Stereoselective Enhancement of Nociception by Opioids in Different Strains of Mice

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Accepted December 26, 1984

Abstract—The effects of Mr2096, Mr2097, diprenorphine, (−)-bremazocine and Mr2266 on jumping latencies were evaluated in Swiss, CXBK, C57BL, CXBH and CBA strains of mice. Mr2096 and Mr2097 respectively produced analgesia and hyperalgesia in these strains of mice. Thus their effects on nociception were mediated by stereoselective opioid receptors. Diprenorphine also produced hyperalgesia which might be mediated by both mu and kappa receptors. Kappa receptors also appeared to mediate hyperalgesia at least in Swiss and CBA strains, as both (−)-bremazocine and Mr2266 shortened the jumping latencies.

Reports have been published on the analgesic response to opioids (1, 2) and hyperalgesic reactions to opioid antagonists (3) in different strains of mice. However, the stereoselectivity of opioid antagonists on nociceptive reactions in different strains of mice has not yet been reported. Therefore, the present experiments were undertaken to elucidate the stereoselectivity of a diastereoisomeric pair of N-tetrahydrofurfurylnormorphones, Mr2096, an agonist, and Mr2097, an antagonist (4), and diprenorphine, an oripavine antagonist, on the jumping response using the hot plate test. Additionally the involvement of kappa receptors in pain control was also examined by using a kappa agonist, (−)-bremazocine (5), and a selective kappa antagonist, Mr2266 (6), in these strains of mice.

Five different strains of mice (Swiss, CXBK, C57BL, CXBH and CBA; all male; 4–6 weeks old; 20–28 g) were obtained from the Laboratory Animal Center, National University of Singapore and were allowed to adapt to the new environment for at least one week. The jumping latencies were measured using the hot plate technique previously described (3, 7). The apparatus consisted of a hot plate maintained at 55°C on which a restraining glass cylinder (height, 17 cm; diameter, 13 cm) was placed. The “cut-off” time was 120 sec. The jumping response was the end point and the jumping latencies were recorded by an experienced observer who was “blind” to treatment schedules. The mice were exposed to the hot plate only once. Control groups received the solvent at the appropriate time. All the tests were conducted between 14:00 hr and 18:00 hr. Groups of 20 mice were used for each treatment. The solutions were administered in a volume of 0.5 ml/20 g. Statistical significance of the data was evaluated by Student’s t-test.

The effects of Mr2096, Mr2097 and diprenorphine on the jumping latencies of Swiss, CXBK, C57BL, CXBH and CBA strains of mice are shown in Fig. 1. In Swiss, CXBK and C57BL strains, low doses of Mr2096 (0.3, 1 mg/kg) produced prolongation of jumping latencies, and higher doses (3, 10 mg/kg) did not produce any significant effect; the falling-off of the analgesic effect of Mr2096 in these strains of mice might be related to its mixed agonist-antagonist properties (4). In the slow responding CXBH and CBA strains, Mr2096 over a wide range of doses (0.3, 1, 3 and 10 mg/kg) produced significant analgesia as measured by the
prolongation of jumping latencies. However, in these strains, the analgesic effect of Mr2096 regressed for 3 and 10 mg/kg.

In Swiss and CXBK strains, low doses (0.3, 1 mg/kg) of Mr2097 and diprenorphine did not produce any significant action on nociception, whereas higher doses (3, 10 mg/kg) shortened the jumping latencies significantly. Facilitation of jumping responses occurred to the following doses of antagonists against the remaining respective strain: Mr2097 and diprenorphine: 3 mg/kg (C57BL); diprenorphine: 3 or 10 mg/kg (CXBH); Mr2097: 3 or 10 mg/kg; and diprenorphine 1, 3 or 10 mg/kg (CBA). Thus it was generally observed that Mr2096 produced antinociception and Mr2097 induced a hyperalgesia, indicating stereoselectivity of opioid receptors in the regulation of nociception in different strains of mice. The hyperalgesia following the injection of Mr2097 was attested by the production of hyperalgesia by diprenorphine, another class of opioid antagonist. The hyperalgesia induced by Mr2097 was possibly mediated by the mu type of opioid receptors because of its structural similarity to naloxone. The hyperalgesia induced by diprenorphine might be mediated by both mu and kappa receptors as it is regarded as a universal antagonist at both sites.

The involvement of kappa opioid receptors in the regulation of nociception was also examined using a kappa agonist, (-)-

Fig. 1. Stereoselective alterations of jumping latencies by opioids in 5 different strains of mice. Ordinates: jumping latencies in seconds. Abscissae: doses of drugs in mg/kg (log scale). Hatched area indicates the mean±S.E.M. for the corresponding control mice. Asterisks indicate significant difference (P<0.05) from corresponding controls. n=20 per each point. Closed circle (●), Mr2096; open circle (○), Mr2097; open square (□), diprenorphine. All the drugs were dissolved in 0.9% sodium chloride solution and injected s.c., 10 min before the test. The respective strain is indicated on the top of the figure.
bremazocine, and a selective kappa antagonist, Mr2266. (-)Bremazocine (1 mg/kg) and Mr2266 (1 mg/kg) produced hyperalgesia in the Swiss and CBA strains but not in others, a finding which was consistent with an earlier report (8).

The present study showed, firstly, that Mr2096 and Mr2097 respectively produced analgesia and hyperalgesia in Swiss, CXBK, C57BL, CXBH and CBA strains of mice. Thus their effects on nociception were mediated by stereoselective opioid receptors. Regarding their mechanisms, the analgesic effect of Mr2096 might arise as a result of mimicking the endogenous opioids released during the thermonociceptive stimuli. The hyperalgesia produced by Mr2097 and diprenorphine could be interpreted as antagonism of endogenous opioids liberated during the heat stress and/or mimicking endogenous antagonistic ligands for which there are some indications (9–13). Secondly, kappa receptors also seemed to mediate hyperalgesia, at least in Swiss and CBA strains of mice, as both (-)bremazocine and Mr2266 shortened the jumping latencies. The hyperalgesia produced by these two drugs might be due to antagonism of endogenous substrates for both kappa and mu receptors released during the thermonociceptive stimuli. In this context, it has been earlier observed that administration of a kappa agonist, U-50488, also produced hyperalgesia in Swiss and CBA strains but not in others (8). Thus it appears that the strains C57BL, CXBK and CXBH might be lacking in kappa ligands and/or kappa receptor levels. In support of kappa receptor mediation of hyperalgesia, it has been recently shown (14, 15) that ethylketazocine produced hyperalgesia in acutely decerebrated dogs as indicated by a shortening of a skin twitch reflex latency.

Acknowledgements: This research work was supported by a research grant (RP 95/81: Functions of Endorphins) by the National University of Singapore. I am indebted to Dr. H. Merz (Boehringer Ingelheim, F.R.G.) for his generous gifts of Mr2096 and Mr2097 and Mr2266; to Dr. D. Romer (Sandoz, Switzerland) for (-)bremazocine; and to Dr. M. Rance (Reckitt & Colman, England) for his generous gift of diprenorphine. I thank Miss Mui-Eng Chua for technical assistance.

References


2 Jacob, J. and Barthélémy, C.: Réactivité nociceptive et sensibilité à la morphine de Souris de diverses souches. Therapie 22, 1435–1438 (1967)


5 Römer, D., Büscher, H., Hill, R.C., Maurer, R., Petcher, I.J., Welle, H.B.A., Bakel, H.C.C.K. and
6 Merz, H.: Structural features of opioid kappa agonists and antagonists. Symposium on kappa receptors and their ligands, April 30, 1982 Toulouse, France.