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Interaction of neuroleptic and cholinergic drugs with central dopaminergic mechanisms

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Neuroleptic drugs have been shown to possess antidopaminergic and antimuscarinic properties (Miller & Hiley, 1974) using *in vitro* assay techniques. Animal behavioural models have now been used in order to examine the relative effects of these actions *in vivo*.

In rats with unilateral lesions of the nigro-striatal dopamine fibres induced by injection of 6-OH dopamine into the substantia nigra methamphetamine causes turning towards the side of the lesion in a dose-dependent fashion. Measurement of this turning behaviour is believed to constitute an *in vivo* measure of the effects of dopamine released from the nigro-striatal pathway on the intact side.

Turning produced by methamphetamine (5 mg/kg) was completely antagonized by the dopamine antagonists pimozide (0.25 mg/kg), α-flupenthixol (1.0 mg/kg) and α-clopenthixol (8 mg/kg). It was partially antagonized by α-flupenthixol (0.2 mg/kg) or chlorpromazine (4 mg/kg). The isomeric trans forms of the thioxanthenes β-flupenthixol (10 mg/kg) or β-clopenthixol (8 mg/kg) were ineffective. These trans isomers are also ineffective in blocking the stimulating effects of dopamine on striatal adenylate cyclase, whereas the α-(*cis*)-isomers are potent blockers. The dopamine antagonists clozapine and thioridazine in doses up to 18 mg/kg had no effect on turning. These are the two neuroleptics which combine antidopaminergic actions with potent antimuscarinic properties (Miller & Hiley, 1974).

The effect of cholinergic drugs on turning behaviour was also examined. Oxotremorine (0.75 mg/kg) plus methylatropine (5 mg/kg) antagonized methamphetamine induced turning, indicating the dopaminergic/cholinergic balance modulating the action of the extrapyramidal system. In addition, scopolamine (10 mg/kg) caused turning in the same direction as amphetamine but was less effective. Pimozide (0.25 mg/kg) or α-flupenthixol (0.2 mg/kg) antagonized the effects of scopolamine.

Low doses of apomorphine (<0.1 mg/kg) produced turning away from the side of lesion, presumably due to a direct action on supersensitive receptors on the lesioned side. This turning was not antagonized by thioridazine or clozapine (18 mg/kg). Apomorphine induced turning was antagonized by oxotremorine (0.74 mg/kg). These results indicate that the effects of cholinergic drugs are not wholly dependent on the integrity of the nigro-striatal system.

d-Amphetamine (4 mg/kg) produced a stimulation of locomotor activity in adult and 11-day old rats. Pretreatment of adults with clozapine (4 mg/kg) or thioridazine (4 mg/kg) 3 h previously or thioridazine (4 mg/kg) 30 min previously had no effect on the amphetamine induced stimulation of locomotor activity. Trifluoperazine (0.4 mg/kg) 3 h previously completely inhibited locomotor activity. Pretreatment of 11-day old rats with 4 mg/kg clozapine or thioridazine 3 h before amphetamine completely inhibited the stimulation of locomotor activity.

It is known that 11-day old rats can respond to catecholaminergic agonists but the response to cholinergic drugs has not yet developed. It is suggested that in adult animals the anticatecholaminergic effects of some neuroleptics may be

modified by their antimuscarinic actions. In 11-day old animals however the anticatecholaminergic effects may be expressed unmodified.

R.J.M. is an M.R.C. Scholar.

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The effects of a new anti-depressant, ORG GB94, on amine uptake mechanisms

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Antagonism of reserpine-induced hypothermia is a widely employed test for the screening of potential anti-depressant compounds. ORG GB94 (1, 2, 3, 4, 10, 14b-hexahydro-2-methyldibenzo[c,f.]pyrazino-[1,2-a] azepine monohydrochloride) is a clinically efficacious anti-depressant (Itil, Polvan & Hsu, 1972) possessing no reserpine antagonistic properties (van Riezen, 1972). In addition to having no dramatic effect on hypothermia induced by apomorphine and tremorine, ORG GB94 fails to antagonize tetrabenazine-induced ptosis. The activity of anti-depressants, as typified by the tricyclics, e.g. desmethylimipramine (DMI), in such systems is attributed to their ability to block the membrane amine pump of central monoaminergic neurones. Differences have been found in the effect of tricyclic anti-depressants and of ORG GB94 on the turnover of rat brain noradrenaline and 5-hydroxytryptamine (Leonard, 1974) and experiments were undertaken to determine whether or not ORG GB94 had an effect on central catecholaminergic uptake systems.

Incubating rabbit brain stem slices in the presence of either DMI or ORG GB94 resulted in a concentration-dependent inhibition of uptake of the noradrenaline analogue(−)-metaraminol [(−)-MA] (for experimental details see Sugrue & Shore, 1969). The ID_{50} values for DMI and ORG GB94 were 4.2×10^{-7} M and 3.0×10^{-6} M respectively. Kinetic studies were undertaken and *Km* values determined from Lineweaver-Burk plots. ORG GB94 (10^{-5} M) and DMI (10^{-6} M) did not alter the V_{max} of (−)-MA uptake by rabbit brain stem slices but did effect a change in *Km* thus indicating that both drugs compete with (−)-MA for the amine attachment site on the carrier. A characteristic feature of DMI is its inability to block the amine pump of central dopaminergic neurones (Dorris & Shore, 1971). Incubating rabbit hypothalamic minces in the presence of either DMI (10^{-5} M) or ORG GB94 (10^{-5} M) resulted in a profound block of (−)-MA uptake. On the other hand, (−)-MA uptake by rabbit striatal minces was essentially unaltered by either drug.

In addition to the above *in vitro* findings, ORG GB94, like DMI, not only antagonizes the pressor response to tyramine but also potentiates the pressor response to noradrenaline in the pithed rat.

The results of this study reveal that ORG GB94 mimics DMI in several experimental situations. Both compounds are competitive inhibitors of the membrane amine pump of central noradrenergic neurones. ORG GB94, like DMI, has no effect on amine uptake by central dopaminergic neurones. Both drugs antagonize and potentiate the pithed rat pressor response to tyramine and noradrenaline respectively. Why ORG GB94 should be so similar to DMI in monoamine uptake studies and yet be essentially devoid of effect in conventional anti-depressant screening tests not only awaits clarification but would also appear to cast doubt on the validity and significance of such models.

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