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Bremazocine-Induced Backwards Walking Behavior in Rats is Mediated Via Opioid Kappa Receptors

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SHEARMAN, G T AND C STENFORS *Bremazocine-induced backwards walking behavior in rats is mediated via opioid kappa receptors* PHARMACOL BIOCHEM BEHAV 24(4) 861–863, 1986 —Bremazocine dose-dependently induced backwards walking behavior in rats after its SC injection Only the (−) but not the (+) enantiomer induced backwards walking Pretreatment with either naloxone or MR 2266 reduced the bremazocine-induced backwards walking. MR 2266 was at least ten times more potent than naloxone. These findings suggest that bremazocine-induced backwards walking is mediated via an agonistic action of the drug with opioid kappa receptors The data may contribute to the discussion concerning opioid kappa receptors and the psychotomimetic effects of some opioid analgesic drugs.

Bremazocine Naloxone MR 2266 Kappa receptors Backwards walking Psychotomimetic activity

BREMAZOCINE is a benzomorphan derivative that has been characterized as a potent long-acting opiate kappa agonist [18]. In addition to its opiate agonistic actions, bremazocine also possesses opiate antagonistic properties [6, 17, 18, 23]. Thus, bremazocine appears to be a mixed agonist-antagonist at opiate receptors.

Several mixed agonist-antagonist analgesic drugs, including cyclazocine, have been reported to induce a behavioral syndrome in rats consisting of lateral head movements, pivoting on the hind paws and backwards walking [1–5, 9, 10, 19] Induction of this syndrome was proposed as a model for predicting the psychotomimetic activity of such drugs in man [8, 11, 19] It was the purpose of this study to determine whether bremazocine would induce backwards walking in rats and to test the hypothesis that this effect is mediated via kappa opioid receptors

METHOD

Male Sprague Dawley rats (Sandoz AG, Basel) weighing between 130 and 190 g were used The animals were housed in groups of 6–10 in Makrolon cages (32×54×19 cm) in a colony room thermostatically maintained at 23±1°C. The room lights were turned on from 6.00 a.m to 6.00 p.m. The animals received food and water ad lib except during the experiment when no food or water was available. On the experimental day the rats were transported to a sound-attenuated observation room, weighed, injected with bremazocine or solvent and placed in groups of three in Makrolon cages described above. The rats were observed continuously for two hours beginning 5 min after bremazocine injection. Naloxone or MR 2266 were injected 10 min before bremazocine The number of times each rat walked backwards was recorded by the experimenter The data were calculated in terms of the percentage of rats walking backwards in the 2 hr observation period as well as the frequency of backwards walking.

All drugs were dissolved in 0.9% saline except MR 2266 ((−)2-(3-furylmethyl)5,9-dimethyl)-2-hydroxy-6,7 (benzomorphan) which was dissolved in a minimal amount of 0 1 N HCl. All drugs were injected SC in a volume of 1 ml/kg Drug doses were calculated in terms of the free base

RESULTS

Data summarized in Fig. 1 show that bremazocine (0.0032–0 32 mg/kg) dose-dependently induced backwards walking after its SC injection in rats. (−)Bremazocine (0.0032–0 32 mg/kg) also induced backwards walking, however, (+)bremazocine (0.32 and 3.2 mg/kg) did not

As shown in Fig. 2, MR 2266 (0.04–2.5 mg/kg) dose-relatedly reduced both the number of rats walking backwards after bremazocine injection as well as the frequency of backwards walking. Naloxone did not significantly (Probit Analysis $p>0$ 05) reduce the number of rats walking backwards but a dose of 10 mg/kg significantly (Student's t-test, $p<0.05$) reduced the frequency of backwards walking induced by bremazocine.

DISCUSSION

The present experiment demonstrated that bremazocine stereo-selectively induced backwards walking behavior in rats and that the bremazocine-induced backwards walking was selectively reduced by pre-treatment with the opioid kappa receptor antagonist MR 2266.

That backwards walking was induced only by (−)bremazocine is in agreement with other data showing that the antinociceptive [18] and certain behavioral effects of

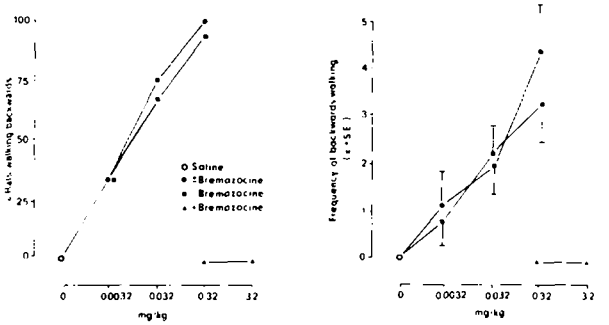

FIG 1 Dose-dependent induction of backwards walking behavior by bremazocine and its (−) enantiomer N = 12 for racemate and for (−) and (+) enantiomer

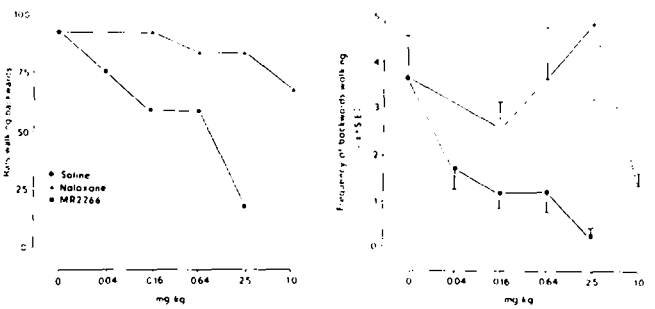

FIG 2 Reduction of bremazocine (0 32 mg/kg)-induced backwards walking behavior by MR 2266 and naloxone pre-treatment N = 12 per dose of each drug

bremazocine [16] are induced by the levorotatory enantiomer Although the dextrorotatory enantiomer was completely inactive in inducing backwards walking, even in doses up to 1000 times higher than the (−) or (±) forms, we found that the levorotatory isomer was as potent as the racemate in this respect. At the present time we cannot explain why the (−) enantiomer was not twice as potent as the racemate

Earlier investigations found that several opioid analgesic drugs with mixed agonistic-antagonistic activity induced a behavioral syndrome in rats including backwards walking [1–5, 9, 10, 19]. Since these studies a classification of opioid receptors was proposed [7,14] and several drugs found to previously induce backwards walking have now been classified as kappa agonists [14,22] Bremazocine can also be classified as a kappa agonist with mixed agonist-antagonist activity [18] and the present data show that this drug also induced backwards walking in rats.

The narcotic receptor antagonists naloxone and MR 2266 each reduced backwards walking induced by bremazocine. MR 2266 was several-fold more potent than naloxone in this respect The sensitivity to antagonism by naloxone and MR 2266 has previously been used as evidence for the involvement of specific opioid receptors [13] MR 2266 is generally accepted to be a more selective opioid kappa receptor antagonist than naloxone [12, 15, 18, 20, 21] Thus the present data showing that MR 2266 is at least ten-fold more potent than naloxone in reducing bremazocine-induced backwards walking suggests that this behavior is mediated via an agonistic interaction of bremazocine with opioid kappa receptors. Previously, MR 2266 was found to be more potent than naloxone in blocking other actions of bremazocine [12, 18, 20] Naloxone very weakly reduced the frequency of bremazocine-induced backwards walking and did not significantly reduce the percentage of rats walking backwards Similarly, it was found that cyclazocine-induced backwards walking was unaffected by naloxone treatment [3,9].

It has been suggested that the induction of backwards walking behavior in rats by opioids with mixed agonist-antagonist activity may be related to the psychotomimetic activity of these drugs in man [8, 11, 19]. The present finding that backwards walking induced by bremazocine is mediated via kappa receptors may contribute to the discussion concerning the role of opioid kappa receptors and the clinical psychotomimetic activity of some opioid analgesics

REFERENCES

1 Buckett, W R and J S Shaw Dopaminergic drugs antagonize the psychotomimetic effects of partial-agonist analgesics *Psychopharmacologia* **42:** 293–297, 1975

2 Collier, H O J and C Schneider Profiles of activity in rodents of some narcotic and narcotic antagonist drugs *Nature* **224:** 610–612, 1969

3 Collier, H O J and C Schneider Some agonist and antagonist properties of morphine antagonists in rodents In *Agonist and Antagonist Actions of Narcotic Analgesic Drugs*, edited by H W Kosterlitz, H O J Collier and J E Villarreal London Macmillan, 1972, pp 128–135

4 Cowan, A Simple in vivo tests that differentiate prototype agonists at opiate receptors *Life Sci* **28:** 1559–1570, 1981

5 Curzon, G , J C R Fernando and A J Lees Backward walking and circling Behavioural responses induced by drug treatments which cause simultaneous release of catecholamines and 5-hydroxytryptamine *Br J Pharmacol* **66:** 573–579, 1979

6 Gambino, M C , P Petrillo and A Tavani Agonist and antagonist properties of some benzomorphans on nociceptive reaction and intestinal transit in rats *Life Sci* **33:** 461–464, 1983

7 Gilbert, P E and W A Martin The effects of morphine and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog *J Pharmacol Exp Ther* **198:** 66–82, 1976

8 Haertzen, C A Subjective effects of narcotic antagonists cyclazocine and nalorphine on the addiction research center inventory (ARCI) *Psychopharmacologia* **18:** 366–377, 1970

9 Holtzman, S G and R E Jewett Stimulation of behavior in the rat by cyclazocine Effects of naloxone *J Pharmacol Exp Ther* **187:** 380–390, 1973

10 Iwamoto, E T and W R Martin Multiple opioid receptors *Med Res Rev* **1:** 411–440, 1981

11 Keats, A S and J Telford Narcotic antagonists as analgesics clinical aspects In *Drug Design Advances in Chemistry*, edited by R F Godd Washington Am Chem Soc, 1964, p 170

12 Leander, J D A kappa opioid effect increased urination in the rat *J Pharmacol Exp Ther* **224:** 89–94, 1983

13 Lord, J A , H Waterfield, J Hughes and H W Kosterlitz Endogenous opioid peptides multiple agonists and receptors *Nature* **267:** 495–500, 1977

14 Martin, W. R , C. G Eades, J. A Thompson, R E Huppler and P. E Gilbert The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog *J Pharmacol Exp Ther* **97**: 517–532, 1976
15 Merz, H , A Langbein, K Stockhaus, G Walther and H Wick Structure activity relationships in narcotic antagonists with N-furyl-methyl substituents In. *Advances in Biochemical Psychopharmacology*, edited by M C. Brande, L S Harris, E L May, J P Smith and J E Villarreal New York Raven Press, 1974, pp 91–107
16 Mucha, R F and A Herz Motivational properties of kappa and mu opioid receptor agonists studied with place and taste preference conditioning *Psychopharmacology (Berlin)* **86**: 274–280, 1985
17 Petrillo, P , M. Amato and A Tavani Bremazocine induces antinociception, but prevents opioid-induced constipation and catatonia in rats and precipitates withdrawal in morphine-dependent rats *Life Sci* **35**: 917–922, 1984
18 Römer, D., H Buscher, R. C. Hill, R. Maurer, T. J Petcher, H B. A Welle, H C C K. Bakel and A M Akkerman Bremazocine. A potent, long-acting opiate kappa-agonist. *Life Sci* **27**: 971–978, 1980
19 Schneider, C Behavioral effects of some morphine antagonists and hallucinogens in the rat. *Nature* **220**: 586–587, 1968
20 Shearman, G T and A Herz Discriminative stimulus properties of bremazocine in the rat *Neuropharmacology* **20**: 1209–1213, 1981
21 Shearman, G T and A Herz. Evidence that the discriminative stimulus properties of fentanyl and ethylketazocine are mediated by an interaction with different opiate receptors *J Pharmacol Exp Ther* **221**: 735–739, 1982
22 Snyder, S H and R A. Goodman. Multiple neurotransmitter receptors *J Neurochem* **35**: 5–15, 1980
23 Von Voigtlander, P F and R A Lewis. U 50,488, a selective kappa opioid agonist comparison to other reported kappa agonists *Prog Neuropsychopharmacol Biol Psychiatry* **6**: 467–470, 1982