THE COMPARATIVE PHARMACOLOGY OF MORPHINE, KETOCYCLAZOCINE AND 2'-HYDROXY-5,9-DIMETHYL-2-ALLYL-6,7-BENZOMORPHAN IN RODENTS

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In 1976, Martin & others described the pharmacological profiles of the three opiate derivatives - morphine, ketocyclazocine and SKF 10047 (2'-hydroxy-5,9-dimethyl-2-allyl-6,7-benzomorphan) in the chronic spinal dog. They described three contrasting ranges of pharmacological actions, varying susceptibility to naloxone antagonism and presence or absence of cross tolerance and dependence between the three compounds. On this basis three types of opiate receptor were proposed to accommodate the three type substances, the μ-receptor (morphine), the κ-receptor (ketocyclazocine) and the σ-receptor (SKF 10047). Other opiate derivatives were then classified as being pure agonists, partial agonists or pure antagonists at each of these receptors.

We have determined whether the differences between the three type substances so apparent in the dog are similarly apparent in rodents. We have compared the intraperitoneal effects of the three compounds on hot plate reaction time and respiratory rate in mice (Bousfield & Rees, 1969), oesophageal temperature and locomotor activity (Animex) in mice, tail flick time (D'Amour & Smith, 1941), rectal temperature and locomotor activity in rats. Behavioural effects were also noted.

Morphine (10-40 mg/kg) produced the predicted range of effects. At a dose of 20 mg/kg it caused a 3-fold increase in hot plate reaction time and a 35% decrease in respiratory rate in mice, a 3-fold increase in tail flick time in rats, a biphasic change in body temperature (primarily hypothermia), and negligible effect on locomotor activity. Behavioural observations included the stilted locomotion and Straub tail so characteristic of the drug. The effects of keto-
-cyclazocine (1.25-80 mg/kg) were similar with respect to the two analgesic tests and respiration. In contrast to morphine there was only hypothermia and this was less marked, and locomotion was considerably reduced. The animals were very sedated, and the incidence of Straub tail was infrequent.

SKF 10047 (10-80 mg/kg) was quite different. The only action shared with mor-
-phine and ketocyclazocine was a decrease in respiratory rate. Analgesia was not detected by either test, and there was no consistent change in body temp-
-erature. The animals became very ataxic, and the minimal lethal dose was relatively low (80 mg/kg).

The qualitative effects of the three type substances in rodents differ suff-
-iciently from those reported in dogs to doubt common mechanisms of action in the three species, and thus the relevance of differential effects being due to different receptor interactions may be questioned.

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