ATTENUATION OF THE PRESSOR RESPONSE TO TYRAMINE BY NRIS

Exordium[1]

> Progress, far from consisting in change, depends on retentiveness. Those who cannot remember the past are condemned to repeat it.
> ~ Santayana, G. The Life of Reason 1905

I frequently find myself saying that history is the key (and I have used that Santayana quotation more than once), and this is exemplified by the enduring misunderstandings of the interactions between MAOIs and the old TCAs; two of the TCAs have sufficient SRI potency to precipitate serotonin toxicity (but IMI is weak and 'on the cusp'). Although the basic pharmacology research that would have enabled an understanding of the relevant interactions, had people studied it in depth, did exist at the time that Pare was writing about MAOIs (1980s) and the pressor response (see my 1998 review [1]), it was either overlooked, or not understood. These mis-understandings have continued creating a widespread disinclination to use MAOIs.

I should make it plain to readers that misunderstandings of the interactions between MAOIs and TCAs are still contained in many, perhaps even most, of the standard texts that are consulted by doctors. This includes many standard textbooks — most egregiously the latest (5th) edition of the APA book[2], journal review articles, the Physician's desk reference, MIMs, the British national formulary, and other similar sources.

Few standard sources have both correct and accurate information about MAOIs.

I did cover this topic briefly in my recent MAOI review [2], but space considerations, and fear of stirring up referees to unnecessary and tedious discussions, disinclined me from covering it as comprehensively as I do here.

It is thus ironic that the other main property of at least some (but not all) of the 'TCAs'[3] is that they have significant potency as NRIs (see my TCA review for details and receptor affinity data [2]), and that NRI property protects patients from the pressor response induced by ingesting tyramine (with, or without, MAOIs). Indeed, it can be assumed that if a drug is not able to strongly inhibit the tyramine pressor response, then it is not an effective NRI (cf. duloxetine and venlafaxine, which both 'fail' that test.

The work by Pare et al. on blocking the MAOI-pressor response, done in the early 1980s, attracted little attention, was little-cited, and Pare himself underrated the results because he did not understand the data: Nathan Kline, who had significant input into those papers, had died in early 1983. No-one else took up the baton. Thus, the work disappeared beneath the snow-storm of trivial papers,

[1] I like this word; I think it is time to rehabilitate it. It means more than 'an introduction', it also insinuates putting things in (historical) context.
[2] despite an assurance to me from the editors that they were going to correct their previous mistakes that I had detailed for them in the 4th edition.
[3] This is a good illustration of why we should adopt neuropharmacology-based nomenclature [18-20]: because the TCAs are a decidedly non-homogenous group of drugs. Regarding them as such, as has habitually been done, strikingly illustrates the misunderstandings and misconceptions that thereby arise. From a pharmacologist's standpoint grouping them together makes no sense, no sense.

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mostly drug-company sponsored RCTs of the super new drugs, showing A>B>C>A — 'Penrose stairs with drugs', as I have previously called it.

> RCTs show A>B>C>A — 'Penrose stairs with drugs'

This commentary clarifies and reinterprets the results Pare obtained in the light of more recent knowledge of receptor pharmacology — especially because MAOIs are undoubtedly still of great therapeutic importance.

Attenuation of the pressor response by NRIs

Tyramine enters the presynaptic neuron by active transport by the NAT, its ingress is inhibited by NRIs (in proportion to their potency), which therefore inescapably attenuate the tyramine pressor effect, because it is dose-related. This was demonstrated experimentally in animals in the early days of pharmacology, by famous pharmacologists, like Sjoqvist and Brodie [3-5], and others.

Here are the relevant papers I have on file, 'for the record', relating to the effect of NRIs on the tyramine pressor response [5-26] — a great many papers to become lost and forgotten you might think.

That would lead to the confident prediction that this would remain the case in humans, even when the pressor response has been potentiated by MAOIs, because that has been experimentally demonstrated in animals [27-29].

The first people to specifically articulate and explore the potential to protect humans from the tyramine-induced pressor response during MAOI-treatment appear to have been Pare and Kline (winner of *two* 'Lasker' awards) [27] with experiments in rats (using TCP and DMI). Kline was a co-author with Pare in the paper on the 'cheese effect' in 1982 [30]. This paper explored the clinical reality of its relevance, which was clearly demonstrated, in a sample of patients being treated for depression who were given an intravenous challenge with tyramine. The six patients who were receiving the weak TCA-NRIs dothiepin (aka dosulepin, K_i ~30) and trimipramine (K_i 2,500 — i.e., totally inactive as an NRI, it is an anti-histamine, like doxepin) showed no significant reduction of pressor sensitivity (as expected), whereas patients on amitriptyline showed definite attenuation of the pressor response. NB. They did also measure levels of desmethyl-amitriptyline (aka nortriptyline), the metabolite of amitriptyline. NTP is more potent as an NRI (K_i ~3), vs amitriptyline (K_i ~60), it is only the NTP levels in this work that are relevant). There were no patients taking desipramine (a still more potent NRI (K_i ~1) in this group [30].

Unfortunately, their second paper [31], without Kline (who died in Feb 1983), which did include one patient taking desipramine, was less helpful than it might have been. This was because, at that time, clear data on the relative potency of the drugs used (amitriptyline, nortriptyline, imipramine, desipramine) was not available, or was inchoate [32-34]. Pare et al. do not appear to have had a clear awareness of their relative NRI potency. It is striking, from their data, that patient '7', who had a therapeutic blood level of desipramine (of the drugs they used, that was the most potent NRI at a K_i ~1), was completely immune to any elevation of blood pressure, even after 100 mg of tyramine. The three patients who had low blood levels of nortriptyline (50µg/l or less) still demonstrated reduced pressor responses, although they did have some elevation of blood pressure.

Despite Pare's perception that his study was unsuccessful, my reinterpretation, with a current understanding of the K_i of these drugs at the NAT from modern HCR data, indicates these results are strongly positive — that being obvious without statistical analysis. They indicate the threshold level of substantive

effectiveness is, not unexpectedly, around a blood level of NTP of >50 µg/l (i.e., around the accepted minimum therapeutic level).

Their imperfect understanding about receptor affinities impaired their interpretation of the results.

We also know, from extensive subsequent research, that NRIs with *high* affinity (around a K_i of 5, or less) for the NAT (e.g. reboxetine, desipramine, protriptyline and nortriptyline) have been demonstrated to completely block, or at least markedly attenuate, the pressor response to tyramine at clinically relevant doses [5-11]. And see also [9, 12-20].

This leads to a confident conclusion about an old and bitter-sweet irony: combinations of (non-serotonergic) TCAs, or specific NRIs, with MAOIs, do not have a risk of significant or serious interaction. They make MAOIs safer by attenuating the pressor response to tyramine (or any other NA releaser): tyramine-sensitivity is markedly reduced if a *potent* NRI is added to the regime.

> NRIs make MAOIs safer by attenuating the pressor response to tyramine

That is not 'just a theory', as I have heard some describe it; it is pharmacological and clinical fact, first investigated 50 years ago, and attested to by the above numerous and replicated experiments in both animals and humans.

The only question up for debate and investigation is whether they do this predictably and reliably, and to a sufficient extent to allow relaxation of the tyramine diet recommendations.

I suggest the failure to understand the literature, besides reflecting insufficient knowledge of pharmacology, is also a reflection of the failure to recognise the clinical and research utility of 'neuroscience-based nomenclature' — indeed, the confusion surrounding TCAs must be one of the most powerful arguments for the rationality and utility of the neuroscience-based nomenclature approach.

As an expert in serotonin toxicity I note that the difficulties experienced by clinicians and researchers, such as Pare and his colleagues, were substantially contributed to by their failure to understand serotonin toxicity, which is evidenced above by their use of imipramine with an MAOI (definitely contra-indicated): at least they had the excuse that it was emerging knowledge, we do not — we have no excuse.

The strategy of using an NRI to attenuate the pressor response might be usefully employed more frequently. It rates as another of Nathan Kline's great ideas, but sadly one which was forgotten.

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