials ($F = 2.07$; $df = 5,54$; $P < 0.084$), individual comparisons showed a highly significant difference between the total number of escape failures in the "helpless" and "nonhelpless" control groups (Dunnett's $t = 5.13$; $df = 6,54$; $P < 0.01$); as in the first experiment, "helpless" controls made considerably more escape failures than "nonhelpless" controls and continued to make a high number of escape failures throughout the acquisition.

In contrast to the results obtained with curative treatment, preventive treatment with hydroxyzine before exposure to inescapable electric shock tended to decrease the total number of escape failures made during acquisition in comparison with "helpless" controls. This effect was statistically significant at the doses of 8 mg/kg^{-1} (Dunnett's $t = 2.70$; $df = 6,54$; $P < 0.05$) and 32 mg/kg (Dunnett's $t = 3.84$; $df = 6,54$; $P < 0.01$) and was most marked at the third acquisition session for all three doses. Diazepam (2 mg/kg), like hydroxyzine, also

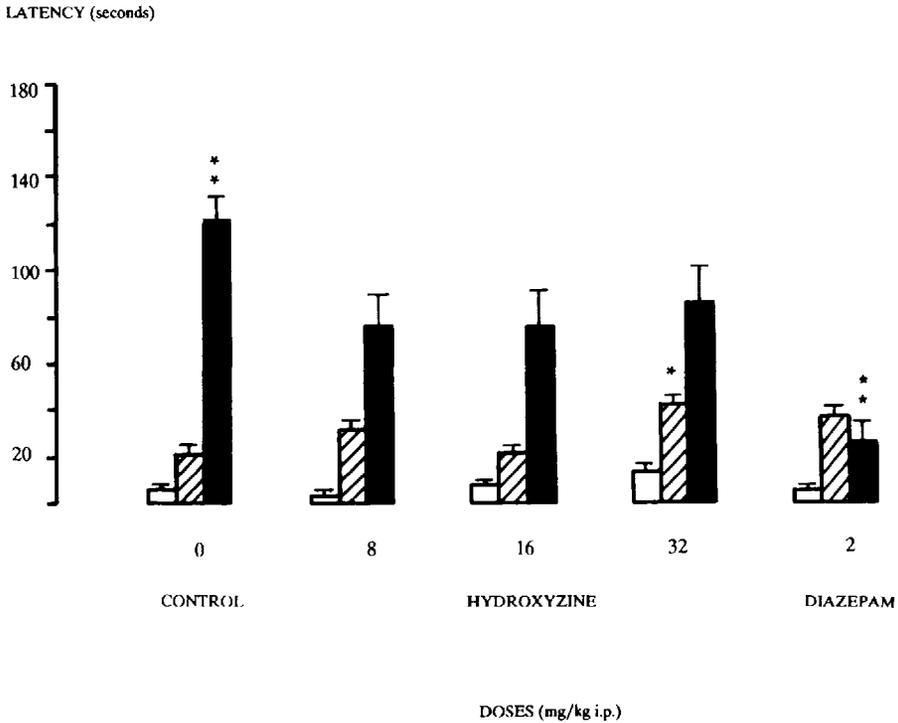


Fig. 3. Passive avoidance test. The effects of hydroxyzine and diazepam given i.p. 30 min before the first session (S1) on the mean (\pm SEM) S1 step-through latencies (blank columns), S1 escape latencies (cross-hatched columns), and S2 step-through latencies (black columns) of a passive avoidance task ($n = 20$ per group). The S1 and S2 latencies in the control group were compared using a Student's t test (paired sample). The treated groups were compared with the control group for each parameter using Dunnett's t test. *, $P < 0.05$; **, $P < 0.01$ (two-tailed).

significantly decreased the total number of escape failures during the three acquisition sessions (Dunnett's $t = 3.89$; $df = 6.54$; $P < 0.01$).

Passive Avoidance Task: Effects of Hydroxyzine and Diazepam on Memory

The effects of hydroxyzine and diazepam on performance in the passive avoidance task are shown in Figure 3. Analysis of variance of the two measures taken during S1 (step-through latency, escape latency) indicate an absence of statistically significant overall differences in the step-through latencies ($F = 2.27$; $df = 4,95$, $P > 0.05$), but a statistically significant overall difference between the escape latencies ($F = 2.582$; $df = 4,95$; $P < 0.05$). Individual comparisons reveal no significant drug effects on the step-through latencies as compared with the control group, whereas with the escape latencies a slight but statistically significant increase was observed with hydroxyzine at 32 mg/kg^{-1} (Dunnett's $t = 2.54$; $df = 5,95$; $P < 0.05$).

At S2 there was a marked and highly significant increase in the step-through latency as compared with S1 in the non-drug-treated control group ($t = 8.210$; $df = 18$; $P < 0.001$), suggesting that the animals had remembered the shock received 24 hr previously. Overall analysis of variance of the S2 step-through latencies showed a highly significant effect of treatments ($F = 5.280$; $df = 4,95$; $P < 0.001$). Individual comparisons indicate that there was

BEHAVIORAL RESPONSE SCORE

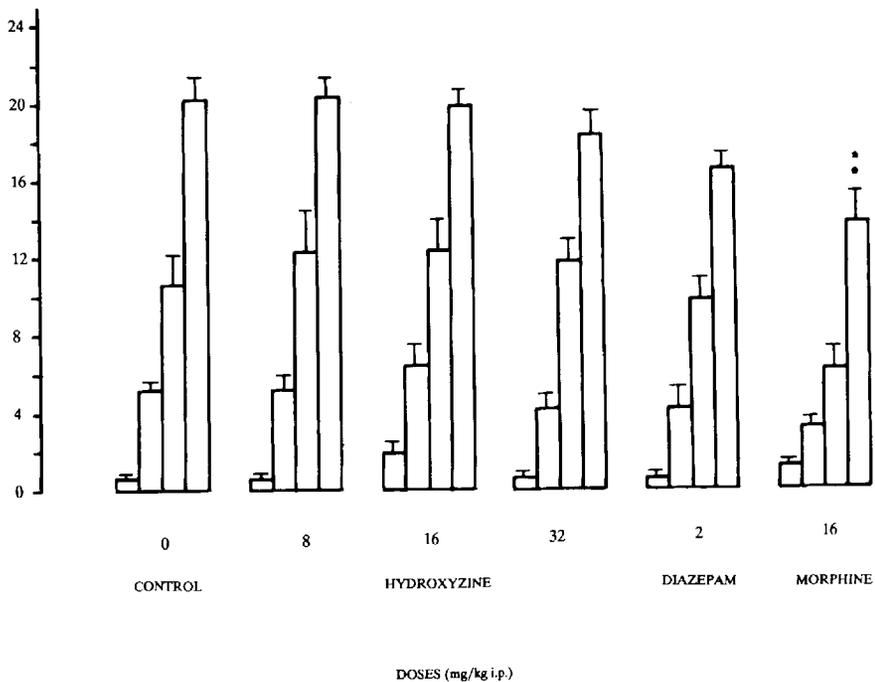


Fig. 4. Shock sensitivity test. The effects of hydroxyzine, diazepam, and morphine on the mean (\pm SEM) behavioral response to four intensities of electric shock (first column = 0.5 mA; second column = 1 mA; third column = 2 mA; fourth column = 4 mA). The behavioral response score at each intensity for each treatment group was compared with the equivalent control scores using Dunnett's *t* test. **, $P < 0.01$ (two-tailed).

a slight, non-dose-dependent and statistically nonsignificant decrease in S2 step-through latencies in the hydroxyzine-treated groups. In contrast, a marked decrease in the S2 step-through latencies was observed in the diazepam-treated group when compared with the control group (Dunnett's $t = 4.53$; $df = 5,95$; $P < 0.01$). These results suggest that diazepam, but not hydroxyzine, caused memory deficits in this learning situation.

Electric Shock Sensitivity: Effects of Hydroxyzine, Diazepam, and Morphine

The behavioral responses to different levels of shock after treatment with hydroxyzine, diazepam, and morphine are shown in Figure 4. Analysis of variance yielded a significant overall treatment effect ($F = 4.221$; $df = 5,30$; $P < 0.01$). Individual comparisons suggest that whereas neither hydroxyzine (8, 16, and 32 mg/kg) nor diazepam (2 mg/kg⁻¹) significantly affected the behavioral response to shock, a clear tendency toward a reduction was observed with the reference analgesic morphine (16 mg/kg), with a highly significant effect at the highest shock intensity (Dunnett's $t = 3.73$; $df = 5,30$; $P < 0.01$).

DISCUSSION

The present experiments have shown that hydroxyzine, when given before exposing rats to a series of inescapable shocks (preventive treatment), blocked the occurrence of acquisition

deficits ("learned helplessness") during the subsequent learning of a conditioned avoidance task, whereas hydroxyzine was without effect when first administered after shock exposure during the learning task (curative treatment). Similar effects were observed with diazepam given in the same experimental conditions. These results suggest, therefore, that hydroxyzine, like diazepam, can prevent the deleterious effects of uncontrollable stress. The results obtained in the passive avoidance task suggest, however, an interesting distinction between hydroxyzine and diazepam. Hydroxyzine, in the dose range that prevented "learned helplessness," had very little effect on the retention of the passive avoidance response as measured by the step-through latency at the second trial, whereas with diazepam clear signs of a memory deficit were apparent. These findings would suggest that the antistress effects of hydroxyzine were not due to poor memory for the aversive stimulation. In contrast, the findings with diazepam would suggest that at least part of its antistress activity in this experimental situation might have been due to deficient memory. Finally, the experiments that measured shock sensitivity suggest that neither hydroxyzine nor diazepam, in contrast to the standard analgesic morphine, altered the animals' response to electric shock. It would not appear therefore that the antistress effects of hydroxyzine or diazepam could be ascribed to reduced shock sensitivity.

The present experiments were successful in reproducing the phenomenon of "learned helplessness," as measured by the increase in escape failures in animals previously exposed to inescapable electric shock [Seligman and Maier, 1967; Martin et al., 1986]. Similarly, the results obtained with diazepam confirm those reported previously with this compound in a similar experimental paradigm in which it was shown that diazepam could prevent the occurrence of "learned helplessness" when given before inescapable shock [Sherman et al., 1979] but was ineffective in reducing the acquisition deficit when first given during the subsequent learning [Sherman et al., 1982; Drugan et al., 1987]. Furthermore, the apparent memory deficits observed with diazepam are consistent with many reported findings, both in animals [Gamzu, 1987; Lenègre et al., 1988a; Porsolt et al., 1988] and in humans [Curran, 1986], indicating that diazepam, like other benzodiazepines, induces amnesia. This interpretation is reinforced by the fact that diazepam did not affect shock sensitivity, another finding in the present experiments that is consistent with the experimental literature [Rosland et al., 1987].

The failure of hydroxyzine to induce signs of memory impairment in the passive avoidance test corroborates similar findings in an analogous situation in the mouse [Lenègre et al., 1988b]. Furthermore, the fact that hydroxyzine, at antistress doses, did not appear to affect memory in mice and rats suggests that hydroxyzine, unlike the benzodiazepines, would not cause memory disturbance in man. This possibility could perhaps account for the clinical observation that anxiolytic doses of hydroxyzine can even facilitate cognitive performance in man [Pishkin and Shurley, 1983], whereas opposite effects have been observed with benzodiazepines [Spinweber and Johnson, 1982].

Taken together, the present findings suggest that hydroxyzine possesses a similar behavioral action to diazepam and the atypical anxiolytic buspirone in preventing the deleterious effects of stress while, like buspirone but unlike the benzodiazepines, not causing the release of behavior suppressed by punishment. These findings confirm clinical data indicating therapeutic effectiveness of hydroxyzine in the treatment of anxiety and suggest that stress-induced avoidance deficits ("learned helplessness") might be a useful paradigm for detecting non-benzodiazepine-like anxiolytic activity.

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