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BRIEF COMMUNICATION

DALDA (H-Tyr-D-Arg-Phe-Lys-NH^2), a Potent μ-Opioid Peptide Agonist, Affects Various Patterns of Locomotor Activities

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MEYER, M. E., B. I. McLAURIN AND M. E. MEYER. *DALDA (H-Tyr-D-Arg-Phe-Lys-NH^2), a potent μ-opioid peptide agonist, affects various patterns of locomotor activities.* PHARMACOL BIOCHEM BEHAV **51**(1) 149–151; 1995.—The central effects of μ-opioid receptor agonist DALDA (ICV 0.00, 0.1, or 1.0 μg) were investigated in rats for 120 min on activity monitors. The durations in seconds of horizontal movement time, rearing time, and stereotypy time were measured during 12 consecutive 10-min time blocks. DALDA (ICV, 0.1 and 1.0 μg) resulted in biphasic effects, inhibition followed by activation for horizontal movement, rearing, and stereotypy times.

μ-Opioid peptide agonists DALDA Locomotor activity Rearing Linear locomotion Stereotypy

THE EFFECTS of various μ-opioid peptide and opiate agonists on locomotor activity has been described in rodents. Central microinjections of several enkephalin, β-casomorphin, and dermorphin analogs result in biphasic effects on locomotor activity. In general, low dosages induce stimulation of activity, whereas, large dosages result in an initial suppression followed by activation [(1,2,4–6); see (8,11) for reviews].

DALDA, (H-Tyr-D-Arg-Phe-Lys-NH$_2$), a dermorphin analog, has been shown to have unprecedented high selectivity and affinity for the μ-opioid receptor (3,9,10). Because of these biological characteristics, DALDA could be a significant research analog in behavioral pharmacology. Recently, it has been reported that DALDA (ICV, 0.1–1.0 μg/side), unlike DAMGO and PL017, elicited significant locomotor inhibition over a 60-min time course without an activation effect (6).

The present study expands the time course for DALDA to ascertain if the biological activity of this peptide would elicit a biphasic inhibition-activation effect on various patterns of locomotor activities in rats. We report here our findings for ICV-injected μ-opioid peptide agonist, DALDA, on horizontal movement, rearing, and stereotypy times in seconds during 12 consecutive 10-min time blocks.

METHOD

Animals

Male Long-Evans rats, weighing 200–225 g, were obtained from Charles River. The rats were individually housed in stainless steel cages, had food and water ad lib, and were maintained on a 12 L : 12 D (0700–1900 h) cycle. The animals were tested in the light phase between 1000–1600 h. The room in which the animals were maintained was at a constant temperature (210 ± 2°C). This study was carried out in compliance with the rules set forth in the NIH Guide for the Care and Use of Laboratory Animals.

Surgery

The animals, while under equithesin anesthesia (0.3 ml/100 g, IP), were cannulated unilaterally with the use of a stereotaxic instrument. Guide cannulae, 7 mm long, fabricated from 23 g hypodermic needles were permanently fixed to the skull with microscrews and dental cement. The guide cannulae were implanted following the coordinates from Paxinos and Watson (7), 0.8 mm posterior to bregma, 1.5 mm lateral to midline

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on the right side to allow injections into the lateral cerebral ventricle (ICV). The vertical depth of the injection cannula was 4 mm below the surface of the skull. The animals were allowed 2 weeks recovery before behavioral testing. During recovery, the animals were not handled or transported except for routine cleaning.

Drugs and Drug Administration

The μ-receptor agonist DALDA (H-Tyr-D-Arg-Phe-Lys-NH_2; mol. wt. 611.1) was obtained from Bachem (Torrance, CA). All peptides were dissolved in distilled water, which was also given for the vehicle control injections (0.00 μg). The drug solutions were made up daily to the appropriate concentrations of 0.1 and 1.0 μg. The 0.5 μl of solution was intracerebroventricularly (ICV) microinjected over a period of 60 s, and the cannulae remained in place for another 30 s. Injection sites were verified by the perfusion of a methylene blue dye solution into the lateral ventricles prior to autopsy.

Apparatus

Immediately following ICV, each rat was placed in an Omnitech Digiscan Animal Activity Monitor (Columbus, OH) for 120 min. In this experiment, data were collected every 10 min. The acrylic cage within the monitor measured approximately 42 cm wide by 42 cm long and 30.5 cm high. The monitor was equipped with 16 beams 2.54 cm apart from front to back and from side to side, as well as 16 beams 2.54 cm apart from side to side on the upper level. Every 100 ms, the computer sampled the status of all of the beams. The Digiscan analyzer converted the patterns of the beams broken into different measures of locomotor activity. The measures analyzed in this study were horizontal movement time in seconds (as long as the animal moved, movement time was incremented); rearing time in seconds (as long as the animal was rearing and activating the upper sensors, rearing time was incremented); and stereotypy time in seconds (as long as the animal was repeatedly breaking the same beam or sets of beams, the monitor considered the animal was emitting stereotypy behaviors).

Statistics

Each independent treatment group consisted of 12 animals chosen at random. The animals were treated only once.

A two-factor mixed design ANOVA was used to analyze the within measures (12 consecutive 10-min time blocks), between the treatment conditions (three dose levels), and the time by dose interaction effect. The significant interaction for the dose by time interval was followed up within time blocks by Dunnett's multiple comparison tests between the control group and the treatment groups. p-Values equal to or less than 0.05 were judged to be statistically significant.

RESULTS

Horizontal Movement Time

Figure 1A illustrates the biphasic effect of horizontal movement time elicited by DALDA (ICV, 0.1–1.0 μg) over the 12 consecutive 10-min time blocks when compared with the control group.

The three treatment groups by 12 10-min time blocks interaction was significant, $F(22, 352) = 11.24$, $p < 0.001$. The subsequent analyses between the 1.0 μg group and the vehicle control group resulted in the attenuation of horizontal movement time at the 10-min interval through the 50-min time block ($ps < 0.01$ and 0.05) and potentiation of horizontal movement time in the 80- through 120-min time block ($ps < 0.01$). Similarly, the 0.1 μg group showed significant suppression of horizontal movement time from the 10-min time block through the 30-min block ($ps < 0.01$ and 0.05) and activation at the 60- and 80- through 120-min time blocks ($ps < 0.05$ and 0.01).

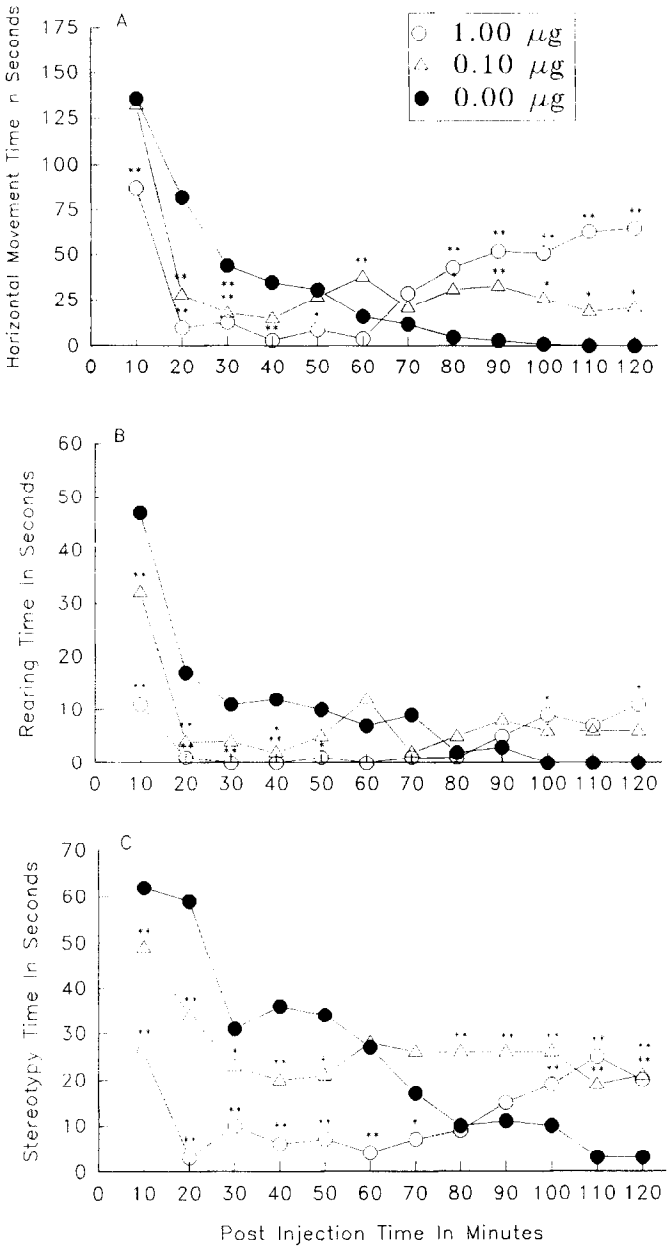

FIG. 1. (A) Significant interaction effects of ICV injected 0.00, 0.1, and 1.0 μg dosages of DALDA on horizontal movement time in seconds over 12 consecutive 10-min intervals. (B) Significant interaction effects of ICV injected 0.00, 0.10 and 1.00 μg dosages of DALDA on rearing time in s over 12 consecutive 10 min intervals. (C) Significant interaction effects of ICV injected 0.00, 0.10, and 1.0 μg dosages of DALDA on stereotypy time in seconds over 12 consecutive 10-min intervals. Significant differences from the vehicle control group (0.00 μg) at each time point: $*p < 0.05$; $**p < 0.01$. For clarity, the error bars have been omitted.

Rearing Time

Figure 1B shows the significant interaction between the three dose levels and the 12 consecutive 10-min time blocks for rearing time, $F(22, 352) = 6.20$, $p < 0.001$. When compared to the control group, the 1.0 μg group rearing time was significantly suppressed from 10- through 50-min time blocks ($ps < 0.01$ and 0.05) and activated at time blocks of 100 and 120 min ($ps < 0.05$).

Stereotypy Time

Figure 1C depicts the significant dose by time course interaction for stereotypy time, $F(22, 352) = 9.54$, $p < 0.001$. The subsequent analyses resulted in significant attenuation of stereotypy time with the 1.0 μg dosage in comparison to the control group during time blocks 10 through 70 min ($ps < 0.05$ and 0.01) and significant potentiation from time blocks 100–120 min ($ps < 0.05$ and 0.01). Similarly, the 0.1 μg group was significantly attenuated from 10–60-min time blocks ($ps < 0.05$ and 0.01) and potentiated from the 80 through the 120 min time blocks ($ps < 0.01$).

DISCUSSION

The results presented in this article provide further information on the role of the μ-opioid receptor agonist, DALDA, in eliciting biphasic changes in various patterns of locomotor behavior following ICV administration. During the 120-min session, the 1.0 μg of DALDA (ICV) elicited a significant biphasic effect with an initial suppression, an intermediate marked inhibition, followed by significant activation for horizontal movement time, rearing time, and stereotypy time. On the other hand, the 0.1 μg dosage initially suppressed locomotion followed with a shorter duration of inhibition and lower level of activation. These biphasic effects were primarily different from ICV DAMGO and PL017 in the duration effects on locomotor activity (6). The behavioral profile of DALDA, in the present study, clearly shows that the initial DALDA-induced suppression was of a significantly longer duration than was observed with DAMGO and PL017. This longer suppression effect may be due the DALDA's very high selectivity and affinity for the μ-opioid receptor.

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