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Monoamine Oxidase Inhibitors and Brain Monoamines in Clinical Conditions

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The amine hypothesis of depression states that at least some cases of endogenous depression are caused by a depletion of certain monoamines in the brain. The hypothesis is supported by the finding that all drugs that elevate mood increase the brain concentrations of free monoamines, such as noradrenaline, whereas drugs that depress mood decrease these concentrations (Schanberg, Schildkraut & Kopin, 1967).

By their enzyme-inhibitory action the monoamine oxidase inhibitors increase the concentrations of monoamines in the brain and can reverse the depressive-like behaviour of animals resulting from amine-depleting drugs such as reserpine. The monoamine oxidase inhibitors were the first group of antidepressants (as distinct from stimulants) to be introduced into psychiatry, and despite adverse publicity are still considered by most experienced psychiatrists to be extremely useful, and indeed essential, drugs, especially for certain cases of depression.

Effect of monoamine oxidase inhibitors on brain monoamines. Measurement of the amount of inhibition of monoamine oxidase by the use of 5-hydroxytryptamine-tolerance tests and changes in the urinary excretion of 5-hydroxyindol-3-ylacetic acid or tyramine have lost favour as being too indirect. What is wanted is a measure of the change in brain amine concentrations brought about by the drug and, if possible, the change in amine activity.

Following on the work of Joyce (1962), we have estimated the concentrations of 5-hydroxytryptamine, noradrenaline and dopamine in the brain stem, hypothalamus and caudate nucleus in

patients who had died of various terminal illnesses and who had been receiving monoamine oxidase inhibitors (MacLean, Nicholson, Pare & Stacey, 1965; B. B. Jones, W. J. Nicholson, C. M. B. Pare, K. Price & R. S. Stacey, unpublished work). The essential findings were that all monoamine oxidase inhibitors had a similar pharmacological effect, as measured by the change in brain amines, provided they were given in doses that were clinically equipotent. Secondly, the maximum concentration occurred at about 2-3 weeks and at a time when a clinical effect would be expected to occur, but thereafter tended to plateau off. Thirdly, although the distribution of individual concentrations are unimodal, there was a wide variation, some patients showing only a small increase in amine concentration.

These findings are interpreted as being very suggestive of the antidepressant effect of the monoamine oxidase inhibitors being mediated through their enzyme-inhibitory properties. The fact that some depressed patients do not respond to the drug may be due in part to some of them needing a larger dose, and Akindele, Evans & Oswald (1970) have shown a correlation between clinical improvement and disappearance of R. E. M. (rapid-eye-movement) sleep, which in certain patients only occurs with large doses of a monoamine oxidase inhibitor. On the other hand, it has been suggested that there may be at least two genetically distinct types of depression, one responding to the monoamine oxidase inhibitors and the other to tricyclic antidepressants, the response to the drugs tending to breed true in the same family (Pare, Rees & Sainsbury, 1962; Pare, 1970).

Brain amines in depression. Studies of brain amines in patients who commit suicide have been somewhat disappointing (Shaw, Camps & Eccleston, 1967; Bourne *et al.* 1968; Pare *et al.* 1969). They showed no evidence whatsoever of a deficiency of noradrenaline or dopamine, but a possible depletion of 5-hydroxytryptamine. These studies measured total brain amines and, of course, do not necessarily reflect the amount of physiologically active amines. These might best be measured by a determination of their metabolites, and indeed there appeared to be a decrease in the amount of 5-hydroxyindol-3-ylacetic acid in suicides compared with controls (Bourne *et al.* 1968; Pare, Yeung, Price & Stacey, 1969), but a study of catecholamine metabolites was impracticable. The suggestion of decreased amounts of 5-hydroxytryptamine and its major metabolites in these studies is, however, made more significant by the finding by Ashcroft *et al.* (1966) and Denker, Malm, Roos & Werdinius (1966) of decreased amounts of 5-hydroxyindol-3-ylacetic acid in the cerebrospinal fluid of depressed patients, and preliminary studies on the cerebrospinal fluid in patients

receiving probenecid suggest that the turnover of brain 5-hydroxytryptamine might be diminished in cases of depression (Van Praag & Korf, 1970).

Thus studies so far suggest that 5-hydroxytryptamine might be decreased in depressed patients, and clinically it has been found that feeding with tryptophan will potentiate the antidepressant properties of monoamine oxidase inhibitors (Coppen, Shaw & Farrell, 1963; Pare, 1963) and possibly even have an antidepressant effect when given by itself (Coppen, Shaw, Herzberg & Maggs, 1967), whereas phenylalanine seems to be ineffective either alone or with monoamine oxidase inhibitors (C. M. B. Pare, unpublished work). In this respect 3,4-dihydroxyphenylalanine (dopa) is of interest, as, although it causes excitement when given in acute experiments with animals, it has been reported to cause depression when given to patients with Parkinson's syndrome (Jenkins & Groh, 1970). A possible explanation lies in the report by Kopin (1970) that 3,4-dihydroxyphenylalanine may result in the formation of dopamine in 5-hydroxytryptamine-producing cells and then act as a false transmitter in place of the 5-hydroxytryptamine.

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COMMUNICATIONS

Inhibition of Rat and Mouse Brain Monoamine Oxidases By (+)-Amphetamine

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The molecular basis of amphetamine's central stimulant action is still disputed, but inhibition of monoamine oxidase [monoamine-oxygen oxidoreductase (deaminating), EC 1.4.3.4] is nowadays almost invariably discounted as a contributory factor, partly on the grounds that amphetamine is too weak an inhibitor (Zirkle & Kaiser, 1964), and partly on the grounds that the stimulation produced by amphetamine differs qualitatively from that displayed by irreversible inhibitors of the hydrazine type (Stein, 1964).

Monoamine oxidase inhibition by amphetamine *in vitro* has previously been studied mainly at substrate concentrations well above the K_m value for this enzyme; such experiments would grossly underrate the degree of inhibition produced by a competitive reversible inhibitor *in vivo*, where the endogenous substrate concentrations are low. K_m

values for rat and mouse brain monoamine oxidase determined at 25°C and pH 7.4 in an air atmosphere with ^{14}C -labelled substrates were about 70 μM , 250 μM and 100 μM for 5-hydroxytryptamine, (-)-noradrenaline and tyramine respectively. At substrate concentrations of 11–20 μM (all well below K_m but still higher than the probable endogenous concentration of free 5-hydroxytryptamine or noradrenaline) oxidation of 5-hydroxytryptamine or noradrenaline by either mitochondrial or microsomal brain fractions was inhibited by 50% by about 6 μM (+)-amphetamine. Slightly higher concentrations (8 μM for rat fractions, 20 μM for mouse fractions) were required to inhibit tyramine oxidation by 50%. These concentrations are well within the range (3–100 μM) reached in the brain by (+)-amphetamine given at doses (0.25–10 mg/kg) sufficient to elicit measurable behavioural changes in either species (Fuller & Hines, 1967; Maikel, Cox, Miller, Segal & Russell, 1969).

Kinetically inhibition is competitive but is not consistent with the enzyme being homogeneous. This is particularly so with tyramine as substrate,