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Motivational properties of kappa and mu opioid receptor agonists studied with place and taste preference conditioning

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Abstract. The reinforcing porperties of various opioid agonists acting preferentially on the kappa and mu opioid receptors were assessed using taste and place preference conditioning procedures.

Kappa receptor agonists produced conditioned aversions. Taste aversions were produced by all of the drugs used, including racemic mixtures of ethylketazocine, tifluadom, and U50-488, and active isomers (+)-tifluadom, (−)-bremazocine, and Mr 2034; corresponding inactive isomers either produced no effect of were less potent. Place aversions were produced by U50-488 and (−)-bremazocine, but not (+)-bremazocine or any of the other kappa receptor agonists tested with the taste procedure. The mu agonists produced predominantly conditioned preferences. Place preferences were produced by morphine, fentanyl and sufentanil. Taste preferences were produced by low doses of these substances; at higher doses the taste preferences were absent or replaced by aversions. Finally, with naloxone and lithium chloride it was shown that the taste procedure was more sensitive to punishing effects than the place procedure.

It is concluded that kappa and mu opioid receptor agonists are effective unconditioned stimuli. From the lower portions of the dose response curves it is further concluded that activation of kappa opioid receptors has aversive properties and activation of mu receptors appetitive reinforcing properties. The findings are also discussed with regard to the prevailing notions of taste conditioning with opiates, and the reinforcing properties of activity of the endogenous opioid peptide systems.

Key words: Mu opioid receptor agonists – Kappa receptor agonists – Naloxone – Lithium chloride – Stereospecificity – Conditioned taste aversion – Conditioned place preference

The application of simple, classical conditioning procedures for the examination of the motivating properties of opiates is based on the observation that animals prefer stimuli paired with appetitive reinforcers and avoid stimuli paired with aversive stimuli (Kumar 1972; Cappell et al. 1973). Using place and taste conditioning paradigms, preference conditioning has been reported for a variety of different opioid agonists including etorphine, heroin, levorphanol, and morphine (Mucha et al. 1982; Spyraki et al. 1982; Stolerman et al. 1978).

Work with competitive antagonists and stereoisomers suggests that opioid receptors are involved in these conditioned behaviours produced by opioids (LeBlanc and Cappell 1975; Mucha et al. 1982; van der Kooy and Phillips 1977). However, despite the existence of at least three different types of opioid receptors (Robson et al. 1983; Wüster et al. 1981), it is not known how activation of these different receptor types is reflected in preference conditioning. Only morphine has been systematically studied in these paradigms (Cappell et al. 1973; Mucha et al. 1982; Stolerman et al. 1978), but morphine produces dose-related conditioned place preference and dose-related taste aversion (Cappell et al. 1973; Mucha et al. 1982; Stolerman et al. 1978). Since only the place conditioning is fully antagonized by naloxone (LeBlanc and Cappell 1975; Mucha et al. 1982; van der Kooy and Phillips 1977), it is possible that different receptor types subserve these two opposing motivational effects. Indeed, although morphine is known to act preferentially on the mu receptor, it does not exclusively do so (Robson et al. 1983). Therefore, to clarify the involvement of different receptor types in opiate-related preference conditioning, it is necessary to gather systematic data for a variety of agonists selective for mu and other opioid receptor types as regards taste and place preference conditioning.

Accordingly, the present study examines taste and place preference conditioning produced with morphine, fentanyl, and sufentanil, agonists preferrring the mu type of opioid recetors (Leysen et al. 1983; Wüster et al. 1981) and ethylketazocine, tifluadom, and U50-488, agonists preferring the kappa type of receptors (Römer et al. 1982; von Voigtlander et al. 1983). To investigate the stereospecificity of the effects of kappa receptor agonists, several enantiomeric pairs, including (−) and (+) bremazocine, Mr 2034 and 2035, and (−) and (+) tifluadom were tested (Römer et al. 1980; Merz et al. 1975; Kley et al. 1983).

Finally, in order to interpret some of the findings, the relative sensitivities of the present taste and place procedures to aversive effects were compared using lithium chloride and naloxone, two drugs previously reported to have aversive properties (Mucha et al. 1982).

Materials and methods

Animals. Experimentally-naive, male, Sprague-Dawley rats were obtained from the Institut für Wissenschaftliche Versuchstierzucht (Gelting, FRG) and Iwanowas (Kissleg,

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FRG) at weights of 200–300 g. They were housed on sawdust bedding in groups of 4–12 with free access to food and water.

Apparatus. Place conditioning was carried out using 30 × 60 × 30 cm (w × l × h) wooden and Plexiglas boxes, each equipped with a loose-fitting (Mucha and Iversen 1984). In training, a box was divided, using a sliding partition, into two equal compartments with the wooden parts painted white or flat black. The floors were either smooth black Plexiglas or textured (diamond pattern) white Plexiglas. In testing, the centre partition was raised 12 cm from the floor and at the bottom of this opening a 5 cm wide, 2 cm high platform (constructed of 1 cm galvanized steel mesh) was fixed along the line of the partition. Rats were filmed during testing through a transparent Plexiglas wall using an Olympus VX-301-E video camera to determine their location. There were three areas in the test box (the black, white, and centre), and the position of the rat was defined by the position of its front paws. The taste conditioning was carried out in stainless steel wire laboratory cages. Food was available in the food hoppers and fluid in one or two drinking bottles. All testing and training was carried out in a room that was dimly lit using a 60 W incandescent bulb positioned so that the light was directed away from the rats. Masking white noise was provided.

Drugs and flavoured solutions. The following drugs (in most cases kindly donated by the respective companies) were used: morphine HCl (Merck Chemical Co., Darmstadt, FRG), naloxone HCl (Endo Laboratories, Garden City, NJ, USA), fentanyl and sufentanil citrates (Janssen Pharmaceutica, Beerse, Belgium), ethylketazocine (±) methanesulfonate (Sterling-Winthrop Research Institute, Rensselaer NY, USA), tifluadom (±) HCl (1-methyl-2-(3-thienylcarbonyl)-aminomethyl-5(2-fluorophenyl)-H-2,3-dihydro-1,4-benzodiazepine) as well as its two isomers (Kali-Chemie Pharma, Hannover, FRG), U50-488H (3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl-benzeneacetamide), methanesulfonate (The Upjohn Co., Kalamazoo, Mich, USA), (+) and (−) bremazocine base (Sandoz, Basle, Switzerland), Mr 2034-TA ((−)5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan) and its (+) isomer, Mr 2035-TA (Boehringer, Ingelheim, FRG), and lithium chloride (Sigma Chemical, Taufkirchen, FRG). The solutions were prepared with saline, except for tifluadom which was dissolved in propylene glycol (33% v/v mixed with saline). The injections were made subcutaneously in volumes of 1–2 ml/kg. Doses were calculated in terms of the free base and are presented in the figures. The bremazocine solutions were prepared using a drop of concentrated HCl.

The two flavoured solutions comprised a) 12.5 mM monosodium glutamate and 128 mM NaCl and b) 1.5 mM citric acid and 0.25 mM saccharin (Stolerman et al. 1978). They were prepared with deionized water and termed "MSG-NaCl" and "Cit-Sacc", respectively.

Conditioning protocols. For place conditioning, rats received three pairings of drug with one set of cues and three pairings of vehicle with the other set of cues. Assignment to particular cues and order of treatment was always balanced for the animals of a particular group and experiment. During a typical session, the rat was injected, then placed for 1 h into its training compartment. The interval between place conditioning sessions was not less than 4 h and not longer than 30 h.

For taste conditioning, rats were first trained to drink in the test cages: they were deprived of water overnight (about 15 h) and then placed for 30 min into their test cages where a water spout was made available. Commencing between 1700 and 1930 hours, 2–4 days later, the water was again removed from the home cages and returned for 30 min at approximately 24-h intervals. As with place conditioning, these rats received three pairings of drug with one flavour cue and three pairings of vehicle with the other. During a taste pairing session, the rat was placed into its test cage and 5 min later a bottle with 4 ml flavoured solution was positioned on the cage. Ten minutes later, the rat was injected and then returned to its home cage. The sessions were carried out between 0830 and 1600 hours and the interval between exposure to the flavour cues was similar to that of the place cues. On the last training day, the rats were again permitted free access to water.

Testing was carried out 1 day following training. For the place conditioning, the rats were placed individually on the centre platform of the test box and the time spent in each compartment during a 15-min period was recorded. For the taste conditioning the rats were placed individually for 24 h into their test cages which were fitted with two bottles each containing 100 ml of one of the two flavoured solutions. The amount consumed of each solution was then measured.

Expt. 1. Stimulus preferences were assessed in control rats in order to determine whether the rats showed unconditioned preferences for either of the cues. Two groups of rats were run, one on the place and one on the taste conditioning procedure; the precise protocols differed from the standard procedure in that saline administration was paired with both of the two alternate stimuli of each procedure. The training period for each procedure was 3 days and testing was on the 4th day.

Expt. 2. Place conditioning produced by mu receptor agonists was assessed. Different doses of morphine, fentanyl, and sufentanil were used to construct dose response curves.

Expt. 3. Place conditioning produced by kappa receptor agonists was assessed in a series of sub-experiments. Initially, dose-response curves were constructed for ethylketazocine, tifluadom, and U50–488. In an additional experiment, place conditioning produced by ethylketazocine (2.5 mg/kg) after six drug pairings, instead of three, was examined. Place conditioning produced by 4 mg/kg U50–488 with a longer time in the training box of 2 h, not the normal 1 h, was also examined; this seemed necessary because the acute effects of this dose during initial experiments lasted longer than 1 h. Finally, stereospecificity of the conditioning with kappa receptor agonists was studied by constructing dose-response curves for (+) and (−) bremazocine. Several doses of Mr 3034 were also tested.

Expt. 4. Taste conditioning produced by the mu receptor agonists was studied in several sub-experiments. We first established dose-response curves; then morphine taste conditioning produced by six pairings was examined. Finally, taste conditioning with 0.004 mg/kg fentanyl was examined with a procedure that differed from the usual one as fol-

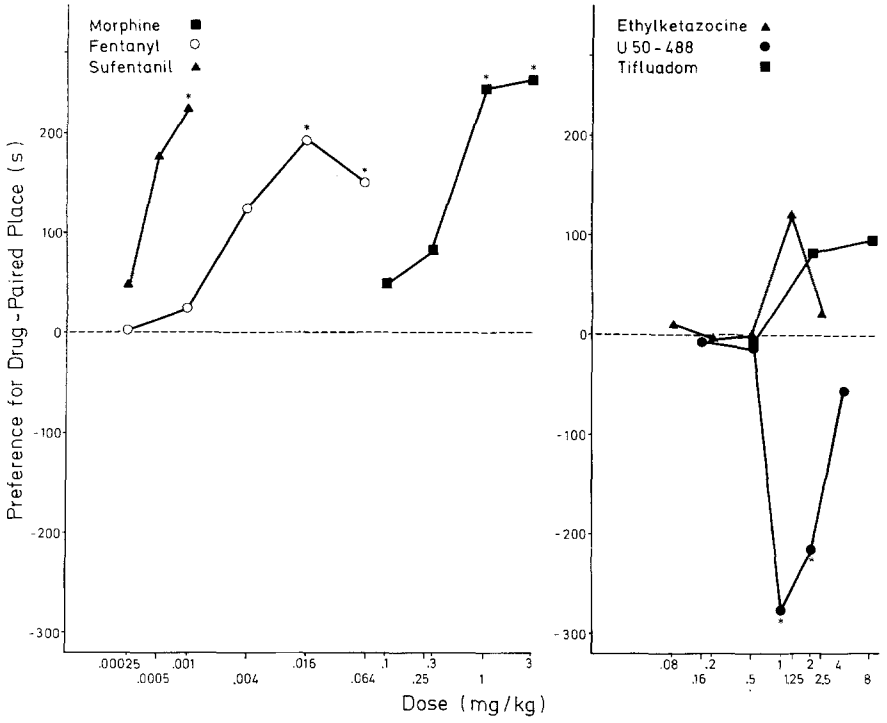

Fig. 1. Place preference scores of rats trained with different doses of mu (*left panel*) or kappa receptor agonists (*right panel*). *Ordinate:* mean difference between time spent on the drug and the vehicle side of the testbox. *Abscissa*: doses of the respective drugs. The data at each point were from 10 to 12 rats, except for eight in the case of sufentanil. The *asterisks* indicate significant preference conditioning

lows: First, the rats were habituated to a 23.5-h water deprivation scheme for 6 days. This scheme was continued until the day before the test, when water was again made freely available. Second, commencing on day 7, the rats were trained during three 2-day cycles: On 1 day, MSG-NaCl solution was given, and on the other, Cit-Sacc. The training was approximately 5 h prior to the usual time of watering. Thirdly, the rats were permitted to consume unlimited amounts of the flavoured solutions during the training trial.

Expt. 5. Taste conditioning was examined for the kappa receptor agonists used in Fig. 1. The stereospecificity of the conditioning was determined by testing for preferences produced by (+) and (−) bremazocine, Mr 2034 and 2035, and (+) and (−) tifluadom.

Expt. 6. Place and taste conditioning was examined for lithium chloride and naloxone.

Data transformations and analyses. Scores of preference for the drug-paired cues were computed as previously reported in the literature. Place preference scores comprise the amount of time spent on the vehicle-paired side subtracted from the amount of time spent on the drug-paired side (Mucha and Iversen 1984). Taste preference scores comprised the difference between the volume consumed of drug-paired and vehicle-paired flavours, expressed as percent of total fluid intake (Stolerman et al. 1978). The data are presented as mean ± SEM. Dose-response curves constructed for the preference scores were analyzed using one-way random factorial analyses of variance and when necessary *t* tests; the taste preference data, however, were first subjected to arcsine transformations (Kirk 1968). Whether an individual dose produced conditioning was evaluated using a sign test by evaluating the number of plus and minus scores (Conover 1971); some animals responded with very high scores on one of the choices of the test and very low on the other, suggesting that the assumption of independence necessary for a parametric test was not always tenable. The accepted level of significance was $P<0.05$.

Results

Expt. 1. Stimulus preference in control rats. In rats receiving control exposure to the training procedures, there was no significant preference for either of the place cues. The mean time spent on the white and black sides were 347 ± 43 and 304 ± 30 s ($n=12$), respectively. Similarly, there was no significant preference for either of the two flavoured solutions. Mean fluid consumed was 24.4 ± 3.5 and 20 ± 3.8 ml for the MSG-NaCl and Cit-Sacc solutions ($n=8$), respectively.

Expt. 2. Place conditioning dose-response curves for mu receptor agonists. All three substances produced conditioned place preference (Fig. 1, left panel). There was a significant linear relation of dose and preference for sufentanil ($F=6.1$; $df=1,21$: $P<0.03$), fentanyl ($F=6.6$, $df=1,47$; $P<0.02$), and morphine ($F=10.7$; $df=1,38$; $P<0.003$); the lowest effective doses were 0.001 mg/kg (224 ± 40 s, $n=8$), 0.016 mg/kg (194 ± 60 s, $n=10$), and 1 mg/kg (247 ± 66 s, $n=12$) for sufentanil, fentanyl, and morphine respectively.

Expt. 3. Place conditioning with kappa receptor agonists. As shown in Fig. 1 (right panel), there was no significant place conditioning with ethylketazocine ($F=0.9$; $df=4,55$) or tifluadom ($F=2.0$; $df=1,27$). U50–488, however, produced conditioned place aversion that followed a biphasic function of dose ($F=10.3$; $df=1,48$; $P<0.003$); the effects were significant at 1 (−317 ± 67 s, $n=12$) and 2 mg/kg (−256 ± 53 s, $n=10$). In view of the unusual shape of the dose-response curve with U50-488, these findings were replicated in a different group of rats. In an additional experiment, a high dose of ethylketazocine (2.5 mg/kg) failed to produce significant conditioning even though it was given over six instead of the usual three pairings (the mean preference score was 88 ± 76 s, $n=8$). In another experiment using

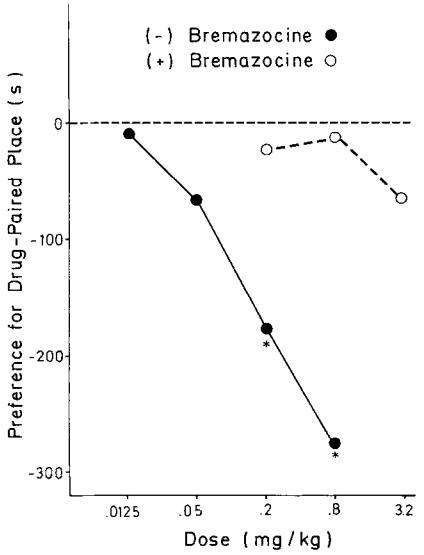

Fig. 2. Place preference scores of rats trained with different doses of the opioid active isomer, (−)-bremazocine, or its inactive form, (+)-bremazocine. The general information is similar to that in Fig. 1

4 mg/kg U50–488 and a 2-h instead of the usual 1-h period in the test box, significant conditioning was also not seen (the mean preference score was -118 ± 63 s, $n=10$).

As seen in Fig. 2, (−) bremazocine produced a significant linear relation of dose and place aversion ($F=5.54$; $df=3,36$; $P<0.01$), whereas (+) bremazocine produced no significant place conditioning ($F=1.44$; $df=2,33$). An analysis of variance of the data from both isomers indicated a significant effect of the isomers ($F=8.62$; $df=1,43$; $P<0.01$). The lowest dose of (−) bremazocine having a significant effect was 0.2 mg/kg (-178 ± 28 s, $n=10$). Mr 2034, also an active isomer (Merz et al. 1979), was tested, but over the doses used (0.1, 0.3, 1, and 3 mg/kg) no significant conditioning was seen ($F=0.18$; $df=3,36$).

Expt. 4. Taste conditioning with mu receptor agonists. All drugs produced taste conditioning (Fig. 3, left panel). Fentanyl produced a significant biphasic function ($F=16.4$; $df=1,42$; $P<0.001$); a taste preference seen at 0.004 mg/kg ($30.8 \pm 8.9\%$, $n=10$) and the taste aversion at 0.64 mg/kg ($-48.8 \pm 14.1\%$, $n=8$) were significant. Sufentanil conditioning was also significantly dose-related ($F=2.3$; $df=6,61$; $P<0.05$). The taste preference at 0.00025 ($28.2 \pm 11.6\%$, $n=10$) and 0.0005 mg/kg ($42.4 \pm 8.9\%$, $n=10$) were significant. The aversion at 0.0125 mg/kg ($-24.4 \pm 18.5\%$; $n=10$) was not itself significant, but the mean preference was significantly lower than that at 0.00025 and 0.0005 mg/kg. Morphine, in contrast, produced only an aversion in this test. There was a significant linear relation of effect and dose ($F=16.7$; $df=1,38$; $P<0.001$); the biphasic trend was not significant ($F=0.5$). The conditioning was significant at 1 mg/kg ($-56.3 \pm 11.6\%$, $n=6$).

With six instead of the usual three pairings, morphine produced (Fig. 3, left panel) a significant biphasic effect ($F=5.9$; $df=1,36$; $P<0.03$). There was a significant aversion at 0.42 mg/kg ($-39.2 \pm 5.4\%$, $n=10$) and a small but significant preference at 0.25 mg/kg ($17.4 \pm 14.3\%$, $n=10$) with eight of the ten rats preferring the solution paired with morphine. Rats acclimated to a 23.5-h water deprivation scheme and allowed unlimited intake of the flavoured solution during a pairing session also showed a significant preference for the solution paired with 0.004 mg/kg fentanyl ($35.6 \pm 8.2\%$, $n=14$).

Expt. 5. Taste preference conditioning with kappa receptor agonists. There was a significant linear relationship between dose and magnitude of effect (see Fig. 3, right panel) for ethylketazocine ($F=4.2$; $df=1,44$; $P<0.05$), tifluadom ($F=13.9$; $df=1,25$; $P<0.03$), and U50–488 ($F=5.9$; $df=$

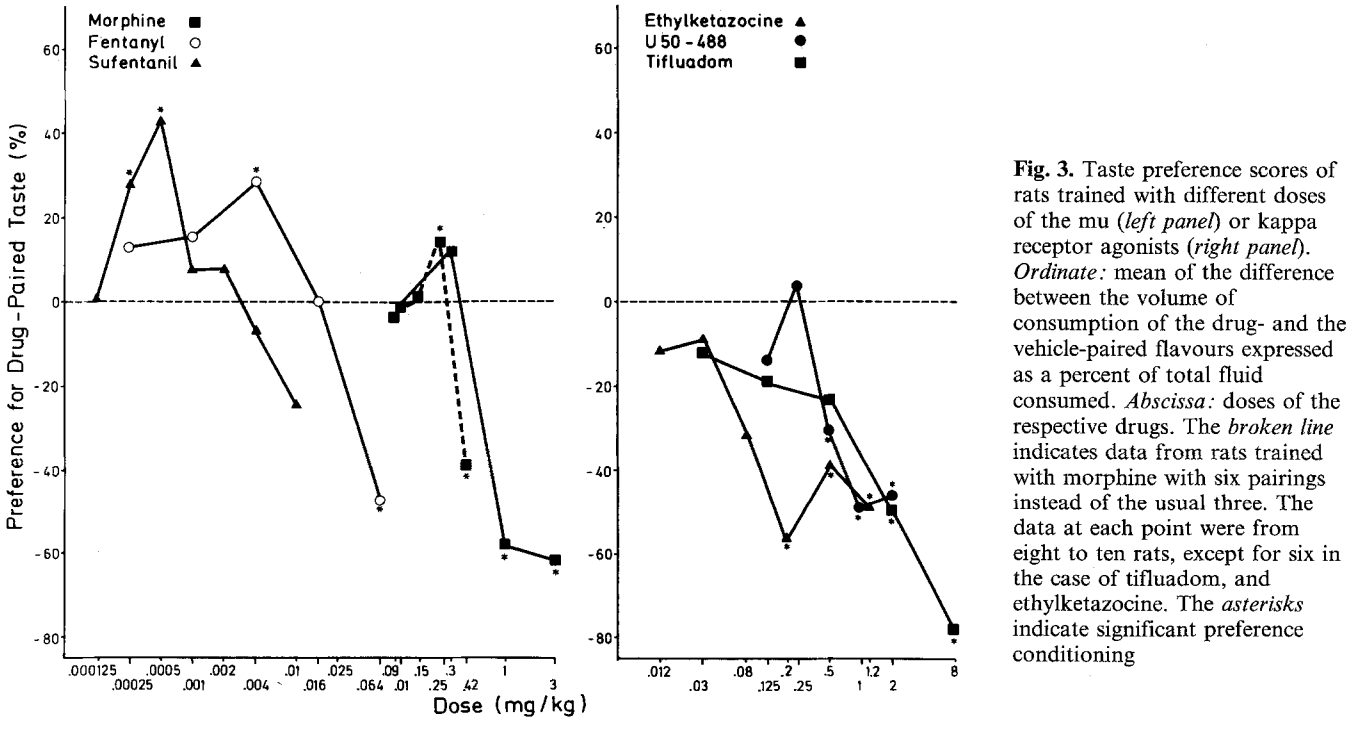

Fig. 3. Taste preference scores of rats trained with different doses of the mu (*left panel*) or kappa receptor agonists (*right panel*). *Ordinate:* mean of the difference between the volume of consumption of the drug- and the vehicle-paired flavours expressed as a percent of total fluid consumed. *Abscissa:* doses of the respective drugs. The *broken line* indicates data from rats trained with morphine with six pairings instead of the usual three. The data at each point were from eight to ten rats, except for six in the case of tifluadom, and ethylketazocine. The *asterisks* indicate significant preference conditioning

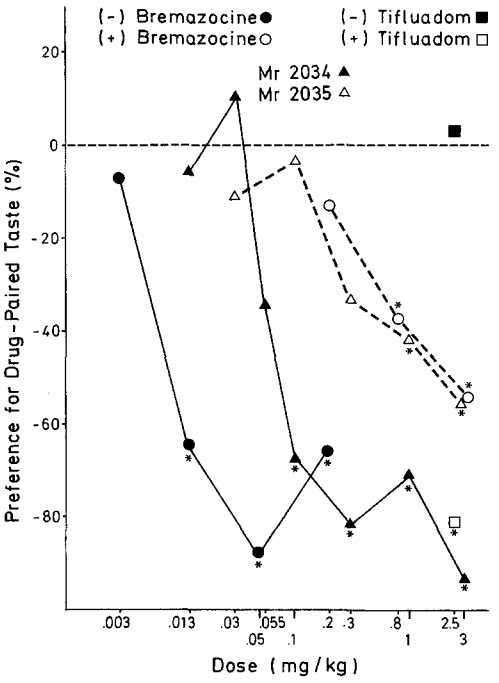

Fig. 4. Taste preference score of rats trained with the opioid active enantiomers (−)-bremazocine, Mr 2034, and (+)tifluadom and the opioid inactive enantiomers of these kappa receptor agonists. The general information is similar to that in Fig. 3

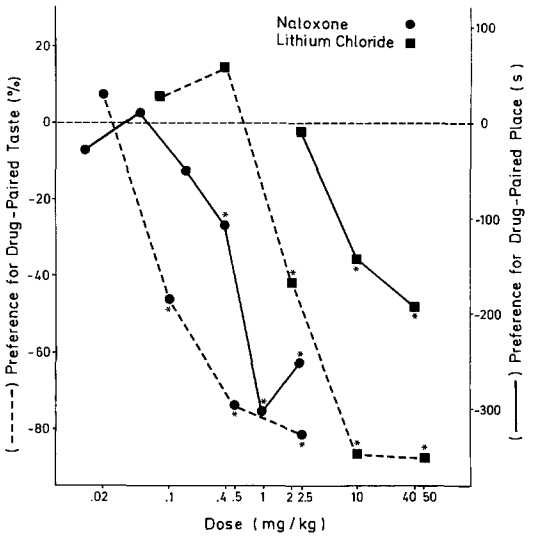

Fig. 5. Place and taste preference scores for rats trained with different doses of lithium chloride and naloxone. For explanation of the ordinates see Figs. 1 and 2. The *abscissa* gives the doses of the respective drugs. The data at each point were from 10 or 12 rats for place and six or eight for taste. The *asterisks* indicate significant preference conditioning

1,35; $P<0.03$). The lowest doses that produced a significant aversion were 0.2 mg/kg ($-55.6\pm16.4\%$, $n=6$), 0.5 mg/kg ($-30.3\pm13.2\%$, $n=8$), and 2 mg/kg ($-49.1\pm18.9\%$, $n=6$) ethylketazocine, U50–488, and tifluadom respectively.

Figure 4 reveals the significant linear relation between dose and aversion for (−) bremazocine ($F=11.5$; $df=1,23$; $P<0.003$) and (+) bremazocine ($F=4.55$; $df=1,16$; $P<0.05$). The (−) isomer, however, was much more potent: the lowest effective dose was 0.013 mg/kg ($-65.0\pm15.4\%$, $n=6$) as compared to 0.8 mg/kg ($-38.6\pm15.0\%$, $n=6$) for the (+)-isomer. Also, at 0.2 mg/kg, the preference score of the (+) isomer group ($12.8\pm13.3\%$, $n=8$) was significantly different from that of the (−) isomer group ($-63.0\pm13.8\%$, $n=8$). Similarly, a significant linear relation between dose and aversion was seen for Mr 2034 ($F=21.3$; $df=1,27$; $P<0.001$) and Mr 2035 ($F=7,6$; $df=1,34$; $P<0.01$) and again the (−) isomer, Mr 2034, was more potent. The lowest effective dose of Mr 2034 was 0.1 mg/kg ($-67.4\pm14.7\%$, $n=10$) and of Mr 2035, 1 mg/kg (-41.4 ± 12.3, $n=8$). Also, analysis of variance indicated a clear difference in the effect of the isomers ($F=32.2$; $df=1,70$; $P<0.001$). Taste conditioning produced by tifluadom was also stereospecific: at the dose run, 2.5 mg/kg, the active isomer (+) (Kley et al. 1983) produced significant taste aversion ($-81.5\pm2.6\%$, $n=8$), but the inactive did not (3.0 ± 24.5, $n=8$).

Expt. 6. Sensitivity of place and taste conditioning as compared with lithium chloride and naloxone. Lithium chloride produced a dose-related aversion to both place and taste stimuli (Fig. 5), as indicated by a significant linear relationship between the magnitude of the aversion and the dose for place ($F=13.4$; $df=1,33$; $P<0.001$) and taste ($F=81.2$; $df=1,31$; $P<0.001$). The lowest dose that produced a significant place aversion was 10 mg/kg (-134 ± 24 s, $n=10$) and a significant taste aversion, 2.0 mg/kg ($-40.1\pm11.2\%$, $n=8$).

Naloxone also produced an aversion to both place and taste stimuli (Fig. 5), as confirmed by a significant linear relationship between the magnitude of the aversion and the dose for place ($F=24.9$; $df=1,76$; $P<0.001$) and taste ($F=35.0$; $df=1,20$; $P<0.001$. The lowest dose that produced significant place conditioning was 0.4 mg/kg (-106 ± 37 s, $n=10$) and taste, 0.1 mg/kg ($-46.9\pm12.6\%$, $n=6$).

Discussion

Drugs acting preferentially on the kappa or on the mu type of opioid receptors were examined for their motivating properties using taste and place preference conditioning procedures. Thus, it was found that all drugs tested were effective unconditioned stimuli (i.e. produced conditioning). The two test procedures were of the two-stimulus, unbiased type, thereby providing information on both appetitive reinforcing and aversive properties of drugs (Mucha and Iversen 1984). This, together with the measurement of dose-response curves revealed the relation between the nature of particular motivating effect and dose and choice of conditioning procedure.

Regarding the kappa opioid receptor agonists, all the racemic opioids (ethylketazocine, tifluadom, and U50–488) produced conditioned aversion: all produced taste aversion and U50–488 produced place aversion. Of the active isomers, all (Mr 2034, (−)-bremazocine, and (+)-tifluadom) produced taste aversion and (−) bremazocine produced place aversion as well. Since the respective inactive isomers failed to produce any conditioning or produced aversion only at high doses, it was concluded that these agonists induce the aversion via activation of specific opioid receptors. Although the obvious interpretation is that these effects are due to activation of the kappa type of receptor, there are data indicating that kappa agonists act as antago-

nists on mu opioid receptors (Petrillo et al. 1984; Wüster et al. 1980). Therefore, it might be considered that this aversive effect is similar to that of naloxone, i.e. due to antagonism of the activity of an endogenous opioid peptide (Mucha et al. 1982; Stolerman et al. 1978). However, this explanation is quite unlikely, since a comparative examination of the aversion produced by naloxone and a kappa receptor agonist in lesion experiments revealed different mechanisms. Destruction of the arcuate nucleus of the hypothalamus, which contains cell bodies of beta-endorphin neurones, attentuated the aversive effect of naloxone, but not that of U50–488 (Mucha et al. 1985).

There are a number of noteworthy differences in the degree of conditioning produced by the various kappa receptor agonists. They comprise: 1) single-phase dose-response curves for the taste conditioning with all the drugs and for place with (−) bremazocine, 2) a U-shaped dose-response curve for the place conditioning with U50–488, and 3) a lack of place conditioning with ethylketazocine, tifluadom, and Mr 2034. The U-shaped curve for U50–488 was repeated in two separate experiments and was similar to the shape of the curve seen for the effect of this drug on food intake (Morley and Levine 1983). In addition, place conditioning was not seen with a high dose of ethylketazocine, even with twice the usual number of pairings. There is no simple explanation for these differences, but consideration of the findings and the fact that U50–488 and (−) bremazocine are the most selective kappa ligands used here (Römer et al. 1980; von Voigtlander et al. 1983; suggest that the lack of place conditioning with ethylketazocine and Mr 2034 may be due to additional activity on different types of opioid receptors; such a reversal of aversion may also occur with high doses of U50–488. The differences in the results of the different tests may be explained by the fact that any weakening of aversive conditioning would likely be seen first with the less sensitive place conditioning procedure. It is also possible that the various drugs act on different subtypes of kappa receptors (Pfeiffer et al. 1981) with activity on the alternative subtypes reflected in variations in the conditioning.

The mu opioid receptor agonists, in contrast to the kappa, produced predominantly conditioned preference. However, again differences were noted in the effects produced by individual drugs. All three mu receptor agonists produced place preference, and, at low doses, fentanyl and sufentanil also produced clear taste preference. At high doses of fentanyl and sufentanil, the taste preference was absent or replaced by aversion, and morphine produced primarily taste aversion.

It was concluded that at low doses mu receptor agonists act as appetitive reinforcers. Conditioned preference produced by such drugs were previously shown to be stereospecific and naloxone reversible (Mucha et al. 1982; van der Kooy et al. 1982). Moreover, the doses producing preference were very similar to those producing generalization to discriminative properties of fentanyl, a response previously concluded to involve mu receptors (Colpaert 1978; Shearman and Herz 1982). The order of potencies found is also similar to those of competition for sufentanil binding (Leysen et al. 1983) and inhibition of electrically-induced twitches in the isolated ileum preparation (Wüster et al. 1981). It is therefore concluded that the appetitive reinforcing effects seen here are due to activation of mu opioid receptors.

The basis of the lack of taste preferences and presence of taste aversion at higher doses of fentanyl and sufentanil is not yet clear. Since it was seen that 0.025 mg/kg sufentanil and 0.25 mg/kg fentanyl are lethal for some of the rats, the aversions may be an expression of toxicity. The taste aversion produced by morphine has been proposed to reflect toxicity (cf. Cappell and LeBlanc 1975; Goudie 1979). However, in contrast to the findings with fentanyl and sufentanil, the morphine doses that produced taste aversion are similar to those producing place preference and are considerably lower than the lethal doses range (30 mg/kg failed to kill any rats), suggesting that another mechanism may be involved. We are currently carrying out further experiments on this issue.

The conditioned taste preference produced by the mu opioid receptor agonists constitute the first demonstration of conditioned taste preferences produced in nondependent rats. This adds to a previous finding of a preference produced by pairing a flavour with recovery from illness by a dopamine agonist (Green and Garcia 1970). It is generally believed that self-administered drugs do not produce any preference for taste cues (Cappell and LeBlanc 1975; Goudie 1979). However, the present study indicates that this notion is no longer tenable. Therefore, like non-drug reinforcers (Ettenberg 1980; Hogan and Roper 1978), opioids can produce conditioned preference with both environmental cues and taste cues serving as conditioned stimuli.

The present data suggest that endogenous opioid activity mediated by mu opioid receptors has motivating properties. It was found here that activities of mu receptors had appetitive reinforcing properties. It was also confirmed that low doses of naloxone have aversive effects (Mucha and Iversen 1984; Mucha et al. 1982); as naloxone has a higher affinity to mu receptors than to other opioid receptor types (Robson et al. 1983), the blockade of the mu receptors probably produces the aversive properties of naloxone.

The results are in line with reports that mu receptor agonists are readily self-administered in laboratory animals (Woods et al. 1979) and that kappa receptor agonists are not (Katz et al. 1982; Römer et al. 1982; Woods et al. 1979). However, the present models, in contrast to self-administration models, can differentiate motivationally neutral from aversive drug effects. Therefore, it is likely that kappa substances are not self-administered because they are punishing.

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