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MIF-1 is Active in a Chronic Stress Animal Model of Depression

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PIGNATIELLO, M. F., G. A. OLSON, A. J. KASTIN, R. H. EHRENSING, J. H. McLEAN AND R. D. OLSON. *MIF-1 is active in a chronic stress animal model of depression.* PHARMACOL BIOCHEM BEHAV **32**(3) 737–742, 1989.—MIF-1 was tested in an animal model of depression that used unpredictable chronic stress. In this paradigm, rats received either no stressors or a daily protocol of a variety of stressors for 20 days, during which time daily, intraperitoneal injections of various compounds were given. The tricyclic antidepressant imipramine (5 mg/kg) and low doses (0.1 and 1.0 mg/kg) of MIF-1 significantly increased activity and decreased defecation in an open field on day 21. No dose of naloxone (0.01–10.0 mg/kg) acted as an antidepressant. A high dose (10.0 mg/kg) of MIF-1 significantly increased the effects of chronic stress and produced hyperalgesia. Chronically-stressed rats were significantly more analgesic than controls. The results indicate that MIF-1 can act as an antidepressant in this model.

MIF-1 Imipramine Naloxone Chronic stress Depression Open field Endogenous opiate system

MIF-1 (prolyl-leucyl-glycinamide) is a tripeptide that has been shown to modulate several forms of behavior (26). Prominent among these are its actions as an antidepressant and opiate antagonist.

The ability of MIF-1 to act as an antidepressant was reported to be dose-related, with lower doses producing antidepressant outcomes and higher doses either having no effect or exacerbating symptoms (3–6, 8, 9). The human EEG profile of a low dose (1.0 mg/kg) of MIF-1 also was similar to that of the tricyclic antidepressant amitriptyline (7). In some of the studies, MIF-1 was shown to be clinically effective within a few days as opposed to the typical delayed onset of improvement seen with tricyclic antidepressants (3,25).

Environmental stress seems to play a substantial role in depressive illness (2, 17, 18, 23, 24). Moreover, chronic low-grade stressors appear to be more detrimental than single occurrences (1,27), as in the case of long-term marital, family, and occupational struggles.

To evaluate the effectiveness of MIF-1 when chronic stress is used as the precipitating factor, the tripeptide was tested in the unpredictable chronic stress animal model of depression developed by Katz (10). Willner considers the model to have high overall validity (27). In this paradigm, rats are exposed to a variety of stressors for three weeks, after which time some animals are exposed to an acute stress followed by an open field test. Acutely-stressed rats show high activity and low defecation in the open field compared with chronically-stressed rats, unless the chronically-stressed rats receive daily, concomitant injections of an antidepressant (11–16, 21, 22).

The investigation was composed of three experiments. In the first experiment, the tricyclic antidepressant imipramine was tested in order to validate the model in our laboratory. The second experiment involved five doses of both MIF-1 and naloxone in order to evaluate the antidepressant and opiate antagonistic effects of MIF-1 in this model. In Experiment 3, attempts were made to reverse the effects of chronic stress by treatment for three weeks after termination of the chronic stress procedure.

EXPERIMENT 1

METHOD

Animals

Forty-eight (48) Sprague-Dawley-derived male rats, 70 days old at the start of testing, were used. They were housed individually and were handled for three days before the start of the experiment. Food and water were freely available for all groups

[1]This investigation was based on the doctoral dissertation of Michael F. Pignatiello at the University of New Orleans. These experiments were approved by the Committee for the Protection of Human and Animal Subjects at the University of New Orleans (#S-11).
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TABLE 1

TWENTY-DAY CHRONIC STRESS PROTOCOL

Day 1	shock (30 10-sec 1-mA shocks, spaced 1-min apart, in an operant chamber)
Day 2	food deprivation (40 hr)
Day 3	cold swim (5 min, 4°C)
Day 4	water deprivation (40 hr)
Day 5	–
Day 6	heat stress (5 min, 40°C)
Day 7	shaker stress (15 min, 1 ft horizontal displacements at 1 ft/sec)
Day 8	light/dark cycle reversal (24 hr light then 24 hr dark)
Day 9	cold swim
Day 10	shock
Day 11	tail pinch (1 min, hemostat clamped 1 cm from base of tail)
Day 12	heat stress
Day 13	food deprivation
Day 14	–
Day 15	light dark cycle reversal
Day 16	cold swim
Day 17	tail pinch
Day 18	shock
Day 19	water deprivation
Day 20	shaker stress

except on those occasions when food or water was removed as part of the chronic stress procedure. A lighting cycle of 12 hr/12 hr (lights on from 0700 to 1900 hr) was automatically programmed.

Apparatus

Open field testing was performed on a white tile floor, with each side of the field measuring 1.22 m (4 feet) in width and 45 cm (1.5 ft) in height. The floor was divided into 16 equally-sized squares, each being 30.5 cm (1 ft) on a side, to allow for assessment of locomotion. The open field was cleaned with water between tests.

Design

A 2×4 between-subjects factorial design was used for this experiment. This design represented two treatment groups (imipramine and diluent) and four stress groups (control, chronically-stressed, acutely-stressed, and chronically + acutely-stressed groups), with an n of six for each condition. Animals in the chronically + acutely-stressed group subsequently will be referred to as the combined-stressed group.

Chronic Stress Procedure

Over the course of 20 days, a series of 18 stressors was given to the animals, one stressor daily except for two days when no stressor was given. The order of chronic stress administration can be found in Table 1. On each day, the time of delivery of the stressor was varied so as to maximize the unpredictable nature of the stressors.

Acute Stress Procedure

On the 21st day, commencing one-half hour into the dark cycle, animals receiving the acute stress were placed in a lighted room for one hour in front of a speaker emitting a 95 dB white noise. After exposure to this noise/light stress, these rats were transported immediately to the open field test room.

Open Field Testing

Testing was carried out in the dark except for a 25-watt GE red light bulb which was placed over the open field area allowing the experimenter to record data. A continuous background masking noise of 40–50 dB was provided by normal operation of the air circulation system. Animals were individually placed so as to face one of the four corners. Placement initiated timing of the test. Four behavioral measures were assessed during a three-min period. The four measures included (a) mean activity score (number of squares which the rat entered with all four feet), (b) mean latency to leave the home square (0–180 sec), (c) mean defecation score (number of boluses at the end of the three minutes), and (d) mean latency to initial defecation (0–180 sec). Since the latency scores mirrored the results of the other activity and defecation scores, they are not reported separately.

Compounds

Rats were given daily, intraperitoneal (IP) injections of either diluent (0.9% NaCl, 0.01 M acetic acid) or 5 mg/kg imipramine HCl, 1 ml/kg. Animals receiving chronic stress were given the injections 15 min before the stressor. Animals not receiving chronic stress were given daily injections sometime during the light cycle. Compounds were coded, with the code being withheld from the experimenter until all data were analyzed. Injections stopped 36 hr before open field testing.

Statistical Analyses

A 2×4 analysis of variance was conducted for each behavioral measure. Tukey's HSD post hoc test was used to assess comparisons between groups with a significance level set at $p<0.05$.

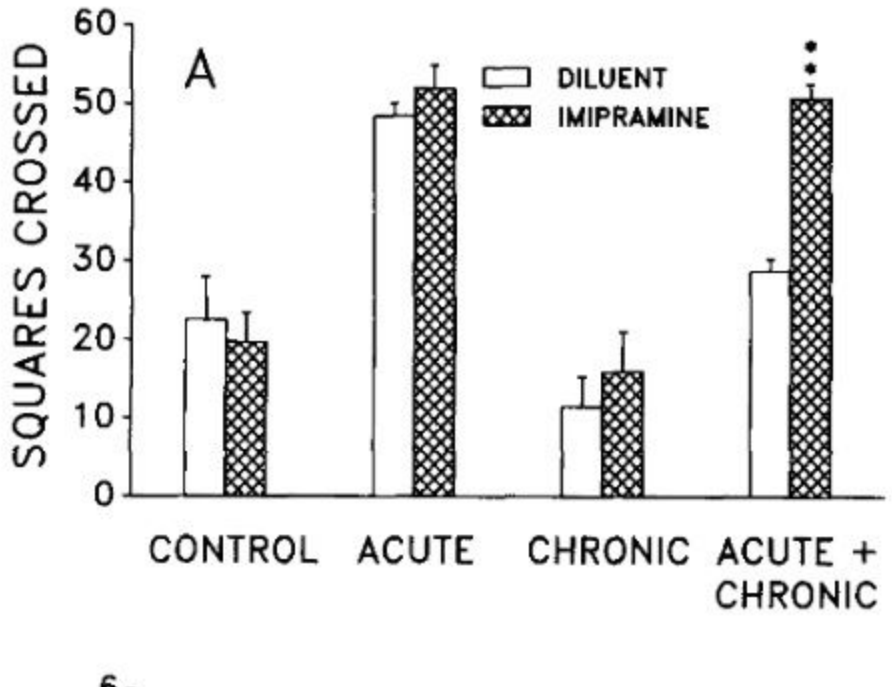
RESULTS

Mean Activity Score

As shown in Fig. 1A, there was a significant main effect for Treatment, $F(1,40)=10.3$, $p<0.01$, with animals that received imipramine exhibiting more activity than animals that received diluent. The main effect for Stress also was significant, $F(3,40)=50.6$, $p<0.01$, indicating that the animal model was successful. Animals in both the acutely-stressed and combined-stressed groups had increased activity compared with animals in both the control and chronically-stressed groups ($p<0.01$). The acutely-stressed animals also had more activity than the combined-stressed animals ($p<0.05$). The Treatment × Stress interaction was significant, $F(3,40)=5.2$, $p<0.01$, with simple main effects tests showing that animals given imipramine had more activity compared with animals given diluent in the combined-stressed group, $F(1,10)=71.6$, $p<0.01$.

Mean Defecation Score

As shown in Fig. 1B, the main effect for Stress was reliable, $F(3,40)=5.3$, $p<0.01$, with the acutely-stressed animals producing fewer boluses than the control animals ($p<0.01$). No other comparisons reached significance. As a result of the significant Treatment × Stress interaction, subsequent tests showed that in the combined-stressed group, animals that received imipramine had reliably less defecation compared with animals that received diluent, $F(1,10)=5.0$, $p<0.05$.



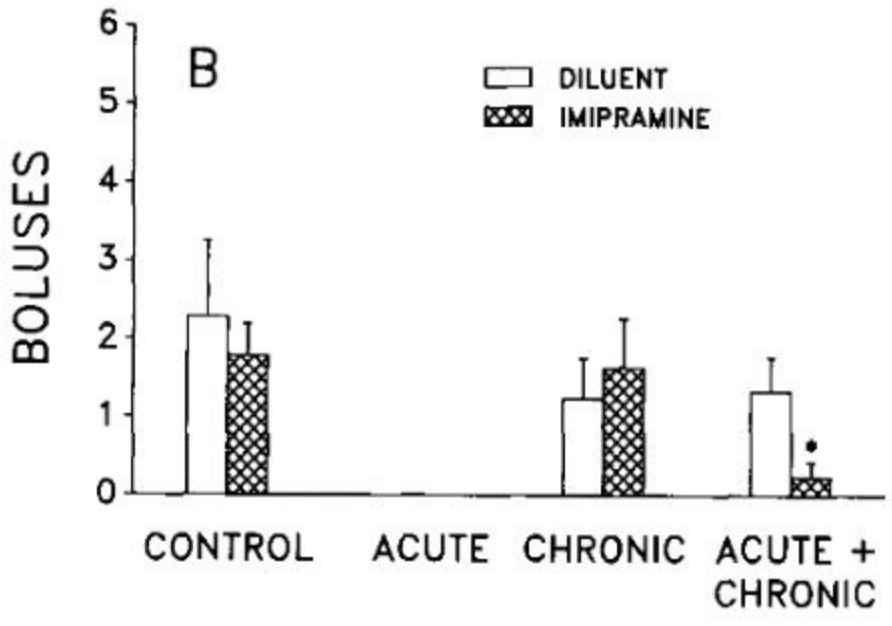


FIG. 1. Effect of diluent and imipramine (5.00 mg/kg) on (A) activity in an open-field maze as measured by the mean number of squares crossed and on (B) defecation in an open-field maze as measured by the mean number of boluses. The asterisks indicate a significant difference between imipramine and diluent at $p<0.01$.

DISCUSSION

The first experiment primarily served to replicate and thus validate Katz's model in our laboratory with imipramine at a dose of 5 mg/kg, which was the optimal dose used previously (12). This validation was desirable since deviations were made from the chronic stress protocol used in Katz's studies, mostly with respect to omission of changes in housing of animals, which could have altered the results. However, this did not occur since the tricyclic antidepressant was found to block the effects of chronic stress in the combined-stressed groups.

EXPERIMENT 2

METHOD

Animals

Two hundred and forty (240) rats were used in this experiment. All laboratory conditions were identical to those in Experiment 1.

Design

Animals were divided into ten groups of 24 rats each representing five doses of MIF-1 and five doses of naloxone. This $2\times5\times4$ between-subjects factorial design represented the two compounds (MIF-1 and naloxone), five doses, and four stress groups.

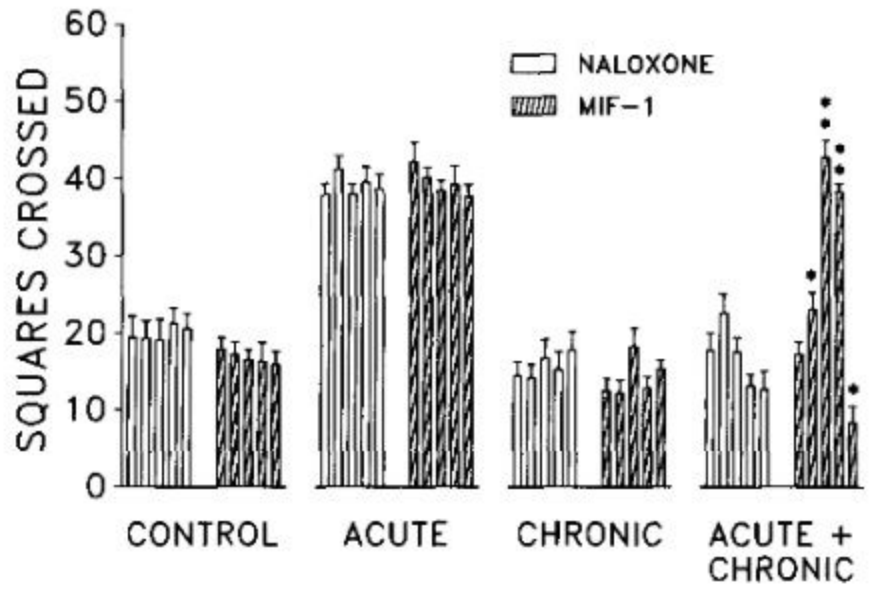


FIG. 2. Effect of naloxone (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg) and MIF-1 (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg; each group of five bars reflects the five doses in ascending order) on activity in an open-field maze as measured by the mean number of squares crossed. The asterisks indicate a significant difference between the dose and its control at $p<0.05$ (*) or $p<0.01$ (**).

Chronic Stress, Acute Stress, and Open Field Procedures

These were identical to those in Experiment 1.

Compounds

Five doses (0.0, 0.01, 0.1, 1.0, and 10.0 mg/kg) of MIF-1 and naloxone were used. As in Experiment 1, the compounds were coded and were administered daily 1 ml/kg, IP. The time of injections was identical to Experiment 1.

Additional Behavioral Measures

Since possible opiate antagonist activity also was being studied in this experiment, all animals were given tail-flick tests on the day after open field testing in order to assess antinociception. Tail-flicks, therefore, were tested 54 hr after the last injections. Four trials were given to each rat. The rat's tail was placed on a grooved tray so that it covered a small opening through which heat emanated from a nichrome heating wire. The temperature of the heating element was adjusted by a thermostat, which was set so as to produce tail-flick latencies of ten sec in preliminary experiments. Of the four measurements, the most deviant was discarded, with the mean of the remaining three times serving as the rat's tail-flick latency.

RESULTS

Mean Activity Score

The results are shown in Fig. 2. The main effects for Stress, $F(3,200)=448.3$, $p<0.01$, and Dose, $F(4,200)=6.8$, $p<0.01$, were significant. All two-way interactions (Compound × Dose, Compound × Stress, and Dose × Stress) were reliable, $F(4,200)=6.8$, $F(3,200)=15.4$, and $F(12,200)=7.1$, respectively, all $p<0.01$, as was the three-way interaction (Compound × Dose ×

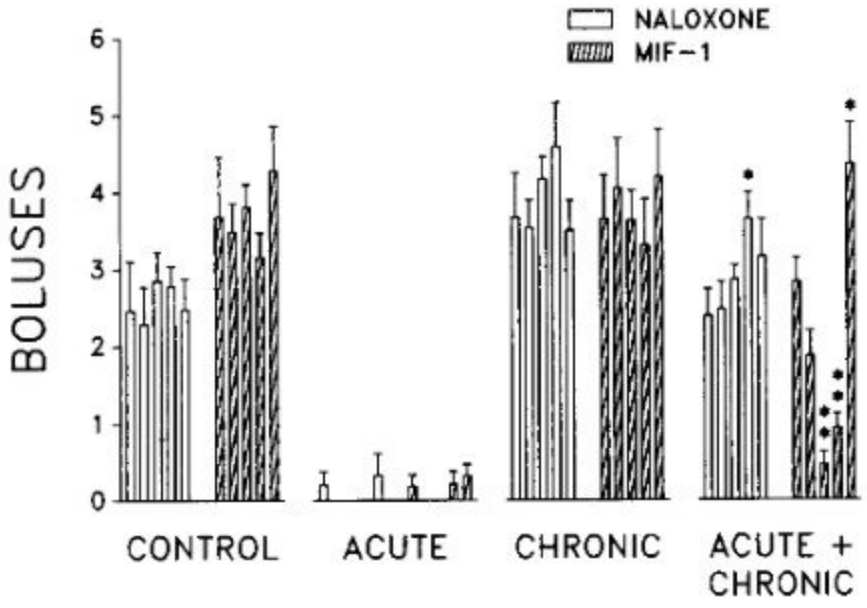


FIG. 3. Effect of naloxone (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg) and MIF-1 (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg; each group of five bars reflects the five doses in ascending order) on defecation in an open-field maze as measured by the mean number of boluses. The asterisks indicate a significant difference between the dose and its control at $p<0.05$ (*) or $p<0.01$ (**).

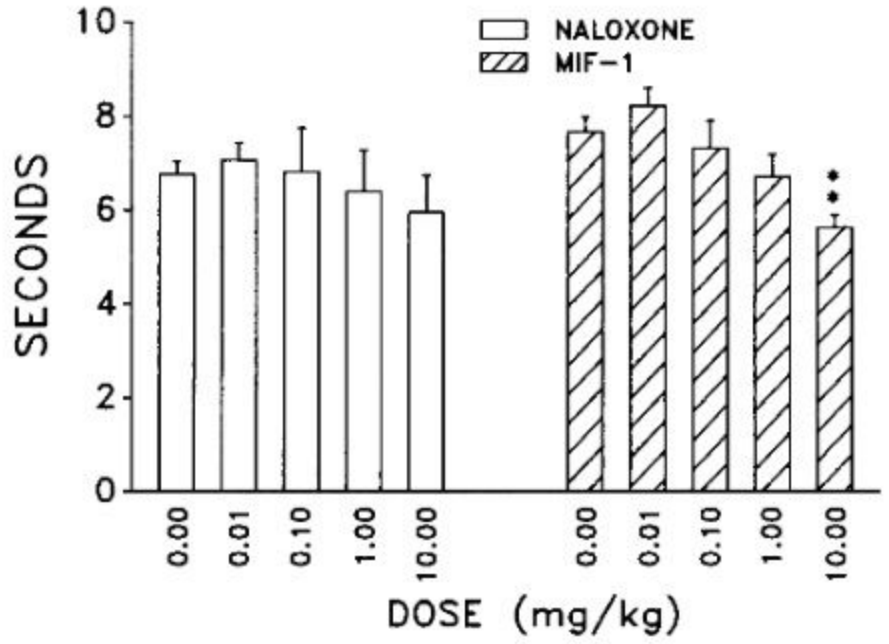


FIG. 4. Effect of naloxone (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg) and MIF-1 (0.00, 0.01, 0.10, 1.00, and 10.00 mg/kg; each group of five bars reflects the five doses in ascending order) on tail-flick latency as measured by mean seconds. The asterisks indicate a significant difference between the dose and its control at $p<0.01$ (**).

Stress), $F(12,200)=6.2$. Subsequent simple main effects tests revealed that significant findings were due to differential activity scores for compound and dose in only the combined-stressed group.

A 2×5 ANOVA conducted on data from the combined-stressed group yielded a significant main effect for Compound, $F(1,50)=56.7$, $p<0.01$, with animals receiving MIF-1 having more activity than animals receiving naloxone. Dose also was significant, $F(4,50)=34.3$, $p<0.01$, with an inverted-U response pattern indicated. Trends analyses yielded a significant quadradic function for Dose, $F(1,55)=28.4$, $p<0.01$. The Compound × Dose interaction also was reliable, $F(4,50)=31.8$, $p<0.01$, indicating that MIF-1 and naloxone produced different responding depending on dose. Simple main effects tests showed that animals that received MIF-1 had more activity than animals that received only naloxone for the 0.1 and 1.0 mg/kg doses, $F(1,10)=99.3$ and $F(1,10)=147.3$, respectively, both $p<0.01$. Trends analyses revealed a significant quadratic function for MIF-1, $F(1,25)=23.3$, $p<0.01$, and linear function for naloxone, $F(1,25)=13.8$, $p<0.01$.

For the combined-stressed group, in comparison with their respective 0.0 mg/kg doses, animals receiving MIF-1 at the 0.01 ($p<0.05$), 0.1 and 1.0 ($p<0.01$) mg/kg doses had more activity, and those that received the 10.0 mg/kg dose of MIF-1 had less activity ($p<0.05$). No dose of naloxone was reliably different from its control dose.

Finally, for all levels of stress, *t*-tests were conducted between the 0.0 mg/kg doses of MIF-1 and naloxone. In none of the four comparisons were the results significant, suggesting increased confidence with these findings.

Mean Defecation Score

The results are shown in Fig. 3. There was a significant main effect for Stress, $F(3,200)=123.8$, $p<0.01$, and Dose, $F(4,200)=3.3$, $p<0.05$. All two-way interactions and the three-way interactions were significant, $F(4,200)=5.7$, $p<0.01$, $F(3,200)=8.2$, $p<0.01$, $F(12,200)=1.9$, $p<0.05$, and, $F(12,200)=2.0$, $p<0.05$, for Compound × Dose, Compound × Stress, Dose × Stress, and Compound × Dose × Stress interactions, respectively. Subsequent simple main effects tests again revealed that all the interactions can be attributable to differential activity in the combined-stressed group.

The 2×5 ANOVA conducted on the data of the combined-stressed group showed a significant main effect for Compound, $F(1,50)=9.8$, $p<0.01$, with animals given MIF-1 having less defecation than animals given naloxone. A significant main effect for Dose was found, $F(4,50)=8.5$, $p<0.01$, with the bolus count resembling a U-shaped function. Trends analyses revealed both a significant quadratic component, $F(1,55)=13.1$, $p<0.01$, and linear component, $F(1,55)=4.5$, $p<0.01$. The Compound × Dose interaction was reliable, $F(4,50)=10.3$, $p<0.01$, which indicated that animals that received naloxone exhibited more defecation than the animals that received MIF-1 only at the 0.1 and 1.0 mg/kg doses, $F(1,10)=85.0$ and $F(1,10)=34.0$, respectively, both $p<0.01$. Trends analyses showed a reliable quadratic function for MIF-1, $F(1,25)=57.8$, $p<0.01$, and linear function for naloxone, $F(1,25)=5.3$, $p<0.05$.

In comparison with their respective 0.0 mg/kg doses, animals given MIF-1 at both the 0.1 and 1.0 mg/kg doses had reliably less defecation ($p<0.01$), while animals given the 10.0 mg/kg dose of MIF-1 had a higher defecation score ($p<0.05$). For naloxone, only the animals given the 1.0 mg/kg dose had significantly higher defecation scores than the animals that received the 0.0 mg/kg dose of naloxone ($p<0.05$). Finally, *t*-test analyses conducted between the 0.0 mg/kg doses of MIF-1 and naloxone were nonsignificant for all four levels of stress.

Tail-Flick Analyses

A 2×5 ANOVA was performed for tail-flick latency, representing the two compounds and five doses. As shown in Fig. 4, there was a significant main effect for Compound, $F(1,220)=5.9$, $p<0.05$, in which animals given naloxone had shorter latencies than animals given MIF-1. There also was a reliable main effect for Dose, $F(4,220)=9.5$, $p<0.01$, with results suggesting hyperalgesia with increasing doses. In comparison with their respective 0.0 mg/kg doses, only animals given the 10.0 mg/kg dose of MIF-1 had shorter latencies ($p<0.01$), whereas no dose of

naloxone was reliably different from the 0.0 mg/kg dose of naloxone ($p>0.17$). Finally, t-tests conducted on the 0.0 mg/kg doses of MIF-1 and naloxone were nonsignificant.

In addition, a $2\times5\times2$ ANOVA was conducted to assess the influence of chronic stress on antinociception. There was a reliable main effect for Stress, $F(1,220)=19.1$, $p<0.01$, with nonchronically-stressed animals having shorter latencies than animals that were chronically-stressed. This result indicated that the chronic stress procedure made these animals less sensitive to pain. None of the two-way nor the three-way interactions were significant.

DISCUSSION

Five doses of both MIF-1 and naloxone were used in order to evaluate the antidepressant and opiate antagonistic effects of MIF-1 in this paradigm. This represents an extension of the system from an animal model of depression to include opiate antagonism. MIF-1 displayed antidepressant properties primarily at lower doses with the most effective doses being 0.1 and 1.0 mg/kg. In this regard, MIF-1 blocked the effects of chronic stress, since animals given these doses responded to the acute stress with increased activation and decreased defecation. No animals given any dose of naloxone responded similarly. Moreover, previous animal and clinical studies using MIF-1 indicate that MIF-1 is effective as an antidepressant only at low doses and that a biphasic inverted-U dose response curve is typically reported (3, 5, 8, 9). Trends analyses performed on the data of animals given MIF-1 in the combined-stressed group produced a significant quadratic function on both measures, supporting the presence of a curvilinear function.

Since the stressors used in the model have previously been effective in eliciting endogenous opiate activity and since the conditions under which they were given (i.e., prolonged-intermittent, inescapable stress, in environments in which animals were previously exposed to the stressors) were optimal for eliciting such activity (19,20), involvement of the opiate system seems likely. Tail-flick analyses indicated that chronically-stressed animals were more analgesic than nonchronically-stressed animals, suggesting that endogenous opiate activity in response to the stressors was present 54 hr after completion of the three-week protocol and was blocked by a dose of MIF-1.

EXPERIMENT 3

METHOD

Animals

One hundred twenty (120) rats were used in this experiment. Laboratory conditions were identical to those of the first two experiments.

Design

A $5\times4\times4$ mixed factorial design was used which represented five groups of compounds, four groups of stress, and four repeated measures. Four weekly open field measurements were taken starting at the end of third week (i.e., end of the stress procedure). The animals were divided into five groups of compounds of 24 rats. Each group then was divided into the four groups of stresses (n = six per stress).

Compounds

The dose level for this experiment was chosen based on the results of the previous two experiments. In addition to diluent and imipramine (5 mg/kg), MIF-1 (0.1 mg/kg) and naloxone (1.0 mg/kg) were used. Tyr-MIF-1 (Tyr-Pro-Leu-Glycinamide) (0.1 mg/kg) also was used at a dose level corresponding to that for MIF-1. Compounds were administered starting with the fourth week and were given on days 22–27, 29–34, and 36–41. Injections were stopped 36 hours before open field testing.

Behavioral Procedure

Chronic stressors were given during the first three weeks of the experiment by the method previously described. No injections were given during these weeks. The acute stress and open field testing were given on day 21, yielding a baseline from which reversal of the "depressed" effect could be evaluated. Acute stress and open field tests then were given each week on days 28, 35, and 42.

RESULTS

Mean Activity Score

There was a significant main effect for Stress, $F(3,100)=212.3$, $p<0.01$, and Time, $F(3,300)=20.4$, $p<0.01$. A significant Stress $\times$ Time interaction, $F(9,300)=5.9$, $p<0.01$, indicated differential activity depending on level of stress and week tested. Simple main effects tests showed that there was a significant increase in activity for animals in the combined-stressed group, $F(3,87)=37.8$, $p<0.01$, with the predominant increase taking place between weeks 4 and 5 (i.e., two weeks after the cessation of stress). Animals in the chronically-stressed group showed a lesser, yet significant, increase in activity over time, $F(3,87)=3.6$, $p<0.05$, while no such increases were found for animals in the control or acutely-stressed groups. No effects of the treatment were significant for this measure, suggesting that the partial spontaneous remission shown by animals predominantly in the combined-stressed group was not dependent on the compound administered.

Mean Defecation Score

There was a reliable main effect for Stress, $F(3,100)=225.0$, $p<0.01$, and Time, $F(3,300)=25.2$, $p<0.01$. A significant Stress $\times$ Time interaction was found, $F(9,300)=7.8$, $p<0.01$. Simple main effects tests showed that decreases in defecation over time were found in all stress groups except the acutely-stressed animals, in which no decrease was observed, mostly due to a floor effect. Defecation decreases in animals in the combined-stressed group, $F(3,87)=27.9$, $p<0.01$, were the most dramatic between weeks 4 and 5. Significant, yet less dramatic, changes were found for the control, $F(3,87)=3.1$, $p<0.05$, and chronically-stressed animals, $F(3,87)=3.9$, $p<0.05$. Once again, the compounds administered did not differentially affect the outcomes for this measure.

DISCUSSION

Experiment 3 was conducted in order to evaluate whether imipramine, MIF-1, Tyr-MIF-1, or naloxone would be effective in reversing the effects of chronic stress if daily injections were administered after the completion of the stress protocol as contrasted to concomitant administration. No differential recovery was observed since partial spontaneous remission was observed in all groups within two weeks, at which time about two-thirds recovery was found. It is possible that if chronic stressors had been continued throughout this phase rather than ending them before the administration of the compounds, differential effects might have emerged. Such a manipulation would be more analogous to

treatment of human depression since stressors do not altogether disappear once therapy has begun.

SUMMARY

This set of investigations support previous studies in which MIF-1 was found to exhibit antidepressant properties. It extends them to an animal model of depression involving chronic stress.

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