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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