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Behavioral Effects of Opioid Peptide Agonists DAMGO, DPDPE, and DAKLI on Locomotor Activities

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MEYER, M. E. AND M. E. MEYER. *Behavioral effects of opioid agonists DAMGO, DPDPE, and DAKLI on locomotor activities.* PHARMACOL BIOCHEM BEHAV 45(2) 315–320, 1993.—The effects of the μ-selective agonist DAMGO (ICV doses of 0.00, 0.01, 0.1, or 1.0 μg), the δ-selective agonist DPDPE (ICV doses of 0.00, 0.1, 1.0, or 10.0 μg), and the κ-selective agonist DAKLI (ICV doses of 0.00, 0.01, 0.1, or 1.0 μg) were tested in rats for 60 min in an activity monitor. The durations in seconds of linear locomotor time, rearing time, stereotypy time, and margin time (thigmotaxis) were measured during six 10-min time blocks. DAMGO (0.1 and 1.0 μg) resulted in biphasic effects, inhibition followed by hyperactivity for linear locomotor, rearing, and stereotypy times, and an inhibition of thigmotaxis. DPDPE (10.0 μg) was associated with monophasic potentiation of linear locomotor activity and mixed effects in stereotypy times. DAKLI did not effect horizontal, rearing, or margin times; only stereotypy times resulted in mixed effects of DAKLI. The differential behavioral profiles were discussed in reference to the three opioid receptor subtypes.

Opioid peptide agonists DAMGO DPDPE DAKLI Locomotor activity Thigmotaxis Rearing Linear locomotion Stereotypy

THERE is an abundance of evidence to show that there are at least three major pharmacologically different opioid receptor subtypes: μ-, δ-, and κ-receptors (2,4,13,17,20,28,29). However, subclassification of the μ-receptor has been suggested, as well as for the κ-receptor. With the development of selective ligands and their availability in [^{3}H]-labeled form, the μ-binding sites have been labeled with DAMGO [D-Ala^2, Me-Phe^4, Gly-ol^5-enkephalin] (6,12), δ-sites with DPDPE [D-Pen^2, D-Pen^5-enkephalin] (2,15), and κ-sites with DAKLI [Arg^{11,13}-dynorphin A1-13-Gly-NH $(CH_2)_5NH_2$] (5).

The effects of various opioid peptide and nonpeptide opiate agonists on locomotor activity has been described in rodents using various routes of administration. Morphine, β-endorphin, and some metabolically stable enkephalin analogs result in biphasic effects on locomotor activity. In general, low dosages induce stimulation of activity whereas larger doses result in an initial suppression followed by hyperactivity (1,7,9,10,22).

Recent studies with mice using DAMGO and DPDPE injected ICV suggests that DAMGO, a selective μ-receptor peptide agonist, induced an increase in horizontal activity (14) and a decrease in rearing without the typical biphasic effect, whereas DPDPE, a δ-peptide agonists, increased the activation of locomotor (3,14,16,26), of circling and grooming, and of rearing activity (3,14,26). Dynorphin A(1-13) and various κ-nonpeptide opioid agonists have been reported to have no effect on locomotor activities (11,25). However, κ-agonists has been reported to produce monophasic locomotor depression (9,23,24), sedation and ataxia (9), and a variety of bizarre postures, rotations, and rigidity of limbs (8,19,21,27).

This study focused upon selective peptide agonists for μ-, δ-, and κ-receptor subtypes, although it is acknowledged that other subtypes may exist. We were interested in the behavioral effects of selective opioid peptides on linear locomotor, rearing, stereotypy, and margin time (an index of thigmotaxis) in a dose by time interaction design following ICV administration.

METHOD

Animals

Male Long-Evans rat weighing 200–225 g were obtained from Charles River. Rats were individually housed in stainless steel cages, had food and water ad lib, and were maintained on a 12 L : 12 D (light 0700–1900 h) cycle. Animals were tested in the light phase between 1000–1600 h. The room in which animals were maintained was at a constant temperature (21 ± 2°C). This study was carried out in compliance with the

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rules set forth in the *NIH Guide for the Care and Use of Laboratory Animals.*

Surgery

Animals, while under Equithesin anesthesia, were cannulated unilaterally with the use of a stereotaxic instrument. Guide cannulae, 7 mm long, fabricated from 21- ga 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 (18), 0.8 mm posterior to bregma, 1.5 lateral to midline 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. Animals were allowed 2 weeks recovery before behavioral testing. During recovery, animals were not handled or transported except for routine cleaning.

Drugs and Drug Administration

The selective μ-receptor agonist DAMGO (Tyr-D-Ala-Gly-*N*-methyl-Phe-Gly-ol; mol. wt. 513.6), the selective δ-receptor DPDPE (Tyr-D-Pen-Gly-Phe-D-Pen; mol. wt. 645.8), and the selective κ-receptor DAKLI (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Arg-Leu-Arg-Gly 5-aminopentylamide; mol. wt. 1801.2) were obtained from Sigma Chemical Co. (St. Louis, MO). All peptides were dissolved in distilled water. Distilled water was also given for the control injections. The drug solutions were made up daily to the appropriate concentrations of 0.01, 0.1, and 1.0 μg for DAMGO and DAKLI and 0.1, 1.0, and 10.0 μg for DPDPE. The 0.5 μl of solution was microinjected over a period of 60 s and the cannulae remained in place for another 30 s. Immediately after the injection procedure, the animal was placed into an activity chamber. Injection was verified by the perfusion of a methylene blue dye solution into the lateral ventricles prior to autopsy. In two animals, verification was not possible and they were replaced.

Apparatus

Immediately following ICV administration, each rat was placed in an Omnitech Digiscan Animal Activity Monitor for 1 h. In the three experiments, data were collected every 10 min. The acrylic cage within the monitor measured approximately 42 × 42 × 30.5 cm. The monitor was equipped with 16 beams 2.54 cm apart from front to back and from side to side on the lower level, as well as 16 beams 2.54 apart from side to side on the upper level. Every 100 ms, the computer sampled the status of all the beams. The Digiscan analyzer converted the patterns of the beams broken into different measures of locomotor activity. The measures automatically analyzed in this study were the linear 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); 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 behavior; this measurement corresponded to grooming, head bobbling and weaving, chewing, etc.); and margin time in seconds (as long as the animal was within 1 cm to the walls of the cage, the margin time was incremented).

Statistics

Each treatment group consisted of 12 animals chosen at random. Each rat was used only once. A two-factor mixed-design analysis of variance (ANOVA) was used to analyze the within-measures (six 10-min time blocks), between the treatment conditions (four dose levels), and the time × dose interaction effect. Significant interactions for the dose × time interval were followed-up with one-way ANOVAs within time blocks and Dunnett's multiple comparison tests between the control group and the treatment groups. p values equal to or less than 0.05 were judged statistically significant. The vehicle control group data was used in the independent analyses for DAMGO, DPDPE, and DAKLI.

RESULTS

Locomotor Effects of DAMGO

Linear locomotion time. Figure 1A (top) illustrates the 60-min time course of linear locomotor activity of rats, in seconds, treated with one of four dose levels of DAMGO (vehicle, 0.01, 0.1, and 1.0 μg/rat, ICV).

The overall ANOVA revealed a significant difference among the four treatment groups, $F(3, 44) = 6.73$, $p < 0.001$. The subsequent analyses between the four dose levels yielded significant hyperactivity in the 0.01- and 0.1-μg groups when compared with the vehicle controls ($p < 0.05$). On the other hand, the 1.0-μg group was hypoactive but not significantly different from the vehicle control group ($p > 0.05$). Over the six 10-min time blocks, there was a significant habituation effect, $F(5, 220) = 57.76$, $p < 0.001$. The four treatment groups × six 10-min time blocks interaction was highly significant, $F(15, 220) = 18.20$, $p < 0.001$. The subsequent analyses between the 1.0-μg and vehicle groups revealed a biphasic effect for DAMGO. At the 10-, 20-, and 30-min time blocks, there were significant suppression or hypoactivity ($p < 0.05$) and at the 50- and 60-min time blocks there were significant potentiation or hyperactivity ($p < 0.05$). The subsequent analyses for the 0.1-μg group and the vehicle control also revealed a biphasic effect for DAMGO, but with less early hypoactivity. At the 10- and 20-min time blocks, there was significant hypoactivity ($p < 0.05$) and at time blocks of 40, 50, and 60 min significant hyperactivity. The subsequent analyses for the 0.01-μg group revealed significant hyperactivity at time blocks of 20, 30, and 50 min.

Rearing time. Figure 1B illustrates the rearing activity of rats, in seconds, treated with one of four dose levels of DAMGO (vehicle, 0.01, 0.1, and 1.0 μg/rat, ICV) over the 60-min time course.

The two-factor mixed ANOVA revealed a significant difference among the four treatment groups, $F(3, 44) = 14.49$, $p < 0.001$. The subsequent analyses between the control and peptide groups yielded a significant suppression of rearing in the 1.0-μg group. Over the six 10-min time blocks, there was a significant habituation effect, $F(5, 220) = 13.70$, $p < 0.001$. The four treatment groups × six 10-min time blocks interaction was significant, $F(15, 220) = 8.35$, $p < 0.001$. The subsequent analyses for the 1.0-μg group showed significant suppression of rearing at 10 to 40 min and for the 0.1-μg group suppression at 10 to 20 min but excitation at 50 min. On the other hand, the 0.01-μg group emitted significant increases in duration of rearing at 20 and 50 min.

Stereotypy time. Figure 1C depicts the stereotypy activity of rats, in seconds, treated with one of four dose levels of DAMGO (vehicle, 0.01, 0.1, and 1.0 μg/rat, ICV) over the 60-min time course.

The ANOVA showed a significant difference among the four peptide groups, $F(3, 44) = 9.26$, $p < 0.001$. However,

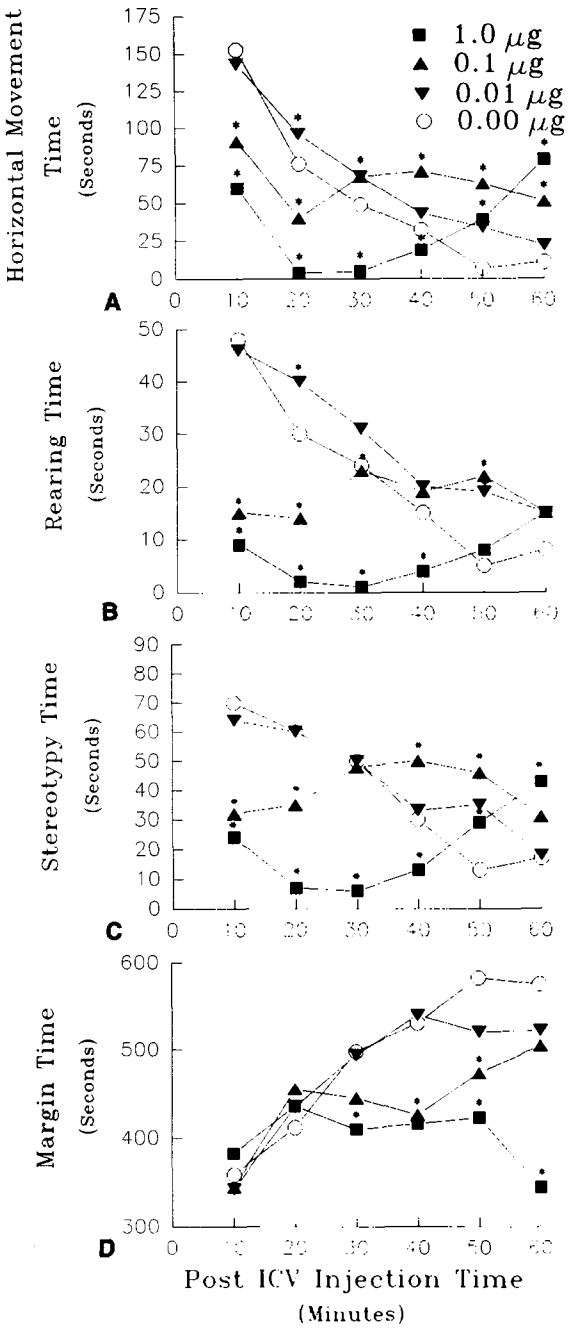

FIG. 1. Effects of several doses of the μ-opioid peptide DAMGO on four measures of locomotor activity, in seconds, over 60 min. (A) Horizontal movement time. (B) Rearing time. (C) Stereotypy time. (D) Margin time. Significant differences from the vehicle control group (0.00 μg) at each time point: $^*p < 0.05$.

only the 1.0-μg group differed from controls with significant suppression of stereotypy time. Over the six 10-min time blocks, there was significant habituation, $F(5, 220) = 8.80$, $p < 0.001$. The four treatment conditions × the six 10-min time block interaction was also highly significant, $F(15, 220) = 12.22$, $p < 0.001$. The subsequent analyses between the 1.0-μg group and controls over the six 10-min time blocks showed biphasic effects with significant suppression between 10 and 40 min and activation of stereotypy behaviors at 50 and 60 min. Similarly, the 0.1-μg group showed significant suppression between 10 and 20 min and activation beyond 40 min. There were no significant effects for the 0.01-μg group except a significant effect at 50 min ($p < 0.05$).

Margin time. The margin time in seconds or thigmotaxis of rats treated with one of four dose levels of DAMGO (vehicle, 0.01, 0.1, and 1.0 μg/rat, ICV) over the 60-min time course is shown in Fig. 1D.

The ANOVA indicated a significant interaction among the four dose levels over the time course, $F(15, 220) = 4.50$, $p < 0.001$. The 1.0-μg group showed significant less thigmotaxis between 30 and 60 min and the 0.1-μg group at the 40- and 50-min time blocks in comparison to vehicle controls ($p < 0.05$). The vehicle, 0.01-, and 0.1-μg groups all showed significant increases in thigmotaxis over the time blocks ($p < 0.05$), whereas the 1.0-μg group showed no significant change ($p > 0.05$).

Locomotor Effects of DPDPE

Linear locomotion time. Figure 2A illustrates the linear locomotor activity of rats, in seconds, treated with one of the four dose levels of DPDPE (vehicle, 0.1, 1.0, and 10.0 μg/rat, ICV) over the 60-min time course.

The overall ANOVA revealed a significant difference among the four treatment groups, $F(3, 44) = 3.81$, $p = 0.02$. The subsequent analyses between the four dose levels yielded significant hyperactivity in all DPDPE dose levels and the vehicle control group ($p < 0.05$). Over the six 10-min time blocks, there was a significant habituation effect, $F(5, 220) = 140.59$, $p < 0.001$. The four treatment groups × six 10-min time blocks interaction was significant, $F(15, 220) = 2.91$, $p < 0.001$. From the subsequent analyses between the 10.0-μg group and the vehicle control resulted in a brief biphasic effect with hypoactivity at the 10-min interval and hyperactivity at every time interval thereafter. During the 10- and 20-min intervals, the 1.0-μg groups showed hyperactivity ($p < 0.05$). Only at the 20-min interval was there significant hyperactivity for the 0.1-μg group ($p < 0.05$).

Rearing time. Figure 2B shows the rearing time, in seconds, of rats treated with one of the four dose levels of DPDPE (vehicle, 0.1, 1.0, and 10.0 μg/rat, ICV) over the 60-min time course. The dose × time course was significant, $F(15, 220) = 1.70$, $p = 0.05$. In addition, the time course analysis revealed a significant habituation effect, $F(5, 220) = 35.29$, $p < 0.001$. The subsequent analyses revealed a significant suppression of rearing in the 10.0-μg group in the 10-min time block and potentiation of rearing in the 20-min block ($p < 0.05$). All other comparisons were not statistically significant, ($p > 0.05$).

Stereotypy time. The stereotypy time, in seconds, of rats treated with one of the four dose levels of DPDPE (vehicle, 0.1, 1.0, and 10.0 μg/side, ICV) over the six 10-min time blocks is shown in Fig. 2C.

The dose × time blocks interaction was significant, $F(15, 220) = 3.93$, $p < 0.001$, as was the differences across the time blocks, $F(5, 220) = 63.76$, $p < 0.001$. The 10.0-μg group differed significantly from controls with the suppression of stereotypy at 10 min and potentiation at 50 min; the 1.0-μg group showed significant suppression at 20- and 30-min time blocks; and the 0.1-μg group was significantly activated at 50 min ($p < 0.05$); all other comparisons were not different ($p > 0.05$).

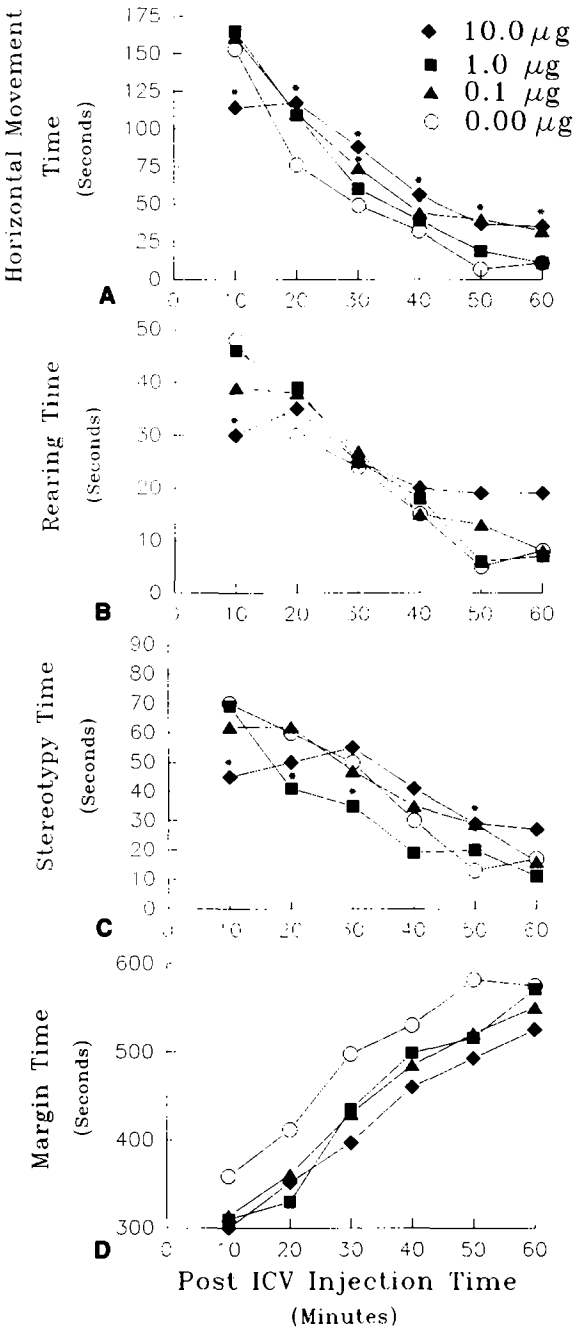

FIG. 2. Effects of several doses of the δ-opioid peptide DPDPE on four measures of locomotor activity, in seconds, over 60 min. (A) Horizontal movement time. (B) Rearing time. (C) Stereotypy time. (D) Margin time. Significant differences from the vehicle control group (0.00 μg) at each time point: $*p < 0.05$.

Margin time. Figure 2D shows the margin time, in seconds, of rats treated with one of the four dose levels of DPDPE (vehicle, 0.1, 1.0, and 10.0 μg/side, ICV) over the time blocks. Only the time block habituation effect was significant, $F(15, 220) = 98.42$, $p < 0.001$. All other analyses resulted in non-significant differences ($p > 0.05$).

Locomotor Effects of DAKLI

Linear locomotion time. Figure 3A illustrates the linear locomotor activity, in seconds, of rats treated with one of four dose levels of DAKLI (vehicle, 0.01, 0.1, and 1.0 μg/side, ICV) over the 60-min time course.

The overall ANOVA failed to reveal significant differences among the four dose levels ($p > 0.05$), nor was there a signifi-

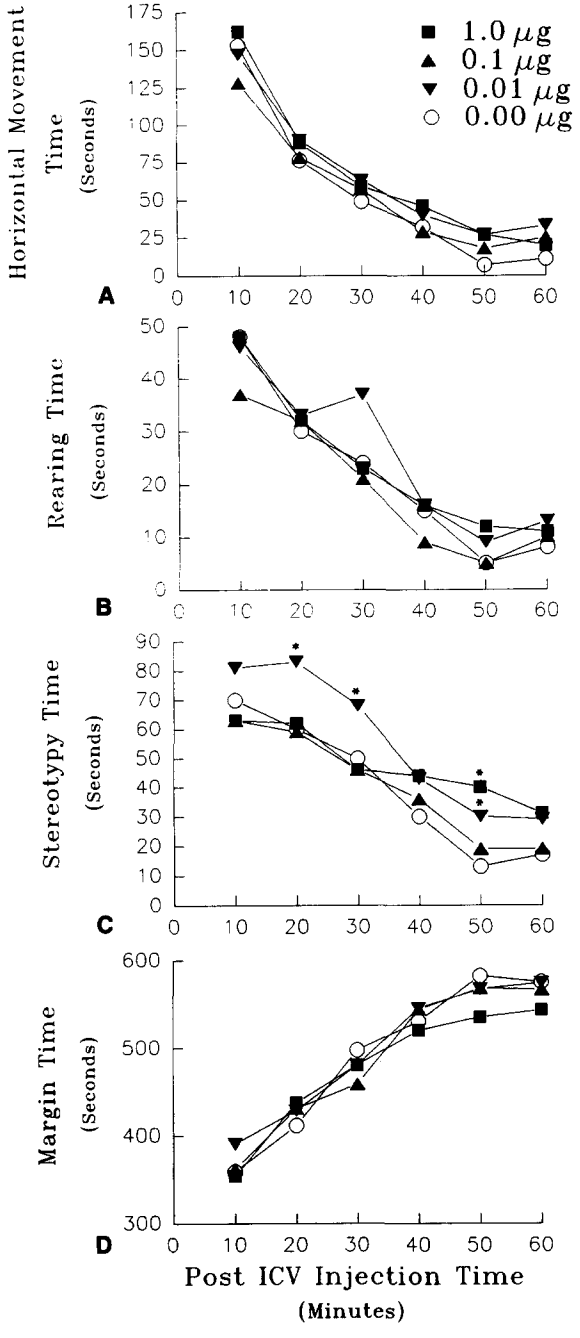

FIG. 3. Effects of several doses of the κ-opioid peptide DAKLI on four measures of locomotor activity, in seconds, over 60 min. (A) Horizontal movement time. (B) Rearing time. (C) Stereotypy time. (D) Margin time. Significant differences from the vehicle control group (0.00 μg) at each time point: $*p < 0.05$.

cant dose × time interaction effects. Over the six 10-min time blocks, there was a significant habituation effect, $F(15, 220) = 28.84, p < 0.001$.

Rearing time. Rearing time, in seconds, of rats treated with one of four dose levels of DAKLI (vehicle, 0.01, 0.1, and 1.0 μg/side, ICV) over the six 10-min time blocks is given in Fig. 3B.

The ANOVA for the between-peptide doses and for the dose × time course resulted in nonsignificant differences ($p > 0.05$); only the habituation effect was significant, $F(5, 220) = 70.66, p < 0.001$.

Stereotypy time. Figure 3C depicts the stereotypy time, in seconds, of rats treated with one of four dose levels of DAKLI (vehicle, 0.01, 0.1, and 1.0 μg/side) over the 60-min time course.

The ANOVA revealed a significant dose effect, $F(3, 44) = 3.47, p < 0.02$; a significant habituation across the time course, $F(5, 220) = 67.04, p < 0.001$; and a significant dose × time course interaction, $F(15, 220) = 1.88, p < 0.03$. The 1.0-μg group's stereotypy time was significantly potentiated in comparison to controls at 50 min, and the 0.01-μg group differed at 20-, 30-, and 50-min time blocks.

Margin time. The margin time, in seconds, of rats treated with one of four dose levels of DAKLI (vehicle, 0.01, 0.1, and 1.0 μg/side, ICV) over the 60-min time course is shown in Fig. 3D.

Only the habituation effect over the six 10-min time course was significant, $F(5, 220) = 107.99, p < 0.001$. All other comparisons were not significantly different ($p > 0.05$).

DISCUSSION

The prototype nonpeptide opiate morphine has been the benchmark in the development of peptide and nonpeptide agonists for the μ-receptor (20). In this study, the effects of the highly selective μ-receptor peptide agonist (20) DAMGO on linear locomotor activity were similar to the effects of morphine in rats. The 1.0-μg dose (ICV) exerted a significant U-shaped biphasic effect with an initial suppression at the 10-min interval, a marked hypoactivity at the 20- and 30-min intervals, followed by significant hyperactivity at the 50- and 60-min intervals. The 0.1-μg dose initially suppressed locomotion by the 30-min interval and for the remaining time blocks this dosage resulted in hyperactivity. On the other hand, the low-dose level, 0.01 μg, like morphine effectively enhanced the locomotor activity without the initial suppression. These dose-response effects generalized to rearing and stereotypy behaviors. DAMGO has a significant effect on thigmotaxis as measured by margin time. In contrast to controls, the 1.0-μg DAMGO-treated group showed little thigmotaxis and the other dose levels resulted in intermediate effects. These biphasic effects were different from mice, where only dose hyperactivity was observed (14). This species difference may be a function of the opioid as mice show especially significant excitation (7,22).

The behavioral profile of DPDPE, a selective δ-receptor peptide agonist (20), in the present study is in part comparable to other reports of a monophasic hyperactivity with various measures of locomotor activity (3,16,26). However, we found that only the 10.0-μg dose of DPDPE resulted in a significant increase in linear locomotor time following the first 10-min time block. The DPDPE linear locomotion effects appeared not to generalize to other behaviors as DPDPE had no significant increase in rearing time, mixed effects on stereotypy time, and no effects on margin time of thigmotaxis. These data differ from that reported in the mouse, where DPDPE, in a dose-dependent manner, increased both horizontal and rearing activities (14,26,27).

The κ-receptor peptide agonist, DAKLI, in this study had no behavioral effects on linear locomotor time, rearing time, or margin time. There were four non-dose-related functions for stereotypy time. The 0.01-μg dose resulted in significant increases of stereotypy time at time blocks 20, 30, and 50 min; at time block 50 min, the 1.0-μg dose also resulted in a significant potentiation of stereotypy. In general, these data strongly suggest that DAKLI has little or no significant effects on various measures of locomotor activities. The data in the present study are similar to those obtained with other κ-receptor peptide agonists. On the other hand, κ-receptor nonpeptide agonists have been found for the most part to cause suppression without the subsequent hyperactivity. These differences between the κ-receptor peptide and nonpeptide agonists leads to an interesting paradox. However, while DAMGO and DPDPE were protected from enzymatic degradation by the D-amino acids at position 2 DAKLI was not. The lack of effect for DAKLI may be the result of: a) rapid metabolism of this peptide, which was not active at the receptor site (8); or b) when dissolved in solution, most of this peptide remained on the walls of the injection tube and was therefore not available (5).

With the dosage levels, route of administration, species, and specific ligands, it appears that the three opioid receptors—μ, δ, and κ—may be associated with different behavioral profiles. The μ-agonist DAMGO had significant biphasic behavioral effects with attenuation followed by potentiation of linear locomotor activity, rearing, and stereotypy and attenuation of thigmotaxis. The monophasic potentiation of linear locomotor activity with DPDPE, a δ-agonist, with a larger dose level than for DAMGO and mixed or no effects on other locomotor activities, suggests a lack of generality across various behaviors. The selective κ-agonist DAKLI, in this present study, did not effect linear locomotor activity, rearing, and thigmotaxis and had mixed effects on stereotypy. However, further peptides that are selective for each opioid receptor subtype should be examined as to their effects upon locomotor activities before concluding that the behavioral effects were due to the activation of the specific receptors.

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