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Alprazolam Reduces Stress-Induced Mortality in Cardiomyopathic Hamsters

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TAPP, W. N., B. H. NATELSON, D. CREIGHTON, C. KHAZAM AND J. E. OTTENWELLER. *Alprazolam reduces stress-induced mortality in cardiomyopathic hamsters.* PHARMACOL BIOCHEM BEHAV 32(1) 331–336, 1989.—These experiments examined the role of several variables involved in the production of serious, stress-induced disease. Experiments 1 and 2 indicated that stress may not be medically dangerous except in animals with a predisposition or vulnerability to disease. Repeated exposure to cold-immobilization produced no detectable ill effects in healthy hamsters, but it was lethal for cardiomyopathic hamsters (CMHs). Experiment 3 showed that stressor intensity was also critical to the outcome of stress. CMHs succumbed when they were stressed in the supine position, but not when they were immobilized in the less stressful prone position. In Experiment 4, we attempted to reduce the stressfulness of cold-immobilization with the anxiolytic alprazolam. Alprazolam effectively blocked stress-induced mortality. In addition, we found that poststress body temperature was a crude predictor of an animal's ability to cope with stress. Alprazolam prevented CMHs from developing stress-induced hypothermia.

Anxiolytic Core temperature Sudden death

FOR decades, stress has been studied because of its ability to activate or suppress a host of bodily functions. These physiological changes and the early demonstration that stress could produce overt disease in animals (20) led to the idea that stress played a role in the genesis of severe human illness. And, this idea has been supported, at least for the outcome of human heart disease [e.g., (19,22)]. However, further investigation has shown that the link between stress and serious disease is more complicated than the original formulation suggested.

Careful evaluation of the disease that develops in stressed animals revealed that the disease is usually not life-threatening and typically disappears despite the continuation of stress [e.g., (14,15)]. These results placed the relatively benign results of stress in animals in direct contrast to the lethal consequences of stress in humans. To explain this discrepancy, Natelson (12) suggested that stress was relatively benign except when stress was administered in the presence of either disease or the predisposition to disease. Then, stress could produce lethal effects. We found initial support for this hypothesis in experiments which used digitalis to predispose guinea pigs to cardiac arrhythmias. We found that stress produced digitalis-toxic cardiac arrhythmias at doses of digitalis which were benign in unstressed controls (14).

The present experiments extended our investigations of the variables that influence stress-induced disease. These experiments examined stress-induced disease in cardiomyopathic hamsters. The cardiomyopathic hamster (CMH) provides a useful model for extending our investigations of the role of predisposition in the production of stress-induced disease. The CMH inherits a heart disease that is active during a discrete period of the animal's life—from 1 to 3 months of age (4). The disease is manifested by multiple foci of myocytolytic necrosis and fibrosis which resemble in part human congestive cardiomyopathies (7). Autonomic involvement in the genesis of CMH disease is suggested by the fact that the course of the disease can be delayed by pharmacological blockade of the sympathetic nervous system (2,10) and by the fact that the cardiac lesions resemble those produced during administration of exogenous catecholamines (5).

During its period of lesion formation, the hamster remains in apparent good health. It is not until many months later that the animal dies due to the development of severe heart failure. We were thus intrigued to learn that treatment with dibenzylene, an alpha adrenergic antagonist which also increases endogenous catecholamines, exacerbated the pathological process and could be lethal (6). We reasoned that stress, known to release catecholamines and to activate the sympathetic nervous system, might also be lethal in these animals. The purpose of this report is first to show data supporting this thinking and then to begin an analysis of the mechanism of this stress-induced effect.

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EXPERIMENTS 1 AND 2

The purpose of these experiments was to evaluate the predisposition hypothesis of stress-induced disease in hamsters. This hypothesis would predict that stress would produce medically serious or lethal consequences in CMHs with covert heart disease but not in healthy hamsters. Therefore, we compared the effects of cold-immobilization in CMHs and healthy hamsters. Cold-immobilization has proven a useful tool in studies of stress-induced gastric disease (18).

Method

The subjects were BIO 14.6 cardiomyopathic hamsters or F1B healthy hamsters (Bio-Research, Cambridge, MA). Hamsters were received in our laboratory at 8–10 weeks of age and were allowed at least 1 week to acclimate to our animal quarters. They were individually housed in shoe-box cages with free access to food and water and were on a 12-hr light, 12-hr dark schedule. Thereafter, at 2.5–3 months of age, hamsters in the stress group were subjected to five consecutive daily 2-hr periods of supine immobilization at 4°C. Hamsters were immobilized by extending their 4 limbs and taping them to the corners of a small board and then covering their bodies with a cloth flap attached to the board with Velcro fasteners. Nonstress hamsters were removed from their home cage and put into another shoe-box cage without food and water for 2 hr over the same five-day period. The 2-hr sessions began at the time the lights went out. This time was chosen because data indicate that immobilization stress can be ineffective when administered during the day (1). Immediately before and after each stress session as well as the next morning after each session, hamsters were checked to see if they were still alive. Thereafter, we checked the hamsters twice daily until ten days past the last death. Two experiments were done. In the first, both CMH and F1B hamsters were used. In the second, only CMHs were used.

Results and Discussion

In Experiment 1, the only animals to succumb were the CM hamsters in the stress group: 5 out of 9 of those animals died; in contrast, none of the 8 nonstressed CMH, none of the 6 stressed F1B and none of the 6 nonstressed F1B died. The increased mortality in the stressed CMH group compared to the stressed F1B group was statistically significant (Fisher's exact test=0.042). The increased mortality in the stressed CMH group compared to the unstressed CMH group was also significant (Fisher's exact test=0.02). Of the stressed CMH that died, none died during the actual 2-hr stress sessions themselves; 3 were found dead either the morning or afternoon after a stress session, and 2 died in the days following the last stress session. Because none of the healthy F1B hamsters were debilitated by stress or succumbed to it, we dispensed with using them for the rest of the experiments reported here.

In Experiment 2, done to replicate our finding that stress had lethal consequences for CMH hamsters, we found that 50% of the 16 stressed CMH died while none of the 7 nonstressed CMH died. This difference was also statistically significant (Fisher's test=0.009). Again, none of the stressed animals died during the 2-hr stress sessions themselves; 7 were found dead the morning or afternoon after a stress session, and one died afterwards. Thus, repeated administration of a stressor has lethal consequences for cardiomyopathic hamsters. The fact that death only occurred in the animals with covert heart disease supports the hypothesis that stress has serious medical consequences only if it occurs to an individual with an organ vulnerability. Stress was a necessary condition, however, because unstressed CMH controls did not die. The repeated stress, itself, was not directly and immediately lethal since no hamster succumbed during the actual stress procedure. Instead, it obviously made the hamster sick. Often, the animal succumbed between stress sessions, but some animals did not succumb until several days to over a week after the end of the stress session.

EXPERIMENT 3

Experiment 1 showed the crucial role of predisposition by a covert disease in affecting the outcome of stress. Experiment 3 examined the role of stress intensity in predisposed animals by determining whether CMHs exposed to a less severe stressor would also succumb. As the less severe stressor, we used cold-immobilization in the prone position. Rats exposed to this stressor develop significantly less gastric erosive disease than rats stressed in the supine position (24).

Method

Young CMHs were received and housed in our animal quarters as described above. Hamsters were randomly divided into 2 stress groups (n=16 each) and a no-stress control group (n=6). The first stress group was exposed to supine cold-immobilization done as detailed above. The second stress group was exposed to immobilization at 4°C using a sheet metal tube which was individually sized to each hamster and thus prevented the animal from moving. Animals in this condition did not have their limbs extended and were maintained in the prone position. Animals subjected to this stressor do not vocalize, while those immobilized in the supine position with limbs extended do; this is additional evidence that the prone restraint stressor was less stressful than the supine restraint stressor. The remainder of the experimental conditions was as detailed above.

Results and Discussion

The only group to show fatalities was the CMH group subjected to supine cold-immobilization. Twelve of 16 hamsters in that group died while none of the 22 hamsters comprising the other 2 groups (tube stress and no-stress control groups) died. The differences between the group exposed to the more intense stressor and the tube stress or no-stress groups were statistically significant (Fisher's test <0.0001 and $=0.003$, respectively). This experiment indicates that a threshold in stressor intensity must be reached in order to see the lethal consequences of stress in these animals. Less intense stress does not have lethal consequences in these animals.

EXPERIMENT 4

In Experiment 3, we showed that reducing stress intensity by altering the environmental stressor could prevent stress-induced mortality. However, that manipulation changes both the physical and psychological characteristics of the stressor. In an effort to begin trying to separate these two, Experiment 4 was designed to test the effects of using an anxiolytic to reduce the stressful effects of cold-immobilization. The anxiolytic we chose was alprazolam which has been shown to attenuate stress-related physiological responses in health (11,25) and disease (21).

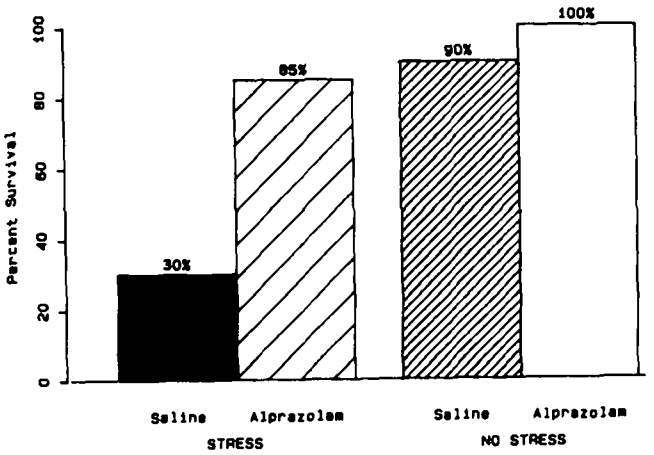

FIG. 1. Percent of animals surviving in Experiment 4 (n=20 per group).

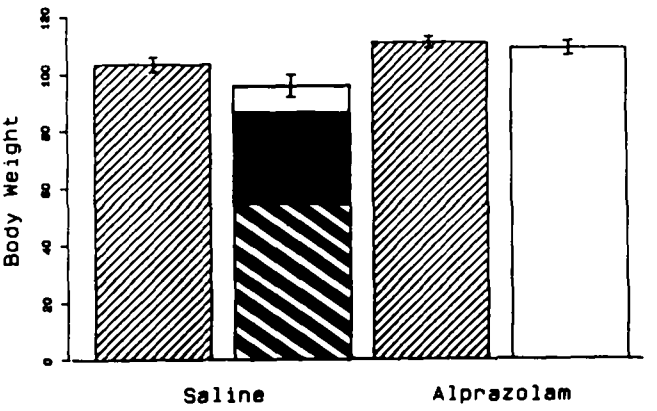

FIG. 2. Body weight (mg±SEM) in unstressed controls (narrow cross-hatched bars) and stressed groups (white bars). Note that weights from all the animals in the saline-stress group (i.e., second bar) are displayed. The heavy cross-hatching depicts the weights of CMH succumbing late while the stipple depicts the weights of the CMH succumbing early. Note animals dying late weigh less than those dying early.

Method

CM hamsters were treated as detailed above and were divided into stress and no-stress groups as well as alprazolam and saline control groups—a 2×2 design. For one week, hamsters were injected intraperitoneally twice daily with alprazolam, 8 mg/kg (range of injectate: 0.14 to 0.24 ml). The first injection was done in the mid-afternoon, and the second injection was done immediately before onset of dark. The dose chosen was one which on first administration produced a noticeable diminution of spontaneous behavior but not sleep; this diminution of spontaneous behavior was no longer remarkable after repeated administration of the drug. On the eighth injection day stress and control handling procedures began.

Because we were concerned that alprazolam might interfere with thermoregulation, we measured rectal temperature. Using a mouse rectal probe inserted about 2 cm up the rectum, temperatures were taken immediately after immobilization and at the end of the stress session; temperatures were not taken from unstressed, control animals because of the evident stressfulness of this procedure. Temperatures obtained by this technique were reliable but somewhat below normal core temperature; we used these measurements because efforts to advance the probe further produced obvious trauma. [Subsequent experimentation showed that these measures correlated highly (r_{14}=.98) with core temperature and were different only by the addition of a constant.] Following the termination of the 5-day stress period, drug and saline treatment continued for another 17 days. Viability was checked twice daily. Autopsies were performed when an animal was found dead; no more than 12 hr transpired between death and autopsy. Autopsy consisted of removal of organs and adsorption of pleural and peritoneal fluid on a preweighed gauze pad. Organs and body cavity fluid were then weighed. Surviving animals were sacrificed at the end of the experiment and autopsied as above.

Results and Discussion

Figure 1 shows the mortality results. As in previous experiments, the saline-treated, stressed hamsters showed a significantly greater mortality than nonstressed controls (Fisher's test=0.0005). However, alprazolam pretreatment blocked stress-induced mortality. Fourteen of 20 saline-stress animals died, but only 3 of 20 drug-treated animals died (Fisher's test=0.0005). There was no significant difference between the incidence of death in the drug-treated, stressed hamsters and drug-treated, unstressed hamsters.

The top of the bars in Fig. 2 depicts the body weights of hamsters that survived to the last day of the experiment. Analysis of variance revealed a significant effect of drug, $F(1,57)=13.4$, $p<0.0001$, in that drug-treated surviving hamsters weighed more than saline-treated controls. There was no significant effect of stress. The second bar from the left depicts data from the entire saline-stress group. This bar has been subdivided to provide body weight data on those animals in this group that succumbed during the experiment. Those hamsters that died in the morning or afternoon after a stress session weighed significantly more [86.7±3.1 g (SEM); stippled part of bar] than those dying thereafter [55.1±1.8 g; cross-hatched part of bar; $t(12)=8.87$, $p<0.0001$]. Assuming that body weight reflects health status, these data suggest that the disease process begun during the stress week continues after stress terminates.

Figure 3 portrays temperature values of the saline- and drug-treated groups for the first 3 stress sessions. Data were only analyzed for statistical significance for the first 3 stress days because of subsequent death in the saline-stress group producing both a selection bias and an unbalanced data set. Analysis of variance for repeated measures revealed a significant interaction between treatment (drug or saline), stressor session, and stress itself, $F(2,72)=9.26$, $p<0.001$. What this complex interaction means is that while temperatures before stress remained the same for both saline- and alprazolam-treated hamsters, the values after stress showed a progressive decline for the saline group and a progressive increase for the alprazolam group. Temperatures on stressor day 1 immediately after immobilization were the same for both groups indicating that alprazolam did not interfere with the hamsters' ability to maintain its temperature in normal am-

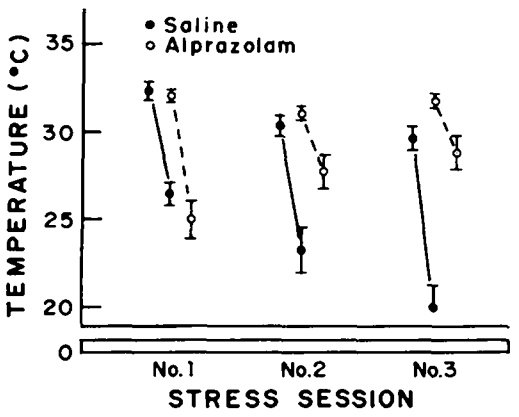

FIG. 3. Temperature (±SEM) of saline- (●) and alprazolam-treated (○) hamsters before and after the first 3 stress sessions. Note that control hamsters show progressively worse thermoregulation while alprazolam-treated hamsters show progressively better thermoregulation.

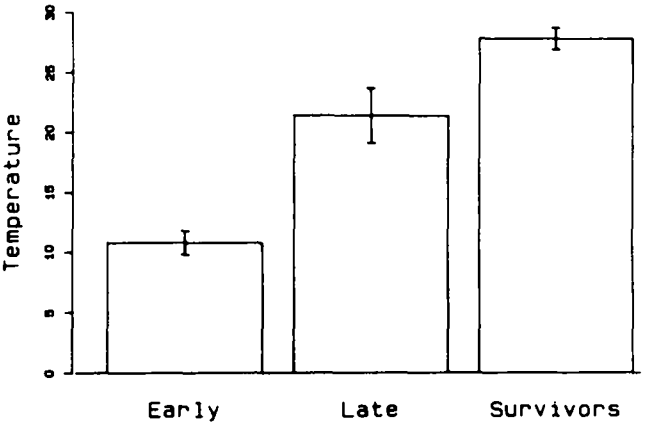

FIG. 4. Relation between last temperature measured (±SEM) and whether the hamster died on the morning or afternoon after a stress session (EARLY group), later than that (LATE group) or survived. Group means differ from each other significantly.

TABLE 1

ORGAN AND BODY CAVITY FLUID WEIGHTS (in mg ± SEM)

Organ	Saline-No Stress	Saline-Stress	Alpraz-No Stress	Alpraz-Stress
Kidney	976 ± 18	1333 ± 72*	1008 ± 17	1030 ± 27
Spleen	122 ± 10	94 ± 8*	135 ± 9	139 ± 7
Liver	3868 ± 114	3811 ± 126	4363 ± 109	4043 ± 152
Body Cavity Fluid	117 ± 20	304 ± 76*	120 ± 24	148 ± 25

*Different from each of the other 3 groups by Dunn's test ($p<0.05$).

bient surroundings. Similarly, both drug- and saline-treated hamsters showed the same magnitude of drop in temperature ($p<0.01$ for both, Dunn's test) after the first 2-hr session of cold-immobilization, but thereafter the patterns began to diverge. On the second stress session, both groups showed significant declines again ($p<0.01$ for saline and 0.05 for drug), but the alprazolam-treated hamsters fell less (27.7°) than the saline-treated hamsters (23.8°; $p<0.01$). On the third stress session, alprazolam-treated hamsters showed no significant fall after the 2-hr stress while the saline-treated hamsters still showed a significant decrease ($p<0.01$); poststress temperatures in the drug-treated hamsters (28.8°) were significantly higher ($p<0.01$) than those in the saline-treated hamsters (20.0°). Thus, alprazolam-treated CM hamsters showed progressive adaptation in terms of their thermoregulatory response to cold-immobilization, while saline-treated CM hamsters showed a progressively worse ability to cope with the cold challenge.

To determine whether thermoregulatory effectiveness was related to stress-induced death, we compared the last temperatures taken from hamsters that died early in the experiment with temperatures from hamsters that died late and from hamsters that survived. Early deaths occurred during the 5 stress days and the first poststress day. Figure 4 depicts the data. A statistically significant difference existed among the three groups, $F(2,17)=48.5$, $p<0.0001$. Hamsters that died early thermoregulated worse than hamsters that died later ($p<0.01$), and animals destined to survive the stress thermoregulated the best ($p<0.05$). Two of the alprazolam-treated hamsters that died did so 48 hr after the fifth stress session, and they too showed very low temperatures following the fifth stress session (13.6° and 19.5°); temperature was not obtained on a third hamster in this group which succumbed the morning after the last stress session. However, survivors in the drug-treated group had significantly higher temperatures on the last measurement day (30.9±0.5°) than saline-treated survivors [28.0±0.9°; $t(21)=2.57$, $p<0.02$]. Thus, hamsters that thermoregulated to the cold stress challenge the poorest succumbed the soonest, while those that protected their temperature better survived into the week after stress, and those that showed the best thermal control acutally survived.

In the autopsy data, analysis of variance revealed significant differences with $p<0.015$ for a number of organs and measures. Table 1 shows the group means and standard errors for the autopsy measures that produced significant F values. Post hoc tests between group means were done using Dunn's test ($p<0.05$). The saline stress group had significantly more body cavity fluid, heavier kidneys, and lighter spleens than each of the other 3 groups. Treatment with alprazolam prevented all these changes. Weights of hearts, adrenals, lungs, seminal vesicles and testes were unaffected

by either stress or drug treatment. Review of these data with a clinical pathologist did not reveal an obvious pathological process causing death. Alprazolam-treated hamsters had heavier spleens and livers than saline-treated controls.

GENERAL DISCUSSION

Stress produced early death in cardiomyopathic hamsters. These animals died more that 4 months before CMHs begin to die in our colony and more than 10 months before the median death age for these animals in our colony (17). Two factors were critical for stress to produce a lethal outcome. First, stress was lethal only in hamsters with a covert heart disease. When hamsters with an inherited cardiomyopathy were stressed, between 50% and 75% of the animals die. But, when healthy hamsters were subjected to the same stressors, none of them died. However, the combination of covert disease and stress is not necessarily sufficient to produce lethal consequences. A second critical factor is that the stressor must be sufficiently intense. When a less intense stressor was administered to CM hamsters, the stress-covert disease combination was not lethal. These data complement our earlier work in which we showed that stress could elicit digitalis-toxic arrhythmias at doses that were not toxic in unstressed controls (14).

Data from both models support the hypothesis that stress alone is not a risk factor for serious medical illness or death. However, stress can be a serious risk factor in individuals with either covert disease or a predisposition to disease. One implication of this conclusion is that the pathogenic effects of stress may not be a major concern in young, healthy individuals. However, stress may have serious pathogenic consequences in people with covert disease, as might be the case in the elderly, or in the individual with some predisposing factor, such as asymptomatic coronary artery disease.

The second important implication of these data is that a possible way exists in which one could intervene to block stress-induced pathogenesis. One could use treatments with anxiolytics which reduce the perceived or effective stress as well as alter physiological responses to stress; this tactic has been used successfully in the past with stress-induced gastric disease (8). We used this tactic in our efforts to reduce the pathological consequences of cold-immobilization by treating with the anxiolytic, alprazolam. Alprazolam reversed all signs of stress-induced disease and prevented stress-induced death in CM hamsters. Alprazolam-treated animals defended their body temperature significantly better than saline controls during cold-immobilization. This is important because there was a clear relationship between survival and an animal's ability to defend its temperature during the stress of cold-immobilization.

Hamsters that died during the earliest phase of the experiment also exhibited the poorest thermoregulation during cold-immobilization. Thermoregulation was less impaired in hamsters that died later in the experiment, and hamsters that survived exhibited the best thermoregulation. We found a qualitatively similar relationship between thermoregulation and stress-induced disease in a study of gastric erosive disease produced by cold-immobilization (16). Like others (3), we showed a correlation between the thermoregulatory response to the stressful challenge and the magnitude of disease that was produced.

To understand the effects of thermoregulation on stress-induced mortality and on alprazolam's protective effect, we must consider the effect of cold challenge, stress, and alprazolam on CMH thermoregulation. CMHs may have impaired thermogenic responses to cold because they have inherited deficits in the quantity and physiological availability of brown adipose tissue, a specialized thermogenic tissue (9,27). However, the brown adipose tissue deficit does not seem to be the only critical element because exposure to cold alone is not sufficient to produce stress-induced mortality. Hamsters that were exposed to the same low temperatures in less stressful immobilization did not get sick and die. Clearly, the presence of a sufficiently intense stressor is crucial to stress-induced mortality, but the cold challenge alone does not provide the required intensity. Furthermore, it seems unlikely that hamsters died of hypothermia per se, because hamsters continued to succumb over the days following the last stress session in ambient temperatures that did not represent a thermoregulatory challenge.

Does alprazolam produce its protective effects by reducing stress or by improving thermoregulation directly? Acute studies suggest that diazepam, the prototypic benzodiazepine, is a hypothermic agent. At room temperature, diazepam blocked restraint-induced hyperthermia in a dose-dependent fashion (23), reduced baseline temperature (23,26), but then, at high but not lower doses, diazepam reduced the magnitude of the hypothermia that develops in rats when they are held by the nape of the neck (23). In the cold (4°C), diazepam produced hypothermia that was not dose-dependent (26).

In contrast, alprazolam was not a direct hypothermic agent at the doses employed in this study. Both alprazolam-treated and control CMHs had the same baseline temperature and the same temperature response to the first cold-immobilization. Differences only emerged during subsequent exposures to the stressor. With repeated exposure, saline-treated controls showed progressively more hypothermia, while alprazolam-treated hamsters showed progressively less hypothermia. These data suggest that alprazolam is not working via a direct effect on physiological thermoregulatory mechanisms. Instead, they suggest that the drug is working as an antistress agent that reduces perceived or effective stressfulness below the intensity required to produce pathogenesis and mortality.

The observations in this report suggest that stress-induced mortality and pathogenesis are the results of a complex chain of circumstances and events. This chain of events is set into motion when an individual with covert or overt diease or some other predisposing condition is subjected to a stressor. To be effective, the stressor must be perceived and interpreted as sufficiently intense or stressful. There follows a cascade of stress responses involving many physiological systems which results in disease in the vulnerable individual. Treatment with alprazolam broke this chain, possibly by reducing the effective intensity of the stressful experience. Another explanation is that the drug directly interfered with the animal's ability to defend its body temperature against the stress of low ambient temperature. Although it is not clear which mechanism was operative, it is clear that alprazolam reduced stress-induced hypothermia and weight loss in cardiomyopathic hamsters. More importantly, alprazolam blocked the lethal consequences of stress in these animals with heart disease. This finding suggests that alprazolam might be a useful therapeutic adjunct for physicians treating the sick during periods of stress.

ACKNOWLEDGEMENTS

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NOTE ADDED IN PROOF

A report on the untoward effects of verapamil in this model has appeared in Res. Commun. Chem. Pathol. Pharmacol. 62:511–514; 1988.