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Long-Term Effects of Inescapable Stress on Daily Running Activity and Antagonism by Desipramine[1]

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DESAN, P. H., L. H. SILBERT AND S. F. MAIER. *Long-term effects of inescapable stress on daily running activity and antagonism by desipramine.* PHARMACOL BIOCHEM BEHAV **30**(1) 21–29, 1988.—The behavioral consequences of exposure to stressors such as inescapable shock are usually transitory if testing is conducted in an environment different from that in which the stressor was administered. The behaviors tested have generally been motivated by discrete stimuli in the environment (e.g., activity in reaction to shock) or have been part of homeostatic regulatory mechanisms (e.g., eating). Here we investigated the effects of inescapable shock on a behavior that is not so tightly tied to motivating and reinforcing conditions, daily activity in a familiar home cage/running wheel environment. Rats lived in the wheel environment for 44–85 days before treatment. Inescapable shock produced only a transient reduction of water intake and body weight, but daily running was depressed for 14–42 days (the maximum period studied) depending on the conditions. This long-term effect on activity occurred despite the fact that shock was administered in an environment very different from the animal's home running wheel environment. The activity reduction was reversed by desipramine in a dose dependent fashion. Indeed, the activity of inescapably shocked animals treated with the optimum dose of desipramine exceeded that of control animals undergoing neither stress nor drug treatment. The maximum effect of desipramine required 7 days of treatment. Desipramine did not affect the activity of control subjects.

Inescapable shock Learned helplessness Activity Desipramine Antidepressants

THERE has been considerable interest in the behavioral changes produced by exposure to stressors in animals. Such changes have been proposed as models of several different psychiatric disorders in humans, particularly depression [46]. An extraordinarily broad range of behavioral alterations have been documented, among which are subsequent reductions in pain sensitivity or reactivity [12], maternal behavior [44], aggressiveness [22], social dominance [31], activity or response initiation in the presence of stressors [2], learning to escape or avoid stressors [27], response perseveration [38], and food and water intake [41].

Although all of these behavioral sequelae of exposure to stressors have not been studied in detail, a common characteristic seems to be that they are quite transitory, at least following an acute stressor. For example, reductions in pain sensitivity/reactivity persist for at most 1 hr following exposure to a wide variety of stressors [7]. Hypoalgesic mechanisms do remain sensitized for a longer period following exposure to a session of 80 inescapable shocks so that hypoalgesia can be readily reactivated, but this sensitization endures for only 48 hr [23]. Similarly, reductions in both motor activity elicited by gridshock [23] and immersion in water [43] persist for at most 48–72 hr following inescapable shock treatment, and alterations in aggressiveness and dominance have a similar timecourse (Maier, unpublished data). Food and water intake remain depressed for only periods ranging to 24 hr following exposure to inescapable shock [41] and other stressors [34]. In parallel fashion, deficits in escape learning produced by inescapable shock often do not occur if 48–72 hr are allowed to intervene between inescapable shock exposure and escape testing [11, 23, 27], although there are conditions under which the effect is more prolonged [11].

Exceptions to this transitory nature of stressor effects have occasionally been reported. The behavioral changes described above are presumed to reflect *nonassociative* or *unconditioned* alterations produced by stress. However, the reported exceptions to the rapid timecourse of decay have involved situations in which behavioral testing occurred in the *same* or similar apparatus to that in which the initial stressor was presented. A number of investigators [13, 19, 28] have found escape learning deficits from 5–7 days after exposure to inescapable shock. However, inescapable shock was delivered in an identical or similar environment to that in

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which later escape testing occurred. Thus the effects observed could have been based on *associative* or *conditioned* changes, and their relative permanence may therefore not be surprising. For example, exposure to stimuli that had been present during shock can produce brain norepinephrine metabolism changes similar to those produced by shock itself [5]. Long-term effects that are observed in environments similar to those in which inescapable shock is delivered could easily reflect *re-arousal* of the effect rather than persistence through time. Glazer and Weiss [11], Maier *et al.* [23] and Overmier and Seligman [27] all administered inescapable shock and subsequent escape testing in very different situations, and found only a transitory effect.

It might seem that these behavioral outcomes would be more enduring if exposure to stressors became chronic. However, this is frequently not the case. There is often an adaptation process such that behavioral effects which would follow an acute exposure do not occur at all following chronic exposure [4]. For example, the reduced swimming that follows a single session of inescapable shock does not occur if 10 sessions of inescapable shock are employed [42].

The transitory nature of stress-induced behavioral change in rats leads to difficulties when such change is used as a model of a long-term psychiatric disorder in humans. For example, many models of depression are based on exposure to stressors and the behavioral changes which have been observed to follow (see [45] for a recent review). Indeed, stressful events often do precede the onset of clinical depression in humans [20]. However, reactive depression has been reported to dissipate with a timecourse that is on the order of months, not hours. Even allowing for differences between rodents (the experimental subjects in almost all of the above studies) and humans, it is difficult to argue that changes which persist for at most 48 hr model a condition that endures for weeks to months following a precipitating episode.

Moreover, studies of pharmacological reversal are difficult to perform with a behavioral phenomenon that dissipates in 24–72 hr without intervention. This is particularly problematic when it would be useful to compare acute and chronic drug effects, as is especially the case with antidepressants. Most antidepressant drugs are not clinically effective after a single administration and require anywhere from a few days to several weeks of use for effectiveness depending on the drug and the study [6,37]. For example, the "behavioral despair" model [30] is probably the most extensively pharmacologically investigated paradigm of stress-induced behavioral change (see [29] for a review). Rats or mice are forced to swim in a confined space. After initial attempts to escape the subjects assume an immobile posture, and on a second immersion the onset of immobility is much more rapid. The latency of onset of immobility in the second immersion is the measure of interest and is delayed by the administration of a variety of antidepressants between the initial immersion and the test. However, the interval between initial immersion and testing is almost always 24 hr, and so the ability of acute and chronic drug administration to reverse the behavior cannot be compared. Even when repeated daily immersions have been employed and chronic drug administration used, the interval between the last immersion day and testing has been only 24 hr (e.g., [16]). Thus the drugs were given on each of the immersion days rather than after the stressor exposure had ended and before or during testing. This is also true of other chronic stress paradigms such as that developed by Katz and his colleagues [35]. Here the animal is exposed to a variety of different stressors over a 3 week period, but the test of behavioral change (open field activity) occurs immediately after the last stress session. Perhaps this difficulty is partly responsible for the fact that the majority of drug studies in this area have administered the pharmacological agent of interest *before* the stressor and have examined prevention rather than reversal of stress-induced behavioral changes.

Of course, it is possible that the unconditioned behavioral changes that have been observed in rats following exposure to stressors simply are all transitory in nature. Indeed, many of the neurochemical changes produced by stressors are equally transitory. For example, the reduced levels of brain norepinephrine produced by exposure to inescapable shock persist for at most 48 hr even after the use of very severe and prolonged shock [43], and frequently are present for only much shorter periods [3].

Alternatively, it is also possible that the use of different stressors or behavioral tests might reveal more enduring changes than those yet observed. A wide variety of different stressors have already been examined. However, the behaviors that have been examined as outcomes of stressor exposure have tended to have several common features. First, the behaviors have been brief, with the testing period ranging from seconds (pain sensitivity/reactivity measures) to at most an hour (shock escape learning). Indeed, many of the most often used tests are very brief. For example, the behavioral despair test is 5 min in duration, the swim test used by Weiss and his colleagues is typically 15 min in duration, and so forth. Even behaviors such as maternal effectiveness, aggression, and dominance have been assessed only in very brief tests. For example, Rapaport and Maier [31] employed a 2 min competition for food test as their measure of dominance. Second, the behavior examined has almost always been elicited or motivated by a discrete environmental stimulus. Thus, activity has been measured in response to shock or to immersion in water, pain sensitivity in reaction to nociceptive stimulation, escape learning in response to shock, maternal behavior by pup retrieval in response to pup removal from the nest, dominance by confrontation with another animal, etc. Third, testing has usually been conducted in a relatively unfamiliar experimental environment. Obviously, these factors are strongly related. Testing has typically involved the measurement of a behavior motivated by a manipulable stimulus administered in a controlled experimental environment.

It is possible that it is these sorts of behaviors that reveal only transitory effects of stressor exposure and that a different type of behavior might display a more enduring impact. It is of interest that the behaviors that seem most disrupted during human depression are often self-initiated, familiar, usual activities that do not have a clear motivating stimulus in the environment and for which lack of performance does not have clear consequences [1]. In searching for an animal behavior that occurs over protracted periods in a familiar environment without an external motivating stimulus and for which depressed performance does not have clear negative consequences, general daily activity is an obvious candidate. Indeed, level of spontaneous activity has been used for the diagnosis and quantification of depression and mania in man [40]. This behavior also differs from others previously examined in that it has a strong circadian pattern, and depression is known to involve disturbances in circadian rhythms [17].

The purpose of the first experiment was to examine whether exposure to a stressor previously used in this lab-

oratory and known to have only transitory effects on activity in reaction to shock, escape learning, pain sensitivity changes, and shock-elicited aggression, would have a prolonged effect on general daily activity in a familiar environment. Rats were allowed to live in an environment consisting of a small cage attached to a running wheel for 44 days. They were then removed from this environment either 1, 2, or 4 times and given a session of inescapable shock identical to that usually used. This occurred in a different room on a different floor of the building. They remained in the running wheel/home cage environment at all other times and activity was assessed over an additional 42 days.

EXPERIMENT 1

METHOD

Subjects

The subjects were 40 male Charles River derived rats bred and raised at the University of Colorado. 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 40 activity cages (Geo. H. Wahmann, Baltimore, MD). Each consisted of 2 compartments mounted on a 70×35×45 cm (L×W×H) galvanized metal frame. A 9×7 cm (L×H) opening in the metal plate separating the compartments provided free and easy access between a 25×15×12.5 cm (L×W×H) wire mesh cage and a 11.5 cm wide 35 cm diameter wire 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 augmented with electrode paste.

Procedure

At 60 days of age the rats were weighed and placed into the activity wheels. They then remained undisturbed in the wheel apparatus for 44 days. Wheel revolutions and water consumption per day were measured for the last 21 of these baseline days. The animals were then divided into 5 groups of 8, with groups being balanced with regard to baseline activity. All animals were then weighed again on Day 1 of treatment (Day 45). Animals in the Control group were simply returned to their home wheels after weighing. Subjects in the Restrained group were placed into the Plexiglas tubes for 2 hr (the duration of the shock sessions) after the weighing and then returned to their wheels. These subjects were also restrained on Days 2, 3, and 4 for a total of 4 days of restraint. Rats in the 1 Day group received a session of inescapable tailshocks in the tubes. There were 100 1.6 mA shocks, each 5-sec in duration, delivered on a 60 sec variable time schedule (range of 15–120 sec). This group was not shocked again. The 2 Day group was treated identically, but they received a second session of inescapable shock 24 hr later. Analogously, the 4 Day group received 4 sessions of inescapable shock. All animals were always immediately returned to their home wheels after treatment and all were weighed on Days 4, 8, 16, and 24 post-treatment. Treatment always occurred between the 4th and 8th hr of the light part of the rat's cycle. Daily wheel revolutions and water consumption were measured for 42 days from the beginning of treatment. In sum, the rats simply lived in the wheels for 44 days, then received either 4 sessions of restraint or 1, 2, or 4 sessions of inescapable shock, and then again remained undisturbed, with the exception of 4 weighings, for 42 days. Two subjects were lost from the experiment, one due to death and the other to procedural error.

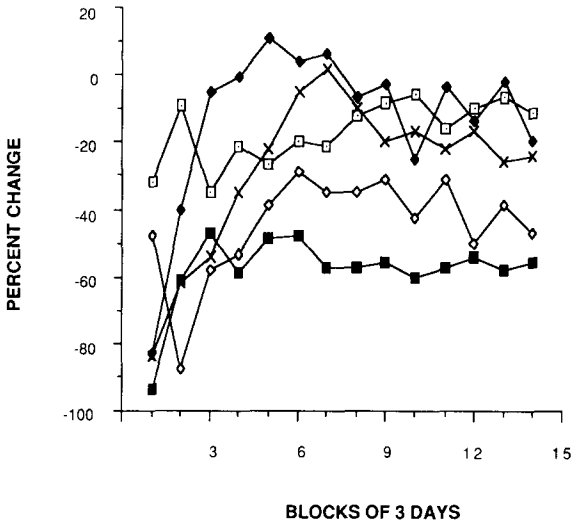

FIG. 1. Mean daily activity as percent change from baseline across blocks of 3 days for groups given no treatment, 1, 2, or 4 days of inescapable shock, or 4 days of restraint. ⊡: control; ◆: restrained; ×: one day; ◇: two days; ■: four days.

RESULTS

Although individual baseline activity became quite stable, there were some differences in activity level among the animals. Because of these differences in activity level from subject to subject the raw activity scores for each day were converted to a percentage change score. 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 wheel revolutions on each subsequent day for each subject was expressed as a percentage of this baseline score.

These data are shown in Fig. 1 which depicts percentage change in activity from baseline for each group across blocks of 3 days. The first day represents the first day of experimental treatment (shock or restraint). Thus the first block of 3 days consists of the shock day and 2 non-shock days for the group which had received 1 day of shock, 2 shock days and 1 non-shock day for the group which had received 2 days of shock, 3 shock days for the group which had received 4 days of shock, and 3 restraint days for the group which had received 4 days of restraint, etc.

Wheel running in the controls showed a slight decline with onset of experimental treatment for the other animals, but recovered to baseline. This decline was probably caused

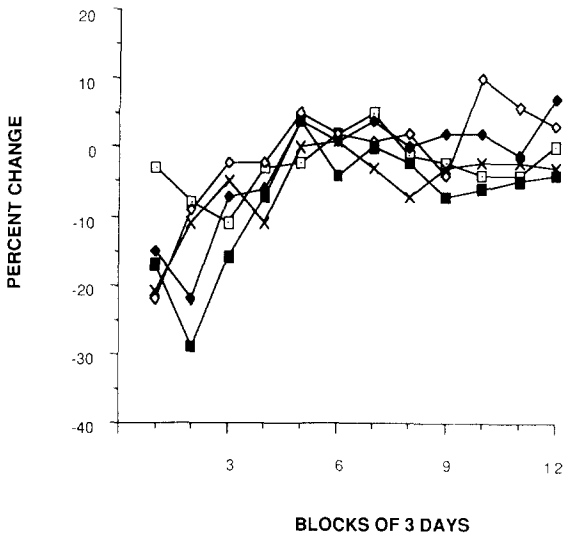

FIG. 2. Mean daily water intake as percent change from baseline across blocks of 3 days for groups given no treatment, 1, 2, or 4 days of inescapable shock, or 4 days of restraint. □: control; ◆: restrained; ×: one day; ◇: two days; ■: four days.

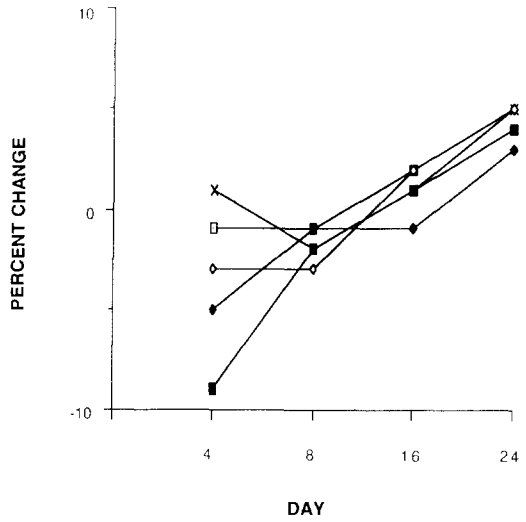

FIG. 3. Mean body weight on Days 4, 8, 16, and 24 as percent change from baseline for groups given no treatment, 1, 2, or 4 days of inescapable shock, or 4 days of restraint. □: control; ◆: restrained; ×: one day; ◇: two days; ■: four days.

by the increased level of experimenter activity in the room (weighing animals, removing animals for transport to the treatment room, etc.). As is evident, both restraint and shock produced a precipitous decline in daily activity ranging from 82 to 94%. Activity in the animals which had been restrained recovered rapidly and returned to baseline by the third block of 3 days. Indeed, an examination of the individual day data indicates that the activity of restrained subjects had recovered to control group levels by Day 6. Since there were 4 days of restraint, the activity reduction thus persisted for only 1–2 days following the last day of restraint. However, exposure to shock produced a more prolonged and graded effect. The activity of animals given 1 session of inescapable shock did not return to control levels until the fifth block of 3 days. Thus a single session of inescapable shock produced a subsequent reduction in daily activity lasting approximately 14 days. The activity of animals given either 2 or 4 days of inescapable shock had not recovered to control levels even at the end of the 42 days of the experiment. Activity was still reduced by 47% and 56% for the 2 and 4 days of inescapable shock groups.

These conclusions were confirmed by a repeated measures analysis of variance. The effects of Groups, $F(4,31)=4.67$, $p<0.005$, blocks of Days, $F(13,403)=14.44$, $p<0.0001$, and the interaction of Groups and Days, $F(52,403)=2.87$, $p<0.0001$, were all reliable. Simple effects tests yielded a significant difference between groups on each of the blocks of Days, with the smallest F being 2.65, with *df* of 4 and 91. Dunnett's comparisons ($p<0.05$) were made between each of the experimental groups and the Control group at each block of 3 days. Activity in the Restrained group was less than the Control only on blocks 1 and 2. Activity in the Restrained group exceeded activity in the Controls on blocks 3–7. Activity after 1 day of shock was significantly less than that of Controls on blocks 1–3. After 2 days of shock activity was significantly below Controls on blocks 2, 3, 4, and 8–14. Activity for the 4 days of shock subjects was different than for Controls on all blocks except block 3.

Recall that body weight was measured before and 4, 8, 16, and 24 days after the beginning of experimental treatment. Because of an error the Control group was not weighed on Day 24 and so this data point is missing. The weight data are shown in Fig. 2 as a percent of change from baseline. Experimental treatment led to a transient weight loss which was fully recovered in all groups by Day 8. This weight loss was most prominent in the group given 4 days of shock and was not present at all after 1 day of shock. Analysis of variance yielded reliable effects of only Days, $F(2,64)=41.96$, $p<0.0001$, and the interaction of Groups and Days, $F(8,64)=9.28$, $p<0.0001$. Simple effects tests indicated that weights differed reliably only on the Day 4 measurement, $F(4,38)=3.25$, $p<0.03$. Dunnett's comparisons ($p<0.05$) yielded a reliable difference from Control weights for only the Restrained and 4 Days groups.

Figure 3 shows daily water intake across 3 day blocks as a percentage change from baseline. As with body weight, restraint and inescapable shock exposure led to a transient reduction. Water intake returned to normal by the second block of 3 days after either 1 or 2 days of inescapable shock. Examination of the individual day data indicates that water intake was fully recovered by 2 days following both the single and double inescapable shock treatment. Levels indistinguishable from Controls were attained by the third block after 4 days of restraint and by the fourth block after 4 days of inescapable shock. Since both of these treatments extended into the second block of 3 days, this indicates that water intake was only depressed for at most 2 days beyond the termination of restraint and at most 5 days beyond the termination of the 4 days of inescapable shock. Examination of the individual day data indicates that water intake had recovered by the fourth day. Analysis of variance yielded reliable effects of Days, $F(11,363)=14.99$, $p<0.0001$, and the interaction of Groups and Days, $F(44,363)=1.95$, $p<0.01$. Simple effects tests revealed a reliable Groups effect on Blocks 1 and 2 only. Dunnett's comparisons ($p<0.05$) indicated that all groups differed from the Controls on the first Block of 3 days, while the Restrained and 4 Days groups differed from the Controls on the second Block.

In sum, the present results confirm the usual transient

effect of exposure to stressors on body weight and water intake. Body weight changes were no longer evident 4 days after even 4 sessions of inescapable shock, and may have not even persisted for this long as a measurement was not made between days 4 and 8. Neither 1 or 2 sessions of inescapable shock had any effect on body weight measured 3 or 2 days later, respectively. Water intake recovered to control levels in anywhere from 2 to 4 days post-stress, depending on the condition. In dramatic contrast, the depression in daily running was much more persistent, but only after exposure to inescapable shock, not after exposure to restraint. It remained for 14 days after a single session of inescapable shock and was still in evidence at Day 42 in the 2 and 4 sessions of inescapable shock conditions.

EXPERIMENT 2

The magnitude and duration of the daily running wheel activity changes produced by exposure to inescapable shock is seemingly unique among the behavioral effects of stressors. This is especially true when it is recognized that testing here occurred in an environment that was quite distinct from the shock environment and one that was highly familiar and "safe." This raises the question of what the present effect might have in common with other "stress effects." The behavioral consequences of exposure to stressors are often quite sensitive to prevention or reversal by antidepressants (see [9] for a review). Experiment 2 thus sought to determine whether the activity reduction produced by inescapable shock might be reversed by antidepressant treatment. This seemed a particularly interesting possibility because antidepressants generally *reduce* or have no effect on activity in "normal" subjects (see [39] for a review).

METHOD

Subjects

The subjects were 40 rats identical to those used in Experiment 1.

Apparatus

The wheels were the same as those used in Experiment 1. However inescapable shock was delivered in a different apparatus. Plexiglas boxes measuring 15.5×12×17 cm (L×W×H) were used. The animals here had more freedom of movement than in the tubes used in Experiment 1. The animal's tail extended from the rear of the boxes and was attached to a rod. Inescapable shock was delivered to the tail via fixed electrodes augmented with electrode paste.

Procedure

The rats were placed in the wheels at 60 days of age and remained undisturbed for 85 days. Activity and water consumption were recorded for the final 49 of these days. The subjects were then divided into 5 groups matched on baseline activity. One group served as a Control and was not disturbed in any way. The remaining 4 groups received 3 daily sessions of inescapable tailshock administered in the Plexiglas boxes. Shock parameters were identical to those used in Experiment 1. Three days after the last shock session the 4 groups began to receive differential treatment. One group (0 mg group) continued without drug. The other 3 groups were given desipramine hydrochloride (Merrell Dow) dissolved in their drinking water at 3 different concentrations—5 mg/100 ml (5 mg group), 10 mg/100 ml (10 mg group), or 20 mg/100 ml (20 mg group). Desipramine solutions were prepared every other day and fresh solution provided. The drug was delivered in the drinking water rather than through injection because frequent removal of the animals from the wheels and injection would have been likely to disrupt activity. This regimen continued for the next 30 days during which activity and water consumption were recorded daily. At the end of the 30 days the Control and 0 mg subjects were switched to desipramine in order to determine the effect of desipramine on baseline activity. They received the concentration that had proven to be most effective in the first stage of the experiment (10 mg). The subjects which had been receiving desipramine were switched to plain water. This regimen continued for 15 days.

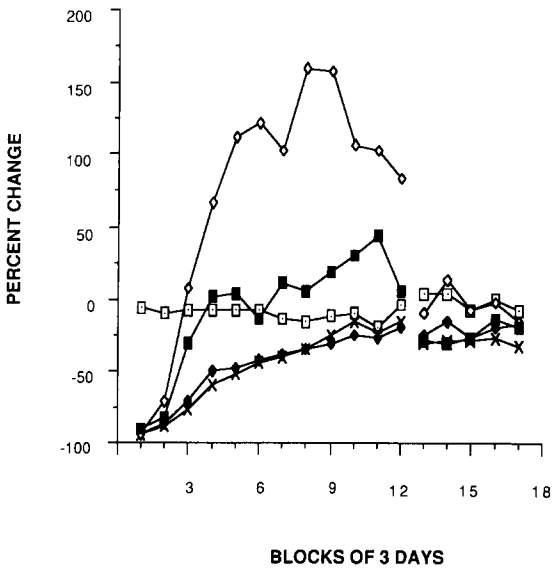

FIG. 4. Mean daily activity as percent change from baseline across blocks of 3 days for groups given no treatment, or inescapable shock combined with 0, 5, 10, or 20 mg concentrations of desipramine in their drinking water. At the break in the figure the Control and 0 mg groups were switched to 10 mg and the 5, 10 and 20 mg groups were switched to 0 mg. ⊡: control; ◆: 0 mg; ×: 5 mg; ◇: 10 mg; ■: 20 mg.

RESULTS

As in Experiment 1 the last 7 days of running wheel activity before experimental treatment were taken as each animal's baseline and wheel revolutions per day were expressed as percent change from this baseline. Figure 4 shows the daily activity for each group collapsed across 3 day blocks. The first block thus represents the days on which shock sessions occurred, the second block the 3 days post-shock before desipramine treatment began, the third block the first 3 days of desipramine administration, etc. The figure shows a break at the point at which drug treatments were switched.

First examine the data for the blocks (1–12) before the drug was switched among groups. The Control group showed quite stable activity across the 12 blocks. Inescapable shock again produced a profound reduction in daily activity, falling to almost zero during the 3 days on which shock treatment occurred. This severe drop occurred despite the fact that most running occurs during the dark part of the day/night cycle, darkness commencing 4–6 hr after the termination of the shock session. Activity recovered gradually

in the animals not given desipramine in their water, reaching Control levels after roughly 27 days. Desipramine had a dramatic and dose dependent effect on this activity reduction. The 5 mg concentration had no effect at all, while the 10 mg concentration elevated activity to levels far in excess of baseline or Control group levels. Examination of the individual day data indicates that the 10 mg concentration began to have an effect rapidly, but that its full effect appeared gradually across days. Percent change in activity compared to pre-stress baseline for the last day before drug administration for this group was −84%, and for each of the first 10 days following initial administration of this dose was −42, −29, 24, 26, 34, 50, 118, 83, 170, 82%. Thus 7 days seemed to be required for peak effectiveness. The 20 mg concentration seemed to have a small effect, but it is to be noted that this is entirely attributable to a single subject that was consuming desipramine in quantities falling in the range of the 10 mg subjects (see below). This subject's activity was enormously facilitated, and if this subject is removed the effect of the 20 mg dose disappears.

These conclusions were confirmed by a repeated measures analysis of variance. Because of the extreme skewness of the data (values could not fall below −100% but rose considerably above +100%) they were converted to logarithmic values for analysis. The effects of Groups, $F(4,32)=2.89$, $p<0.04$, Blocks, $F(11,352)=122.60$, $p<0.0001$, and the interaction of Groups and Blocks, $F(44,352)=9.41$, $p<0.0001$, were all reliable. Simple effects tests yielded reliable overall Group differences on Blocks 1–6, with the smallest F being 2.91 and *df*'s=4,55. Dunnett's comparisons ($p<0.05$) with the Control indicated that the 0 mg group differed from the Control on Blocks 1–6, as did the 5 mg group. The 10 mg group differed from the Control on all Blocks except Block 3, and the 20 mg group differed from the Control on Blocks 1, 2, 10, and 11.

Now examine the data after the drug switch (Blocks 13–17). Recall that the Control and 0 mg groups now received 10 mg in their water, while the 5, 10, and 20 mg groups now received 0 mg. The elevated activity of the animals that had been receiving 10 mg rapidly returned to Control and baseline levels. Importantly, the 10 mg concentration did not have a detectable effect when now administered to the nonshocked subjects and those that had been shocked but whose activity had been allowed to recover. The 10 mg concentration had no effect even though actual consumption (see below) was identical to that which the 10 mg group consumed before the switch and which was effective in reversing the impact of inescapable shock. This suggests that the drug does not in itself elevate running wheel activity at the dose that was effective in reversing the activity reduction produced by the inescapable shock. Analysis of variance applied to Blocks 13–17 did not yield reliable effects of Groups or the interaction of Blocks and Groups.

Mean daily water intake across blocks of 3 days is shown in Fig. 5. As in Experiment 1, exposure to inescapable shock produced a reduction in water intake that recovered to control levels relatively rapidly. The addition of desipramine to the water (Blocks 3–12) depressed water intake, and did so for as long as the drug remained in the water. This effect was concentration dependent, with the reduction being greatest for the 20 mg concentration, intermediate for 10 mg, and smallest for 5 mg. Water intake increased rapidly when desipramine was removed from the water (Blocks 13–17). Conversely, the addition of desipramine to water for the Control and 0 mg groups depressed intake.

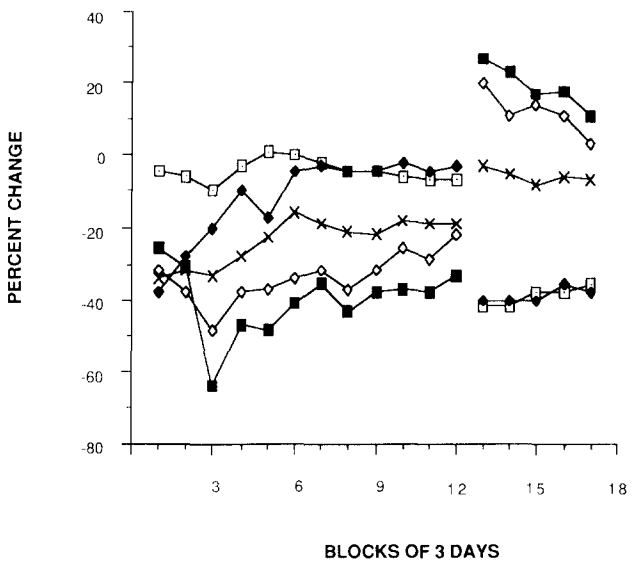

FIG. 5. Mean daily water intake as percent change from baseline across blocks of 3 days for groups given no treatment, or inescapable shock combined with 0, 5, 10, or 20 mg concentrations of desipramine in their drinking water. At the break in the figure the Control and 0 mg groups switched to 10 mg and the 5, 10 and 20 mg groups were switched to 0 mg. ⊡: control; ◆: 0 mg; ×: 5 mg; ◇: 10 mg; ■: 20 mg.

Analysis of variance of the data from Blocks 1–12 revealed reliable effects of Groups, $F(4,32)=16.58$, $p<0.0001$, Blocks, $F(11,352)=16.34$, $p<0.0001$, and the interaction of Groups and Blocks, $F(44,352)=5.51$, $p<0.0001$. Simple effects tests yielded reliable Group differences on all Blocks. The smallest F with 4 and 79 *df* was 6.97. Dunnett's comparisons ($p<0.05$) revealed that the 0 mg group differed from the Control on only Blocks 1 and 2. The 5 mg, 10 mg, and 20 mg groups all differed from the Controls at each Block. Analysis of the data after the shift (Blocks 13–17) indicated reliable effects of Groups, $F(4,32)=19.73$, $p<0.0001$, Blocks $F(4,128)=4.27$, $p<0.0001$, and the interaction of Groups and Blocks, $F(16,128)=2.59$, $p<0.0001$. Simple effects tests again yielded reliable Group differences on each Block, with the smallest F being 11.83 with 4 and 40 *df*.

Because the drug was administered in the drinking water each animal determined its own actual dose. Figure 6 shows the number of mg of desipramine ingested per day for each of the drug groups across blocks of 5 days. As can be seen, the 3 groups ingested distinctly different amounts of drug in accord with the amounts placed in the water. Indeed, there was only a single subject that overlapped between groups, with one subject in the 20 mg group ingesting an amount of desipramine in the 10 mg group range. The mean amount of desipramine ingested per day across the entire 30 days of administration was 1.86, 3.33, and 5.39 mg for the 5, 10, and 20 mg groups, respectively. The Control and 0 mg groups consumed an average of 3.22 and 3.11 mg after they were switched to the 10 mg concentration in the water. Analysis of variance yielded reliable effects of Groups, $F(2,22)=91.85$, $p<0.0001$, Blocks, $F(5,110)=18.96$, $p<0.0001$, and the interaction of Groups and Blocks, $F(10,110)=4.45$, $p<0.0001$. Newman-Keuls post hoc comparisons ($p<0.05$) indicated that each group differed from the other on each Block. Since the animals weighed approximately 400 g at this stage of the

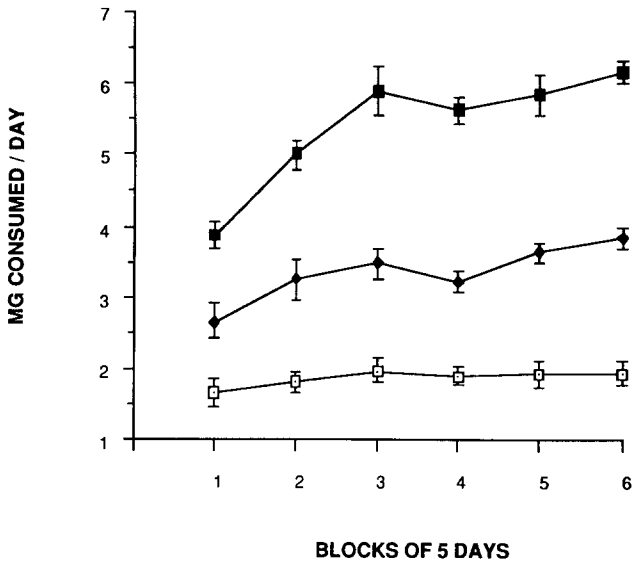

FIG. 6. Mean daily consumption of desipramine across blocks of 5 days for the 5, 10, and 20 mg groups. ⊡: 5 mg; ◆: 10 mg; ■: 20 mg.

experiment, the 5, 10, and 20 mg groups were receiving approximately 4.0–5.0, 8.0–9.0, and 13.0–14.0 mg/kg per day.

GENERAL DISCUSSION

The results of these experiments are quite clear. Exposure to inescapable shock depressed water intake and body weight for a short period of time, consistent with previous reports of behavioral changes following exposure to stressors. Thus water intake was reduced for 2–4 days following the last exposure to inescapable shock, depending on the conditions. Similarly, body weight had recovered to control levels by 4 days post-shock, and might have proved to recover even earlier if a measurement had been made. In dramatic contrast, the same shock conditions in the same subjects depressed daily running wheel activity for 14–42 days (the maximum period measured), depending on the number of exposures to inescapable shock and the apparatus in which inescapable shock was administered. It is to be noted that restraint did not have a prolonged impact on activity, even though the 4 days of restraint had a more pronounced effect on water intake and body weight than did either 1 or 2 days of shock.

The impact of desipramine was also quite clear. Desipramine depressed water intake in a dose dependent fashion. However, it is unclear whether this reduction was caused by the actions of the drug or by the taste it imparted to the water. The 5 and 20 mg concentrations had little effect on the activity reduction produced by inescapable shock. However, the 10 mg concentration reversed the activity reduction and led to an elevation of activity well above baseline levels. Activity returned to baseline levels when the drug was discontinued. In contrast, the 10 mg concentration had no effect at all on the activity of nonshocked animals or animals that had been shocked but whose activity had been allowed to recover before drug administration.

The duration of the changes in daily running wheel activity following inescapable shock stand in dramatic contrast to many of the behavioral consequences of exposure to stressors that have been studied. For example, we have employed the identical 4 day inescapable shock procedure used in Experiment 1 and have examined the persistence of subsequent shuttlebox escape learning deficits. Escape learning deficits were not demonstrable for more than 3 days following the last shock session (unpublished data). As noted above, there are a small number of reports of learning deficits persisting for 7 days, but here testing was conducted in an environment identical or similar to the environment in which inescapable shocks had been administered. These deficits could thus reflect a conditioned reactivation of the processes which underlie the escape learning deficit rather than an ongoing persistence across the 7 day interval. However, in the present studies persistent activity deficits occurred in an environment that had few if any cues in common with the environment in which inescapable shock was administered. The animals in Experiment 2 were not even handled again after being returned to the wheels after their last shock session, and so one cannot even point to handling cues as a mediator associated with shock. Moreover, the animals lived in the wheel environment for many days before shock was first administered, and thus even if there were cues in common they should not have become associated with shock because they were highly familiar. Familiar "safe" cues do not readily become associated with shock [21]. Finally, even if some cue present in the wheel environment had become associated with shock, the association should have extinguished well before 42 days of exposure with no further shock. The activity changes here observed thus reflect a long-term *unconditioned* effect of inescapable shock. The processes responsible must persist for the 14–42 days rather than being re-initiated during testing.

An obvious possibility is that the animals were injured during exposure to inescapable shock and thus ran less because they were unable to do so or because running produced pain. However, the animals were observed carefully and no injuries were detected. Reversal of the running reduction by desipramine is also inconsistent with this explanation since desipramine should not have produced recovery from injury. Desipramine has been reported to produce analgesia, but the effect is small and occurs only at doses higher than those used here [15]. Finally, other behavioral changes which also depend on locomotion (e.g., shuttlebox escape, swimming, activity in the presence of aversive stimuli, etc.) recover rapidly after exposure to the same inescapable shock procedure as was used here.

The depression of daily running must represent a long-term change in the processes which control and motivate daily activity. It is important to re-emphasize that the long-term change here observed reflects a change in daily activity, not in the organism's ability to locomote or respond to environmental stimuli that elicit locomotion. Locomotion in response to a shock stimulus, for example, is recovered in 2–3 days after exposure to inescapable shock [23]. Thus it is reasonable to look towards processes known to be involved in the control of daily activity. Daily activity in rats is a rhythmic behavior and follows a diurnal cycle, with most activity concentrated in the dark period [33]. Mechanisms controlling circadian rhythms are therefore obvious candidates as processes which might have been altered by inescapable shock. Circadian rhythms are thought to be controlled by one or more pacemakers each governing multiple oscillators [26]. Running wheel activity itself appears to be governed by the action of more than one oscillator [8]. An interesting possibility is that inescapable shock produced a long-term disruption in either a pacemaker or an oscillator

involved in regulating activity patterns so that the processes initiated at each active phase of the cycle ceased to occur. Activity in inescapably shocked subjects may not so much have been depressed as "uninitiated." The implication is that inescapable shock not only reduced overall running but destroyed its circadian pattern. Evaluation of this possibility will require a more fine-grained recording of activity than was performed in the present studies. Interestingly, depression has been argued to involve an alteration in circadian rhythms [17]. In this regard it might be noted that imipramine has a pronounced effect on the activity of the suprachiasmatic nuclei [44], the structure thought to constitute the brain's major pacemaker [25]. Moreover, the effect of imipramine is to shift activity toward the pattern seen in the dark (active) part of the cycle.

It might seem that this argument suggests that drinking should also have been disrupted for a long period of time since drinking also follows a diurnal pattern and is controlled by circadian processes [46]. However, drinking is also under strong homeostatic control and responds to deprivation with increased consumption. In contrast, running activity often is not increased by deprivation [14,24] and often decreases [36]. Thus running may be subject to fewer control mechanisms than drinking with less internal regulation.

The effects of desipramine observed in this study are complex but resemble those noted in man and experimental animals. First, we found that desipramine had little effect on activity in normal rats, even in chronic doses. Similarly, tricyclic antidepressants appear to have little impact on humans with normal affect. Moreover, as already noted, if tricyclic antidepressants do alter spontaneous activity in rats, the effect is generally sedative [39]. Second, desipramine had a potent stimulatory effect in rats that had been made hypoactive by inescapable shock. Indeed, inescapably shocked rats treated with desipramine displayed much greater activity than did control rats exposed to neither stress nor drug treatment. Moreover, the stimulatory effect of desipramine decreased several weeks post-stress, as the depressed activity of stressed rats returned to normal. Third, while some effect of desipramine was apparent within 24 hr of initial drug administration, a maximal effect required 7 days of treatment. Similarly, antidepressant treatment in man [6] and certain antidepressant behavioral effects in rodents [28] have been reported to require chronic drug administration. Finally, we observed a strongly curvilinear relationship between dose and behavioral effect. Only the intermediate dose of 8.0–9.0 mg/kg had a clear impact. This would represent a higher dose than typically employed in human clinical practice (300 mg in a 75 kg patient represents 4 mg/kg). However, a comparison of plasma or brain levels would be more relevant. A curvilinear relationship between plasma level of drug and antidepressant activity has been reported in man for desipramine [10] and other antidepressants [32].

These results may have cautionary implications for research on desipramine pharmacology in rats. First, the biochemical effects of tricyclic drugs have been generally studied in "normal" rats. But the effects of these drugs may be quite different in rats in other behavioral states such as that induced here. Certainly, the behavioral effect of the drug was very different in untreated and inescapably shocked animals. Second, the biochemical effects may depend strongly on dose. Many studies have used doses of 10 mg/kg or higher, and our results suggest that this may not be an effective dose range for stimulant properties of desipramine. The U-shaped dose response curve suggests a competing sedative effect activated at higher doses.

The sensitivity of the running reduction to desipramine should not be taken to mean that the present paradigm is either generally or specifically responsive to antidepressants. Such a conclusion would require investigation of a wide variety of pharmacological agents that both do and do not have antidepressant effectiveness. However, the duration and nature of the behavioral change isolated here does seem to more closely resemble human reactions to exposure to severe stressors than many others which have been studied.

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