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The opioid κ-selective compound U-50,488H does not inhibit intestinal propulsion in rats

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The selective κ-compound U-50,488H, at doses producing strong central pharmacological effects (0·5–32 mg kg^{-1} i.p.) did not delay the intestinal transit of a charcoal meal and had little or no antagonist action against morphine-induced constipation. It appears that κ-opioid receptors are probably not involved in the mechanisms responsible for opioid-induced constipation.

Opioids produce a variety of pharmacological effects in-vivo generally attributed to interaction at multiple opioid receptor types deignated as μ, κ and σ by Martin et al (1976).

In an attempt to investigate the role of κ-type opioid receptors in the mechanisms involved in opioid-induced constipation, we studied the pharmacological effects on rat intestinal propulsion of U-50,488H (*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzenacetamide), a compound reportedly selective at κ-binding sites in-vitro and at κ-receptors in-vitro and in-vivo (Piercey et al 1982; Lahti et al 1982; VonVoigtlander et al 1983; Gillan et al 1983).

Materials and methods

Overnight fasted male CD-COBS rats (Charles River, Italy, 150–180 g) were tested for intestinal transit (Fiocchi et al 1982) 5 min after a charcoal meal according to our standard procedure (Tavani et al 1980), and 4 min after the meal they were tested for 55 °C hot-plate reaction (licking time, cut-off 30 s) scored as analgesic index [(time with drug – time pre-drug)/(30 – time pre-drug)].

Drugs were dissolved in distilled water and were injected intraperitoneally (i.p.) (Tavani et al 1980) and doses were calculated for the following salts: U-50,488H methanesulfonate hydrate (gift from Dr P. F. Von-Voigtlander, the Upjohn Company, Kalamazoo, USA) and morphine HCl (Salars, Como, Italy).

The results in Fig. 1 were processed statistically by two-way analysis of variance and Tukey's test.

* Correspondence.

Results

Fig. 1 shows the effects of various doses of U-50,488H on nociception and intestinal transit in the same rat. U-50,488H, at doses that doubled progressively from 0·5 to 32 mg kg^{-1} i.p. given 10 min before the test meal, did not affect the intestinal transit of charcoal, but the highest doses showed a tendency to prolong the hot-plate reaction. At 32 mg kg^{-1}, rats presented alterations in their gross behaviour (slow movements, flaccid-

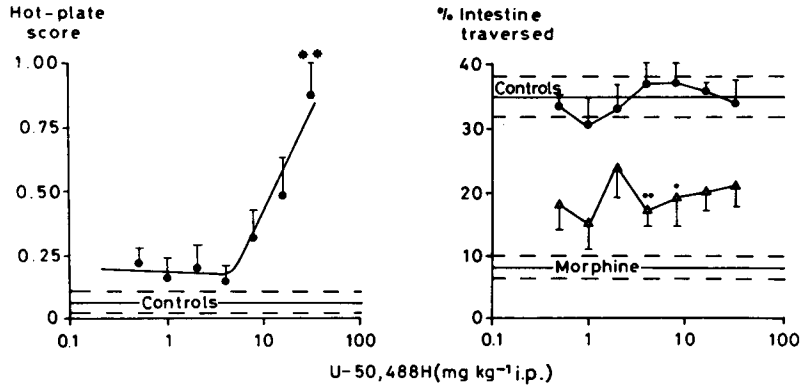

FIG. 1. Effect of U-50,488H and morphine on nociception and intestinal transit in rats. Each point represents (mean and s.e.) response from 6 to 12 animals. Distilled water (controls) or 0·1 mg kg^{-1} i.p. morphine (morphine) were injected 5 min before the test meal. U-50,488H and distilled water (●) or U-50,488H and morphine (△) were injected i.p. respectively 10 and 5 min before the test meal. Hot-plate score and % intestine traversed by charcoal were determined respectively 4 and 5 min after the meal, as described in Materials and methods. $^{**}P < 0·01$ from controls; $^{*}P < 0·05$ and $^{**}P < 0·01$ from the group injected with the same dose of U-50,488H and distilled water, by two-way analysis of variance and Tukey' test.

ity) and 6 out of 7 rats tested did not react in the hot-plate test.

In accordance with previous results (Tavani et al 1980), we found (Fig. 1) that a low dose of morphine (0·1 mg kg^{-1} i.p.) 5 min before the test meal markedly delayed the intestinal transit of charcoal. U-50,488H administered 5 min before morphine at doses from 0·5 to 32 mg kg^{-1} i.p. partly prevented morphine-induced inhibition of intestinal propulsion, but this effect was not dose-related and the interaction between morphine and U-50,488H was not significant in our statistical test. In similar experiments in which 8 mg kg^{-1} i.p. of U-50,488H were administered 30 and 60 min before killing the animals, we observed no effect on intestinal transit and no antagonism of morphine-induced delay of intestinal propulsion (data not shown).

Discussion

The existence of stereospecific opioid binding sites in the rat intestine has been reported (Manara et al 1980; Monferini et al 1981) and it has been suggested that these sites should be predominantly δ-binding sites (Leslie et al 1980).

Recently we studied the intestinal effects of bremazocine and ethylketazocine (Gambino et al 1983), reported to be a 'κ-agonist' in-vivo (Römer et al 1980; Martin et al 1976), but not selective ligands, at the μ-, δ- and κ-sites in-vitro (Magnan et al 1982). Bremazocine proved to be a pure antagonist of morphine-induced constipation in the charcoal meal test and ethylketazocine a pure agonist, this latter finding being in agreement with other reports (Porreca et al 1982a, b). From these results we deduced that the κ-type opioid receptors probably do not play a major role in the mechanisms of opioid-induced constipation, and that bremazocine and ethylketazocine's effects depend on interaction at μ- and δ-sites. The present finding that U-50,488H a selective κ-agonist (Piercey et al 1982; Lahti et al 1983; VonVoigtlander et al 1983; Gillan et al 1983), even at high doses producing strong central pharmacological effects, does not delay intestinal transit of the test meal, further supports our hypothesis. On the other hand the weak, if any, antagonist properties of U-50,488H on morphine-induced constipation might depend on the residual cross-reactivity of U-50,488H at μ- and δ-binding sites (Gillan et al 1983) although it cannot be excluded that U-50,488H may interact at different sites in the gut inducing any pharmacological effect opposite to constipation induced by morphine.

In summary although our results suggest that κ-receptors are probably not involved in mechanisms responsible for opioid-induced constipation, at present we cannot definitely exclude the presence of κ-receptors in the rat intestine.

In-vivo pharmacological experiments with even more selective opioid κ-compounds or in-vitro binding assays with [^{3}H]bremazocine suppressed at μ and δ-sites in the rat intestine are required to clarify whether κ-sites are present or not in this tissue.

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