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J. Pharm. Pharmacol. 1982, 34: 666–667
Communicated April 19, 1982

0022–3573/82/100666–02 $02.50/0

Tolerance and cross-tolerance studies with morphine and ethylketocyclazocine

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It is generally believed that the in vivo effects of opioids are mediated by subclasses of opiate receptors that have been designated as μ, κ and σ (Gilbert & Martin 1976; Martin et al 1976). In this model, agonists are specific for particular receptor subtypes, and the ultimate effects are initiated by an interaction of agonist with receptor subtype. For example, the benzomorphan, ethylketocyclazocine (EK), is thought to cause analgesia in pressure and writhing tests by interacting with κ receptors whereas morphine is active in the same tests through an interaction with μ receptors (Tyers 1980). The view that an effect, in a particular test for analgesia, can be initiated through two distinct receptor subtypes is inconsistent with conventional models of drug action. Traditionally, a pharmacological effect has been associated with a receptor rather than the agonist, with a single effect being mediated through only one receptor subtype. Our previous (Cowan et al 1978) and present studies (involving pressure and heat stimuli, respectively) with EK and morphine suggest that this more traditional view is also applicable to the opioids. Specifically, we believe that morphine and EK, prototype ligands at μ and κ receptors, respectively, cause analgesia in rats through agonist actions on a common receptor.

Methods

Male, Sprague Dawley rats (180–220 g; Zivic-Miller) were implanted s.c. with two pellets each containing 75 mg of morphine alkaloid or with two placebo pellets. The pellets were wrapped in nylon mesh in order to facilitate their removal 72 h after implantation. Dose-response curves for analgesia were obtained with morphine and EK 24 h after pellet removal. The procedure employed was the tail flick test with water at 58 °C as the nociceptive stimulus. Each animal served as its own control. The analgesic effect was calculated using a 15 s cutoff time and the following formula:

% of maximum possible effect = [(test time–control time) × 100]/(15–control time).

Testing took place 30 min after challenging the rats with s.c. morphine sulphate (Mallinckrodt) or ethylketocyclazocine methane sulphonate (Sterling-Winthrop). Doses are given in terms of the salt.

Results and discussion

Doses of morphine necessary to produce analgesia in placebo (control) rats ranged between 2·5 and 20 mg kg^{-1}, s.c. while doses for EK in placebo rats were between 0·2 and 2·5 mg kg^{-1}. In each case, a maximum effect was obtained. In morphine-pelleted animals, the dose necessary to produce analgesia increased to 10–80 mg kg^{-1} for morphine and 10–120 mg kg^{-1} for

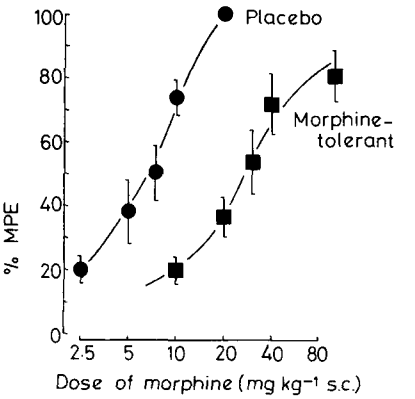

FIG. 1. Percent of maximum possible (analgesic) effect (% MPE) ± s.e. after morphine in either placebo (●) or morphine (■) tolerant rats. Groups of 8–10 animals were used at each dose in the tail flick test.

* Correspondence.

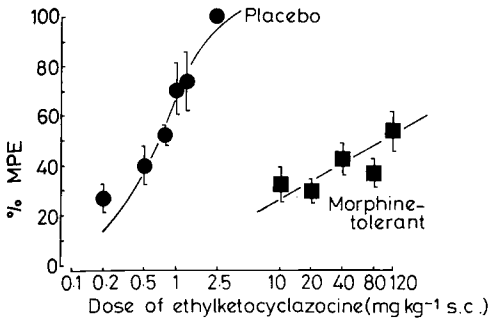

FIG. 2. Percent of maximum possible (analgesic) effect (% MPE) ± s.e. after ethylketocyclazocine in either placebo (●) or morphine (■) tolerant rats. Groups of 8–10 animals were used at each dose in the tail flick test.

EK. The rightward displacement of both the morphine (Fig. 1) and the EK (Fig. 2) dose-response curves demonstrates tolerance to morphine and cross-tolerance to EK in morphine-pretreated animals. The morphine dose-response curve from morphine-tolerant animals is steep and parallel to that obtained with naive animals, while the EK curve in morphine-tolerant rats is shallow with a low maximum. While morphine gave a near maximum effect (80%) in tolerant rats at the highest dose employed, EK elicited only a 53% effect at the highest dose tested (120 mg kg^{-1}). Tolerance to morphine produced approximately a four-fold shift in the morphine dose-response curve but about a 100-fold shift in the EK dose-response curve. This suggests that pretreatment with morphine induces cross-tolerance to EK more easily than tolerance to morphine.

Supporting evidence from a different endpoint should be considered. We have shown that tolerance develops to both morphine and EK in the rat charcoal meal test (Green 1959) and that two-way cross-tolerance exists between these compounds in this procedure (Porreca et al 1982). Moreover, the slowing of gastrointestinal transit by morphine and EK is antagonized to the same extent by naloxone (subcutaneous A50 values were 133 and 300 μg kg^{-1}, respectively).

In contrast to these similarities between morphine and EK, it should be noted that EK does not substitute for morphine in rats receiving an i.p. infusion of morphine (Teiger 1974) (Dr M. E. Feigenson, Sterling-Winthrop, personal communication). Information on the important question of whether morphine substitutes for EK in rats infused with EK has yet to be reported. Also, Chang et al (1981) have recently identified a benzomorphan-selective binding site in rat brain homogenates. Critically, however, these workers found that although benzomorphans (such as EK) bind to this site with high affinity, they also bind to morphine and enkephalin sites with equal or even greater affinities.

On the basis of our data, we suggest that it is more appropriate to pair a receptor subtype with a specific opiate effect rather than with a specific opiate compound. From this perspective, differing profiles associated with the acute administration of opioids may reflect differences in affinity for the particular receptor subtype, but an agonist may interact with more than one receptor subtype. Common effects (such as tail flick analgesia or inhibition of gastrointestinal transit) would be initiated by common receptor subtypes. This interpretation is more in keeping with traditional models of drug action.

It is a pleasure to thank Sterling-Winthrop for ethylketocyclazocine and Endo for naloxone. The study was supported by Grant DA 02322 from the National Institute on Drug Abuse.

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