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EDITORIAL

Monoamine oxidase inhibitor efficacy in depression and the 'cheese effect'[1]

It is widely agreed that the monoamine oxidase (MAO) inhibiting group of drugs have a useful role to play in the treatment of depressive illness. However, there is no generally accepted set of criteria to distinguish patients likely to respond from those who are therapy-resistant, and any precise division can only be made in retrospect (Pare & Sandler, 1959). MAO inhibitors employed in clinical practice are, without exception, 'suicide' inhibitors, compounds which are themselves metabolized to form a product which combines irreversibly – and lethally – with the active centre of the enzyme (for recent review, see Singer *et al.* 1979). Although a number of competitive, reversible inhibitors, synthesized by several different drug companies, are now undergoing evaluation, their clinical effectiveness has yet to be proved.

Since the early days, it has been tacitly or explicitly (Pare & Sandler, 1959) assumed that these drugs produce their therapeutic benefit by allowing a build-up within the brain of a particular monoamine substrate of the enzyme. Indeed, such an assumption has been one of the main props of the monoamine hypothesis of depressive illness (Schildkraut, 1965). Recently, this interpretation of MAO inhibitor action has been further refined. MAO can be subdivided pharmacologically by its sensitivity to the inhibitor, clorgyline, into two forms (Johnston, 1968): MAO A which prefers the 'classical' neurotransmitters, noradrenaline and 5-hydroxytryptamine as substrates, and MAO B which preferentially oxidizes certain less well-studied monoamines (see Singer *et al.* 1979). Lipper *et al.* (1979) have now suggested that inhibition of the A form of the enzyme, in their case with clorgyline itself, is a necessary prerequisite for therapeutic benefit in depressive illness. They indicated that the relatively selective MAO B inhibitor, pargyline, only possesses antidepressant activity in a dose large enough to bring about some degree of MAO A inhibition in addition. On the surface of it, this hypothesis received support from the recent double-blind trial of Mendis *et al.* (1981) which failed to demonstrate any therapeutic benefit deriving from the selective MAO B inhibiting drug, (−)-deprenyl, in patients with primary depressive illness. Even leaving to one side the counter-evidence of certain, admittedly open, studies where improvement was reported in response to deprenyl (Varga & Tringer, 1967; Tringer *et al.* 1971; Mann & Gershon, 1980) and the fact that the trial of Mendis *et al.* (1981) was a limited one, because the drug was and is in short supply, deprenyl is sufficiently atypical an MAO inhibitor to make it inadvisable for us to take for granted any straightforward explanation of its mechanism of action.

MAO inhibitors have enjoyed a modest success which would have been considerably greater but for one important adverse reaction, the 'cheese effect', the profound and sometimes disastrous rise in blood pressure which generally follows the administration of tyramine-containing foods to subjects under treatment. And yet there is little doubt that deprenyl, otherwise another powerful 'suicide' MAO inhibitor, is quite free from the 'cheese effect' at the 10–20 mg per day dosage schedule commonly employed in clinical practice (Elsworth *et al.* 1978). Indeed, only during a 50 mg per day dosage schedule and then with intravenous tyramine challenge, has any flicker of a hypertensive response been observed (Mendis *et al.* 1981). At first sight, such virtual absence of the 'cheese effect' is puzzling, for selective inhibition of MAO B with deprenyl, although real enough, probably represents an acute pharmacological response within a particular dosage range (Glover *et al.* 1980; Murphy *et al.* 1981): prolonged administration of the drug in clinically useful dosage seems likely to inhibit both forms of the enzyme in the human brain within a period of weeks although, for

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obvious reasons, there are few direct data. Chronic deprenyl treatment, for example in parkinsonian patients, still has the same safety margin as short-term administration (Elsworth *et al.* 1978) so that some explanation, other than a simplistic one involving selective inhibition of gastrointestinal MAO B while allowing MAO A to continue its metabolic action on tyramine unchecked (Knoll, 1976), must be invoked.

How do we resolve these problems? Recently, Sandler *et al.* (1980) were able to show that MAO inhibition itself, on the one hand, and the 'cheese effect', probably representing facilitation of noradrenaline release from its peripheral binding sites in response to tyramine, on the other, may derive from two separate and distinct actions of the same drug. In the pig, tyramine is predominantly metabolized by MAO B, which is widespread throughout its tissues with the exception of gastrointestinal mucosa which contains MAO A (Squires, 1972). However, pre-treatment of this animal with doses of clorgyline insufficiently large to produce any substantial degree of MAO B inhibition nevertheless resulted in a typical 'cheese effect' after intravenous tyramine challenge; and, conversely, pre-treatment of the pig with sufficient deprenyl to bring about almost complete MAO B inhibition in an animal which, to all intents and purposes, only possesses MAO B, followed by intravenous tyramine injection (to by-pass any gut MAO A barrier), resulted in no hypertensive response (Sandler *et al.* 1980).

Thus, there is a *prima facie* case to suggest that, with the exception of deprenyl, all the MAO inhibitors so far employed in clinical practice possess two, perhaps unconnected, pharmacological actions. If one were to accept, for the purposes of argument, that it may be the second of these actions, the central counterpart of the 'cheese effect', rather than MAO inhibition proper, which is responsible for the therapeutic benefit of the MAO inhibitors (Mendis *et al.* 1981), then many of the pieces of information we have which fail, at the present time, to fit into the clinical jigsaw might slot into place:

(1) A cheese effect has been reported following pre-treatment with compounds like isoniazid (Robinson *et al.* 1968; Smith & Durack, 1978; Lejonc *et al.* 1979; Morgan, 1980) and indomethacin (Lee *et al.* 1979), neither of which has any MAO-inhibitory action. In this connection, it is interesting to recall isolated reports (Salzer & Lurie, 1953; Joshi, 1976), never adequately followed up, suggesting that isoniazid itself possesses a beneficial effect in some patients with depressive illness.

(2) Although (+)-tranylcypromine is a more effective MAO inhibitor than the (−)-isomer (Fuentes *et al.* 1976; Reynolds *et al.* 1980*a*, *b*), (−)-tranylcypromine may be a clinically more effective antidepressant (Escobar *et al.* 1974) and, indeed, has been shown by Reigle *et al.* (1980) to release central noradrenaline more vigorously. (−)-Deprenyl is a more effective MAO inhibitor than the (+)-compound and it may not be entirely irrelevant that the early and optimistic Hungarian open studies (Varga & Tringer, 1967; Tringer *et al.* 1971) employed (±)-deprenyl. (+)-Deprenyl behaves pharmacologically in a manner very similar to amphetamine (Knoll & Magyar, 1972). The pharmacological waters may be muddied further by the fact that (+)-deprenyl seems likely to be metabolized to the pharmacologically-active (+)-methamphetamine and amphetamine (*cf.* Reynolds *et al.* 1978).

(3) Reports have started to appear of a beneficial effect of L-tyrosine administration in some patients with depressive illness (Gelenberg *et al.* 1980; Goldberg, 1980). It seems perfectly feasible that, rather than the conversion of tyrosine to catecholamine (Melamed *et al.* 1980) being responsible for the improvement, direct decarboxylation of tyrosine to tyramine by L-aromatic amino acid decarboxylase with subsequent liberation of noradrenaline, i.e. a central 'cheese effect', is responsible. The facts that L-tyrosine is a relatively poor substrate for this enzyme (Lovenberg *et al.* 1962) and that human brain is characterized by highly variable enzyme activity (Sacks *et al.* 1979) provide a likely explanation for the capricious nature of the clinical response to L-tyrosine. Although polar compounds like tyramine are traditionally unable to cross the blood–brain barrier (Weil-Malherbe *et al.* 1959), we cannot rule out the possibility that tyramine traverses this barrier in low concentration, to a degree varying from individual to individual. The single case study of Pickar *et al.* (1979) may well be instructive in this regard: they found that the intravenous administration of tyramine to a patient with bipolar affective disorder led to a lightening of affect.

If, then, the beginnings of a case for a central counterpart of the 'cheese effect', i.e. central noradrenaline liberation by tyramine, being responsible for the positive response to MAO inhibitor

therapy, are beginning to emerge, it may even be possible to bolster it with some further evidence. Sandler *et al.* (1979) recently provided data pointing to a deficit of endogenous tyramine production in patients with depressive illness. If such deficient production is also manifest centrally, then we may be one step nearer to identifying a further factor in the pathogenesis of depressive illness and, indeed, to rehabilitating, albeit in a new guise, the hard-pressed (Baldessarini, 1975) noradrenaline hypothesis of depression.

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