DOPAMINE ELEVATION MAO-A, B OR BOTH?

I particularly acknowledge the assistance of Professor John Finberg in preparing this commentary.

INTRODUCTION

There is an enduring lack of appreciation of the fact that inhibiting both subtypes of MAO elevates human brain levels of dopamine to a greater extent than selective blockade of MAO-B. That being the case, why are the anti-parkinsonian drugs — selegiline and rasagiline — selective for MAO-B?

The answer to this question is rooted in the historic concerns about the dangers of MAOI drugs — see this commentary about the history of MAOI drugs. Both the development of the (weak) selective reversible inhibitor of MAO-A, moclobemide*, and the development of rasagiline, the irreversible selective inhibitor of MAO-B, represent attempts to minimize perceived disadvantages resulting from the tyramine pressor response.

Evidence

The direct evidence comes only from animal experiments, so far. Experimental work in humans is now possible (PET studies) but has not yet been undertaken. It seems people are too busy doing 'systematic reviews' and 'meta-analyses' to do any good original work. As Professor Ioannidis recently pointed out there are now more meta-analyses of antidepressant trials than actual original trials! What a farcical situation research has now become — it is like a ploughman going up and down the field over the same furrow, over and over.

30/10- MAOIs need to inhibit MAO by close to 100% in order to be effective, because MAO is in a large excess.

Nature rarely supports inefficiency, so why it is in such excess? what is it doing? is there a hypothesis as to explain this?

MAOIs increase the free amine within the neurons, since the amines are constantly synthesized, and the vesicular storage capacity is limited. Then the concentration gradient for reuptake from the synapse back to the internal compartment is altered, there is a smaller concentration gradient synaptic to inside, so net reuptake is reduced, and more amine remains in the synaptic space, leading to a greater effect at the receptors[1]. In various studies both at Finberg's lab and others, they found that MAOI treatment does not affect the initial rate of amine reuptake, but in vivo, using microdialysis, we find an increase in free amine in the extracellular space. (I enclose an article on this).

Microdialysis shows a small increase in striatal resting dopamine level in intact rats but a potentiation of the depolarization-induced release. Selegiline behaved similarly. By comparison, clorgyline caused a massive increase in KCl-induced DA[2].

In the DA lesioned striatum, rasagiline produced a small increase in L-dopa-induced DA release, but clorgyline increased this many fold [3]

* It is regrettable that other similar MAO-A selective drugs developed as prospective ADs never made the cut and have never been widely or extensively used in clinical practice. It is particularly regrettable because a couple of them were more potent than moclobemide, which is so weak as to be of doubtful utility — even in overdose it cannot do anyone any harm.

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A similar result was reported about the same time by Abercrombie (attached). Other microdialysis studies in **rats** have shown the greater effect of MAO-A than MAO-B inhibition on DA levels — it is not valid to assume the same happens humans.

Finberg's paper on rasagiline and other brain amines in rats, shows the greater effects of clorgyline and tranylcypromine than rasagiline on DA metabolism. I quote JF

> Because of the cheese effect no one has been prepared to give MAO-A or A+B inhibitors to patients, not only because of the tyramine problem but also because of interaction with L-dopa. I suppose that if an ambitious clinician was prepared to start his patient (advanced PD, not responding to L-dopa) on an A+B inhibitor, and then give very small doses of L-dopa initially, it might be possible to see a good clinical effect, but none are prepared to do this. It would be possible using PET or SPECT to look at effects on in vivo DA levels in people after MAO-I but again no-one has done this yet [2-5].
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> To account for this apparent mismatch, we have hypothesized that MAO-A protein may be translated in the cell body and segregated to the axon terminals [6]; this hypothesis is supported by the discovery that MAO-B is absent from the mitochondria of the axon terminals (Arai et al., 2002), as well as by the documentation of MAO-A mRNA in the 5-HTergic cells (Luque et al., 1995, 1996; Jahng et al., 1997; Filipenko et al., 2002; Wylie et al., 2010). The proposed compartmentalization may facilitate the specific degradation of 5-HT in the synaptic terminal; further, the expression of MAO-B in the somata of 5-HTergic neurons may serve protective functions for 5-HT.

References

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