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-

tic agonist, (Brown, unpublished observations, 1979), which, on the basis of the present interpretation, would be predicted to markedly inhibit catalepsy. Preliminary results suggest that this is the case.

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The effect of metoclopramide and haloperidol on tardive dyskinesia

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Tardive dyskinesia is a movement disorder which occurs in patients on long-term neuroleptic therapy, and has been attributed to the development of supersensitivity of dopamine receptors in the central nervous system (Marsden, 1975). Metoclopramide (MCP) has recently been reported to produce tardive dyskinesia (Lavy, Melamed & Penchas, 1978; Kataria, Traub & Marsden, 1978) but despite other evidence that MCP blocks dopamine receptors (Day & Blower 1975; Ahtee, 1975; Goldberg, Volkman & Kohli, 1978) it does not appear to have antipsychotic activity (Borenstein & Bles, 1965).

We have compared the effects of single intravenous doses of MCP (10, 20 and 40 mg), haloperidol (HL) (5 and 10 mg) and placebo (saline) in 8 patients (age 55 to 85 years, 6 female) with tardive dyskinesia secondary to long term neuroleptic treatment. The study was double blind and the order of drug administration randomised, with an interval of at least 7 days between each treatment. The patients' severity of dyskinetic movement (N.I.M.H. Psychopharmacology Research Branch 1975) and parkinsonism (Calne, Reid, Vakil, *et al.*, 1971) was rated immediately before, and at 1, 3 and 6 h after drug administration. In addition video recordings were made at the same time for later rating for dyskinesia by 4 observers. The total dyskinesia score for each patient at each time point was summed, and the results analysed by the Wilcoxon signed rank test (Siegel, 1956). The scored drug effects on dyskinesia were found to be similar both at the time of the study and from video playback. Patients improved significantly during the day whilst on placebo, and after all active treatments. The effects of HL 10 mg and MCP 40 mg on dyskinesia were significantly greater than placebo at 3 h ($P < 0.05$ and < 0.02 respectively) and of HL 5 and 10 mg and MCP 40 mg at 6 h ($P < 0.01$). No significant changes in parkinsonian features were noted.

These findings suggest that the dose of MCP used for studies of its antipsychotic activity (Borenstein & Bles, 1965) may have been too low. The effect of dopamine receptor antagonists on tardive dyskinesia may provide a useful method for investigating these drugs in man.

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