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Annotation

Monoamine Oxidase Inhibitors: Rehabilitation from Recent Research?

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For a long time, monoamine oxidase inhibitors (MAOIs) have been the Cinderella drugs of psychopharmacy. Although they were introduced just before the tricyclic antidepressants (TCAs), they rapidly became second-line treatments. Several factors contributed to this, in particular the dietary restrictions, the scattered reports of death from overdose and/or toxic interactions, and the unfavourable reports on the efficacy of phenelzine in depression from, among others, the Medical Research Council trial (1965). For a number of years afterwards, prescription of these drugs was limited to a few enthusiasts. More recently, however, their popularity has increased owing firstly to a re-evaluation of their effectiveness in tricyclic-resistant depression and in anxiety disorders, and secondly to growing awareness of the exaggerated claims made about their dangerousness (Pare, 1985).

Therapeutic re-evaluation and new indications

Depression

One of the earliest reports on the antidepressant actions of MAOIs noted their effectiveness in treating atypical depression (West & Dally, 1959), and these findings have been subsequently confirmed and extended (see review by Quitkin *et al* (1979) and Nies & Robinson (1982)). In contrast to patients with endogenous or melancholic depressions, these present a range of phobic, anxious or hysterical symptoms, excessive tiredness and hypersomnia, somatic complaints, and reversal of diurnal variation in mood, sleep pattern, and energy. MAOIs appear to be more effective than TCAs in treating patients with the above symptom profiles. This has been substantiated in a number of placebo-controlled trials comparing phenelzine with imipramine (Liebowitz *et al*, 1985, 1988) and amitriptyline (Robinson *et al*, 1985), which reported that patients with atypical depression responded better and more rapidly to phenelzine. The efficacy of MAOIs in endogenous or melancholic depression is less well proven, and while it is clear that a number of such patients do respond (McGrath *et al*, 1984), it is hard to predict them from clinical profiles.

Anxiety

In this area, as in depression, the observations of the earliest researchers have been rediscovered under the impetus of the newer diagnostic classifications of anxiety. Sargant & Dally (1962) and King (1962) both reported the value of a range of MAOIs in the treatment of anxiety disorders. Subsequent work in the UK in the 1970s (Kelly *et al*, 1970; Lipsedge *et al*, 1973; Tyrer *et al*, 1973) emphasised their value in disorders in which phobic anxiety was a major component. The resurgence of interest in phobic disorders, as redefined in DSM-III-R (American Psychiatric Association, 1987) – and especially the growing importance of panic disorder – have stimulated research interest in the USA. The original observations of Kelly *et al* (1970) that these drugs primarily reduced anxiety attacks have been well substantiated (Sheehan *et al*, 1980; Buiges & Vallejo, 1987). Although other effective drug treatments exist (e.g. TCAs, benzodiazepines), phenelzine is at least as efficacious as these, and perhaps more so (Sheehan *et al*, 1980). It has the additional advantage that, unlike TCAs, it does not seem to provoke anxiety attacks at the start of treatment. Furthermore, in contrast to the benzodiazepines, there is no good evidence of the development of tolerance, and few reports of acute withdrawal reactions (Lydiard & Ballenger, 1987; Dilsaver, 1988).

Perhaps more surprising are the accumulating reports that MAOIs are of considerable value in patients with social phobia (Liebowitz *et al*, 1985, 1986), a condition previously considered to be more appropriately treated by behavioural rather than psychopharmacological means (Marks, 1985). Thus, it appears that MAOIs have considerable anti-anxiety properties, although this effect is not immediate, and in contrast to that of the benzodiazepines, it appears gradually over several weeks of treatment. The neuropharmacological basis for this is discussed below.

Other disorders

In comparison with depression and the anxiety disorders, little has been published on the effects of MAOIs in other psychiatric conditions. Recent reports

suggest that MAOIs may be helpful in bulimia (Walsh *et al*, 1984; Kennedy *et al*, 1985), in patients with chronic pain and coexistent depression (Davidson & Raft, 1985), and in obsessive–compulsive disorder (Jenike *et al*, 1983). Finally and perhaps surprisingly, immediate benefit was seen in a group of patients with attention deficit disorder and hyperactivity treated with a range of MAOIs (Zametkin *et al*, 1985); this argues for a specific stimulant-like action of MAOIs in this condition.

Newer MAOIs

The pharmacology of MAOIs has advanced significantly in two directions in the last 20 years. The first significant development was the separation of type A and type B monoamine oxidase (MAO) isoenzymes, and the subsequent synthesis of inhibitors selective to each. Type A MAO preferentially metabolises noradrenaline and serotonin, whereas type B has selectivity towards dopamine, and therefore is not involved in the 'cheese reaction' to dietary tyramine (Blackwell, 1963). This offered the hope that MAO-B inhibitors would be safe antidepressants (Quitkin *et al*, 1984), but unfortunately, they appear to be effective only at doses where it is likely that the specificity to MAO-B would be lost when substantial MAO-A inhibition might also occur (Sunderland *et al*, 1985). However, these findings are useful in suggesting that changes in either noradrenaline or serotonin may be responsible for the mood effects of MAOIs. There is good evidence that the prototypical MAO-A inhibitor, clorgyline, is an effective antidepressant, and at least as effective as TCAs (see Murphy *et al*, 1987). It is unclear whether it offers any advantage in terms of side-effects or therapeutic response over the presently available non-selective MAOIs, although it has been claimed to be effective even at low doses in patients with bipolar affective disorder (Robinson *et al*, 1985).

While the selective MAO-B inhibitors (pargyline, selegiline) probably have limited use in psychiatry, there is hope that they will be of benefit in conditions of dopamine deficit, such as Parkinson's disease (Schachter *et al*, 1980); deprenyl (selegiline) is presently licensed in the UK for this use.

The second major advance is in the development of short-acting (reversible) selective MAO-A inhibitors (Youdim & Finberg, 1985). These differ from previously available MAOIs, which bind irreversibly with the MAO enzyme (Singer & Salach, 1981), and which require synthesis of new enzyme to restore function. Such drugs include moclobemide and brofaromine, which appear to have antidepressant actions equivalent to those of TCAs (Larsen *et al*, 1984; Bieck & Antonin, 1988; Schiwy *et al*, 1988). They have much shorter functional half-lives than conventional MAOIs (Schoerlin *et al*, 1987), which should make them safer and easier to use. The reversible nature of their inhibition could also minimise reactivity to tyramine, since in theory, this amine could compete with the MAOI, and thus some would be metabolised in the periphery (Youdim & Finberg, 1985). Further studies are needed, however, to confirm the evidence that these new compounds have less propensity for potentiation of tyramine (Korn *et al*, 1984) and to investigate whether they are as effective as conventional MAOIs in treating tricyclic-resistant cases of depression.

The potential for a third significant advance is in the development of targeted MAOIs. At the simplest level, this involves inventing new drugs that work only in the brain. For instance, a pro-drug (MD 72394) has been developed that is activated by decarboxylation; when administered with a peripheral decarboxylase inhibitor, MAO inhibition can be limited to the brain (Palfreyman *et al*, 1984). A refinement of this is the synthesis of MAOIs that are selective for specific neurons: these would be substrates for selective uptake sites, and therefore would be concentrated in the appropriate neurons – an example may be amiflamine, which shows some selectivity for serotonergic neurons (Ask *et al*, 1984). Finally, an MAOI that was also an uptake blocker could be of great benefit, as the uptake blockade would both potentiate the MAOI as well as reduce access of tyramine to the neurons.

MAOI combination treatments

These have long been accepted to be some of the most powerful treatments in psychopharmacology. For depression, combinations with TCAs (Sargant, 1963; Sethna, 1974), lithium (Nelson & Byck, 1982), or *l*-tryptophan (Coppen *et al*, 1963; Baldessarini, 1984) have proved to be effective in resistant cases. Although the benefits may be great, risks may be enhanced, and therapy of this type should be carefully supervised. The combination with TCAs seems the most hazardous, especially with the more selective serotonin reuptake blockers, e.g. clomipramine (Beaumont, 1973) and fluoxetine (Graham & Ilett, 1988). Animal pharmacological work by Marley & Wozniak (1983) showed that it is the TCAs with serotonin reuptake inhibition which are especially dangerous. However, once established, it appears that those tricyclics which significantly inhibit noradrenaline reuptake lower the risk of

'cheese reactions' by prevention by tyramine uptake (Pare *et al*, 1982). The newer MAOIs, especially the reversible ones, should be safer in such combinations, although studies are needed to confirm this.

In the anxiety disorders, the combination of MAOIs and benzodiazepines is often highly effective (Tyrer, 1982). A sensible strategy would appear to be one in which a short course of a benzodiazepine is used for its acute anxiolytic action, while effective MAO inhibition is obtained; the benzodiazepine can then be reduced and stopped after a few weeks with minimal risk of tolerance or withdrawal symptoms.

How do MAOIs work?

Although from a number of different chemical series, all MAOIs interact with the active site of MAO to inactivate this enzyme, in both brain and peripheral tissues. Some also have other effects; for instance, tranylcypromine has amphetamine-like properties (Tyrer, 1982). The inhibition of MAO leads to accumulation of monoamine neurotransmitters (Spector *et al*, 1963), which is presumed to initiate the antidepressant effects of these drugs. Indeed, increased throughput of noradrenergic synapses can be demonstrated (Murphy *et al*, 1986). However, since a therapeutic response takes several weeks to appear, the acute changes are clearly not a sufficient explanation for it. Thus it has been suggested that adaptive changes in receptor number or second-messenger function may be critical (see Murphy *et al*, 1984; Youdim & Finberg, 1985).

More recently, ideas have focused on pre-synaptic mechanisms. Studies from the US National Institute of Mental Health have demonstrated that MAOIs substantially attenuate whole-body noradrenaline turnover (Hauger *et al*, 1988) – an effect presumably mediated by increased autoreceptor inhibition and consequent reduction in noradrenergic neuronal activity (Blier & de Montigny, 1987). It has been suggested that this increases noradrenergic synaptic efficiency (Ross *et al*, 1985; Rudorfer *et al*, 1987), inefficiencies of which may underlie depression (Rudorfer *et al*, 1985). This change could also contribute to their effectiveness in panic disorder, although a different underlying pathology (e.g. paroxysmal noradrenergic overactivity) is likely to exist in these patients (Charney & Redmond, 1983; Charney & Heninger, 1986). We have suggested that TCAs work in panic disorder by stabilising noradrenergic function (Nutt & Cowen, 1988; Nutt & Glue, 1989), and the pre-synaptic effects of MAOIs are consistent with this theory.

Conclusion

MAOIs clearly still have a place in the treatment of depressive and anxiety disorders, both as alternatives to the TCAs, and as first-line choices in their own right in some conditions (e.g. atypical depression). One of the major problems – irreversibility of action – appears to have been overcome with the imminent introduction of newer drugs, such as moclobemide and brofaromine. Although initial claims that these compounds will be significantly less likely to show interactions with foodstuffs require more comprehensive clinical evaluation, if these are correct, they could lead to the full rehabilitation of MAOIs.

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