Pharmacology Biochemistry & Behavior, Vol. 28, pp. 227–233. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Kappa Receptors Mediate the Peripheral Aversive Effects of Opiates

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Received 16 January 1987

BECHARA, A. AND D. VAN DER KOOY. *Kappa receptors mediate the peripheral aversive effects of opiates.* PHARMACOL BIOCHEM BEHAV **28**(2) 227–233, 1987.—Previous evidence has suggested that endogenous and exogenous opioids produce positive reinforcing effects through an action on central nervous system opiate receptors and aversive effects through an action on peripheral opiate receptors. In order to investigate the pharmacological specificity of the opiate aversive effects to peripheral opiate receptor subtypes, drug naive rats were administered various subcutaneous or intraperitoneal dose of the specific kappa receptor agonist U50,488 (0.005–16 mg/kg) and run in a place conditioning paradigm. The results were compared to previously published data on the motivational effects of morphine, collected using identical experimental procedures [1]. Regardless of the route of administration, the majority of doses of U50,488 produced conditioned place aversions, whereas increasing doses of morphine produced conditioned place preferences [1]. Only a low dose of morphine (0.05 mg/kg intraperitoneally but not subcutaneously) was shown to produce significant place aversions, suggesting a local gut effect [1]. Vagotomy blocked the aversive properties of morphine [1], and in the present report shifted the motivational effects of moderate doses of U50,488 into preferences. U50,488 produced aversions at a dose that was 5 times lower than the low dose of morphine that produced aversive effects. Even at very high doses, U50,488 did not produce the conditioned place preferences seen with morphine. These high dose aversions induced by U50,488 were attenuated by a low intraperitoneal dose of the kappa antagonist Mr2266. In order to investigate the possible actions of peripheral, endogenous kappa agonists, a dose-response curve was generated in the place conditioning paradigm from separate groups of naive rats injected with various intraperitoneal doses of the specific kappa antagonist Mr2266 (0.001–10 mg/kg) or its inactive isomer Mr2267 (0.01–10 mg/kg). The results were compared to previously published data on naltrexone (0.01–10 mg/kg) [1], collected using identical experimental procedures. Mr2266 was 10 times more potent than naltrexone in producing preferences at low doses. The inactive isomer, Mr2267 was ineffective in producing place preferences over the doses at which Mr2266 was effective. The results suggest that the primary site of the aversive effects of both exogenous and endogenous opioids is the peripheral kappa receptor.

Kappa receptor Morphine U50,488 Mr2266 Naltrexone Opiate aversions Place conditioning

SEPARATE neural substrates have been proposed [1,2] to subserve the paradoxical positive reinforcing and aversive effects of opiates. In rats, the positive reinforcing effects of morphine are demonstrated when the drug is paired with visual and textural environmental stimuli [16,31]. These positive reinforcing effects of morphine were shown to be produced through an action on brain opiate receptors [1, 2, 25, 29]. In contrast, morphine produces primarily aversive effects when paired with taste stimuli (conditioned taste aversion) [3,28] or under certain conditions when the drug is paired with visual and textural environmental stimuli [1]. These aversive effects of morphine were shown to be produced through an action on peripheral opiate receptors, especially those in the gut [1,2]. Opiate receptors have been classified into three major subtypes, mu, delta and kappa [19,33]. All three subtypes are present on elements in the gut [7,9]. Furthermore, opiate receptors are present on vagal sensory neurons [27,34], and vagotomy [1] as well as peripherally acting opiate antagonists [2] block the aversive effects of morphine without affecting the positive reinforcing effects of morphine. Although morphine is known to act preferentially on the mu receptor, it does not exclusively do so [22]. Therefore, the present study investigates the pharmacological specificity of the gut opiate receptor subtypes mediating the aversive effects of opiates.

A great deal of physiological and pharmacological work has shown that opiates produce gut smooth muscle contraction and constipation through an action on mu and delta type opiate receptors, located on various intrinsic elements of the enteric nervous system [5,9]. None of these effects, however, have been shown to be mediated through an action on kappa receptors [5, 7, 9], which are also present in the gut [5, 7, 9]. Four pieces of evidence point to the kappa receptor as an attractive candidate substrate for peripheral opiate aversive effects. These are the predominance of kappa receptors on primary sensory neurons [32], the anatomical location of opiate receptors at the distal ends of vagal sensory axons in the gut [27,34], the importance of the vagus in mediating the aversive effects of opiates [1], and previous evidence suggesting that systemic stimulation of kappa receptors produces aversion [15]. The present set of experiments were designed to investigate whether the kappa receptor mediates the peripheral aversive effects of opiates.

EXPERIMENT 1

A sensitive place conditioning paradigm [26] was used to

investigate the pharmacological specificity of the receptor subtypes responsible for the mediation of opiate aversive effects. The motivational effects of various doses of the most specific kappa agonist available (U50,488; [24,30]) were investigated. These effects were compared to previously published data on morphine [1] (a mu selective agonist [19,33]), which was collected using identical experimental procedures.

In addition, an experiment was performed in order to determine whether endogenous opioids could produce aversive effects similar to exogenous opioids through action on peripheral kappa receptors. Low doses of naltrexone have previously been shown to produce conditioned place preferences due to an antagonism of endogenous opioids acting on peripheral opiate receptors [1]. Given a certain potency of the motivational effects of the kappa agonist U50,488 in relation to morphine, then we would predict that Mr2266, the most selective kappa antagonist available [14, 30, 33], should show a similar relative motivational potency to naltrexone, although the antagonist motivational effects should be generally opposite to the agonist effects. To test this prediction, we ran a dose-response curve for the specific kappa antagonist Mr2266, administered intraperitoneally (IP). These results were compared to a dose-response curve for naltrexone (IP), which was obtained from previously published data that employed the identical paradigm and procedures [1]. A dose-response curve for the non-active isomer Mr2267 was also obtained as a control for the stereospecificity of the motivational effects of the antagonist at the opiate receptor.

Subjects

All animals used in these experiments were adult male Wistar rats (Charles River) weighing between 300–350 grams. Subjects were housed individually in suspended grey wire cages in a room kept at a temperature of 22°C and lit between 0900 to 2100 hr. Purina rat chow and water were continuously available throughout the experiments.

Method

Twenty groups of animals (n=6–12) were used in this experiment. Place preference procedures were identical to those described previously [16]. Briefly, conditioning took place in two boxes which differed in colour, texture and smell. One box had black walls and a black Plexiglas floor which was wiped with a 2% vinegar solution just prior to placing each rat inside. The other box had white walls and a wood chip floor which gave off a slight smell of wood.

After handling the animals for six consecutive days, place conditioning was carried out. Separate groups of drug naive rats were administered various (IP) or subcutaneous (SC) doses of the specific kappa receptor agonist U50,488 (0.005–16 mg/kg) one day and a vehicle injection on the next, for a total of eight days (i.e., 4 drug pairings). Similar conditioning procedures were applied to separate groups of drug naive rats administered various IP doses of the antagonist drug Mr2266 (0.001–10 mg/kg) or its non-active isomer Mr2267 (0.01–10 mg/kg).

Following drug injection, each rat was immediately placed into one box and on alternate days, when injected with vehicle, it was placed in the other box. Each pairing lasted 30 minutes. The order of drug and vehicle presentation and the choice of environment paired with drug injection were counterbalanced within each group.

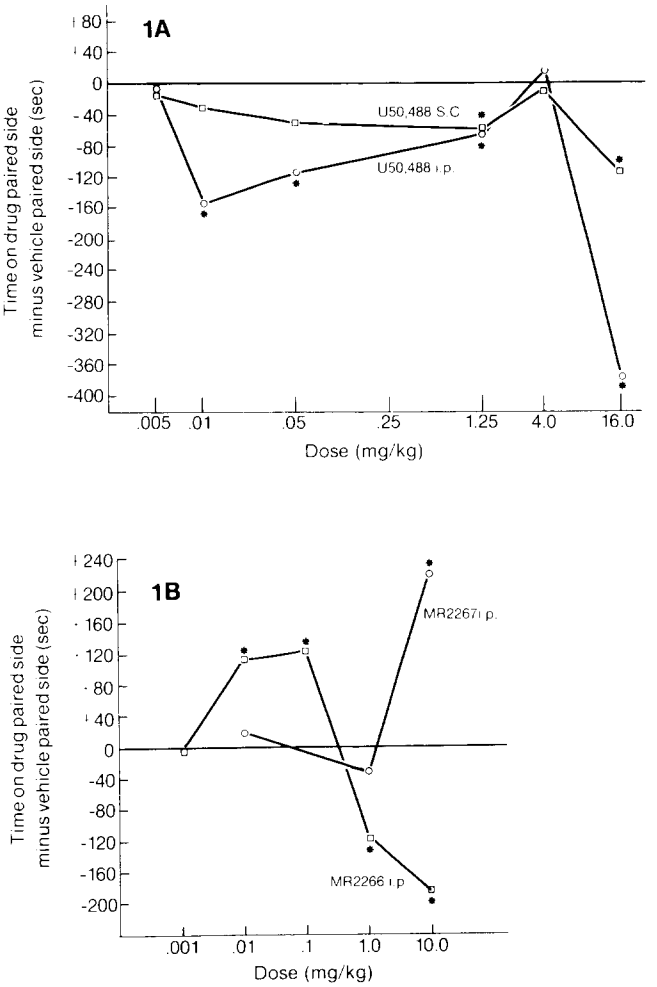

FIG. 1. (A) The effects of various doses of U50,488 (SC and IP) in the place conditioning paradigm. Each point represents the mean for (n=7–12) rats. For reasons of clarity, SEM's are not included in the graph, but the SEM for the U50,488 IP point at 0.01 mg/kg is ±67.0. *Indicates significant place conditioning ($p<0.05$). (B) Effects of various doses of Mr2266 and Mr2267 (IP) in the place conditioning paradigm. Each point represents the mean for (n=7–12) rats. For reasons of clarity, SEM's are not included in the graph, but the SEM for Mr2266 IP point at 0.01 mg/kg is ±58.4. *Indicates significant place conditioning ($p<0.05$).

On the ninth day, each rat was placed into a larger rectangular test box which consisted of environments exactly the same as the two conditioning boxes at each end separated by a smaller grey area (neutral zone). The time spent for each rat on both of the two ends was recorded over a 10 minute period. Evidence exists that this unbiased method of running place preference conditioning is the most reliable [18,26].

Results and Discussion

We previously demonstrated that, regardless of the route of administration, increasing doses of morphine produced conditioned place preferences, except at a low dose of morphine (0.05 mg/kg) IP (but not SC) that produced significant place aversions [1]. On the other hand, the majority of doses of U50,488 produced conditioned place aversions, and in-

creasing doses of U50,488 failed to produce conditioned place preferences. Moreover, U50,488 IP produced conditioned place aversions at lower doses than the dose of morphine IP that produced aversions (Fig. 1A). An analysis of variance on the data from IP and SC injections of U50,488 (0.005–16 mg/kg) revealed a significant effect of dose, $F(5,42)=3.0$, $p<0.05$, route of administration, $F(1,42)=13.7$, $p<0.05$, and time spent in drug versus saline paired environments, $F(1,42)=30.8$, $p<0.05$. Most importantly, this analysis revealed a significant interaction of dose with time spent in each environment and with the route of administration, $F(5,42)=2.94$, $p<0.05$. These results demonstrate that the aversions produced depended upon both the dose of the drug and route of drug administration. Thus, a dose of 0.01 mg/kg of U50,488 (IP) produced significant place aversions, $t(11)=3.2$, $p<0.05$, whereas the same dose administered SC had no significant effect. At one high dose (4 mg/kg IP or SC) U50,488 did not produce significantly less time on the drug versus vehicle paired side of the test box, although at one very high dose (16 mg/kg) significant place aversions (SC $t(7)=5.0$, $p<0.05$; IP $t(7)=8.5$, $p<0.05$) were again observed.

Although morphine is 4–50 times more potent than U50,488 in producing analgesia in rats [30], U50,488 was five times more potent that morphine in producing aversions. The lowest doses that produced place aversions were 0.01 mg/kg of U50,488 IP (Fig. 1A) versus 0.05 mg/kg of morphine IP [1]. Even at high doses, U50,488 never produced conditioned place preferences, whereas, morphine produced place preferences as the dose increased [1]. These results suggest that peripheral kappa receptors mediate the aversive effects of opiates, whereas, central opiate receptors mediate the positive reinforcing effects. Although morphine does not interact with kappa receptors at low doses [19], the intraperitoneal administration of the drug may result in local concentrations at the target tissue sites (i.e., gut opiate receptors) that are sufficient for the activation of other opiate receptor subtypes [22]. Therefore, the results cannot reveal whether the aversive effects from the low dose of morphine (IP) were mu or kappa receptor mediated effects. It should be noted that anomalous results occured at a dose of 4 mg/kg U50,488 which produced no significant motivational effects and at a dose of 16 mg/kg of U50,488, which produced large place aversions (Fig. 1A). These intriguing results were investigated in Experiments 2 and 3.

A similar profile, but of opposite motivational valence, was seen in the place conditioning with opiate antagonists. Low doses of Mr2266 (Fig. 1B) and, as previously reported, naltrexone [1] produced positive reinforcing effects, whereas higher doses of both drugs produced conditioned place aversions. Moreover, Mr2266 produced positive reinforcing effects of lower doses than the dose of naltrexone that produced conditioned place preferences. Only a very high dose of the inactive isomer Mr2267 produced significant place conditioning. An analysis of variance on the overlapping data from the Mr2266 and Mr2267 dose response curves revealed a significant interaction of dose with drug and with time spent in vehicle versus drug paired environments, $F(2,19)=6.5$, $p<0.05$. This suggests that the production of preferences or aversions depended upon the drug and the dose of the drug that was administered. Mr2266 produced preferences at doses as low as 0.01 mg/kg (IP), $t(11)=2.6$, $p<0.05$, while doses higher than 0.1 mg/kg (IP) produced significant place aversions (Fig. 1B). Mr2267, the inactive isomer, failed to produce any significant motivational effects over the portion of the dose-response curve where Mr2266 produced preferences (Fig. 1B). Only the highest dose of Mr2267 produced significant place preferences, $t(5)=4.4$, $p<0.05$. Lower doses did not produce any motivational effects. The neutral motivational effects observed with lower doses of Mr2267 indicate that the motivational effects produced by Mr2266 are receptor mediated effects.

Although naltrexone is about 12 times more potent than Mr2266 at blocking morphine analgesia [30], Mr2266 was ten times more potent than naltrexone in producing positive reinforcing effects in the place conditioning paradigm (Fig. 1B). The lowest doses that produced place preferences were 0.01 mg/kg of Mr2266 IP versus 0.1 mg/kg of naltrexone IP [1]. Although naltrexone and Mr2266 can cross the blood-brain barrier effectively at higher doses (as shown by indirect evidence from analgesic antagonism studies [30]), previous evidence has suggested that the positive reinforcing effects of low IP doses of naltrexone resulted from a local antagonism of endogenous opioids acting on peripheral opiate receptors [1]. Hence, we interpret the higher potency of Mr2266 in producing positive reinforcing effects as evidence that endogenous opioids acting primarily on peripheral kappa receptors produce aversive effects.

Higher doses of Mr2266 produced conditioned place aversions similar to naltrexone. The place aversions observed at higher doses might be due to antagonism of endogenous opioids acting on central opiate receptors [1, 16, 17, 23]. These results, however, do not address the issue of the opiate receptor subtype mediating the high dose central aversive effects of the antagonists. The conditioned place preferences observed at the highest dose of the non-active isomer Mr2267, $t(5)=4.4$, $p<0.05$, suggest that there may be some antagonistic activity of this drug on peripheral opiate receptors at very high doses.

Taken together, the aversive effects produced by low IP doses of U50,488 or morphine [1], and the positive reinforcing effects produced by low IP doses of Mr2266 or naltrexone [1] support the idea that exogenous as well as endogenous opioids produce aversive effects through an action on peripheral opiate receptors. However, the differences in potency between kappa versus mu selective opioid drugs to produce motivational effects suggest that the activation of peripheral kappa receptors is primarily responsible for the aversive effects of opioids.

EXPERIMENT 2

In light of the evidence that the positive reinforcing effects of opiates are due to central mechanisms [1, 25, 29], we hypothesized that higher doses of U50,488 (which can cross the blood-brain barrier effectively as shown by indirect evidence from studies on analgesic and diuretic effects of U50,488 [8, 21, 24]) might produce some positive reinforcing effects through an action on central opiate receptors. These central effects would then counteract the peripheral aversive effects resulting in apparently neutral motivational effects of U50,488 at certain doses (4 mg/kg in Experiment 1). Studies in a companion paper [2] demonstrated that the blockade of peripheral opiate receptors with a quaternary opiate antagonist (which does not cross the blood-brain barrier effectively) attenuated low dose IP morphine place aversions and high dose morphine induced conditioned taste aversions without affecting the positive reinforcing effects of morphine. Moreover, it has previously been demonstrated that vagotomy blocks morphine induced conditioned taste aversions, but not morphine induced conditioned place prefer-

TABLE 1
VAGOTOMY VERIFICATION DATA

Group	Survival	Terminal Body Weight (g) Mean ± SEM	Terminal Stomach Weight (g) Mean ± SEM	Ratio of Stomach Weight / Body Weight Mean ± SEM	Ratio of Stomach Weight / Body Weight Range
Control	8/8	371 ± 12	9.1 ± 1.3	0.025 ± 0.004	0.01–0.035
Vagotomy	6/9	305 ± 11	37.7 ± 4.8	0.123 ± 0.02	0.086–0.164

All rats in the vagotomy group had stomach weight/body weight ratios greater than the rejection criterion (0.033) of the control group ratio of stomach weight to body weight. The rejection criterion is the upper boundary of the 99% confidence interval for the mean of the control group.

ences [1]. On the basis of the above evidence, we predicted that administration of 4 mg/kg (IP) of U50,488 should produce positive reinforcing effects in vagotomized animals. Experiment 2 was designed to test this prediction.

Method

Two groups of animals (n=6–8) served as subjects. Both groups underwent place conditioning with 4 mg/kg U50,488 (IP), as described in Experiment 1. Two weeks before conditioning, the vagotomy group received subdiaphragmatic vagotomies, according to a previously reported technique [4], and the control group received sham operations. Briefly, each rat was first anaesthetized with sodium pentobarbital, the abdomen was opened, and the stomach was lifted out. A 15 mm section of both the anterior and posterior vagus nerve was excised at the juncture of the esophagus and stomach in the vagotomy group. For removal of the section of the posterior vagus, both the nerve and the gastric artery were ligated and cut. Control surgeries were similar except that neither nerves nor artery were cut. To maintain body weight during postoperative recovery, some vagotomized rats were given a wet mash of Purina laboratory pellets mixed in water. All rats were given 21–28 days to recover before behavioral training began.

In order to verify the vagal transection at the end of the experiment, we employed a method that involves measurement of food retention in the stomach [11]. Stomach weight measurement is a reliable index of vagal destruction and is more conservative than the electrophysiological techniques traditionally used [11]. Following behavioural testing, all rats received food and water ad lib for 5 days. On the morning of verification, food was removed from all cages. Six hours later, body weights were measured prior to lethal injections of sodium pentobarbital. The abdomen was opened and the stomach was removed and weighed. A ratio of stomach weight to body weight was calculated for each rat, and a rejection criterion was established by calculating a 99% confidence interval of the mean for controls. A vagotomy was considered complete if the stomach weight/body weight ratio exceeded the upper limit of the control group confidence interval. Data from vagotomized rats with ratios falling within the confidence interval were discarded.

Results and Discussion

Three of the nine rats receiving subdiaphragmatic vagotomy died postoperatively. None of the control rats died prior to verification. Rats with complete vagotomies show excessive gastric retention of food after a period of fasting. In addition, control rats typically weigh more than vagotomized rats [6,10]. The stomach weight/body weight ratio of each of the surviving vagotomized rats exceeded the 99% confidence interval of the control animals and were thus considered complete (see Table 1). Typically, the stomachs of vagotomized rats contained large amounts of food, whereas the stomachs of control rats were empty.

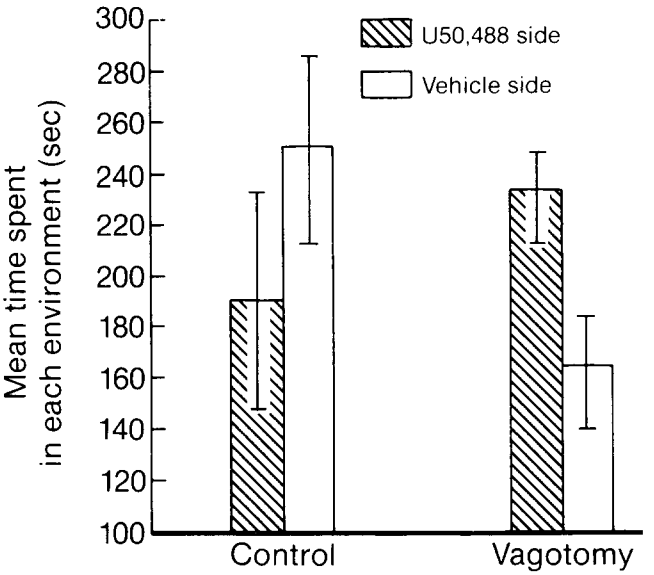

FIG. 2. Effects of vagotomy and sham surgery (control) on the motivational effects of 4 mg/kg U50,488 (IP) in the place conditioning paradigm. Bars are means±SEM of time spent in drug and in saline paired environments for (n=6–8) rats.

Administrations of 4 mg/kg of U50,488 (IP) induced clear conditioned place preferences in vagotomized animals, $t(5)=3.1$, $p<0.05$, but not in sham operated animals, $t(7)=0.8$, $p>0.05$ (Fig. 2). These results suggest that higher doses of U50,488 can produce positive reinforcing effects via central mechanisms. However, the receptor subtype(s) mediating these central effects cannot be determined. Nevertheless, these results might explain why the IP and SC administration of 4 mg/kg U50,488 in normal animals failed to produce any motivational effects. That is, the central positive reinforcing effects may balance the aversive peripheral effects at this dose of U50,488.

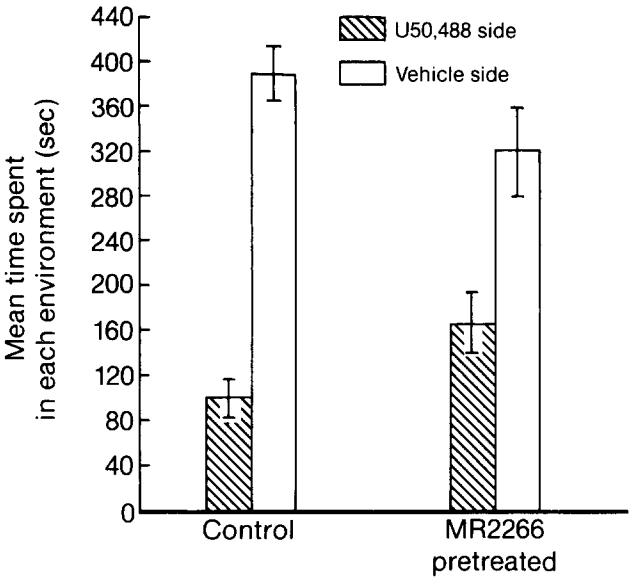

FIG. 3. Effects of blockade of kappa receptors with Mr2266 (0.1 mg/kg IP) on the high dose U50,488 (16 mg/kg IP) aversions. Bars are means±SEM of time spent in drug and in saline paired environments for (n=8) rats.

EXPERIMENT 3

In Experiment 1, we found that a dose of 16 mg/kg of U50,488 produced large conditioned place aversions. This was surprising in light of the data observed with a dose of 4 mg/kg U50,488 in Experiment 2, which suggested that moderate doses of the drug were beginning to have central positive reinforcing effects. We hypothesized that the very high doses of U50,488 might be producing aversive effects through peripheral, non-kappa specific actions. This hypothesis was tested by determining whether the aversive effects of 16 mg/kg U50,488 IP could be blocked by pretreatment with Mr2266, the most selective kappa antagonist available [14, 30, 33].

Method

Two groups of animals (n=8) were used for this experiment. Control animals received IP vehicle pretreatments prior to place conditioning with the kappa agonist U50,488 (16 mg/kg, IP). The experimental animals received identical treatment and conditioning except that the vehicle pretreatments were replaced by IP pretreatments with 0.1 mg/kg of the kappa antagonist Mr2266. In order to avoid assessing any motivational effects of the antagonist drug itself, Mr2266 pretreatments were paired with both environments. The dose of the antagonist was chosen on the basis of a dose response curve generated for Mr2266 (Experiment 1).

Results and Discussion

Treatment with Mr2266 IP blocked a significant portion of the place aversion produced by 16 mg/kg U50,488 IP (Fig. 3). An analysis of variance on the data from both control and experimental groups revealed a significant interaction of group with time spent in drug versus saline paired environments, $F(1,14)=6.2$, $p<0.05$. Thus, the conditioned place aversions observed in control animals were significantly higher than those observed in Mr2266 pretreated animals, $t(14)=1.9$, $p<0.05$. These results suggest that a significant component of kappa aversions can be attributed to action on peripheral kappa receptors. The incomplete blockade of conditioned place aversion by the antagonist suggests that a non-kappa specific mechanism may be responsible for the mediation of some of the aversive effects of high doses of U50,488. Presumably, these non-kappa specific aversive effects overwhelm any positive motivational effects of the drug caused by its action on central opiate receptors (see Experiment 2). These non-kappa specific mechanisms might be non-opiate receptor mediated or might involve the activation of alternate opiate receptor subtypes in the gut (that might also mediate aversive effects). However, it is also possible that very high doses of U50,488 could produce some aversive effects by activating a presently uncharacterized aversive system in the brain. Indeed, it has been suggested that some kappa aversive effects are due to an interaction with the sigma receptor subtype in the brain [12,13]. Kappa receptor stimulation has recently been reported to produce psychotomimetic effects in humans [20]. However, this study [20] did not reveal whether these psychotomimetic effects were due to activation of central or peripheral kappa receptors. Our preliminary results show that the microinjection of U50,488 (1–10 μg) into the lateral ventricle of drug naive rats resulted in neutral motivational effects or in conditioned place preferences (in preparation).

GENERAL DISCUSSION

The present set of experiments reveal that kappa receptors located outside the blood-brain-barrier are primarily responsible for mediating the aversive effects of opiates. The higher aversive potency of drugs acting primarily on kappa opiate receptor, suggests that it is specifically the kappa opiate receptor subtype that is responsible for the mediation of opioid aversive effects. Although morphine is 4–50 times more potent than U50,488 in producing analgesia in rats [30], U50,488 was 5 times more potent than morphine in producing aversions. Even at very high doses, U50,488 never produced the conditioned place preferences seen with morphine. Similarly, although naltrexone is about 12 times more potent than Mr2266 at blocking morphine analgesia [30], Mr2266 was 10 times more potent than naltrexone in producing positive reinforcing effects. Taken together, these results suggest that peripheral kappa receptors mediate the aversive effects of both endogenous and exogenous opioids.

The identification of the kappa opiate receptor as a primary site for opioid aversive effects helps narrow down the peripheral element where the opiate receptors mediating aversive effects are localized in the gut. A great deal of previous work has implicated mu and delta receptors on intrinsic enteric nervous system elements as the receptors producing gut smooth muscle contraction [5,9]. Kappa receptors, although present in the gut, have not as of yet been assigned any functional role. Given the evidence that peripheral kappa receptors mediate aversive effects ([15], the present results), that kappa receptors are predominant on primary sensory neurons [32], and that vagotomy abolishes aversive opioid effects [1], we hypothesize that the kappa receptors mediating the stimulus effects underlying conditioned place and taste aversions are situated on vagal sensory neurons in the gut.

We still do not know, however, whether the anatomical and pharmacological specificities of opiate aversive effects

are absolute specificities. First, are there any aversive effects produced by action on mu and delta receptors in the periphery, and are these effects the same as produced by kappa receptor activation? In light of the data that drugs acting on kappa receptors are most potent in our aversive behavioral assays, are the mu and delta receptors localized only to gut elements that, when activated, produce null or even positive motivational effects? Furthermore, Werz and Macdonald have reported that some individual sensory neurons in the dorsal root ganglia have mu, delta and kappa receptors on them, although more neurons have only kappa receptors on them [32]. Is it the vagal neurons possessing only kappa receptors that are responsible for mediating all aversive effects, or can the mu and delta receptors on other vagal sensory neurons also produce aversions? (although their smaller numbers might reduce the apparent potency of mu and delta agonists in whole organism biological assays). Since morphine does not exclusively act on the mu receptor [22], experiments employing gut application of more specific mu and delta agonists may help answer this question. Similar arguments concerning absolute specificities can be posed concerning the positive reinforcing effects produced by central opiate actions. Several lines of evidence have led to the view that the positive reinforcing effects of opioids may be due to an action on central mu receptors [15, 25, 29]. Does the activation of kappa receptors in the central nervous system also produce positive reinforcing effects? We have shown that vagotomy results in the selective kappa specific agonist, U50,488, producing conditioned place preferences at moderately high doses. Are these effects due to action at a kappa receptor in the brain or simply due to the fact that high doses of kappa agonists begin to act on other receptors in the brain (for example mu receptors)? Experiments currently underway employing brain tissue microinjections of kappa, delta and mu specific agonists in the place conditioning paradigm will help to answer this question.

In conclusion, the aversive effects of endogenous and exogenous opioids appear to have both anatomical and pharmacological specificity. The primary site of these effects seems to be a peripheral kappa receptor.

ACKNOWLEDGEMENTS

Supported by the Medical Research Council of Canada. We thank Dr. H. Merz for the gifts of Mr2266 and Mr2267, and Dr. R. J. Collins for the gift of U50,488. We also thank fellow members of the Neurobiology Research Group/University of Toronto for their valuable comments.

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