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Adinazolam Both Prevents and Reverses the Long-Term Reduction of Daily Activity Produced by Inescapable Shock[1]

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MAIER, S. F., L. H. SILBERT, W. M. WOODMANSEE AND P. H. DESAN. *Adinazolam both prevents and reverses the long-term reduction of daily activity produced by inescapable shock.* PHARMACOL BIOCHEM BEHAV **36**(4) 767–773, 1990.—The behavioral consequences of exposure to stressors such as inescapable shock are usually quite transitory if testing is conducted in an environment different from that in which the stressor was administered. Daily running activity is an exception in that it remains depressed for several weeks following experience with inescapable shock. In the present experiments we found the administration of the triazolbenzodiazepine adinazolam able to both reduce this long-term activity reduction produced by inescapable shock when acutely administered before the inescapable shock, and to reverse the effect when chronically administered after the inescapable shock. Classic 1,4-benzodiazepines such as diazepam have been able to prevent such effects when acutely administered before inescapable shock, but cannot reverse these effects when provided after the inescapable shock. Conversely, classic antidepressants such as desipramine have been unable to prevent these behavioral effects when given before inescapable shock in acute form, but can reverse the effects with chronic administration following the inescapable shock. Our observations that adinazolam can both prevent and reverse the effects of inescapable shock are consistent with reports that this agent has both anxiolytic and antidepressant effects in clinical use.

Inescapable shock Learned helplessness Activity Adinazolam Antidepressants Anxiolytics

SEVERAL of the triazolbenzodiazepines have the unusual property of having features characteristic of both the classic 1,4-benzodiazepine anxiolytics and the antidepressants. For example, adinazolam (1-dimethylaminomethyl triazolbenzodiazepine, Deracyn) has been shown to have actions similar to the classic 1,4-benzodiazepines. Thus, adinazolam binds to benzodiazepine receptors with high affinity (28), antagonizes bicuculline- and penetetrazol-induced seizures (15), reduces the corticosteroid response to stressors (15), antagonizes the anxiogenic effects of FG 7142 and penetetrazol (10), prolongs hypoxic survival time (13), and so forth. Moreover, adinazolam has been shown to be an effective anxiolytic both in animal model systems (10) and in human clinical trials (5).

In contrast to the 1,4-benzodiazepines which do not act as effective antidepressants (27), adinazolam has been shown to exert strong antidepressant effects in double-blind placebo control studies (9). Indeed, adinazolam proved to be as effective as imipramine in ameliorating the depressive symptomology of a population of carefully diagnosed patients suffering from endogenous depression (2). This was so even for patients with more severe, melancholic depression. However, adinazolam does not have many of the biochemical effects that are typical of most antidepressants. It does not have a pronounced impact on either norepinephrine or serotonin uptake as do many of the tricyclic antidepressants, does not alter monoamine metabolism as do the monoamine oxidase inhibitors, and does not down-regulate cortical beta-adrenergic receptors (15). On the other hand, adinazolam does have some effects on serotonergic and noradrenergic systems which are shown by many antidepressants. For example, chronic treatment with adinazolam sensitizes hippocampal pyramidal neurons to serotonin (6), attenuates the hyperactivity of beta-adrenergic receptors produced by reserpine administration (13), and potentiates the action of norepinephrine on blood pressure (15). Finally, alprazolam (1-methyl triazolbenzodiazepine, Xanax) is another triazolbenzodiazepine, introduced as an anxiolytic, which has been found to have useful antidepressant properties.

Even though adinazolam has received extensive study and has been tested with a variety of drug screens, there is surprisingly

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little information concerning its activity in animal systems designed to model various aspects of depression [see (35) for an insightful discussion of the distinction between drug screens and animal models]. All that is known is that adinazolam has been reported to reduce the hyperactivity produced by olfactory bulbectomy (22), as do many effective antidepressants. Further study of adinazolam in animal model systems would provide information about both adinazolam as a drug and the animal systems as models of clinical phenomena.

Numerous behavioral effects have been argued to bear a resemblance to human depression and to constitute models of depression. Many of these involve behavioral states generated by stressors of different kinds. A difficulty with these models is that the behavioral changes produced by stressors are generally quite transitory. For example, exposure to inescapable shock (the "learned helplessness" model) reduces pain sensitivity/reactivity (21), social dominance (25), aggressiveness (20), maternal behavior (34), activity in the presence of subsequent shock (21), learning to escape stressors (23), food and water intake (32), etc. However, the reduction in pain reactivity persists for only 1 hr following the inescapable shock, and can be differentially reactivated by subsequent shock for only 48 hr (21). Similarly, reductions in motor activity elicited by both placement in water (33) and gridshock (21) persist for no more than 48–72 hr following inescapable shock. Food and water intake remain depressed for approximately 24 hr (32), as do aggressiveness and dominance (Maier, unpublished data). Deficits in escape learning generally persist for only 48–72 hr after inescapable shock (21), although there are cases in which this effect is more prolonged (16). It should be noted that more persistent behavioral effects can be observed if testing occurs in a similar or identical environment to that in which the stressor was delivered, and the subject is kept in an environment different from the testing environment (e.g., the home cage) in the interval between stressor exposure and testing (30). However, here the behavior could be the result of an *associative* or *conditioning* process, rather than a behavioral state persisting through time. That is, long-term effects that are observed in environments similar to those in which the inescapable shock or other stressor occurred could reflect *rearousal* of the effect.

However, we (7) have recently reported that one particular kind of behavior, daily running activity, is depressed for a prolonged period following exposure to inescapable shock. In these experiments rats were first allowed to live in an apparatus consisting of a cage attached to a running wheel. The rats were free to enter the running wheel at any time and remained undisturbed until a stable baseline of total daily running was established. In different experiments this period has been anywhere from 3 to 6 weeks. The rats were then removed from the apparatus, brought to a different area of the building, and given exposure to inescapable shock. In different experiments anywhere from 1 to 4 such sessions were provided. The rats then remained undisturbed in the running wheel cages, and total daily running and daily water intake assessed for up to 6 weeks.

Exposure to inescapable shock led to the expected transitory reduction in water intake, persisting for only 48 hr. In contrast, daily running wheel activity was depressed and remained so for 14–42 *days*, depending on the conditions of the experiment. It is important to recognize that this persistent activity deficit occurred in an environment that had few if any cues in common with the environment in which inescapable shock was administered. Moreover, the rats lived in the wheel apparatus for many days before the shock sessions and so the stimuli present were highly familiar "safe" stimuli. Thus, even if there was some stimulus in common between the wheel and the shock environment it would not likely have become associated with shock (18). The activity changes revealed in these studies would thus appear to reflect long-term unconditioned effects of inescapable shock that persist for 14–42 days rather than an effect reinitiated during testing. Finally, it should be noted that the change is a change in daily activity, not a change in the organism's ability to locomote. Locomotion in response to an eliciting stimulus recovers in 2–3 days after exposure to inescapable shock (21).

This offers an ideal paradigm with which to investigate putative antidepressant drugs. Indeed, we found that desipramine reversed the activity reduction when added to the subject's drinking water, and required 7 days for peak effectiveness (7). The desipramine was not initiated until 2 day after the last of 3 shock sessions, and so the effect obtained was a true reversal. The purpose of Experiment 1 was to examine the impact of adinazolam in this same paradigm.

EXPERIMENT 1

METHOD

Subjects

The subjects were 48 Sprague-Dawley rats obtained from Holtzman. They were 60 days of age at the time they were removed from their home cages and placed in the activity wheel apparatus for the remainder of the experiment. They were maintained on a 12:12-hr light/dark cycle, and had food and water continuously available.

Apparatus

Housing and activity measurements were conducted in 48 activity cages (Geo. H. Wahmann, Baltimore, MD). Each consisted of 2 compartments mounted on a $70 \times 35 \times 45$ cm ($L \times W \times H$) galvanized metal frame. A 9×7 cm ($L \times H$) opening in the metal plate separating the compartments provided free and easy access between a $25 \times 15 \times 2.5$ cm ($L \times W \times H$) wire mesh cage and a 11.5 cm wide 35 cm diameter mesh wheel. The wheel was attached to a counter which recorded revolutions of the wheel. Food and water were continuously available in the cage part of the apparatus.

Inescapable shock and restraint occurred in Plexiglas tubes measuring 23.5 cm in length and 7 cm in diameter. The rat's tail extended from the rear of the tubes and was taped to a rod extending from the rear of the tube. Electric shock was delivered to the rat's tail through electrodes attached to the tail and coated with electrode paste.

Procedure

The rats were placed in the wheel apparatus and remained undisturbed for 28 days. Wheel revolutions per day were measured. The animals were then divided into 6 groups of 8, with groups being balanced with regard to baseline activity. Animals in the Control group remained undisturbed and constituted a home cage control. Rats in the Shock group received 3 sessions of inescapable tailshocks in the tubes, 1 session per day. A session consisted of 100 1.6-mA shocks, each 5-sec in duration, delivered on a 60-sec variable time schedule (range of 15–120 sec). The animals were returned to their home wheels immediately after treatment. Treatment always occurred between the 4th and 8th hr of the light part of the rat's cycle. Two other groups also received 3 sessions of shock. These groups received adinazolam dissolved in their drinking water beginning 24 hr after the last shock session. One group received a concentration of 5 mg/100 ml while the other received a concentration of 20 mg/100 ml (Shock-5 mg and

Shock-20 mg groups). The 2 final groups were given adinazolam in their drinking water at the same concentrations, but were not administered shock (5 mg and 20 mg groups). Daily wheel revolutions and water consumption were measured for 18 days from the beginning of treatment. Three subjects were lost from the experiment, no two in any one group.

RESULTS

There were large differences in baseline activity between animals. Each animal's daily wheel revolutions were thus expressed as a percentage of its own baseline in order to prevent high activity animals from contributing disproportionately to the group data. The last 7 days of baseline activity before experimental treatment were averaged for each animal and treated as that subject's baseline. The number of revolutions on each subsequent day for each subject was expressed as a percentage of this baseline. Moreover, overall activity in all of the animals occasionally fluctuated with colony conditions or showed a long-term trend. For example, activity was reduced on days on which the cage trays were changed. To take account of such factors the percent change from baseline score for the Control group was subtracted from the percent change score for each of the other groups on each day. This normalizes the data and expresses it as percent change relative to a home cage control.

Figure 1 presents the activity of each of the experimental groups relative to the Control group, across blocks of 3 days. The Control group is of necessity at 0 (no change relative to the Control), so that any difference from 0 is a change from that observed in controls. Exposure to inescapable shock produced a profound reduction in daily activity, with running in the wheels almost entirely ceasing. This was so even though the shock sessions occurred at a time of day far removed from when the rats were normally active. Most of the rat's running occurs during the dark part of the cycle and the shock session was administered between the 4th and 8th hour of the light part of the cycle. Thus, there was a minimum of 4 hr between the end of the shock session at which time the animals were returned to the wheel apparatus, and the start of the dark interval. Moreover, this activity reduction was persistent and was still clearly evident 12 days later. Even at the final data point the Shock group was 20% below Control. Adinazolam itself had very little effect on activity, although there was a tendency for the high dose to have an initial sedative effect. The high dose of adinazolam had little effect on the activity of inescapably shocked subjects. The low dose of adinazolam had little effect on the activity reduction produced by shock over the first 3 days of treatment. However, in contrast to the high dose, the low dose then reversed the activity reduction during the next 3 days, and eventually produced hyperactivity in the previously shocked rats.

These conclusions were confirmed by a repeated measures analysis of variance. The effects of Groups, $F(5,38)=4.63$, $p<0.05$, blocks of Days, $F(5,190)=19.91$, $p<0.001$, and the interaction of Groups and Days, $F(25,190)=4.55$, $p<0.001$, were all reliable. Subsequent Dunnett's tests ($p<0.05$) comparing each of the experimental groups and the Control at each Block of Days were conducted. The Shock group differed from the Control on Blocks 1, 2, 3, and 5. The Shock-5 mg group differed from Control on Blocks 1, 2, 4, 5, and 6. The Shock-20 mg group differed from the Control on Blocks 1, 2, 3, 4, and 5. Neither the 5 mg or 20 mg groups that had not received shock differed from the Control on any Block.

The mean water intake across blocks of 3 days is shown in Fig. 2. Water intake was reduced on the 3 shock days in all 3 shocked groups, but recovered to Control levels by the very next block of

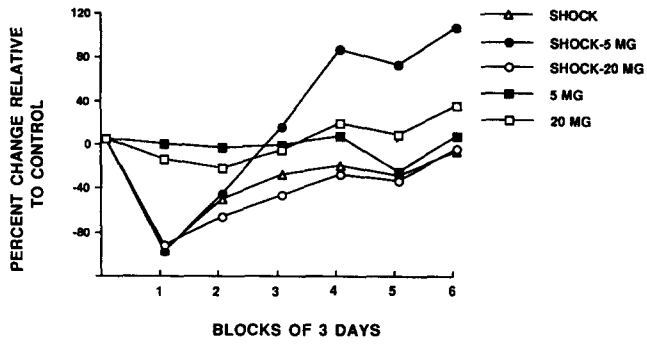

FIG. 1. Mean daily activity as percent change from baseline expressed as a difference from Control, across blocks of 3 days, for groups given inescapable shock (Shock), inescapable shock followed by adinazolam at a concentration of 5 mg/100 ml in the drinking water (Shock-5 mg), inescapable shock followed by 20 mg/100 ml adinazolam (Shock-20 mg), no shock and 5 mg/100 ml adinazolam (5 mg), or no shock and 20 mg/100 ml adinazolam (20 mg).

days. The nonshocked rats that were given adinazolam came to drink somewhat more than Control, as did the Shock-5 mg group. A repeated measures analysis of variance yielded a reliable effects of Blocks, $F(5,190)=43.47$, $p<0.001$, and the interaction of Groups and Blocks, $F(25,190)=2.39$, $p<0.001$. Simple effects analysis designed to examine the reliable interaction indicated a reliable Group effect ($p<0.05$) only on trial Block 5.

The amount of adinazolam consumed during Blocks 2 through 6 can be calculated from the water intake data, and is shown in Fig. 3. Shocked and nonshocked animals at each drug concentration consumed equivalent amounts of adinazolam. The subjects that received the higher concentration of adinazolam in their water consumed much more adinazolam than did the animals that received the lower concentration. The rats weighed roughly 400 g at the stage of the experiment when they began to consume adinazolam. Thus, the doses per day were roughly 6–8 mg/kg and 23–31 mg/kg for the low- and high-dose groups, respectively. A repeated measures analysis of variance yielded reliable effect of Groups, $F(3,25)=48.19$, $p<0.001$, and Blocks, $F(5,125)=19.40$, $p<0.001$.

In sum, a daily dose of adinazolam in the range of 6–8 mg/kg was effective in gradually alleviating the activity reduction pro-

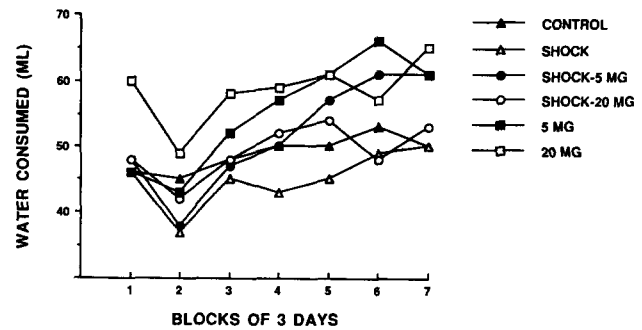

FIG. 2. Mean daily water intake, across blocks of 3 days, for groups given inescapable shock (Shock), inescapable shock followed by adinazolam at a concentration of 5 mg/100 ml in the drinking water (Shock-5 mg), inescapable shock followed by 20 mg/100 ml adinazolam (Shock-20 mg), no shock and 5 mg/100 ml adinazolam (5 mg), or no shock and 20 mg/100 ml adinazolam (20 mg).

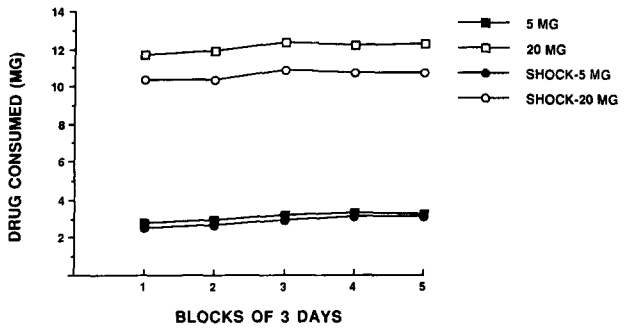

FIG. 3. Mean amount of adinazolam consumed, across blocks of 3 days, for groups given inescapable shock followed by adinazolam at a concentration of 5 mg/100 ml in the drinking water (Shock-5 mg), inescapable shock followed by 20 mg/100 ml adinazolam (Shock-20 mg), no shock and 5 mg/100 ml adinazolam (5 mg), or no shock and 20 mg/100 ml adinazolam (20 mg).

duced by 3 sessions of inescapable shock. Indeed, inescapably shocked subjects that received this dose of adinazolam eventually became more active than Control subjects. In contrast, a dose in the 23–31 mg/kg range was without effect. Here it need only be noted that this pattern is identical to that found with desipramine (7). Desipramine also was ineffective at a high dose (13–14 mg/kg) but was quite effective at a lower dose (8–9 mg/kg). Moreover, the shocked animals given the effective dose eventually became much more active than controls, even though desipramine had no effect in nonshocked subjects.

EXPERIMENT 2

A variety of evidence suggests that different mechanisms are involved in the reversal and the prevention of the behavioral changes produced by inescapable shock (learned helplessness effects) and a number of proposals have been made. For example, Petty (24) has argued that the available evidence suggests that the reversal of the behavioral changes requires a facilitation of serotonergic processes, whereas prevention of the changes requires a facilitation of GABAergic processes during exposure to the inescapable shock treatment. Indeed, the classic 1,4-benzodiazepines such as chlordiazepoxide and diazepam, which facilitate GABAergic transmission (3) have been shown to prevent learned helplessness effects when administered before the inescapable shocks (8,19). Interestingly, neither chlordiazepoxide or diazepam were able to reverse learned helplessness effects when given after the inescapable shock and before testing (8,19). Consistent with the above hypothesis, chronic administration of adinazolam is able to facilitate the effects of serotonin (31) and, as we have just shown, reversed the effects of inescapable shock on activity. Because adinazolam binds to benzodiazepine receptors (28) and facilitates GABAergic processes (15) after acute administration, it might be expected that adinazolam should also be able to prevent learned helplessness effects. The purpose of Experiment 2 was to investigate this possibility. Rats were exposed to 3 sessions of inescapable shock as in Experiment 1, and daily running measured. However, in Experiment 2, adinazolam was administered before each shock session rather than after the shock sessions had terminated.

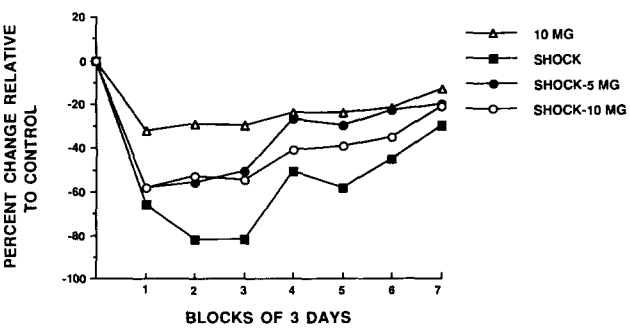

FIG. 4. Mean daily activity as percent change from baseline expressed as a difference from Control, across blocks of 3 days, for groups given inescapable shock (Shock), inescapable shock preceded by 5 mg/kg adinazolam (Shock-5 mg), inescapable shock preceded by 10 mg/kg adinazolam (Shock-10 mg), or no shock and 10 mg/kg adinazolam (10 mg).

METHOD

Subjects

The subjects were 40 rats similar to those described in Experiment 1.

Apparatus

The apparatus was the same as that used in Experiment 1.

Procedure

After baseline activity had stabilized (28 days) the rats were divided into 5 groups. One group served as a home cage control and was not disturbed (Control). Three groups received 3 sessions of inescapable shock as described in Experiment 1. Two of these groups received an IP injection of adinazolam 30 min before each of the shock sessions. The adinazolam was dissolved in saline and administered at either 5 or 10 mg/kg for the 2 groups. These groups are labeled as Shock-5 mg and Shock-10 mg. The final group received 3 injections of adinazolam, 10 mg/kg, but was not shocked (the 10 mg group). Activity was measured for 18 days.

RESULTS

The running wheel activity of each of the groups, calculated in a fashion identical to Experiment 1 as a difference from the Control, across blocks of 3 days, is shown in Fig. 4. Inescapable shock again produced a profound reduction in activity which persisted for the entire duration of the experiment. Activity was still 35% below Control 15 days after the last exposure to shock. The 3 daily injections of 10 mg/kg adinazolam led to an activity reduction which was still 15% relative to the Control 15 days after the last injection. Even though adinazolam administered to nonshocked animals reduced activity, both the 5 and 10 mg/kg doses mitigated the activity reduction produced by shock.

A repeated measures analysis of variance applied to these data yielded reliable effect of Groups, $F(4,31)=5.10$, $p<0.01$, and Blocks, $F(6,186)=25.31$, $p<0.001$. Dunnett's test comparisons of each of the groups with the Control ($p<0.05$) indicates that each of the groups differs from the Control. Subsequent Newman-Keuls comparisons ($p<0.05$) indicates that the Shock group differs from all of the other groups, that the Shock-5 mg and Shock-10 mg groups both differ from the Control, that the 10 mg group differs from the Control, and that the Shock-5 mg, Shock-10 mg, and 10 mg groups do not differ among themselves.

Adinazolam administered before each of the shock sessions blunted the activity reducing effects of inescapable shock. It might seem that the effect of adinazolam in preventing the activity

reduction (Experiment 2) was smaller than its effect in reversing the reduction once it was established (Experiment 1). However, it should be carefully noted that adinazolam administration for 3 days was followed by a reliable long-term *reduction* of activity in Experiment 2. It is not clear why this occurred. It could have been the result of the adinazolam itself, or the removal of the subjects from the wheels and the injection procedure, or an interaction between the two. Whatever the cause, the prolonged reduction in activity produced by the adinazolam injections would work *against* the prevention effect shown by the adinazolam injections in shocked subjects.

GENERAL DISCUSSION

In Experiment 1 adinazolam reversed the activity reducing effects of inescapable shock when administered beginning 24 hr after the termination of the last 3 sessions of inescapable shock. This occurred when a concentration of 5 mg/100 ml was provided in the subject's drinking water. Moreover, the effect was gradual in that the drug required 8 days to exert its maximal effect. Interestingly, the drug did not simply return the inescapably shocked subject's activity to its own baseline or to control levels, but led to activity far in excess of these levels. These very high levels of activity were maintained for the duration of the experiment. In contrast, the higher drug concentration (20 mg/100 ml) had no effect. Finally, the drug itself reduced activity slightly upon initial administration, with this effect disappearing with continued administration.

The pattern of the "therapeutic" effect obtained for adinazolam is identical to that produced by desipramine in the same paradigm (7). Desipramine was also added to the drinking water after 3 sessions of inescapable shock. Here too a lower concentration (10 mg/100 ml) reversed the activity reduction, while a higher concentration (20 mg/100 ml) had no effect. It is worth noting that a curvilinear relationship between plasma level of drug and antidepressant activity in humans has been reported for desipramine (11) and other antidepressants (26). We are unaware of any information on the dose-response relationship of adinazolam as an antidepressant in man. Moreover, the effective concentration of desipramine did not merely return activity to normal, but led to hyperactivity as in the present study. Adinazolam, in common with other antidepressants, has been shown to induce mania in some human patients (2). Similar to adinazolam, desipramine had very little impact on activity in nonshocked subjects.

In contrast to adinazolam and other antidepressants such as desipramine, the classic 1,4-benzodiazepines do not reverse or even reduce learned helplessness effects when administered after inescapable shock. Chlordiazepoxide (8), diazepam (19), and lorazepam (30) have been tested in reversal paradigms and have had no effect. Thus, when administered after inescapable shock, adinazolam resembles antidepressants rather than more traditional anxiolytics.

In Experiment 2 the acute administration of both 5 mg/kg and 10 mg/kg of adinazolam administered before each of the 3 inescapable shock sessions reduced the impact of the inescapable shock on subsequent activity. Thus, adinazolam exerted a "prophylactic" as well as a "therapeutic" effect with regard to the running wheel activity reduction produced by inescapable shock. The prophylactic activity of adinazolam resembles the action of the 1,4-benzodiazepines rather than the antidepressants. The acute administration of chlordiazepoxide (8), diazepam (19), and lorazepam (30) before inescapable shock reduces the magnitude of learned helplessness effects. In contrast, the acute administration of imipramine before inescapable shock does not reduce the magnitude of the subsequent behavioral changes observed (29). The pattern of the present results is thus consistent with the unusual clinical efficacy of adinazolam as both an anxiolytic and an antidepressant. The acute administration of anxiolytics prevent learned helplessness effects while chronic antidepressant treatment reverses them, and adinazolam here had both properties. Adinazolam is the only compound that has been tested with learned helplessness paradigms that, to our knowledge, has both properties.

The present experiments also lend further support to the notion that some of the behavioral changes produced by inescapable shock have similarities to depression. A difficulty has been that the behavioral changes examined have dissipated rapidly, usually over the course of 24–48 hr. The occurrence of human depression may well involve the occurrence of stressors as precipitating factors (17), but the resulting condition persists for months rather than hours. Even allowing for differences between rats and humans, it is difficult to argue that a behavioral change that persists for only hours models behavioral changes that last for months. There are cases in which a behavioral change has been observed to last long after inescapable shock, but testing has always involved the administration of electric shock (e.g., shock escape learning) and/or the behavior has always been one that was measured in an environment identical or similar to that in which the original inescapable shock took place. Environments similar or identical to the inescapable shock environment would be expected to produce *conditioned* changes through standard associative mechanisms, particularly if the subject has not been exposed to the test environment in the interval between inescapable shock and testing. The usual procedure of simply maintaining the subjects in their home cages during the interval would prevent extinction of the association between the test environment and the inescapable shock. Thus, in these instances, it is not possible to determine whether inescapable shock produced a change in the organism's state that *persisted* for the period of time between inescapable shock and testing, or whether any state change dissipated but the shock and/or environmental cues of the testing situation rearoused the state in question or alternatively led directly to the behavioral effect observed by producing conditioned responses. Depression involves a persistent state change, even if it is precipitated by environmental stressors (12).

However, the reductions in running observed in the present studies reflect a persistent change occurring in an environment with no identifiable cues in common with the inescapable shock environment and in which the subjects live continuously. It is worth noting that the behaviors that have been examined in prior studies that have dissipated rapidly are all behaviors that are either elicited or motivated by a discrete, identifiable, potent stimulus (e.g., escape to shock, activity in the presence of shock, swimming when placed in water, tail-flick to radiant heat, etc.), or are tightly tied to homeostatic processes (e.g., eating, drinking). Running in the wheels has a very different character. It is not elicited or motivated by a discrete stimulus that drives the behavior, and there are no obvious negative consequences for the organism if it fails to emit the behavior. Moreover, there does not appear to be a homeostatic process driving the behavior in the sense that deprivation of running does not enhance subsequent running (14). Interestingly, the behaviors that are most altered in depression seem to have this same character. They are often self-initiated, familiar, usual activities that do not have a clear motivating stimulus and for which lack of performance does not have clear and immediate consequences (1). It is therefore of importance that a behavioral change in rats that bears a resemblance to that seen in depression is sensitive to adinazolam, a compound shown to have efficacy for depression.

Although our experiments do not have strong implications for elucidating the mechanisms which underly the activity change produced by inescapable shock, they are at least consistent with a

number of current formulations. For example, Petty (24) has suggested that inescapable shock produces later behavioral changes by altering GABAergic processes, but that these effects are reversed by serotonergic changes. The fact that acute adinazolam administration does impact on GABA systems (15), while chronic adinazolam alters serotonergic processes (31) is consistent with this formulation. However, adinazolam would also be expected to alter other systems that have been proposed to be involved in mediating learned helplessness effects, such as the locus coeruleus-dorsal bundle noradrenergic system (33). Thus, no strong conclusions can be drawn in this regard.

The present results join those we reported for desipramine (7) in suggesting a caution with regard to research on antidepressant pharmacology. The biochemical effects of antidepressants have been generally studied in "normal" rats that have not been exposed to any particular experimental procedures. However, the effects of these drugs could be quite different in subjects that are in other than normal behavioral states, such as those associated with depression. In the present studies the behavioral impact of adinazolam was far different in untreated and inescapably shocked rats. In untreated rats activity was not affected, while activity far in excess of normal resulted when adinazolam was given to rats that had been exposed to inescapable shock. A similar difference might occur with regard to the pharmacology and biochemistry of adinazolam and other drugs. Thus, for example, it could be that adinazolam would alter receptor function in an inescapably shocked animal, even though it does not do so in a "normal" animal (15). For example, the triazolbenzodiazepine alprazolam does not influence dihydroalprenolol binding in cerebral cortex in normal rats, but does antagonize the increase in such binding induced by chronic reserpine treatment (4). An appreciation of the neuropharmacological effects of antidepressants that is relevant to antidepressant efficacy might require the use of subjects that are in a state similar to depression.

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