Assessment of physical dependence in rats after continuous intraperitoneal infusion of morphine or ketocyclazocine

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Previous workers have induced physical dependence to morphine in rats by either multiple injection schedules (Hanna, 1960), pellet implantation (Blasig, Herz, Reinhold & Zieglgansberger, 1973) of the use of 'slow-release' emulsions (Laska & Fennessy, 1978). All of these methods involve problems associated with either the determination of the actual dose absorbed or the maintenance of a constant level of exposure to morphine. In the present study an alternative strategy, based on the method described by Teiger (1974), was employed which overcame both of these problems. Using this method dependence was induced by continuous infusion of drug solutions into the peritoneal cavity by means of previously implanted cannulae.

Groups of male rats (Sprague-Dawley, 150–250 g, $n = 6$–7) were used. Morphine (1–100 mg/kg per 24 h) or ketocyclazocine (10–100 mg/kg per 24 h) was continuously infused into the peritoneal cavity (240 μl/h) over a period of 48 hours. At the end of this time abstinence was precipitated by the injection of the opiate antagonist naloxone (3 mg/kg, s.c.). Various signs of abstinence were either measured (weight loss, escape attempts, shaking episodes, writhing episodes) or assessed on an all or none basis (teeth chattering, ptosis, diarrhoea). The degree of weight loss precipitated by naloxone were directly proportional to the dose of morphine or keto-cyclazocine infused. Other signs, such as writhing or shaking, were not linearly related to the dose of analgesic infused but actually declined at higher doses. Martin, Eades, Thompson, Huppler & Gilbert, (1976) have hypothesised that there are distinguishable opiate receptors and suggested that morphine should be considered as the prototype agonist for the μ receptor whilst ketocyclazocine should be considered as the prototype agonist for the k receptor (Martin, *et al.*, 1976). Experiments were conducted to investigate whether keto-cyclazocine could substitute for morphine and suppress the abstinence signs produced in rats abruptly withdrawn from morphine but ketocyclazocine (10–70 mg/kg per 24 h) was without effect in suppressing the signs of abstinence produced in rats during the acute phase of withdrawal from morphine (200 mg/kg per 24 h).

These results indicate that the technique of continuous intraperitoneal infusion provides an improved method of inducing physical dependence to opiate drugs in rats. By careful observation of the signs of abstinence precipitated after naloxone challenge the degree of dependence can be related directly to the dose of opiate administered. Results of cross suppression tests using morphine and ketocyclazocine indicate a distinction between analgesics which interact with the so-called μ and k receptors.

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Dependence, tolerance and cross-tolerance induced by morphine and ethylketocyclazocine

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The proposed k-agonist ethylketocyclazocine neither precipitates nor suppresses the abstinence syndrome in morphine-dependent monkeys (Villarreal & Seevers, 1972).

Mice and guinea-pigs were pretreated with a single subcutaneous injection of a slow-release emulsion (Collier, Francis & Schneider, 1972) containing morphine (300 mg/kg) or ethylketocyclazocine (30 mg/kg). The animals were allowed between 2 and 96 h of exposure to the emulsion prior to testing.

Tolerance in mice was assessed *in vivo* by challenging pre-treated animals with standard doses of agonists (morphine, 40 mg/kg; ethylketocyclazocine,