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Antinociceptive actions of morphine and buprenorphine given intrathecally in conscious rats

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Morphine injected into the spinal subarachnoid space in animals produces focal analgesia (Yaksh & Rudy, 1977; Yaksh, 1978). In the present study the antinociceptive effects of morphine and buprenorphine injected intrathecally or subcutaneously were compared in the rat (male, 200–270 g, AH-PVG/C). Chronically implanted cannulae (PP10, Portex Ltd) allowed injections (total 15 µl) of drugs or placebo (artificial cerebrospinal fluid in g/l NaCl 7.46; KCl 0.19; $MgCl_2$ 0.19; $CaCl_2$ 0.14) to be made into the subarachnoid space at the level T_{13}–L_1. Antinociceptive activities were determined in dose groups of 6 rats against hind-paw 'lick' response latencies in the hot-plate (55°C) test and in the hind-paw pressure ('analgesimeter', Ugo Basile) test. Drugs were injected either intrathecally at 10, 30 or 60 min or subcutaneously at 30 min prior to determination of nociceptive thresholds. Different groups of rats were used for each pre-treatment time. Experiments were carried out blind using a randomised dosing schedule. Data were analysed for linearity and regression using methods of Finney (1964). Results obtained are given in Figure 1.

After intrathecal injection the peak (30 min) antinociceptive potencies of buprenorphine or morphine were similar in both tests but the buprenorphine

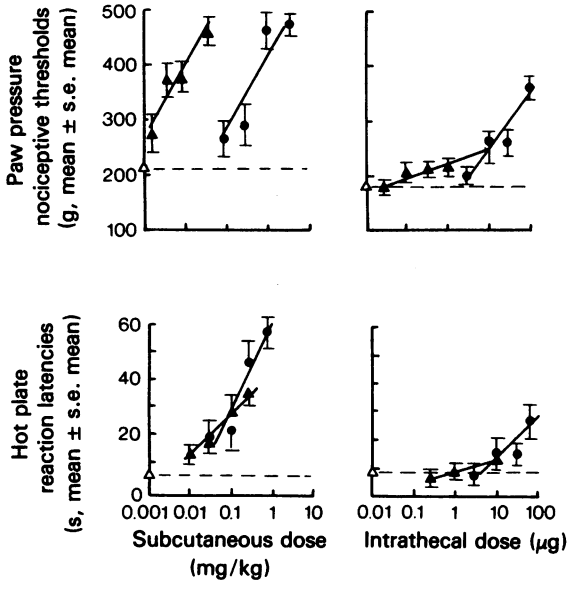

Figure 1 Effects of morphine (●) and buprehorphine (▲) given intrathecally or subcutaneously in the hot-plate (55°C) and paw pressure tests in the rat.

dose-response curve was shallower than that produced by morphine. Similar results were obtained when the drugs were given subcutaneously in the hot-plate test but in the paw-pressure test buprenorphine was considerably more potent than morphine and the slopes of the dose-response curves were not significantly different. The intrathecal doses of buprenorphine required to produce an antinociceptive effect in the paw pressure test were greater per total body weight than the ED_{50} given subcutaneously. This indicates, together with the unexpectedly slow onset time, that the action of buprenorphine given intrathecally in the paw pressure test results from diffusion into the plasma. It is concluded that the predominant site of action of buprenorphine is supraspinal.

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In vivo antagonism of analgesia and respiratory depression induced by proposed μ and κ opiate agonists

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The existence of two types of opiate receptor has been proposed *in vivo*, the μ (morphine sensitive) and the κ (ketocyclazocine sensitive) receptors (Martin, Eades, Thompson, Huppler & Gilbert, 1976).

We have investigated the effects of the proposed μ receptor agonists morphine (10–40 mg/kg i.p.) and methadone (5–20), and the proposed κ receptor agonists ketocyclazocine (1.25–80) and ethylketocyclazocine (1.25–20) on hot plate reaction time and respiratory rate in groups of 12 Manchester strain mice (25 ± 3 g). The effects of the pure narcotic antagonist naloxone (0.2–5) and the partial agonist SKF 10047 (0.2–10) (Martin *et al.*, 1976) upon the actions of the agonists were also observed. Antagonists were injected 5 min prior to the agonists.

All four agonists produced dose-dependent increases in hot plate reaction time and depression of respiratory rate. Both naloxone and SKF 10047 caused a dose-dependent antagonism of these agonist actions.

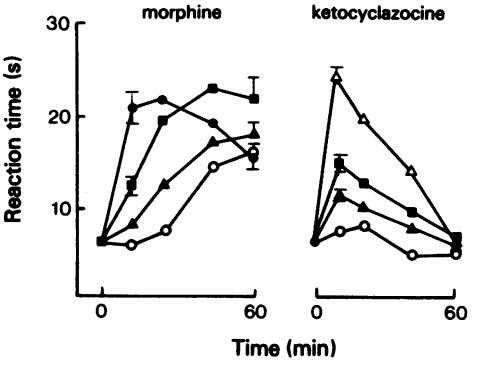

Figure 1 The hot plate reaction times of mice given (●) morphine (40 mg/kg) and (△) ketocyclazocine (20 mg/kg) alone, and in the presence of three doses of naloxone (■, 0.2 mg/kg; ▲, 1 mg/kg; ○, 5 mg/kg). Limits at 10 and 60 min following injection are ±s.e. mean.