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Opiates and classical conditioning: Selective abolition of conditioned responses by activation of opiate receptors within the central nervous system

(conditioned fear/morphiceptin/μ receptors/periaqueductal gray/periventricular region)

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ABSTRACT **It has previously been shown that opiates produce selective abolition of aversively motivated classically conditioned responses in the rabbit. The experiments reported here show that these effects are mediated by specific activation of opiate receptors within the central nervous system in that this central activation is both necessary and sufficient to produce opiate-induced abolition of conditioned responding. Further characterization suggests that selective activation through opiate–μ-receptor interactions within the periaqueductal gray/periventricular region of the fourth ventricle may be critical in mediating this abolition.**

In recent literature, it is suggested that opiate-sensitive processes are involved in the modulation of various aspects of learning and memory formation (1–3). Among these reports are findings that microadministration of opiate agonists into the amygdala complex can alter the retention of passive-avoidance conditioning and the acquisition of fear-motivated conditioned heart-rate responses (4, 5). Such findings have led to the speculation that opiate-sensitive mechanisms within the amygdala may provide a common substrate for the effects of opiates on memory processes and regulation of emotional states including fear (6). On the other hand, peripherally administered opioid peptides have been reported to affect both acquisition and consolidation of avoidance responses (7–9). Such effects are time dependent, suggesting that these peptides acted to alter some aspect of learning and memory processes. Moreover, these effects occur at doses that indicate that the primary site of action may be in the peripheral rather than the central nervous system.

We have recently reported that intravenous (i.v.) administration of morphine produces complete and naloxone-reversible abolition of a simple aversively motivated learned response—the classically conditioned eyelid/nictitating membrane (NM) response in the rabbit (10). Morphine has no effect on performance of the unconditioned reflex response nor on tone-conditioned stimulus-evoked neuronal activity in the primary auditory pathway. Further, the conditioned response (CR) is selectively abolished on the trial immediately following morphine injection, before the animal has experienced the next aversive unconditioned stimulus (US). It would appear that morphine is acting selectively and possibly directly on the associative process—that is, some as yet to be localized portion of the neural circuitry that is essential for the expression of the learned response.

As a first step in the localization and characterization of the opiate-sensitive process in question, we felt that it is necessary to determine the relative contributions of peripheral and central opiate-sensitive sites in the mediation of the opiate-induced abolition of aversively motivated conditioned responding. To this end, we report a series of experiments in which we determined the relative effects of both systemic and central administration of several opiate agonists and antagonists on the expression of the CR. Collectively, these results indicate that the selective opiate action on the CR is mediated by activation of opiate receptor-mediated processes within the central nervous system in that this central activation is both necessary and sufficient in producing the opiate-induced abolition of the CR. Further characterization suggests that selective activation through opiate–μ-receptor interactions within the periaqueductal gray/periventricular region of the fourth ventricle may be critical in mediating this abolition.

MATERIALS AND METHODS

Forty male New Zealand albino rabbits (*Oryctolagus cuniculus*) weighing 2 to 3 kg were used. Animals were maintained on a 12/12 light/dark cycle with ad lib food and water.

Training and Testing. General training and testing procedures have been described (11–13). Briefly, training consisted of short-delay classical conditioning with a tone conditioned stimulus (CS; 1 kHz, 85 dB, 350 msec) and a corneal air-puff US (2.1-N/cm^2 pressure, 100 msec coterminate with the CS). Trials were delivered every 20–40 sec (mean = 30 sec). Eight paired CS–US trials and one CS-alone test trial constituted a block, 13 blocks per day. Animals were trained to a behavioral criterion of eight CRs in any nine consecutive trials and then given two additional blocks of training (baseline conditioning) before test procedures began. A CR was defined as a NM extension during the CS period of at least 0.5 mm. Conditioned and unconditioned responses were determined by calculating the peak NM-response amplitudes (expressed in mm) during the CS and US periods, respectively.

Intracerebroventricular (ICV) Microinfusion Studies. Prior to training, a chronic indwelling guide cannula (22 gauge, Plastic Products, Roanoke, VA) was stereotaxically implanted under halothane anesthesia into the rostral region of the fourth ventricle of each rabbit. Cannulae were positioned midsagitally, 13.0 mm posterior to bregma. Care was taken to avoid damage to the superior sagital sinus. Dorsal/ventral position was adjusted until free flow of cerebrospinal fluid was established (11.5–13.5 mm ventral to bregma) via an internal cannula (28 gauge) that was positioned within and extended 1.0 mm beyond the guide cannula. The internal cannula was connected to a microsyringe by polyethylene tubing (PE 10) during surgery, which allowed the flow of cerebrospinal fluid to be monitored. After localization, the guide cannula was secured with dental

Abbreviations: CS, conditioned stimulus; US, unconditioned stimulus; CR, conditioned response; NM, nictitating membrane; i.v., intravenous; ICV, intracerebroventricular; ANOVA, analysis of variance.

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acrylic and skull screws. A headstage designed to accommodate the stimulus delivery/micropotentiometer assembly was secured about the surface of the skull immediately rostral to the exposed portion of the cannula. The internal cannula was then removed and replaced with an internal stylet that was secured by a screw cap. Animals were allowed a minimum of five days of recovery before training began. At the completion of testing, animals were deeply anesthetized with sodium pentobarbital (Nembutal) and perfused through the heart with 10% formalin. The fixed brains were then mounted in albumin for subsequent histological verification of the cannula placement by localization of the cannula track.

To assess the effects of central administration of opioid peptides on the classically conditioned NM response, a microinfusion procedure was established. After baseline conditioning, the internal stylet was removed and replaced with an internal cannula connected to a microsyringe via polyethylene tubing. Only animals with patent cannulae as determined by free flow of cerebrospinal fluid through the cannulae at the time of testing were used. Appropriate compounds dissolved in Ringer's solution were administered in a 20-μl volume and delivered at a rate of 0.2 μl/sec. Total infusion time was 100 sec. All solutions were prepared immediately prior to administration.

In our initial microinfusion study, 17 rabbits were given baseline conditioning and then assigned to one of five groups such that baseline CR performance was comparable across groups. Animals were administered, via microinfusion, either Ringer's solution (n = 3); 200 nmol of morphiceptin (n = 5), a highly selective opiate agonist for μ receptors (14); 200 nmol of morphiceptin together with 20 nmol of naltrexone hydrochloride (n = 4); or 200 nmol of the (D-Pro^2) analogue of morphiceptin (n = 5), a stereoisomer that has been shown to be void of opiate agonist activity (14, 15). To allow for adequate diffusion of substances, a 5-min period intervened between completion of the microinfusion and resumption of training. Animals were then tested for an additional three blocks.

In a second study, after baseline conditioning, 16 rabbits were assigned to one of five treatment groups in the manner described above. Animals received either Ringer's solution (n = 3) or various amounts of [*N*-Me-Phe^3-D-Pro^4]morphiceptin, a long-lasting, potent, and selective μ-receptor agonist (§): two groups received 12 nmol (n = 3 for both groups) and the remaining two groups received either 6 nmol (n = 4) or 3 nmol (n = 3) by the microinfusion procedure described above. To allow adequate time for diffusion of substances within the ventricle, training was resumed 30 sec after completion of the microinfusion. After an additional three blocks of training, animals in one of the 12-nmol groups received naloxone hydrochloride at 2.5 mg/kg in 0.5 ml of physiological saline and administered via an acute catheter implanted prior to conditioning in the marginal ear vein. Animals in the remaining four groups each received an equal volume of the saline vehicle administered in an identical fashion. Test trials were resumed 30 sec after completion of the i.v. injection. All animals were then tested for a final three blocks.

I.v. Infusion Studies. Each rabbit was surgically prepared under halothane anesthesia with a headstage as described above. Animals were allowed a minimum of five days recovery before training began. To assess the effects of peripherally administered opiate agonists on the conditioned NM response, an i.v. infusion procedure was used. Prior to training, an acute catheter (25 gauge) was implanted in the marginal ear vein. Immediately prior to administration, appropriate compounds were dissolved in 0.5 ml of physiological saline. All compounds were administered at a constant rate over a 30-sec period.

In our initial experiment, after baseline conditioning, each animal (n = 4) was administered a series of i.v. injections of [*N*-Me-Phe^3-D-Pro^4]morphiceptin: the first (1.2 nmol) immediately after baseline conditioning, the second (12 nmol) three trials later, and the third (120 nmol) after an additional three trials. These dosages corresponded to 0.1, 1.0, and 10.0 times the highest dosage administered ICV (see previous study). Animals were given a total of three blocks of conditioning after the initial injection. Thereafter, all subjects were administered morphine sulfate at 7.5 mg/kg i.v. by the procedure described above as a control measure. The animals were then given a final two blocks of testing.

In a second study, after baseline conditioning, each animal (n = 3) was administered morphine sulfate (5 mg/kg) i.v. and, three blocks later, was administered a series of four i.v. injections of naloxone methobromide, a quaternary derivative of naloxone that does not cross the blood–brain barrier in any appreciable amount (16, 17). Three conditioning trials intervened between each sucessive i.v. injection. These doses corresponded to 1, 25, 50, and 100 times the molar dosage of naloxone (275 nmol/kg—i.e., 0.1 mg/kg) previously shown to completely reverse the morphine effect on the CR (9). This range was selected to normalize the potency differences; quaternary naloxone is 1.5–5% as potent (16, 17). One block after the final injection of naloxone methobromide, a control injection of naloxone hydrochloride (0.1 mg/kg) was administered i.v. to each subject. Thereafter, all animals were subjected to a final two blocks.

RESULTS

ICV Microinfusion Studies. ICV infusion of morphiceptin completely abolished the CR; however, concurrent administration of morphiceptin with the opiate antagonist naltrexone produced no effect (Fig. 1*B*). The D-Pro^2 analogue of morphiceptin also had no affect on the CR. These observations were statistically reliable. A two-way mixed analysis of variance (ANOVA) showed a significant drug–block interaction [$F(3,12) = 3.556$; $P < 0.05$]. *Post hoc* Newman–Keuls analysis showed that the post-morphiceptin blocks were reliably different from all other groups ($P < 0.05$). No other comparisons were significant. As previously reported for i.v. morphine, the effect of morphiceptin was selective in that there were no effects on the amplitude of the unconditioned response (Fig. 1*A*). A separate two-way mixed ANOVA showed no significant main or interaction effects. Marked recovery of the CR was observed in the morphiceptin-treated animals during the fourth through the sixth blocks (data not shown).

The potent long-lasting analogue of morphiceptin, [*N*-Me-Phe^3-D-Pro^4]morphiceptin, similarly abolishes the CR (Fig. 2). This effect is dose dependent and, at the highest dose administered (12 nmol), completely abolished the CR in most instances for the six blocks tested. In fact, two animals given extended testing showed no recovery of the CR until the 11th and 13th blocks (45–55 min; data not shown). A two-way mixed ANOVA confirmed these observations, showing a significant block effect [$F(2,22) = 8.99$; $P < 0.001$] and a significant drug–block interaction [$F(8,22) = 3.302$; $P < 0.025$]. *Post hoc* Newman–Keuls analysis showed no reliable differences for the preinjection means. For the three blocks post-ICV infusion, both 12-nmol groups were reliably different from the vehicle group ($P < 0.05$). For the blocks after i.v. injection, the 12-nmol/saline group was reliably different from the vehicle group, the

§ Chang, J.-K., Wei, E. T., Killian, A. & Chang, K.-J., International Narcotic Research Conference, North Falmouth, MA, June 14–18, 1982, p. 5.

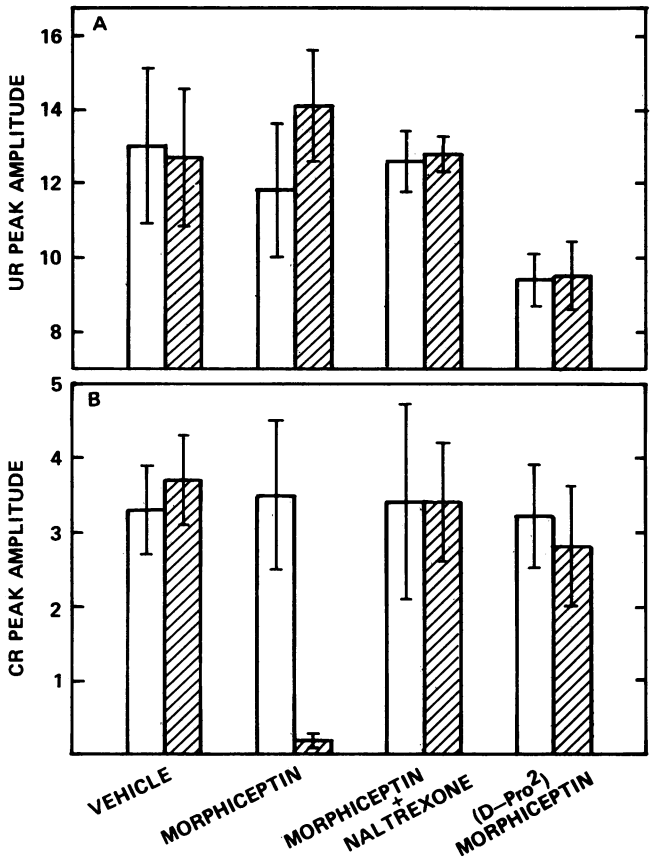

FIG. 1. Mean UR (*A*) and CR (*B*) amplitudes (expressed in mm) during two blocks of pre-infusion baseline conditioning (□) and the three blocks after ICV infusion (▨).

3-nmol group, and the 12-nmol/naloxone group ($P < 0.05$ for each). No other comparisons were reliable. Again, this opioid effect was selective to the CR as there were no effects on the unconditioned response ($F < 1$ for main and interaction effects). The effect remained selective to the CR even in two pilot animals given 25 and 50 nmol, respectively (data not shown).

I.v. Infusion Studies. I.v. administration of the morphiceptin analogue [*N*-Me-Phe^3-D-Pro^4]morphiceptin in doses ranging from 0.1 to 10.0 times those required to produce complete abolition of the CR when administered centrally produced no effect on conditioned responding (Fig. 3). In contrast, subsequent i.v. administration of morphine produced marked abolition of the CR. These observations were confirmed statistically. A one-way repeated-measures ANOVA showed a significant trials effect [$F(2,6) = 6.741$; $P < 0.05$]. Newman–Keuls analysis showed that the CR amplitudes for blocks following injection of morphine were reliably different from all other blocks ($P < 0.05$). No other comparisons approached significance.

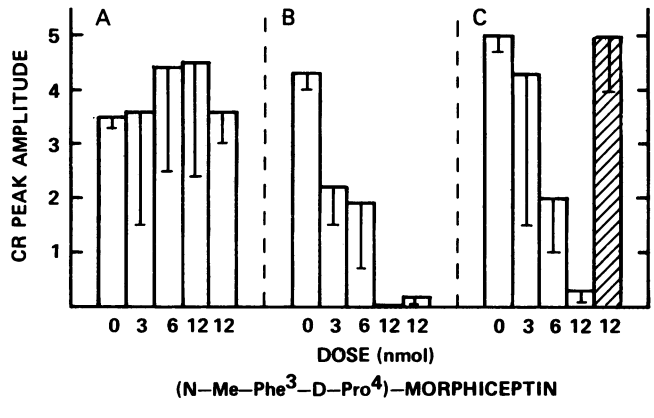

FIG. 2. Mean CR amplitudes (in mm) during two blocks of pre-infusion baseline conditioning (*A*), three blocks following ICV infusion of [*N*-Me-Phe^3-D-Pro^4]morphiceptin (*B*), and the subsequent three blocks following i.v. infusion (*C*) of the saline vehicle (□) or naloxone at 2.5 mg/kg (▨).

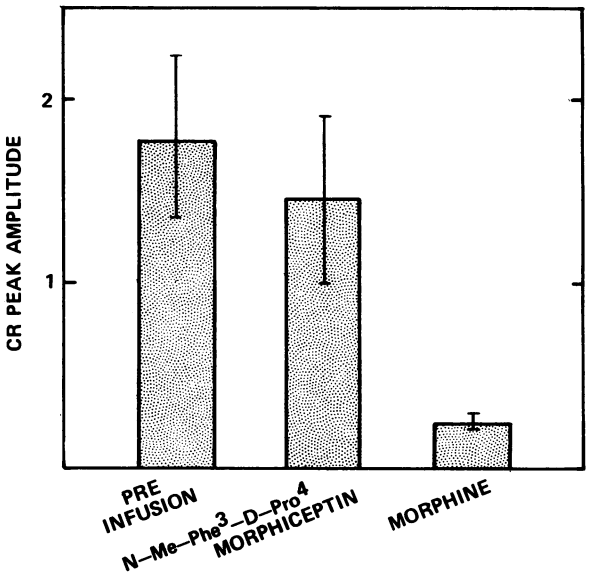

FIG. 3. Mean CR amplitudes (in mm) during two blocks of baseline conditioning, during serial i.v. infusions of [*N*-Me-Phe^3-D-Pro^4]morphiceptin (three blocks), and following i.v. infusion of morphine (two blocks).

In the second study, serial i.v. administration of quaternary naloxone had no effect on normalizing the morphine-induced abolition of the CR (Fig. 4). Such doses ranged from 1 to 100 times the molar dose of naloxone used to subsequently reverse this effect on CRs. These observations were statistically reliable. A one-way repeated-measures ANOVA indicated a significant treatment effect [$F(3,6) = 7.333$; $P < 0.025$]. *Post hoc* Newman–Keuls analysis showed that the post-morphine and -quaternary naloxone blocks were reliably different from the pre-injection and post-naloxone blocks ($P < 0.05$). No other comparisons were significant.

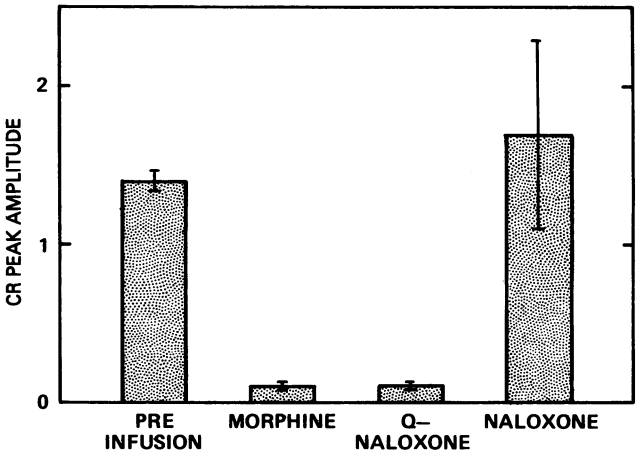

FIG. 4. Mean CR amplitudes (in mm) during pre-infusion baseline conditioning (two blocks) followed by i.v. administration of morphine (three blocks), serial doses of quaternary naloxone (two blocks), and finally naloxone (two blocks).

DISCUSSION

In our initial studies, we demonstrated that morphiceptin, a highly selective μ-receptor agonist, when infused into the fourth ventricle, produced a pronounced abolition of the CR and that this effect was prevented by concomitant infusion of the opiate antagonist naltrexone. Administration of the (D-Pro^2) analogue of morphiceptin, which has previously been shown to be void of opiate agonist activity (14, 15) also was ineffective in the present study in abolishing the CR. The fact that this isomer was ineffective supports the steric specificity of the morphiceptin–recognition site interaction under investigation.

Central administration of the potent long-lasting analogue [*N*-Me-Phe^3-D-Pro^4]morphiceptin similarly produced a marked abolition of the CR. This effect was dose dependent and could be completely reversed by subsequent administration of the opiate antagonist naloxone. When viewed in concert, the effects of these substances on the expression of the CR are consistent with the known pharmacological properties that opiate agonists display through binding at recognition sites characterized as opiate receptors—i.e., high affinity, reversibility, stereospecificity, and the blockage or reversibility of such agonist–receptor interaction by opiate antagonists.

Preliminary analysis indicates that the periaqueductal gray/periventricular region of the fourth ventricle is a particularly sensitive site for producing this opiate–receptor-mediated abolition of the CR, relative to other sites studied. Microinfusion of comparable amounts of morphiceptin into the lateral ventricles produced an abolition of the CR; however, this effect typically had a delayed onset and a considerably shorter and more variable action. Moreover, bilateral microadministration of this peptide into either the medial septal region or the amygdaloid complex had no effect on the CR.

In spite of these observations, it could be argued that, although administered centrally, these opiate agonists are being transported from the cerebrospinal fluid to the circulation and ultimately acting at opiate-sensitive sites in the periphery. However, the results from our systemic studies argue against this position. First, i.v. administration of [*N*-Me-Phe^3-D-Pro^4]morphiceptin in doses ranging from 0.1 to 10 times those effective via central infusion had no effect on the CR. Second, serial systemic administration of the opiate antagonist quaternary naloxone, which does not cross the blood–brain barrier in any appreciable amount, had no effect on morphine-induced abolition of the CR. The range of doses used was comparable in potency with the dose of naloxone subsequently used to completely reverse the effect of morphine.

Collectively, these observations are consistent with the position that the effects of opiates on learned responses are mediated by activation of μ-receptor-mediated processes within the central nervous system. Furthermore, this effect was selective to the CR. None of the opiate agonists tested affected the performance of the unconditioned reflex response. It may be argued that opiates are acting on some critical component(s) of the circuitry that codes the learned response, possibly localized to the periaqueductal gray/periventricular region of the fourth ventricle. This region has also been shown to be a particularly sensitive site in the production of opiate-induced analgesia in the rabbit (18). It is possible that opiate abolition of the CR shares a neural substrate common to that involved in modulation of slow pain and the production of analgesia.

Theoretical treatments of aversive learning emphasize two processes: conditioned fear and the later development of specific adaptive learned motor responses (19–22). Conditioned heart rate changes are generally considered an index of learned fear (23, 24). They develop early in aversive classical conditioning and then fade as conditioned striated muscle responses (eyelid/NM) are established (25–28). We have recently found that central administration [*N*-Me-Phe^3-D-Pro^4]morphiceptin completely abolishes the learned heart rate response in the rabbit (29). Further, the effects of opiates on eyelid/NM CRs decrease markedly with overtraining (unpublished observations). We have recently shown that the ipsilateral cerebellum is essential for learning, and for retention and relearning of the conditioned eyelid/NM response, even in animals given extensive overtraining (30–33). We suggest that in aversive learning the process of learned fear may be necessary for the initial development of specific adaptive learned skeletal muscle responses (e.g., eyelid/NM) and that certain opioids may exert their selective action on both specific and autonomic responses by a common action on a "learned fear" system in the brain (see also refs. 10, 34, 35). As the specific motor response (e.g., eyelid/NM) becomes well learned, the cerebellar circuitry may develop functional autonomy.

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