ELSEVIER

European Journal of Pharmacology 316 (1996) 137–143

ejp

Involvement of δ- and μ-opioid receptors in the potentiation of brain-stimulation reward

Christine L. Duvauchelle [1], Sheila M. Fleming[1], Conan Kornetsky *

Boston University School of Medicine, Laboratory of Behavioral Pharmacology, 80 East Concord Street, L-602, Boston, MA 02118, USA

Received 10 July 1996; revised 12 August 1996; accepted 20 August 1996

Abstract

A rate-free method of determining brain-stimulation reward thresholds was used to identify the rewarding effects of the δ-opioid receptor and μ-opioid receptor agonist peptides, [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and [D-Ala^2–MePhe^4–Gly(ol)^5]enkephalin (DAMGO). The nucleus accumbens-delivered opioid receptor agonists produced marked lowering of the threshold for ventral tegmental area brain-stimulation reward. No change in baseline thresholds was seen after peripheral administration of the nonpeptide δ-opioid receptor antagonist, naltrindole. However, an unexpected finding was that naltrindole blocked the threshold-lowering effects of both DPDPE and DAMGO. These data demonstrate nucleus accumbens activation of δ- and μ-opioid receptors and ventral tegmental area brain-stimulation reward share common brain substrates. In addition, the interference of both δ- and μ-opioid receptor mediated reward by naltrindole may have implications for therapeutic use.

Keywords: DAMGO ([D-Ala^2–MePhe^4–Gly(ol)^5]enkephalin); DPDPE ([D-Pen^2, D-Pen^5]enkephalin); Opioids; Opioid receptor antagonist; Naltrindole

1. Introduction

Using both brain-stimulation reward and conditioned place preference it has been found that many brain sites are involved in the rewarding effects of δ- and μ-opioid receptors. The infusion of δ-opioid receptor agonists into the ventricles (De Witte et al., 1989), ventral pallidum, rostral caudate (Johnson and Stellar, 1994) and ventral tegmental area (Jenck et al., 1987) results in the facilitation of brain-stimulation reward. In addition, conditioned place preferences have been associated with intracerebroventricular (i.c.v.) δ-opioid and μ-opioid receptor agonists and intra-ventral tegmental area infusions of a μ-opioid receptor specific agonist (Bals-Kubik et al., 1990; Bals-Kubik et al., 1993; Shippenberg et al., 1987).

It is clear that there are positive effects when these peptides are directly infused into a number of brain sites. However, there have been mixed results in experiments in which these receptor agonists are directly infused into the nucleus accumbens, a site most commonly associated with positive reinforcement (e.g., see Koob, 1993). Rats self-administered both δ-opioid receptor preferring [Met^5]enkephalin (Goeders et al., 1984) and μ-opioid receptor preferring morphine (Olds, 1982) directly into the accumbens, yet δ- and μ-opioid receptor stimulation within the accumbens facilitated brain stimulation in one study (West and Wise, 1988), while having no effect at another (De Witte et al., 1989). Additionally, intra-accumbens [D-Ala^2–MePhe^4–Gly(ol)^5]enkephalin (DAMGO) did not produce conditioned place preferences (Bals-Kubik et al., 1993). Thus, there are discrepancies regarding δ- and μ-opioid receptor involvement in nucleus accumbens-derived reward.

A positive correlation exists between opioid-induced levels of motor activity and reward value (Johnson and Stellar, 1994; Johnson et al., 1993). Intracerebroventricular (i.c.v) infusion of μ-opioid receptor selective DAMGO and δ-opioid receptor selective [D-Pen^2–D-Pen^5]enkephalin (DPDPE), nucleus accumbens-infused DAMGO and δ-opioid receptor selective [D-Thr^2, Leu^5]–enkephalyl–Thr^6 (DTLET), have been shown to increase locomotor activity (Meyer and Meyer, 1993; Meyer et al., 1994; Dauge et al., 1988). Therefore, a major cause for the discrepancies in results between investigators in the above mentioned

* Corresponding author. Tel.: (1-617) 638-4320; Fax: (1-617) 638-4329; e-mail: ckornets@acs.bu.edu

[1] Present address: Department of Psychology, Arizona State University, Box 871104, Tempe, AZ 85287-1104, USA.

PII S0014-2999(96)00674-7

brain-stimulation reward and conditioned place preference experiments is suggested in an analysis of the time after peptide infusion that the behavior is studied. In those above-mentioned studies (e.g., De Witte et al., 1989; Bals-Kubik et al., 1993), behavioral testing or conditioning occurred immediately after peptide infusion. In experiments on the effects of comparable doses of opioid peptides on locomotor activity, the time of the onset of increased motor effect and peak changes for intra-accumbens DAMGO were 30 and 90 min, respectively. For an accumbens-infused δ-opioid receptor agonist (DTLET), these changes peaked 60 min after infusion (Dauge et al., 1988). Thus, proper timing of the behavioral testing period is crucial in order to test during the time of increased motor effect and avoid the sub-optimal or hypolocomotor effect.

There are no published studies, as of yet, comparing the effects of intra-accumbens μ- and δ-opioid receptor specific agonists on rate-independent brain-stimulation reward thresholds. In the present study, intra-accumbens infusions of μ- and δ-opioid receptor selective opioid peptides, DAMGO and DPDPE were tested to determine their effects on the threshold for rewarding ventral tegmental area stimulation. In order to test the specificity of naltrindole for δ-opioid receptors, effects of DPDPE on brain-stimulation reward rats were challenged with the δ-opioid receptor antagonist, naltrindole. Although we did not expect to see an effect, we also tested a high dose of naltrindole with accumbens-infused DAMGO. Opioid peptide effects on brain-stimulation reward were tested at periods shown to yield optimal activity levels (Dauge et al., 1988; Meyer et al., 1994; Meyer and Meyer, 1993). Threshold determinations were made using a rate-independent measure of reward thresholds (Esposito and Kornetsky, 1977).

2. Methods

2.1. Subjects

Twenty-eight male F-344 rats (Charles River Laboratories, Wilmington, DE, USA) served as subjects. Animals were group housed and handled approximately one month prior to surgery. Thereafter, animals were individually housed in hanging wire cages. Food and water were available ad libitum, except during self stimulation sessions. Animals were maintained on a 12 h light/dark cycle with the lights on at 7:00 a.m.

2.2. Surgery

Once the animals reached 300–325 g in weight, they were anesthetized with pentobarbital (Nembutal®, 50 mg/kg) and chloral hydrate (160 mg/kg). Atropine (250 μg/rat) was given prophylactically to control secretions. With the incisor bar raised to 5.0 mm, a single stainless steel electrode (0.2 mm, Plastics One, Roanoke, VA, USA) and bilateral stainless steel cannulae (22 g, Plastics One) were stereotaxically implanted into the ventral tegmental area (AP = −2.7 mm, ML = +0.7 mm, DV = −8.8 mm) and nucleus accumbens (AP = +3.0 mm, ML = +1.7 mm, DV = −5.2 mm), respectively. The nucleus accumbens guide was positioned 2.5 mm above the intended injection site to avoid diffusion up the guide after intracranial injections. Electrode and cannulae were adhered to the skull with surgical screws and cranioplast dental cement. Following surgery animals were administered 0.05 cm^3 Gentimicin® intramuscularly and were allowed one week postoperative recovery.

2.3. Brain-stimulation reward

Animals were trained in a plastic chamber (23 × 23 × 38 cm) with a cylindrical manipulandum (15 × 7.5 cm) on the right wall inside a sound-attenuating chamber (63 × 44 × 58 cm, MED Associates, St. Albans, VT, USA). There were four evenly spaced cams on one endplate of the manipulandum that, when rotated, operated a microswitch resulting in the delivery of a stimulus. A constant current stimulator (MED Associates) delivered biphasic symmetrical square-wave pulses. Each stimulus had a 500-ms train at a frequency of 160 Hz with a pulse width of 0.2 ms and a delay of 0.2 ms between the positive and negative pulses.

Thresholds were determined by a rate-independent procedure (Esposito and Kornetsky, 1977; Kornetsky and Esposito, 1979; Markou and Koob, 1991) involving the use of discrete trials systematically presented over a range of stimulus intensities. A trial began with the delivery of a non-contingent stimulus of a half-second duration. A response of one-quarter wheel turn of the manipulandum within 7.5 s of this stimulus resulted in the delivery of a contingent stimulus, identical in all parameters to the non-contingent stimulus, and terminated the trial. Failure to respond after the non-contingent stimulus had no consequence and the trial was terminated after 7.5 s. The interval between trials varied around a mean of 5 s and responses made during the intertrial interval resulted in a 15 s delay before the start of the next trial.

Stimuli were presented in an alternating descending and ascending series with a step size of 3 μA. At each current intensity, five presentations (trials) of a non-contingent current (0.5 s) were delivered in succession before the next lower or higher intensity was presented. The first descending current column began with a previously determined stimulus intensity (supra-threshold) which was shown to elicit a contingent response. Three or more responses at a particular intensity were arbitrarily scored as a plus for the interval while less than three responses was considered a minus score. A descending column (e.g., current presentations of decreasing intensities) was conducted until two successive current presentations received minus scores. An ascending column began with the lowest intensity of the

previous descending column and continued upward until there were two successive intensities with at least three out of five responses. Calculating the mean of the midpoints (μA) between the intervals in which the animal made more than two responses and less than three resulted in the threshold for a column. The session threshold was determined as the mean of the column thresholds.

Animals required approximately six 1-h training sessions to learn the task and approximately five sessions to establish a stable threshold. Once stable thresholds were determined, animals started their designated drug treatment. Animals received drug treatment no more than three times per week. Each animal ran a pre-injection (baseline) session consisting of four columns followed by six (DPDPE animals) or eight column (DAMGO animals) post-injection (test) sessions. Drug or vehicle were delivered after baseline sessions.

2.4. Intracranial drug infusion procedure

Infusions into the nucleus accumbens were administered bilaterally with 28 gauge injector needles (Plastics One) which projected 2.5 mm beyond the guide. Each needle was connected to polyethylene tubing (PE-20, Intramedic, Clay Adams) which was attached to a 25 μl Hamilton syringe. Drug was delivered by a syringe pump (Razel Scientific, Stamford, CT, USA) at a rate of 0.5 μl/45 s. Infusion of the drug was confirmed by the movement of an air bubble across a set distance within the PE-20 tubing. Injectors were left in the guides for 90 s following infusion to allow for diffusion from the tips. In order to control for handling effects and to minimize potential damage to brain structures on non-test days, animals were handled in the same manner as on test days and were given mock infusions. For these 'infusions,' injector needles were lowered,

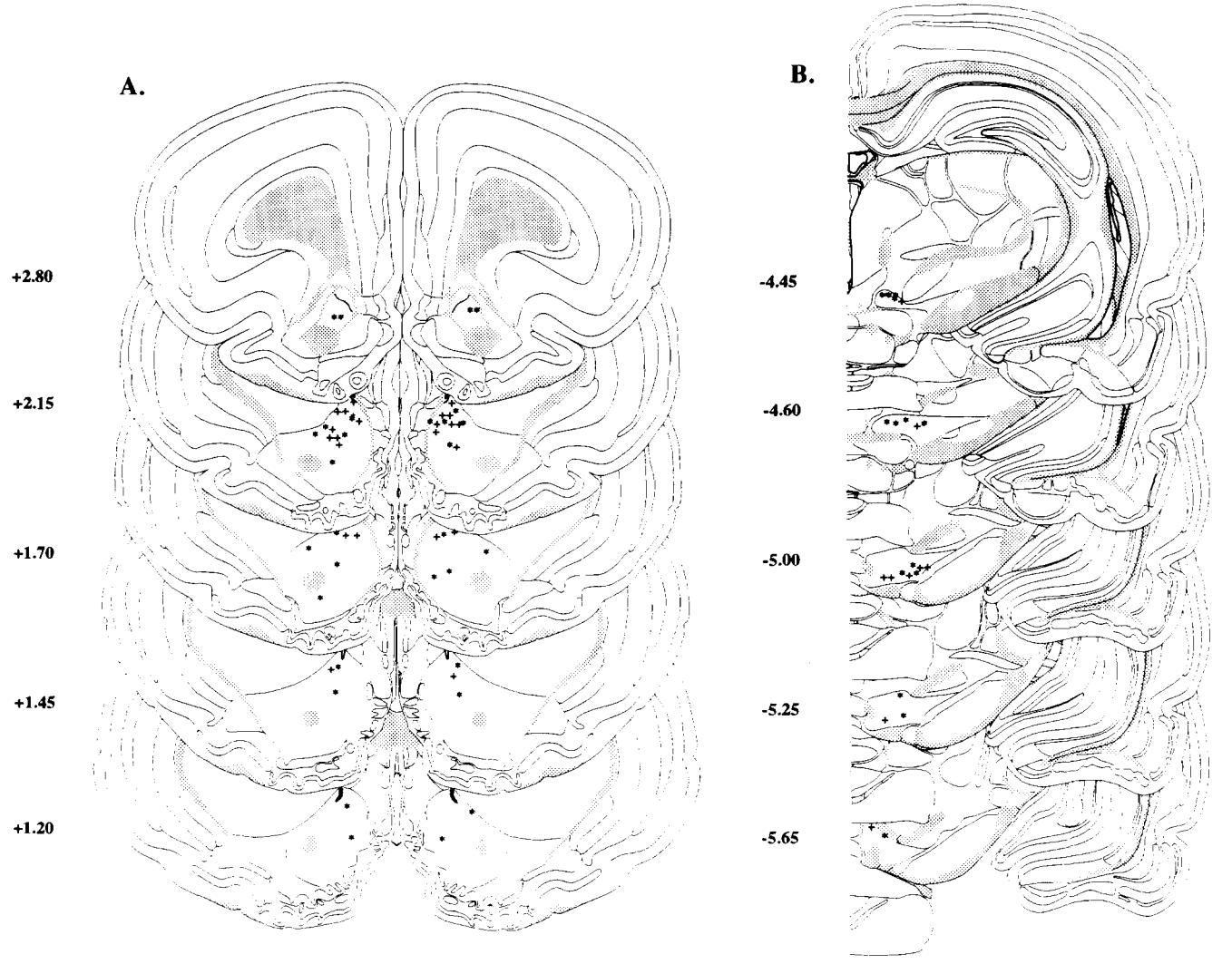

Fig. 1. Histological representation of the location of (A) injector tips within the nucleus accumbens and (B) electrode tips within the ventral tegmental area. The (+) symbol indicates placements in animals that received DAMGO into the area, and the (*) symbol indicates placements in animals receiving DPDPE into the regions. Note that some sites in the ventral tegmental area region are obscured due to multiple placements in the same location. The diagram was drawn with the assistance of Brain Maps® (Swanson, 1992). Numbers to the left indicate mm from bregma. Due to a subsequent infection in the colony, the brains of two animals were not available for histology.

but did not exceed the length of the cannulae and no liquid was infused.

2.5. Drug preparation

The δ-opioid receptor antagonist naltrindole (Research Biochemicals, Natick, MA, USA) and the μ-opioid receptor agonist DAMGO (Peninsula Laboratories, Belmont, CA, USA) were dissolved in 0.9% saline. The δ-opioid receptor agonist DPDPE (Sigma, St. Louis, MO, USA) was dissolved in distilled water. All drugs were prepared the day of testing.

2.6. Histology

At the completion of the experiment, rats were euthanized by an injection of pentobarbital and perfused with a 10% formalin solution. Frozen brain sections were sliced at 20 μm and stained with cresyl violet. Fig. 1 represents the location of the injector needles in the nucleus accumbens and the electrode tips in the ventral tegmental area. As shown, all were within their intended targets.

2.7. Data analysis

Threshold values were calculated for the post-injection sessions, with the test day score minus the mean of the non-test day scores taken as the dependent measure. Because of subject variability in brain stimulation reward thresholds, threshold data was standardized using a *z*-transformation based on the mean and standard deviation of all control days.

One-way repeated measures analysis of variance (ANOVA) was calculated on data from experiments 1 and 2. Fisher's Least Significant Difference (LSD tests, Protected *t*-tests) were used for post hoc analyses. In addition, a Student's *t*-test was also used to compare differences between two groups in experiment 2.

2.8. Experiment 1: Effects of μ and δ-opioid receptor agonists on brain-stimulation reward thresholds

Rats received DAMGO bilaterally (0.0, 0.125, 0.25 and 0.5 and 0.75 μg/0.5 μl per side) 75 min prior to determination of the brain-stimulation reward thresholds. DPDPE (0.0, 2.5, 5.0 and 7.5 μg/0.5 μl per side) was infused bilaterally 45 min prior to test. The times of testing were based on the reported times that DAMGO (Dauge et al., 1988; Meyer et al., 1994) and DPDPE (Dauge et al., 1988) had their maximum locomotor effects.

3. Results

For animals receiving intra-accumbens DAMGO (n = 7), a one-way ANOVA revealed a significant effect of dose, $F(4,24) = 3.48$, $P = 0.022$. Post hoc tests showed that the 0.25 and 0.5 μg doses reliably lowered brain-stimulation reward thresholds when compared to saline (see Fig. 2A).

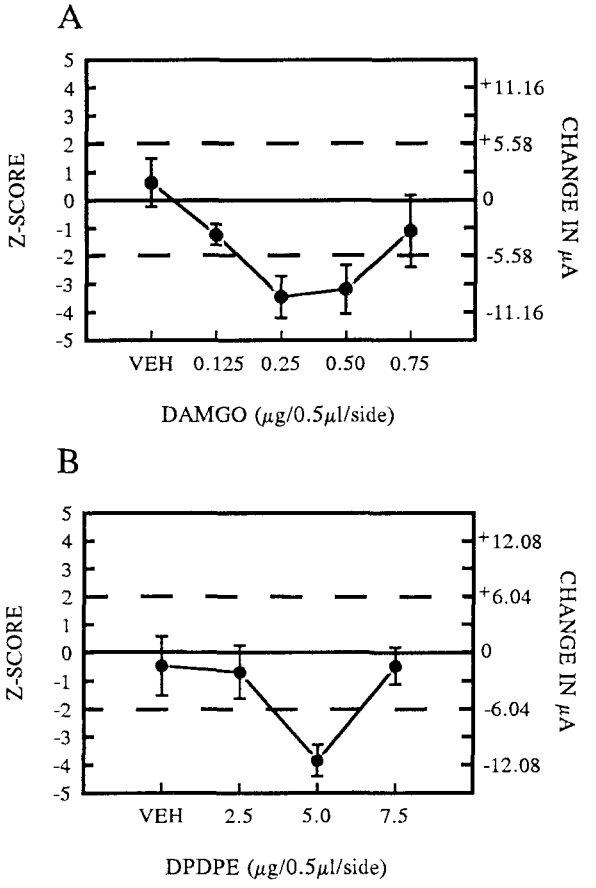

Fig. 2. Mean ± S.E.M. standard score (*z*-score) changes in reward threshold. A *z*-score of ±2.0 indicates the 95% confidence limits based on the mean and standard deviation for all non-drug days. The right side of the graphs depict the mean threshold change in μA. Note: the n contributing to the mean at any dose varied inasmuch as not all animals were tested at each dose. (A) DAMGO: $n = 6$ for saline 0.25 and 0.5 μg doses, $n = 5$ for 0.125 and 0.75 μg doses. (B) DPDPE: $n = 6$ for vehicle and 2.5 μg doses, $n = 8$ for 5.0 μg dose, $n = 4$ for 7.5 μg dose. Drugs were administered bilaterally.

ANOVA calculated from the data of animals receiving DPDPE ($n = 9$) revealed a significant threshold lowering effect, $F(3,24) = 12.59$, $P < 0.0001$. As illustrated in Fig. 2B, post hoc analysis confirmed only the 5.0 μg dose caused a lowering of the brain-stimulation reward threshold.

3.1. Experiment 2: Effect of the δ-opioid receptor antagonist naltrindole

In order to determine possible changes in brain stimulation threshold, animals were given naltrindole alone (0.0, 2.0, 8.0 and 15.0 mg/kg, s.c.) 15 min prior to test session.

In addition, the dose producing the greatest facilitation of brain-stimulation reward in DPDPE-treated animals (5.0

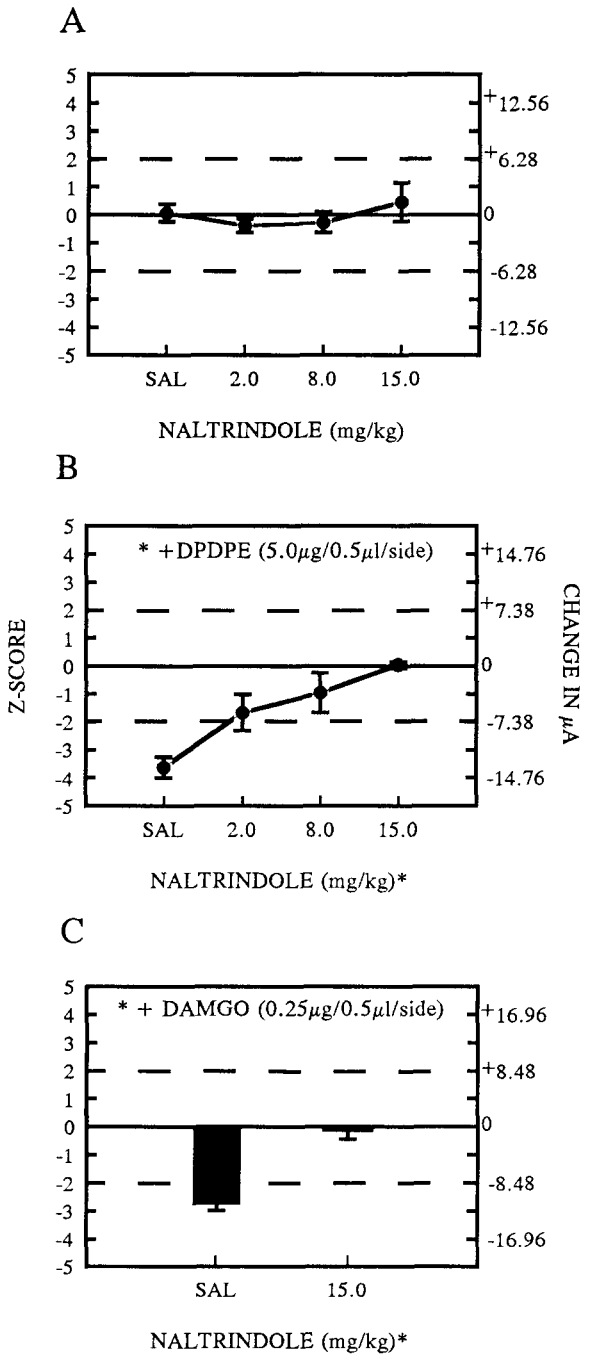

Fig. 3. The mean (±S.E.M.) standard score changes for the effects of naltrindole (s.c.), naltrindole plus 5.0 μg/0.5 μl intra-accumbens DPDPE, and 15.0 mg naltrindole plus 0.25 μg/0.5 μl intra-accumbens DAMGO. Note the n contributing to the mean at any dose varied inasmuch as not all animals were tested at all doses. (A) Naltrindole: $n = 6$ for saline, $n = 5$ for 2.0, 8.0 and 15.0 mg doses. (B) Naltrindole plus 5.0 μg/0.05 μl DPDPE: $n = 6$ for saline, $n = 4$ for 2.0 and 8.0 mg doses, $n = 5$ for 15.0 mg dose. (C) Natrindole 15.0 mg plus 0.25 μg/0.5 μl DAMGO: $n = 5$. DAMGO and DPDPE were administered bilaterally.

μg/0.5 μl, infused 45 min prior to test) was tested against drug challenges of naltrindole (0.0, 2.0, 8.0 and 15.0 mg/kg, s.c.). The optimal dose of DAMGO (0.25 μg/0.5 μl, infused 75 min prior to test) was also tested against the high dose of naltrindole (15.0 mg/kg).

3.2. Results

As illustrated in Fig. 3A, naltrindole ($n = 6$) did not significantly alter the brain-stimulation reward threshold ($F(3,15) = 1.318$, n.s.) Post hoc tests further confirmed that no dose of naltrindole affected brain-stimulation reward thresholds in any direction.

As illustrated in Fig. 3B, naltrindole ($n = 6$) significantly blocked the effect of DPDPE, $F(3,15) = 16.39$, $P < 0.0001$. Post hoc analysis revealed that all doses of naltrindole significantly blocked the rewarding effect of DPDPE.

As seen in Fig. 3C, a δ-opioid receptor antagonist challenge (NTI, 15.0 mg/kg, s.c.; $n = 5$) of μ-opioid receptor agonist (DAMGO) facilitation of reward resulted in a full blocking of the brain-stimulation reward threshold lowering effects of DAMGO, $t(4) = -4.36$, $P = 0.012$.

4. Discussion

In experiment 1, DAMGO and DPDPE infusions into the nucleus accumbens lowered the threshold for brain stimulation reward. These results demonstrate intra-accumbens infusions of both μ- and δ-opioid receptor agonist specific peptides increase an animal's sensitivity to rewarding brain-stimulation.

Although i.c.v. and ventral tegmental area infusions of μ-opioid receptor agonists have been shown to produce positive reinforcing effects in the conditioned place preference and brain stimulation reward tests (Bals-Kubik et al., 1990; Bals-Kubik et al., 1993; Jenck et al., 1987), the results obtained with DAMGO in the present study are apparently not in accordance with studies showing an inability of intra-accumbens DAMGO to produce place preferences (Bals-Kubik et al., 1993) or to facilitate brain stimulation rates of response (De Witte et al., 1989). In these discrepant studies, testing was initiated immediately after intra-accumbens infusions and its duration did not exceed 45 min. Since intra-accumbens DAMGO has a biphasic effect in which the first 45 min reflect decreased locomotion, we tested only at time intervals that were reported to yield increases in locomotor behavior (Meyer et al., 1994; Dauge et al., 1988).

Increased locomotor activity levels often coincide with positive motivational states (Johnson et al., 1993; Johnson and Stellar, 1994). Therefore, since the earlier studies of brain-stimulation reward used comparable doses of DAMGO, discrepant findings may be due to using a rate-dependent measure of brain-stimulation reward during functionally different phases of the drug effect. The hypolocomotor phase of the DAMGO effect may not be as rewarding as the hyperlocomotor phase. Because hypo-

motility may also interfere with operant responding, the decreased response rate for brain stimulation may reflect motoric function rather than, or in addition to, decreases in positive reinforcing effect. Because the rate-independent brain-stimulation reward threshold procedure used in the present study is independent of motor effects (Markou and Koob, 1991) the threshold lowering effect of DAMGO is unlikely the result of an increase in locomotor action.

Using different procedures, a number of investigators have concluded that the reinforcing effects of δ-opioid receptor agonists are the result of activation of nucleus accumbens δ-opioid receptors. For example, i.c.v. DPDPE results in conditioned place preference (Shippenberg et al., 1987), brain stimulation response rates are facilitated by the δ-opioid receptor agonist DTLET (De Witte et al., 1989), and methionine enkephalin is self-administered into the nucleus accumbens (Goeders et al., 1984). In the present study, our finding that DPDPE lowers the threshold for brain-stimulation reward is compatible with the findings of these investigators.

Since we did not conduct a binding study to specifically look at the spread of drug, we cannot be sure that the effects we see are specific to the nucleus accumbens. It is possible that the effects were due to diffusion to surrounding areas. We did the following measures to minimize spread of drug to distal sites: we (1) placed the guide cannula 2.5 mm above the injection tip site to minimize drug spread up the length of the guide and (2) slowly infused a low drug volume (0.5 μl) and left injector in site for 90 s. The diffusion hypothesis further breaks down based on findings in the study by Dauge et al. (1988), in which the same dose of DAMGO (0.25 μg) was dissolved in twice the vehicle volume (1.0 μl) as that used in our study. If diffusion plays a role in this locomotion and our reward findings, our effects on reward should be on more proximal sites at higher concentrations than the locomotion effects. However, our findings of optimal effects on DAMGO reward occurring approximately 90 min post nucleus accumbens drug-infusion coincides with the study by Dauge et al. (1988), showing the highest levels of locomotion occurring at 90 min post nucleus accumbens infusion. Given that identical time course and the positive correlation between opioid-induced levels of motor activity and reward value, if the results from both studies are due to drug diffusion, this scenario is unlikely to produce the coinciding effects of reward and motor behavior seen between the studies.

Naltrindole significantly blocked the threshold-lowering effects of DPDPE at all doses tested, supporting the view that the effect of DPDPE on brain-stimulation reward is specific to δ-opioid receptors; to our surprise however, we found that the high dose of naltrindole (15.0 mg/kg, s.c.) also blocked the reward potentiating effects of DAMGO, suggesting less specificity. Although naltrindole (Portoghese et al., 1988) and DAMGO (Zimmerman and Leander, 1990) are believed to be highly specific for their respective receptor types, particularly in studies of antinociception (Calcagnetti and Holtzman, 1991; Drower et al., 1991), naltrindole does possess significant antagonist potencies at both μ and κ opioid receptors in the guinea pig ileum assay (Portoghese, 1991). In addition, naltrindole blocked the rewarding effects of cocaine in brain stimulation reward (Reid et al., 1993) and conditioned place preference (Menkens et al., 1992). Because naltrindole alone did not affect baseline behaviors in the present and above-mentioned studies (Reid et al., 1993; Menkens et al., 1992), this profile of activity suggests it may have potential as an adjunct treatment for drug abuse.

This rate-independent method of determining brain-stimulation reward thresholds is useful in confirming brain areas and receptors contributing to positive reinforcing events, and predicting treatments that can interfere with these events. In addition, the results obtained from this study further indicate that both μ- and δ-opioid receptor selective agonists DAMGO and DPDPE have a common action on the brain reward system as measured by rewarding intracranial self-stimulation.

Acknowledgements

This research was supported in part by NIDA grants DA02326, DA05100 and NIDA Research Scientist Award KO5-DA00099 to C.K.

References

Bals-Kubik, R., A. Ableitner, A. Herz and T.S. Shippenberg, 1993, Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats, J. Pharmacol. Exp. Ther. 264, 489.

Bals-Kubik, R., T.S. Shippenberg and A. Herz, 1990, Involvement of central μ and δ opioid receptors in mediating the reinforcing effects of beta-endorphin in the rat, Eur. J. Pharmacol. 175, 63.

Calcagnetti, D.J. and S.G. Holtzman, 1991, δ opioid antagonist, naltrindole, selectively blocks analgesia induced by DPDPE but not DAGO or morphine, Pharmacol. Biochem. Behav. 38, 185.

Dauge, V., P. Rossignol and B.P. Roques, 1988, Comparison of the behavioural effects induced by administration in rat nucleus accumbens or nucleus caudatus of selective μ and δ opioid peptides or kelatorphan an inhibitor of enkephalin-degrading-enzymes, Psychopharmacology 96, 343.

De Witte, P., C. Heidbreder and B.P. Roques, 1989, Kelatorphan, a potent enkephalinases inhibitor, and opioid receptor agonists DAGO and DTLET, differentially modulate self-stimulation behaviour depending on the site of administration, Neuropharmacology 28, 667.

Drower, E.J., A. Stapelfeld, M.R. Rafferty, B.R. De Costa, K.C. Rice and D.L. Hammond, 1991, Selective antagonism by naltrindole of the antinociceptive effects of the δ opioid agonists cyclic[D-Penicillamine^{2}–D-Penicillamine^{5}]Enkephalin in the rat, J. Pharmacol. Exp. Ther. 259, 725.

Esposito, R. and C. Kornetsky, 1977, Morphine lowering of self-stimulation thresholds: lack of tolerance with long term administration, Science 195, 189.

Goeders, N.E., J.D. Lane and J.E. Smith, 1984, Self-administration of

methionine enkephalin into the nucleus accumbens, Pharmacol. Biochem. Behav. 20, 451.

Jenck, F., A. Gratton and R.A. Wise, 1987, Opioid receptor subtypes associated with ventral tegmental facilitation of lateral hypothalamic brain stimulation reward, Brain Res. 423, 34.

Johnson, P.I. and J.R. Stellar, 1994, Comparison of δ opiate receptor agonist induced reward and motor effects between the ventral pallicum and dorsal striatum, Neuropharmacology 33, 1171.

Johnson, P.I., J.R. Stellar and A.D. Paul, 1993, Regional reward differences within the ventral pallidum are revealed by microinjections of a μ opiate receptor agonist, Neuropharmacology 32, 1305.

Koob, G.F., 1993, Neural mechanisms of drug reinforcement, Ann. NY Acad. Sci., 171.

Kornetsky, C. and R.U. Esposito, 1979, Euphorigenic drugs: Effects on the reward pathways of the brain, Fed. Proc. 38, 2473.

Markou, A. and G.F. Koob, 1991, Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations, Physiol. Behav. 51, 111.

Menkens, K., E.J. Bilsky, K.D. Wild, P.S. Portoghese, L.D. Reid and F. Porreca, 1992, Cocaine place preference is blocked by the δ-opioid receptor antagonist, naltrindole, Eur. J. Pharmacol. 219, 345.

Meyer, M.E., B.I. McLaurin, M. Allen and M.E. Meyer, 1994, Biphasic effects in intraaccumbens μ-opioid peptide agonist DAMGO on locomotor activities, Pharmacol. Biochem. Behav. 47, 827.

Meyer, M.E. and M.E. Meyer, 1993, Behavioral effects of opioid peptide agonists DAMGO, DPDPE, and DAKLI on locomotor activities, Pharmacol. Biochem. Behav. 45, 315.

Olds, M.E., 1982, Reinforcing effects of morphine in the nucleus accumbens, Brain Res. 237, 429.

Portoghese, P.S., 1991, An approach to the design of receptor-type-selective non-peptide antagonists of peptidergic receptors: delta opioid antagonists, J. Med. Chem. 34, 1757.

Portoghese, P.S., M. Sultana and A.E. Takemori, 1988, Naltrindole, a highly selective and potent non-peptide δ opioid receptor antagonist, Eur. J. Pharmacol. 146, 185.

Reid, L.D., C.L. Hubbell, M.D. Glaccum, E.J. Bilsky, P.S. Portoghese and F. Porreca, 1993, Naltrindole, an opioid δ receptor antagonist, blocks cocaine-induced facilitation of responding for rewarding brain stimulation, Life Sci. 52, PL 67.

Shippenberg, T.S., R. Bals-Kubik and A. Herz, 1987, Motivational properties of opioids: evidence that an activation of δ-receptors mediates reinforcement processes, Brain Res. 436, 234.

Swanson, L.W. (1992) Brain Maps: Structure of the Rat Brain (Atlas and Computer Graphics Files) (Elsevier, Amsterdam).

West, T.E.G. and R.A. Wise, 1988, Nucleus accumbens opioids facilitate brain stimulation reward, Abst. Soc. Neurosci. 14, 1102.

Zimmerman, D.M. and J.D. Leander, 1990, Selective opioid receptor agonists and antagonists: research tools and potential therapeutic agents, J. Med. Chem. 33, 895.