inhibited. Inhibition of the glucagon-sensitive system by chlorpromazine (5×10^{-4}M) was non-competitive. In this system α and β-flupenthixol were both equally effective at 10^{-4}M, and haloperidol was ineffective at 10^{-4}M. This does not parallel the neuroleptic properties of these compounds. The effects of neuroleptics on the glucagon or noradrenaline-sensitive adenylate cyclases occurred at concentrations at which other membrane bound enzymes are also affected and probably reflect the general membrane stabilizing effects of neuroleptics rather than direct drug/receptor interactions of the type that occur with the dopamine-sensitive system.

Richard Miller is an M.R.C. Scholar.

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Some effects of age upon irreversible inhibition of cardiac MAO

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It has been suggested, from evidence derived from the use of irreversible inhibitors such as clorgyline that the monoamine oxidase (MAO) in many tissues exists in two forms, called 'species A' and 'species B' (Johnston, 1968). At present, it is not clear whether these two species of enzyme represent differences in localization, e.g., intra- and extraneuronal MAO (Goridis & Neff, 1971), or differential binding of membrane lipid to the same enzyme protein (Tipton, Houslay & Garrett, 1973). In the rat heart, tyramine is metabolized solely by species A while benzylamine is metabolized by both A and B (Lyles & Callingham, 1974). With this latter substrate, the pattern of inhibition produced by clorgyline depends upon the age of the animal.

Hearts were removed from male Wistar rats and male CFLP mice and homogenized in 0.001 M potassium phosphate buffer at pH 7.4. Assay of MAO activity involved the use of ^{3}H-tyramine and ^{14}C-benzylamine as substrates. Inhibitor concentrations varied from 5×10^{-11} to 5×10^{-4} M.

In rats of mean body weight 151 g, benzylamine oxidation produced a double sigmoid inhibition curve with clorgyline. The plateau region of this curve, which occurred at inhibitor concentrations of 5×10^{-8} to 5×10^{-7} M, suggested that species A represented about 35% of the total enzyme activity. In younger rats of body weight 63 g, the plateau shifted to indicate a smaller (23%) proportion of species A. In rats weighing 36 g, the inhibition curve was essentially a single sigmoid typical of species B. However, in older rats weighing 317 g and 414 g, the plateau shifted in the opposite direction suggesting an increased proportion of species A (50% and 70%, respectively). Confirmation of this was obtained using the MAO inhibitor deprenyl. This compound while producing similar inhibition curves to clorgyline, is more active on species B. Benzylamine oxidation again resulted in a double sigmoid inhibition curve, and the plateau region also shifted to indicate an increase in the proportion and amount of species A with increase in the age of the rat. On this evidence, it is suggested that the increase in the specific activity of rat heart MAO seen in the growing rat is mediated largely by an increase in the amount of species A.

In the adult mouse heart, the inhibition curves using clorgyline were different from those in the rat. Using tyramine as substrate, a double sigmoid curve was found, with species A representing about 20% of the total activity. However, benzylamine produced a single sigmoid curve characteristic of species B.

It would appear that the use of the irreversible MAO inhibitors, clorgyline and deprenyl, with a variety of substrates can be used to investigate the possibility of selective changes in the nature of the enzyme that may accompany changes in its specific activity.

Supported by a grant from the British Heart Foundation. G.A.L. is a Medical Research Council Scholar.

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Tricyclic antidepressants and monoamines: the relationship between uptake blockade and potentiation of neuronal responses

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It has previously been reported that the tricyclic antidepressants imipramine and desipramine can potentiate the responses of single brain cells to micro-electrophoretically applied monoamines (Bradshaw, Roberts & Szabadi, 1974). The potentiating effect of the antidepressants is generally ascribed to the efficacy of these drugs in blocking the uptake of monoamines into nervous tissue (Schildkraut, 1965). In order to investigate this hypothesis we have examined whether the tricyclic antidepressants can potentiate neuronal responses to the monamines in situations where uptake mechanisms are unlikely to be involved.

Single spontaneously active neurones were studied in the cerebral cortex and corpus striatum of the halothane-anaesthetized rat. All the drugs were applied by microelectrophoresis. Repeated responses to monoamines were compared following a brief application of an antidepressant (desipramine or iprindole).

1. It has been reported that iprindole is ineffective in blocking the uptake of noradrenaline (NA), 5-hydroxytryptamine (5-HT) and dopamine (DA) into brain tissue (Ross, Renyi & Ögren, 1971). We have found, however, that responses of single neurones to NA, 5-HT and DA can be potentiated by iprindole (18 cells in the cerebral cortex, 6 cells in the corpus striatum).

2. Although desipramine is a powerful inhibitor of NA uptake, its effects on the uptake of DA are very weak (Shore, 1972). We have found that responses of single striatal neurones to DA are potentiated by desipramine (7 cells).

3. In previous experiments we have found that cortical neurones can respond to microelectrophoretic application of mescaline, and that these responses are pharmacologically similar to those evoked by NA and 5-HT (Bevan, Bradshaw, Roberts & Szabadi, 1974). It has been reported that mescaline has an extremely low affinity for NA uptake mechanisms in the periphery (Iversen, 1967). Nevertheless, we have found that responses of cortical neurones to mescaline can be potentiated by desipramine (10 cells).

These findings indicate that uptake blockade cannot fully explain the potentiating effects of the tricyclic antidepressants on neuronal responses to the monoamines. An alternative explanation could be that the potentiation seen in our experiments is due to a post-synaptic effect of the antidepressants (Bradshaw, Roberts & Szabadi, 1974).

The authors wish to acknowledge financial support from the Mental Health Trust & Research Fund and the Scottish Home & Health Department.

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