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.

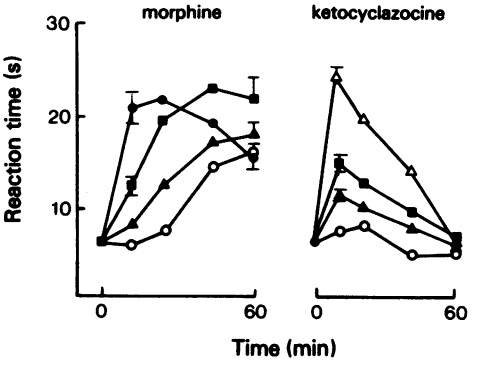

Figure 1 The hot plate reaction times of mice given (●) morphine (40 mg/kg) and (△) ketocyclazocine (20 mg/kg) alone, and in the presence of three doses of naloxone (■, 0.2 mg/kg; ▲, 1 mg/kg; ○, 5 mg/kg). Limits at 10 and 60 min following injection are ±s.e. mean.

The respiratory depressant action of the four agonists were equally antagonised by either naloxone or SKF 10047, the two antagonists being of similar molar potency. In contrast, the analgesia produced by the κ agonists was more readily antagonised than that produced by the μ agonists, and in every instance, naloxone was a more effective antagonist than SKF 10047.

An apparent difference between the μ and κ agonists was seen 60 min following antagonist injection (Figure 1). Both the respiratory depression and the degree of analgesia seen in animals injected with morphine or methadone and an antagonist, was *greater* than that seen in animals given only the agonist. In contrast, animals injected with κ agonists exhibited similar degrees of analgesia and respiratory depression irrespective of antagonist administration.

Correlations between hot plate reaction time and respiratory rate (at peak effect) indicated differences between μ and κ agonists, and suggested that differences in the characteristics of the antagonism of analgesia and respiratory depression also exist.

S.J.W. is an S.R.C. student

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The effects of agents acting at pre- and postsynaptic α-adrenoceptors on haloperidol catalepsy

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Noradrenergic involvement in neuroleptic-induced catalepsy has been reported by a number of workers (Al-Shabibi & Doggett, 1978; Pycock, 1977; Honma & Fukushima, 1977). Although catalepsy is thought to be due mainly to dopaminergic effects of neuroleptics (e.g. Fog, 1972), changes in noradrenergic activity have been shown to have a modulating effect. As α-adrenoceptor agonists and antagonists have been found to differ in their selectivity for peripheral pre- and postsynaptic receptors (Drew, 1976), it is possible to determine the relative importance of these receptors for their effects on catalepsy.

The effects of a range of α-adrenoceptor agonists and antagonists with varying selectivity after s.c. injection were studied on the duration of catalepsy produced by pretreatment with haloperidol (0.2 mg/kg s.c.) in male T.O. mice (20 to 30 g). Catalepsy was measured as the posture holding time after placement of the forelegs on a 7 cm high bar, up to 3 h after injection of haloperidol.

The agonist, methoxamine, at 5 mg/kg, which is selective for postsynaptic α-adrenoceptors markedly enhanced haloperidol catalepsy. Clonidine did so slightly at a dose of 0.5 mg/kg. A very low dose of clonidine however (0.01 mg/kg), which is thought to act mainly on presynaptic receptors, decreased the catalepsy. The selectively postsynaptic antagonist, prazosin, antagonised haloperidol catalepsy at low doses (1 to 2.5 mg/kg), but enhanced it at a higher dose (5 mg/kg); whereas the predominantly presynaptic antagonists, yohimbine (2.5 to 5 mg/kg) and piperoxane (10 to 20 mg/kg), caused potentiation.

These results suggest that modulation of noradrenergic activity, either by direct action on postsynaptic α-adrenoceptors or by affecting transmitter release via presynaptic receptors, may influence neuroleptic-induced catalepsy. Enhancement of noradrenergic activity by presynaptic antagonists which would increase noradrenaline release or by postsynaptic receptor stimulation, resulted in potentiation of haloperidol catalepsy. In addition, the drugs with these effects, methoxamine, yohimbine and piperoxane, when administered alone occasionally produced catalepsy and also increased spontaneous abnormal posture holding in the home cage. The effects of low doses of the postsynaptic antagonist, prazosin, and the presynaptic agonist, clonidine, in inhibiting the catalepsy, further support these results. Higher doses of both these drugs led to an enhancement of catalepsy. This could represent postsynaptic agonist action by clonidine, but an analogous argument is unlikely for prazosin, as it has little presynaptic activity (Cambridge, Davey & Massingham, 1977). Sedation, which was marked at these higher doses with both drugs, may be a second factor in the modulation of haloperidol catalepsy.

Confirmation of the effect of presynaptic receptor stimulation on catalepsy may be sought by the use of guanfacin (BS100-141), a highly selective presynap-