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Factors That Modulate Inescapable Shock-Induced Reductions in Daily Activity in the Rat

W. W. WOODMANSEE, L. H. SILBERT AND S. F. MAIER[1]

Department of Psychology, Campus Box 345, University of Colorado, Boulder, CO 80309

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WOODMANSEE, W. W., L. H. SILBERT AND S. F. MAIER. *Factors that modulate inescapable shock-induced reductions in daily activity in the rat.* PHARMACOL BIOCHEM BEHAV **45**(3) 553–559, 1993.—Most behavioral and neurochemical changes produced by inescapable shock dissipate in 1–3 days. However, daily running activity is depressed for 14–42 days following one to three sessions of inescapable shock. In the present experiments, we sought to determine whether factors known to be important in the development of the short-term effects of exposure to inescapable shock would also be important in the production of the long-term effect of inescapable shock on daily activity. Three factors were examined: a) the escapability of the shock; short-term behavioral changes generally do not occur if the shock is escapable; b) naltrexone pretreatment; the opioid antagonist naltrexone typically prevents many of the short-term behavioral sequelae of inescapable shock; c) treatment with the anxiogenic β-carboline FG-7142; administration of this compound alone frequently mimics inescapable shock in its ability to transiently disrupt behavior. The inescapable shock-induced reduction in daily activity did not depend upon escapability of the stressor. In addition, naltrexone did not prevent and FG-7142 did not induce the reduction in daily activity associated with stressor exposure.

Inescapable shock Learned helplessness Activity Naltrexone FG-7142

EXPOSURE to aversive events leads to both conditioned and unconditioned changes. Conditioned alterations in either behavior or neurochemistry are long lasting and depend for their occurrence upon reexposure to environmental stimuli that had been present during the presentation of the stimuli (4,16). Conversely, unconditioned changes are assumed to dissipate rapidly and do not require the presence of stimuli that had been present during the aversive stimulation. Unconditioned neurochemical and behavioral sequelae of aversive events such as a session of inescapable shock typically persist for only 48–72 h. For example, inescapable shock-produced escape learning deficits (11), reductions in shock-elicited movements (11), reductions in food and water intake (5,18), reductions in struggling when placed in water (19,20), reductions in shock-elicited aggression (13), reinstatable analgesia (10), increased freezing following a shock (12), and monoamine changes (1,19) all disappear within 48–72 h after exposure to inescapable shock.

Desan, Silbert, and Maier (5) and Maier, Silbert, Woodmansee, and Desan (15) reported an exception to this pattern. They found that one to three sessions of inescapable shock led to a reduction in daily running wheel activity that persisted for 14–42 days, depending upon experimental parameters and conditions. In their experiments, animals were first allowed to live in the running wheel apparatus for 4–6 weeks to establish a baseline of running. Thus, the running wheels became a highly familiar environment before any shock was administered. The inescapable shock session that followed was conducted on a different floor of the building while rats were restrained in Plexiglas tubes to minimize the possibility that there would be stimuli in common between the shock environment and the running wheel. Animals were then returned to the wheel and remained undisturbed for the duration of the experiment. It is therefore unlikely that reductions in activity could represent conditioned effects, but running was still severely reduced for a period of weeks. Thus, it would appear that the reduction in running produced by inescapable shock is not a conditioned change but is nevertheless more persistent than is typical of unconditioned consequences of stressors. Further, the reduction in running could not be easily attributed to unobserved physical damage because the reduction in activity could be reversed by desipramine (5).

Little is known about this long-term effect of inescapable shock on daily activity. The time course of the activity change following inescapable shock suggests that perhaps it may be mediated in ways different from other consequences of inescapable shock that have been studied. Here, we explored several factors known to modulate the impact of inescapable

[1] To whom requests for reprints should be addressed.

shock on other behaviors, that is, the strategy was to examine the impact of variables that are known to modulate the effects of inescapable shock on other behaviors on daily running following inescapable shock. The question of interest was whether daily running is simply a more sensitive behavioral endpoint or whether inescapable shock-produced changes in daily activity are mediated in a fundamentally different manner than endpoints previously investigated.

Three variables were chosen for study. First, the sensitivity of this paradigm to stressor controllability was examined because both the behavioral and neurochemical sequelae of inescapable shock depend upon its inescapability (2,12). Second, sensitivity of the inescapable shock-induced reduction in daily activity to blockade by the opioid antagonist naltrexone was explored. The administration of naltrexone before inescapable shock blocks the resulting escape deficit (7), reduced movement in response to shock (7), and reinstated analgesia (14) observed 24 h later. Finally, we explored whether the activity deficit can be induced by the anxiogenic β-carboline FG-7142. The application of FG-7142 to restrained rats mimics many of the short-term behavioral effects of inescapable shock, such as poor escape (8), reinstated analgesia (6), and decreased social interaction (17), all measured 24 h later.

EXPERIMENT 1

Experiment 1 set out to determine whether the prolonged reduction in daily activity observed following inescapable shock is a function of shock controllability. Animals were exposed to either one or three sessions of escapable or inescapable tail-shock. Comparisons in daily running wheel activity before and after experimental manipulation were made to animals not exposed to tail-shock.

METHOD

Subjects

Subjects were 48 male Sprague-Dawley rats obtained from Holtzman Laboratories. They were approximately 60 days of age (250–275 g) at the time of arrival. Immediately upon arrival, animals were placed in activity cages, where they remained for the duration of the experiment. Animals were maintained on a 12 L : 12 D cycle with lights on at 0700 h. Food and water were available at all times.

Apparatus

All animals were housed in activity cages (Geo H. Wahmann, Baltimore, MD) for the duration of the experiment. The activity cages consisted of two compartments mounted to a galvanized metal frame 70 × 35 × 45 cm. One compartment was a 11.5 × 35-cm (width × diameter) wire mesh wheel. The other compartment was a 25 × 15 × 2.5-cm wire mesh cage. The frame separated the two compartments, but a 9 × 7-cm (length × height) opening in the metal frame provided easy access between the two compartments. A counter attached to the wheel recorded daily revolutions. All food and water were available from the cage part of the apparatus.

Escapable and inescapable shock occurred in clear Plexiglas wheel turn boxes measuring 14 × 11 5 × 17 cm. A Plexiglas aluminum spoke wheel (9.5 cm in diameter and 7 cm wide) was mounted in the front wall such that the wheel protruded 2.8 cm into the chamber and was 4.0 cm from the floor. Each wheel had 12 aluminum spokes, 7 cm long and 0.5 cm in diameter, by which the animal could easily turn the wheel with any downward movement. The spokes were parallel to the wheel's axis and were spaced equidistant along the wheel perimeter. Each quarter turn of the wheel was detected by a microswitch mounted on the exterior of the wheel turn box. The rat's tail extended from the rear of the chamber at floor level and was taped to a 9-cm Plexiglas rod. Electrodes for shock delivery were attached to the rat's tail with electrode paste. Shock sources were modeled after the Grason-Stadler Model 700.

Procedure

All rats were placed in individual activity cages upon arrival, where they lived undisturbed until the treatment phase of the experiment. The pretreatment phase was 37 days. Daily wheel revolutions were measured, and upon reaching a plateau in running wheel activity animals were divided into six groups of eight rats. Each group was balanced in terms of pretreatment baseline activity such that all the groups had a similar average activity score. One group of animals served as the home cage control group and was allowed to live undisturbed for the entire experiment. The remaining groups of animals received either one or three sessions of escapable or yoked inescapable (yoke) shock in the wheel turn boxes. Finally, the last group of animals was restrained in the wheel turn boxes for three sessions. One session of shock for animals in the escape group consisted of 100 1.6-mA escape trials occurring on a random-interval 60-s schedule (range 30–90 s) The response requirement for each trial ranged from 1–16 quarter-turns of the wheel and depended upon the animal's performance on the previous trial. The procedure for shock delivery was as follows. A quarter-turn of the wheel was defined as an escape response. Responses during the first 0.8 s of the trial were ignored and did not terminate the shock. One response or one quarter-turn of the wheel following the 0.8-s delay was sufficient to terminate shock for the first five trials. The response requirement was adjusted on the sixth trial based upon the animal's performance on the first five trials. The response requirement was increased to two quarter-turns if the animal's escape latencies on the previous three trials were under 5 s. After four consecutive trials with escape latencies under 5 s, the response requirement was incremented by two. The response requirement was increased by three if five consecutive trials under 5 s were obtained. This pattern of increasing response requirement continued until a maximum of 16 quarter-turns were required to terminate shock. If the animal responded to the shock between 5 and 10 s after shock onset, the escape requirement on the next trial remained unchanged. If the escape latency on a trial was greater than 10 s, the response requirement was decreased by one on the following trial. If the animal did not escape within 30 s, the shock was terminated and the response requirement went back to one quarter-turn and the process resumed. This procedure is designed to assure that subjects learn an instrumental escape response rather than merely reflexively turning the wheel in response to shock. It is the standard escape training protocol employed in this laboratory. Animals in the inescapable groups received identical amounts of shock to animals in the escapable groups; the only difference was that the shock was uncontrollable for these animals. Each animal in the inescapable group was paired with an animal that could escape the shock and was simply given the same amount of shock on each trial. The only difference between these groups was that the shock was uncontrollable for yoked animals in that turning the wheel was without consequence. Restrained animals

were placed in the wheel turn boxes for a time comparable to the duration of the shock sessions but did not receive shock. Animals were immediately returned to their home activity cages following treatment. All treatments occurred between 1000 and 1500 h, during the light part of the rat's cycle, and all animals in the same group were treated on the same day(s). Wheel revolutions were measured for 18 days following treatment.

RESULTS

Baseline running wheel activity differed widely between animals. Each animal's daily wheel revolutions were expressed as a percent of its own baseline activity to allow comparison of activity between animals. Daily wheel revolutions for the 7 days prior to treatment were averaged for each subject and served as the subject's baseline activity score. Daily wheel revolutions for each day following treatment are computed as a percent of the subject's baseline score. Treatment of the different groups was staggered over several days of the experiment. As a result, the first posttreatment day was a different calender day for the different groups. This necessarily made statistical analysis difficult because it is important to make comparisons between groups on the same days of the experiment to control for general fluctuations in the conditions of the experimental colony room. The data were therefore expressed as a change relative to the home cage control group. The mean percent change from baseline for the control group was subtracted from each animal's percent change score for each day posttreatment. The transformed posttreatment day scores were grouped into blocks of 3 days by averaging the percent change scores over 3 days in blocks until the end of the experiment. Data in this form were analyzed by a repeated-measures analysis of variance (ANOVA). The results are shown in Fig. 1. As can be seen, 3 days of restraint had little effect on activity. In fact, restrained animals showed a slight increase from baseline activity relative to home cage controls. In contrast, both one and three sessions of inescapable shock produced a large reduction in activity that persisted for 9–12 days. Importantly, this reduction in activity was of similar magnitude following escapable and inescapable shock. These results were confirmed by a repeated-measures ANOVA. Results indicated the main effect of group, $F(4, 160) = 3.778$, $p = 0.0126$, main effect of blocks of days, $F(5, 160) = 91.929$, $p < 0.0001$, and interaction, $F(20, 160) = 4.064$, $p < 0.0001$, were all reliable. Simple effects analysis showed a significant effect of group on blocks 1, 2, and 3 ($p < 0.01$). Newman-Keuls posthoc tests ($p < 0.05$) on each of the reliable blocks yielded the following results. For the first 6 days posttreatment (blocks 1 and 2), all animals that received tail-shock demonstrated a reliable reduction in running wheel activity as compared to animals in the restrained control group. This reduction in activity was independent of number of sessions and controllability of the stressor. On block 3, the same general pattern held with the exception that animals that received three sessions of inescapable shock no longer differed reliably from the restrained controls.

EXPERIMENT 2

Experiment 1 demonstrated that the decrease in daily activity produced by tail-shock is not sensitive to the controllability of the stressor. Animals that received escapable shock were not prevented from exhibiting the activity reduction as measured in the running wheel. Because controllability of the stressor plays a critical role in the development of many of the short-term behavioral consequences of shock, replication is desirable. Hence, Experiment 2 was partly devoted to a replication of the controllability manipulation. This experiment was also designed to determine the effects of the opioid antagonist naltrexone on the changes in daily activity produced by inescapable shock.

METHOD

Subjects

Subjects were 48 male Sprague-Dawley rats obtained from Holtzman Laboratories similar to those described in Experiment 1.

Apparatus

All animals were housed in activity cages (Geo H. Wahmann), identical to those described in Experiment 1, for the duration of the experiment.

Escapable and inescapable (yoke) shock occurred in clear Plexiglas wheel turn boxes identical to those described in Experiment 1.

Inescapable shock was delivered to some animals while restrained in a Plexiglas tube measuring 23.5 cm in length and 7 cm in diameter. The rat's tail extended from one end of the tube and was secured to a rod extending from the tube. Electrodes for shock delivery were attached to the rat's tail with electrode paste.

Procedure

Forty-eight rats were placed in individual activity cages upon arrival, where they lived undisturbed until the treatment phase of the experiment. The pretreatment phase lasted 36 days in this experiment. Upon reaching a plateau in running wheel activity, animals were divided into six groups of eight rats. Each group was balanced in terms of pretreatment baseline activity such that all groups had a similar average activity score. One group of animals served as the home cage control group and was allowed to live undisturbed for the entire duration of the experiment. Two groups of animals received three sessions of escapable or inescapable (yoke) shock in the wheel turn boxes. The escape training protocol was identical to that employed in Experiment 1. The remaining three groups of animals were used to determine opioid involvement in the shock-induced reduction in running wheel activity. Sixteen animals received three sessions of inescapable shock on 3 consecutive days while restrained in Plexiglas tubes. One session of shock consisted of 100 1.6-mA shocks, 5 s in duration, with an average intertrial interval of 60 s (range 15–120 s). Half of these animals received an IP injection of saline 20 min prior to shock and half received an IP injection of naltrexone (10 mg/kg) 20 min prior to shock. This dose was chosen because it was midway between the 7-mg/kg dose previously found to be effective in reversing stress-induced escape learning deficits (7) and the maximal dose of 14 mg/kg tested. Injections were given after the animal had been removed from its home cage environment and transported to the treatment room. The last group of animals was given a total of three IP injections of naltrexone (10 mg/kg), one injection per day for 3 days. These animals were removed from their home cages, transported to the treatment room, given the injection of naltrexone, and restrained in Plexiglas tubes for the duration of an average shock session (90 min). Animals in the naltrexone-only group were restrained but did not receive tail-shock. All animals

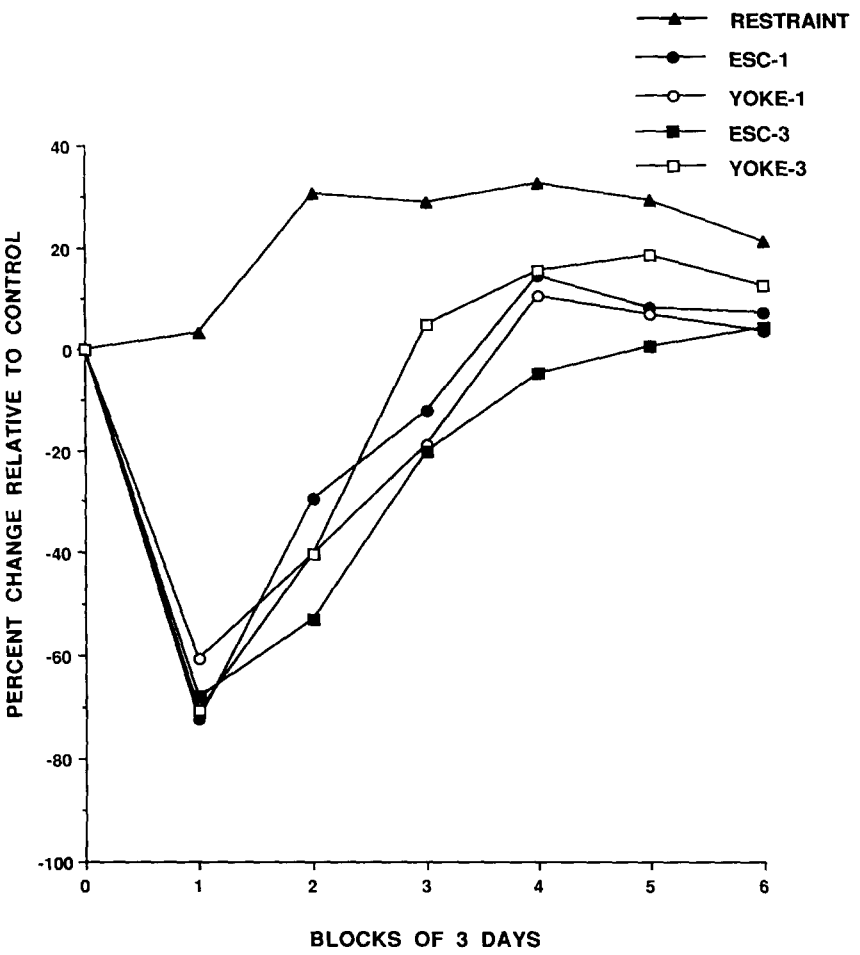

FIG. 1. Mean daily activity for all experimental groups, across blocks of 3 days, as percent change from baseline expressed as a difference from control. Animals received either one or three sessions of escapable (ESC-1, ESC-3) or inescapable shock (YOKE-1, YOKE-3). One group received three sessions of restraint (RESTRAINT).

were immediately returned to their home activity cages following treatment. All treatments occurred between 1000 and 1500 h, during the light part of the rat's cycle, on the same 3 days of the experiment. Wheel revolutions were measured for 18 days following treatment.

RESULTS

The data were treated as in Experiment 1 and are shown in Fig. 2. Daily running wheel activity was suppressed by exposure to tail-shock and was again unaffected by shock controllability. In addition, the opioid antagonist naltrexone had no effect on daily running wheel activity, nor was it able to block the reduction in daily activity produced by inescapable shock. Statistical analysis revealed a significant effect of groups, $F(5, 185) = 5.147$, $p < 0.001$, a significant effect of blocks of days, $F(5, 185) = 29.629$, $p < 0.0001$, and a significant interaction of groups and days, $F(25, 185) = 3.646$, $p < 0.0001$. Simple effects analysis to examine the interaction showed a significant effect of group on blocks 1, 2, and 5 ($p < 0.05$). Further analysis using the Newman-Keuls posthoc test demonstrated the following. The inescapable shock + saline group was significantly ($p < 0.05$) different from the home cage group and naltrexone-only group on blocks 1 and 2. The inescapable shock + naltrexone group was significantly different from the home cage group and naltrexone-only group on blocks 1 and significantly different from the naltrexone-only group on block 2. The groups of animals receiving either escapable or inescapable yoke shock differed from both home cage controls and naltrexone-only animals on blocks 1 and 2. There was no effect of controllability on any of the blocks of 3 days following treatment. The naltrexone-only group did not differ from the home cage control group on any of the blocks of days examined.

EXPERIMENT 3

The purpose of Experiment 3 was to determine whether the anxiogenic, FG-7142, would mimic inescapable tail-shock in producing a reduction in daily running wheel activity.

METHOD

Procedure

Upon arrival, 24 rats were placed in individual activity cages, where they lived undisturbed until the treatment phase of the experiment. In this experiment, the pretreatment phase lasted 41 days. Upon reaching a plateau in running wheel

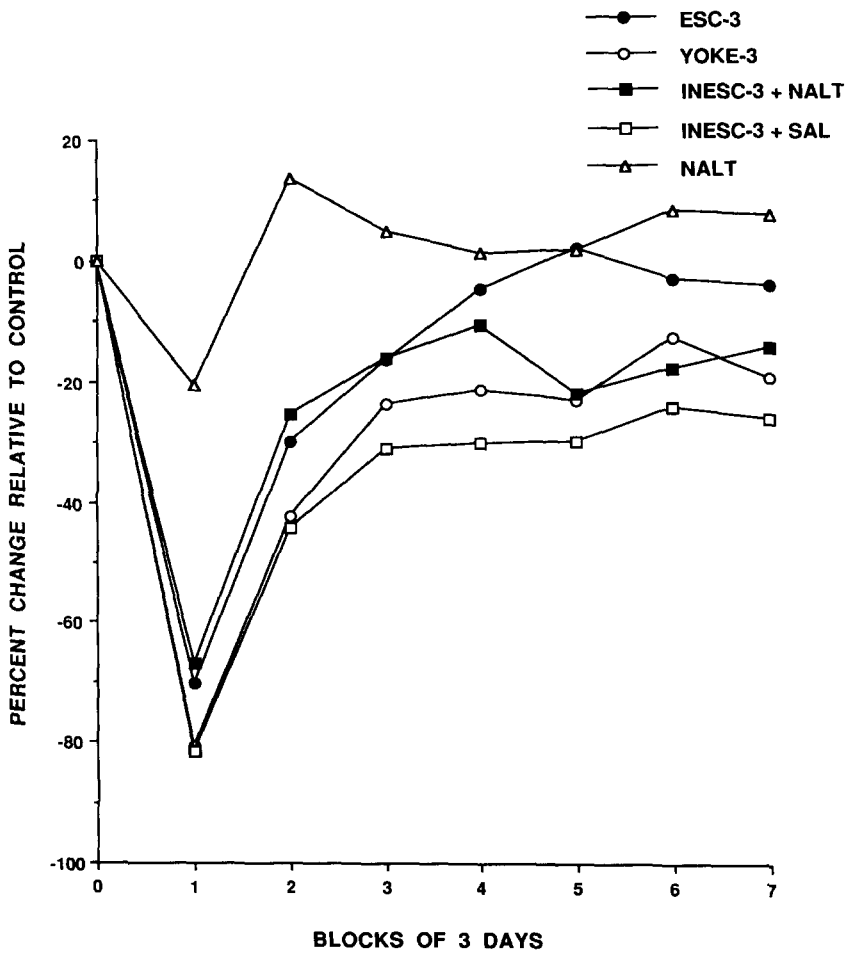

FIG. 2. Mean daily activity for all experimental groups, across blocks of 3 days, as percent change from baseline expressed as a difference from control. Animals received either three sessions of escapable shock (ESC-3), three sessions of inescapable shock (YOKE-3), three sessions of inescapable shock and naltrexone (INESC-3 + NALT), three sessions inescapable shock and saline (INESC-3 + SAL), or no shock and three injections of naltrexone (NALT).

activity, animals were divided into three groups of eight rats equated for average activity level. One group of animals served as the home cage control group and was allowed to live undisturbed for the entire duration of the experiment. One group of animals received three sessions of inescapable shock on 3 consecutive days while restrained in Plexiglas tubes. Finally, the last group of animals received a total of three IP injections of FG-7142 (10 mg/kg) on 3 consecutive days. This dose of FG-7142 is identical to that used by Drugan et al. (6) and Short and Maier (17) to mimic inescapable shock. Injections were given after the animal had been removed from its home cage environment and transported to the treatment room. Animals were then restrained in a Plexiglas tube for the duration of a shock session. All animals were immediately returned to their home activity cages following treatment. All treatments occurred between 1000 and 1500 h, during the light part of the rat's cycle, on the same 3 days of the experiment. Wheel revolutions were measured for 21 days following treatment.

RESULTS

Daily wheel revolutions were expressed as a percent of its own baseline activity as in the prior experiments. Figure 3 presents the activity of the experimental groups relative to the home cage control in blocks of 3 days. Three sessions of shock had a profound effect on daily running wheel activity such that activity was substantially reduced from control for the duration of the experiment. Administration of the anxiogenic compound, FG-7142, prior to restraint had absolutely no effect on daily running wheel activity. These results were confirmed by a repeated-measures ANOVA. The main effect of group, $F(2, 108) = 7.723$, $p < 0.01$, and the main effect of blocks of days, $F(6, 108) = 6.299$, $p < 0.0001$, were reliable. Analysis of simple effects yielded significant effect of groups on block 1, 2, 3, 4, and 5 ($p < 0.05$). Newman-Keuls posthoc analysis on blocks 1-5 revealed that animals receiving three sessions of inescapable shock differed significantly on blocks 1-5 from both home cage controls and animals receiving three injections of FG-7142. Animals receiving FG-7142 did not differ from home cage controls on any block of 3 days examined.

GENERAL DISCUSSION

The results of these experiments are clear in showing that the reduction in daily running produced by inescapable shock

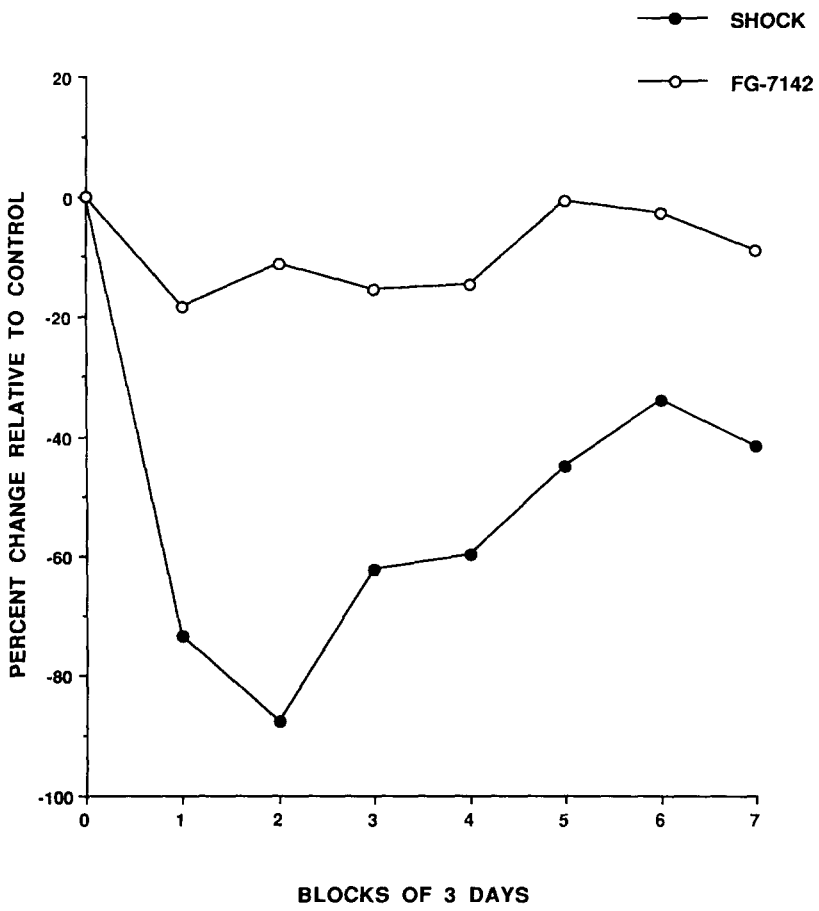

FIG. 3. Mean daily activity for all experimental groups, across blocks of 3 days, as percent change from baseline expressed as a difference from control. Animals received either three sessions of inescapable shock (SHOCK) or no shock and three injections of FG-7142 (FG-7142).

responds differently than do many of the other behavioral consequences of inescapable shock. It proved to be insensitive to shock controllability and so should be viewed as a consequence of exposure to shock per se rather than to inescapable shock. Further, the reduction in running was unaffected by naltrexone administered before shock and was not induced by FG-7142.

It is difficult to isolate the crucial differences(s) between the behavioral consequences of inescapable shock that dissipate rapidly and the daily activity reduction. Both are unconditioned reactions. As noted previously, shuttlebox escape deficits, reduced activity in reaction to shock or being placed in water, reduced shock-elicited aggression, potentiated "opioid" analgesia in reaction to small amounts of shock, increased freezing following shock, and decreased social interaction in a novel environment are the behavioral sequalae of inescapable shock that have been shown to dissipate in 48–72 h. The time courses of other behavioral consequences of inescapable shock have not been measured. The behaviors above can be characterized as being either unconditioned responses (UCRs) to shock or other aversive events or reflections of fear conditioned to cues paired with aversive events or elicited by novelty [see (13) for a more complete argument]. Both UCRs to noxious stimuli and conditioned fear can be considered different types of defensive behavior (3,9), with the former being responses to the actual presence of an aversive event and the latter a reaction to signals for such events. Thus, the short-term changes produced by inescapable shock can be summarized as inhibited defensive UCRs and facilitated fear (13).

Daily running is neither a defensive UCR nor is it a behavior that is part of the fear response. Clearly, the neural circuitry that underlies defensive UCRs and fear must be sensitive to stressor controllability, naltrexone, and FG-7142. The implication of the present results is that the neural circuitry that mediates daily running is not sensitive to these factors. Speculations concerning the nature of these systems go beyond the present data.

There has been a tendency to suppose that stressor controllability modulates all of the sequalae of stressor exposure. The conception has been that controllability determines the "amount" of stress that results, as if "stress" were a simple dimension that can be scaled in magnitude. If this were the case, then controllability should modulate all outcomes of stressors. The present data suggest that this may not be the case. There has also been a natural tendency to attempt to explain the behavioral consequences of inescapable shock by invoking a single underlying mechanism. However, the pres-

ent data suggest that this may be a poor strategy. Inescapable shock leads to multiple and widespread neural changes [see (2) for a review], and different behavioral endpoints may be caused by different sets of these changes. Thus, different behaviors might be expected to respond differently to behavioral and pharmacological variables, and the task will be to determine which behaviors are produced by which sets of neural changes.

ACKNOWLEDGEMENTS

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