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Recent Developments in the Regulation of Monoamine Oxidase Form and Function: Is the Current Model Restricting Our Understanding of the Breadth of Contribution of Monoamine Oxidase to Brain [dys]Function?

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Abstract: Historically, much of the focus on monoamine oxidases and their substrates has been in the area of depression and the monoamine neurotransmitters serotonin (5-hydroxytryptamine), noradrenaline, and to a lesser extent, dopamine. With both forms of monoamine oxidase (A and B), the production of hydrogen peroxide as a byproduct of the reaction between the monoamine oxidases and their monoamine substrates has also implicated monoamine oxidase-sensitive events in intrinsic cell death pathways, particularly those centered on oxidative stress and peroxyradical-mediated mechanisms. Consequently, and perhaps not unexpectedly, the inhibition of monoamine oxidase has been considered as adjunctive therapy in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, both of which involve a significant oxidative stress component. Yet the literature also provides ambiguities; indeed, not all of the functions of monoamine oxidases are dependent on catalytic activity nor can they all be ascribed to expression levels of the monoamine oxidase protein *per se*. Recent reports strongly suggest that the functions of monoamine oxidases also rely on post-translational modifications, epigenetic influences, interactions with other proteins, the cell phenotype and its localization to specific subcellular compartments. These recent developments certainly complicate the issue, yet they need to be duly considered when implicating monoamine oxidases and their inhibitors in both *in vitro* and *in vivo* pathological contexts.

Keywords: Monoamine oxidase; oxidative stress; apoptosis; phosphorylation; splice variant; catalytic independent; mitochondria; nucleus; Alzheimer disease; Parkinson's disease.

INTRODUCTORY COMMENTS

Neurodegenerative diseases are progressive diseases with symptoms that usually manifest following profound and irreversible cellular damage. In certain instances, such as with Huntington's disease, family history and genetics play an unequivocal role in the onset of the disease. In this particular disease the number of the trinucleotide 'CAG' repeats in exon1 of the *huntingtin* gene is inversely correlated with age of onset, i.e. the more repeats there are, the earlier and the more aggressive the disease [1, 2]. In other cases, the neurodegenerative diseases only emerge in the aged population, although there is debate as to whether the diseases, for example Alzheimer's Disease (AD), are 'age-related' or 'aging-related' [3]. The current review will examine the contribution of the enzyme, monoamine oxidase (MAO[1]), to mental health and to neurodegenerative disease with a particular emphasis on its role in the pathology of AD. We will provide some of the basic information required to familiarize the reader with MAO and we will examine some of the evidence, albeit oftentimes ambiguous, regarding the role(s) of MAO in neurodegeneration. We will occasionally include discussions of other pathologies in which MAO has been implicated to support or, in some cases, apparently disagree with our arguments. It is known that there are two isoforms of MAO, denoted MAO-A and MAO-B, with distinct potentials for contributions to neurodegeneration. Several recent reviews have examined the roles of MAO-B and some of its selective inhibitors, including dual/multi-target (e.g. MAO and acetylcholinesterase) inhibitors, in Parkinson's disease- and in AD-related dementias [4-7]. In addition, an overview with a particular focus on the contribution of cell signalling and pro-/anti-apoptotic pathways in MAO-A inhibitor-mediated neuroprotection was recently published [8]. Rather than simply iterating the contents of these excellent reviews, the present review will comment on less obvious contributions by MAO-A, but the details will be contrasted and compared with MAO-B-related information when appropriate. While some of our comments might be provocative, they are certainly not intended to be critical. Our objective is to consider recent developments in the field, how these developments fit into the existing literature and, by extension, to provide novel perspectives on unintentional biases in the literature. We hope to highlight biases that might have steered the field away from a deeper understanding of MAO form and [patho]physiological function, and how these bi-

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[1]The consensus for gene and protein nomenclature will be used throughout this review. Upper case letters will be used to designate the protein, regardless of species (e.g. MAO-A). Instances where upper case letters are italicized will refer to the human gene (for example *MAO-A*), whereas the mouse/rat gene will be italicized and will only have the first letter in upper case (for example, *Mao-A).* All mRNA and cDNA will follow the gene symbol formatting convention, for example *MAO-A* mRNA and *Mao-A* cDNA.

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ases could have led to some of the intricacy and ambiguity in the associated literaure.

THERE ARE TWO ISOFORMS OF MAO

MAO is a flavin adenine dinucleotide (FAD)-containing amine oxidase whose putative physiological function is the oxidative deamination of biogenic and xenobiotic monoamines. The reaction with MAO uses oxygen and results in the generation of the short-lived corresponding aldehyde as well as ammonia and hydrogen peroxide (H_2O_2) as reaction by-products. If these by-products are not detoxified, their accumulation is invariably toxic. For example, if H_2O_2 is not inactivated by glutathione peroxidase, then it can be converted by transition metal-mediated Fenton reactions to toxic hydroxyl radicals that can initiate lipid peroxidation and cell death [9]. This is exacerbated in situations where free radical scavenging or buffering systems may be compromised such as in the elderly [10] and/or during neurodegenerative processes [11]. There is strong evidence that oxidative stress plays a crucial role in the initiation and progression of AD [12, 13]. This is supported by the observation that reactive oxygen species, such as H_2O_2, can mediate the neurotoxicity associated with the β-amyloid peptide [14, 15] and by the elevated oxidative damage in transgenic mouse models of AD [16, 17].

MAO, initially named tyramine oxidase given its ability to deaminate tyramine [18], was subsequently given the more inclusive designation, MAO, once the biogenic monoamines epinephrine, norepinephrine, serotonin (5-hydroxy tryptamine, 5-HT) and dopamine were also identified as substrates [19]. Two isoforms of MAO, i.e. MAO-A and MAO-B, have been identified according to differences in their specificities for inhibitors [20-22] and substrates [22-25]. MAO-A is inhibited by clorgyline at low nanomolar concentrations and this irreversible inhibitor has been used to estimate the turnover rate of MAO-A to be 2 days and recovery of MAO-A activity and protein levels after treatment with clorgyline to occur within 14 days [26]. MAO-B is inhibited by the irreversible inhibitor selegiline (l-deprenyl) at low concentrations, and studies using radiolabeled selegiline estimate the half-life of MAO-B in human brain to range between 30 and 40 days [27, 28]. Serotonin, noradrenaline, and adrenaline are preferential substrates for MAO-A, and benzylamine and β-phenylethylamine for MAO-B, yet there appears to be a functional mismatch between the specific isoform and its preferred substrate. Indeed, MAO-A (mRNA and protein) is highly expressed in catecholaminergic neurons of the locus coeruleus (and it is not found in serotonergic neurons), whereas MAO-B (mRNA and protein) is preferentially expressed in serotonergic neurons of the raphé nuclei, in histaminergic neurons and in glial cells [29-36]. This pattern of mismatch is conserved across species and is thought to be a means of mitigating off-target effects by amines diffusing in from adjacent regions/synapses [32, 33]. This notion is clearly illustrated by the fact that MAO-A is localized to noradrenergic nerve terminals of the rat pineal gland, while MAO-B is concentrated in juxtapositioned (serotoninergic) pinealocytes [37]. Dopamine is a substrate for both isoforms in humans [38, 39] and preferentially for MAO-A in rats [23, 40]. In most species, dopamine, tyramine, and tryptamine are common substrates for both MAO isoforms [22, 41, 42]. However, these substrate specificities are not absolute as both enzymes show broader substrate preference at high substrate concentrations [24]. This is an important consideration as MAO-B is known to play a central role in dopamine degradation in glia/ astrocytes, yet MAO-A has also been detected in glia [43]. This, in combination with the therapeutic potential of non-selective MAO-A/B inhibitors [44], suggests that glial MAO-A could contribute to dopamine degradation when levels of this substrate are in excess [45].

The role of MAO-B in neurodegeneration has been widely studied and recently discussed [4-7, 46]. In contrast, the degradation of serotonin, noradrenaline and dopamine (and any associated cellular dysfunction) by MAO-A has been historically associated primarily with the neurobiology, and treatment, of depression [44, 47, 48] rather than any neurodegenerative phenotype. However, aspects of depression and progressive neurodegeneration could certainly rely on overlapping molecular mechanisms and could account for the recent spate of reports in the literature associating comorbid depression with many other disorders, including an increased risk of dementia and AD.

MAO-A and MAO-B are encoded by two different genes [49] located tail-to-tail on the Xp11.23-Xp 22.1 short arm [50, 51]. Both genes are comprised of 15 exons that span at least 60kb with an identical exon-intron organization that suggests duplication of a common ancestral gene [52]. Tissue-specific differences in the regulation of *MAO-B* transcription could rely on polymorphisms including a C-1,114T in the 5′ region, a variable number 'GT' repeat in intron 2, and a G-to-A point mutation in intron 13 of the *MAO-B* gene [53]. A variable number tandem repeat (VNTR) polymorphism in the *MAO-A* promoter has five alleles containing 2, 3, 3.5, 4, or 5 copies of a 30-bp tandem repeat. Of these alleles, only those with three or four copies of the VNTR are common in different human populations, and those with 3.5 and 4 copies of the VNTR are transcribed much more efficiently than the alleles with 3 and 5 repeats [54]. These differences in transcription efficiency could account for the significant variability in MAO-A activity in different human skin fibroblast cultures [55] and could account for risk in Parkinson's disease [56], AD [57], impulsivity [58] and other neuropsychiatric disorders [59], although there is still debate as to the role of VNTRs in mood and depression [60]. It should be noted that imaging studies have clearly demonstrated that seemingly modest increases in MAO-A binding capacity (i.e. 34%) can account for the depressive phenotype in treatment-naive depressed patients [61] as well as the depression associated with post-partum [62] and following smoking cessation [63]. It is interesting that prenatal exposure to cigarette smoke, which has long been known to contain an MAO inhibitory substance [64], is consistently associated with increased rates of behavioural problems, irritability, and attention-deficit/hyperactivity disorder [65], adolescent onset of drug dependence [66], and risk of violent offenses [67] and criminal arrest [68] in the offspring. MAO-B inhibition could clearly be contributing to the reduced incidence of Parkinson's disease in smokers [69] (with a possible predisposition to smoking by any one of the polymorphisms in the *MAO-B* gene already discussed [53, 70]). However, the neuropsychiatric and conduct disorders men-

tioned above would be more in keeping with a reduction in MAO-A availability as corroborated by recent neuroimaging studies [63, 71]. This long-lasting effect in the offspring strongly suggests an epigenetic modification, as does the much earlier finding of a region-dependent "daily rhythm of MAO" in human brain extracts [72]. An epigenetic component to the regulation of MAO function is now a strong consideration in the relevant literature. Indeed, hypermethylation of the *MAO-B* promoter has recently been linked to smoking [73] and epigenetic regulation of the *MAO-A* gene has been associated with several behavioural phenotypes [31, 74, 75] including a gender-specific propensity for nicotine dependence [76]. Tranylcypromine, a non-selective MAO inhibitor, is also a potent inhibitor of the histone demethylase, LSD1 [77], while the deacetylation (and activation) of the *MAO-A* promoter has been linked to anxiogenic behaviour in the rat [31] and diurnal fluctuations in mood and MAO-A appear to be linked to components of the circadian clock [78]. These transient changes in MAO-A expression associated with epigenetic influences are not in accord with the earlier estimates of turnover rates and half-life for MAO-A that fall within the range of days to weeks [26]. Finally, it is vital to understand that the *MAO* gene could undergo tissue-specific splicing, as proposed for tissue differences in imidazoline binding [79] and as shown to occur following insertional mutagenic disruption of the *Mao-A* gene in mice [80]. We will re-visit the potential contributions by splice variants in our subsequent discussion.

RECENT OBSERVATIONS REVEAL AN EFFECT OF MAO-A THAT IS INDEPENDENT OF ITS CATALYTIC ACTIVITY

Exon 12 is the most conserved exon between *MAO-A* and *MAO-B* (and across species), ostensibly because of the importance of the functional domain that it encodes, i.e. a 33-amino acid expanse that contains the Ser-Gly-Gly-Cys-Tyr pentapeptide that flanks the cysteine406 residue (Cys406) to which the cofactor FAD covalently binds [81]. It is important to note that FAD is not an absolute requirement for full functionality of the MAO-A enzyme, but that it might play a substantive role in maintaining the structural integrity and stability of the enzyme [82, 83]. This seemingly minor observation has a significant impact on the interpretation of MAO-A function. Indeed, we have recently shown that overexpression of an MAO-A protein bearing the Asp328Gln substitution (already known to inhibit MAO-A activity [84]) was able to alter cell proliferation and *de novo* DNA synthesis in the human HEK293 cell line [85]. Furthermore, this same catalytic-*dead* variant was able to induce the expression of Bcl-2 and Bcl-XL, two anti-apoptotic/pro-survival molecules that also have been associated with pharmacological *inhibition* of MAO-A [86, 87]. Interestingly, we observed similar effects in breast cancer cells overexpressing a catalytic-*dead* Cys406-substituted MAO-A variant (Mousseau, Kuski, Pennington, *unpublished data*), which, as mentioned above, would mitigate FAD binding. These data strongly suggest that MAO-A-mediated events are not necessarily predicated solely on its catalytic activity. Until recently, the basic premise was that the catalytic activity of a given sample preparation was a valid reflection of the availability and expression of MAO-A protein within the sample. With the commercial availability of relatively specific antibodies, it has become clear that this premise is flawed. Without this knowledge, the effect(s) of MAO have been attributed exclusively to catalytic reactions and not to any uncharacteristic catalytic-*independent* influences. This recent development certainly primes any debate on the exact role of MAO-A in physiological or pathological phenotypes.

Indeed, there is clear ambiguity in the relevant literature. For example, AD-related pathology is thought to rely primarily on the MAO-B isoform [88, 89] since MAO-B activity and *MAO-B* mRNA have been reported to be increased in platelets of AD patients [90, 91], as well as in the hippocampus, thalamus, and cerebral cortex, which are regions that undergo extensive neuronal cell death during AD [92, 93]. The MAO-B increase could be due to the local infiltration of glial cells in these areas as MAO-B is mainly expressed in this cell type, a significant proportion of which are found in the proximity of β-amyloid plaques (a hallmark of AD pathology) [32, 88, 94]. MAO-A activity and *MAO-A* mRNA are also reported to be elevated in several areas of the AD brain including the occipital cortex, frontal lobe of neocortex, parietal cortex, and locus coeruleus [93, 95, 96] as well as in the caudate nucleus, thalamus and white matter [97]. Although there are also reports of decreases in MAO-A activity in AD brains [95, 98], it is important to realize that a substantial amount of MAO-A (i.e. 75-80%) needs to be inhibited before any effects on MAO-A-mediated cell function would be notable [99, 100]. Furthermore, the 17-31% decrease in MAO-A activity in the AD locus coeruleus, where nearly 70~80% of the neurons are lost [95, 98, 101], suggests that the average MAO-A activity per *surviving* neuron is actually increased [95]. Such a localized hyperactivation of MAO-A could certainly account for the accumulation of toxic MAO-mediated metabolites in AD brains [102]. Similarly, in the earliest stages of AD, such a 'hyperactivated' form of MAO-A in MAO-A-immunoreactive cholinergic neurons in the nucleus basalis of Meynert and any H_2O_2-associated increase in oxidative stress could account for the excessive loss of cholinergic neurons in this structure [98] as well as in MAO-A-expressing serotoninergic neurons in the dorsal raphé nucleus and noradrenergic neurons in the locus coeruleus [103-107]. We will re-visit the potential for a hyperactivated state of MAO-A in an AD-related context a little further on. For the moment, it is clear that estimating MAO-A activity without demonstrating corroborative changes in protein expression presents a significant bias in defining an MAO-A-mediated contribution to earlier stage disease progression based on extrapolations made using post-mortem, *i.e.* terminal stage, tissues (or any other model preparation, for that matter).

Estrogen, a neuroprotective hormone, can selectively decrease MAO-A activity and *Mao-A* mRNA levels in many brain areas [108, 109] and is thought to explain, in part, the increased risk of AD in estrogen-deficient, post-menopausal women. In serum withdrawal-induced neuronal apoptosis, MAO-A activity is selectively increased as is the activation of the pro-apoptotic enzyme caspase-3 [110, 111]. Parenthetically, impaired caspase-3/-9 expression following targeted siRNA-mediated MAO-A knockdown or R1-mediated repression of *Mao-A* transcription correlates with dysregulated apoptosis and disturbed neurodevelopment in an *in*

vitro model of embryogenesis [112]. H_2O_2 generated by MAO induces cell apoptosis in kidney [113], while MAO-A, but not MAO-B, can bind with an endogenous neurotoxin to reduce mitochondrial membrane potential ($\Delta\psi_m$), thus providing additional mechanisms linking MAO-A to apoptotic cell death [114].

Yet, as with the discussion on AD above, the role of MAO-A in normal aging is equally ambiguous [96, 115-117] and if we examine the cancer literature, where MAO-A has recently been associated with disease progression, a similar ambiguity emerges. For example, *MAO-A*/*Mao-A* mRNA is decreased across all cancers (regardless of species) and this generalized decrease is proposed as a marker for tumour progression [118]. Yet our own studies reveal that the MCF-7 cell line has virtually no MAO-A activity, but the highly aggressive MDA-MB-231 breast cancer cell line has very high MAO-A activity (Satram-Maharaj, Nyarko, Kuski, and Mousseau, *unpublished data*). MAO-A activity is also increased in experimental breast cancer in rats [119]. Paradoxical increases in serotonin (which would contradict a putative concurrent increase in MAO-A activity) in human breast cancer are thought to support tumour growth [120]. MAO-A protein is also induced in high-grade prostate cancer [121], yet, again paradoxically, serotonin is concurrently increased [122] to the point that it (e.g. serotonin) is also proposed as a valid marker for prostate tumour progression [123]. It is interesting that these reports base their conclusions on MAO-A protein expression and do not include any estimate of MAO-A activity. Without any evidence to the contrary, the MAO-A protein detected in these reports could be in an *inactive* form and, as our work with the MAO-A(Asp328Gln) catalytic-*dead* variant shows [85], could be promoting proliferative phenotypes *via* non-catalytic-based *de novo* DNA synthesis and/or induction of anti-apoptotic Bcl-2-related proteins.

Could a pool of catalytic-*dead* MAO-A protein influence brain function? While this has never been pointedly examined, there is evidence, albeit indirect, in support of this possibility. For example, our recent work demonstrates that mice expressing the AD-related M146V-substituted presenilin-1 (PS-1) protein express significantly more cortical MAO-A protein than their wildtype littermates [124]; however, MAO-A activity in these mice remains comparable to wildtype levels, which suggests that the *de novo* pool of MAO-A protein is somehow rendered *inactive*. In these PS-1(M146V) mice there is a significant disruption of cortical cytoarchitecture and laminar organization [124] that is a phenotype reminiscent of the disrupted cortical lamination observed in both prenatal PS-1-null mice [125] and postnatal PS-1 conditional knockout mice [126]. This certainly implicates the PS-1 variant itself in this phenotype. Yet, similar permanent cytoarchitectural alterations are also evident in the somatosensory cortex of MAO-A-deficient mice [80], which, presumably, do not bear a PS-1 defect. One could argue that it is the hyperserotoninergic tone that is observed in both PS-1(M146V) [124] and MAO-A-deficient [80] mice that is the commonality underlying the cytoarchitectural alteration in these different strains of mice. This, again, is a reasonable assumption given the similar cortical disruptions associated with hyperserotoninergic (but not noradrenergic) tone produced by administration of the MAO-A inhibitor clorgyline to normal mice during their first week of life [127] or to the clorgyline-induced neurodevelopmental changes observed during *in vitro* embryogenesis [112]. Yet one could also argue that it is MAO-A in its *inactive* state that is also partly responsible for these effects. While such a pool is present in the PS-1(M146V) mice [124] and an inactive human MAO-A protein does exert phenotypic changes *in vitro* [85], how would this mechanistically relate to the original Mao-A-deficient mouse generated by Cases and colleagues [80]? In fact, this is where it is important to recall that these mice were generated by insertional mutagenesis (i.e. the gene for interferon-β was inadvertently inserted antisense into exon2 –and thus disrupting normal transcription- of the *Mao-A* gene); the authors clearly demonstrated that the normal, i.e. full length, *Mao-A* transcript was absent, but that there was evidence of exon skipping, resulting in four detectable *Mao-A* splice variants. This raises the distinct possibility that 'exon-deleted' MAO-A proteins exist and while any MAO-A protein expressed in these mice would clearly be devoid of catalytic activity (not surprising, given the loss of exon2 and the portion of the FAD-binding domain encoded by this exon), the existence of inactive MAO-A protein variant(s) based on the remaining exons could certainly be contributing to various phenotypes. Finally, one must extend these suppositions to the 'knock-out' mouse used by the Shih laboratory and generated as a result of a spontaneous A863T point mutation in the *Mao-A* gene coding sequence that results in a 'TAA' codon and a premature 'stop' during the translation of the MAO-A protein [128]. There is a complete loss of MAO-A catalytic activity in these mice, as would be expected of the truncated gene product, but the possibility of exon skipping has never been examined (or excluded). Thus, the possibility that a deletion mutant MAO-A protein could be triggering such profound developmental changes in these two 'knock-out' mice and potentially exerting some influence on the proliferation of neural stem cells, as observed recently in *Mao-A*/*B* 'knockout' mice [129], is certainly intriguing and warrants further investigation. Could similar splice variants be contributing to the behavioural and cognitive phenotypes in the human kindred bearing a point mutation in exon8 of the *MAO-A* gene and functional deletion of the MAO-A protein [130]? This is also worthy of consideration.

Finally, one has to wonder whether a catalytic-*dead* MAO-A protein could affect other neurodegenerative diseases with a MAO-based causative mechanism. For example, Parkinson's disease has been historically associated with an MAO-B-sensitive etiology as well as therapies based on the putative MAO-B-selective inhibitors selegiline and rasagiline [5]. Rasagiline can also prevent the caspase activation and oxidative stress associated with an *in vitro* α-synuclein model of parkinsonism [131]. Recent work, however, has suggested that not all of the pathology in rodent models of Parkinson's disease can be ascribed solely to MAO-B [132]. Indeed, some of the neuroprotective effects of rasagiline, particularly its ability to induce anti-apoptotic proteins such as Bcl-2-related proteins [133], might reflect MAO-A-mediated mechanisms in human SH-Sy5y neuroblastoma cells [8, 87]. In fact, there is a reasonable evidence that the N-propargyl moiety (found in many MAO inhibitors, e,g, pargyline, clorgyline, selegiline, rasagiline, ladostigil)

can exert effects and activate cellular signalling cascades (particularly those associated with neuroprotection/rescue) independent of any catalytic inhibition of the targeted MAO enzyme [5, 44, 134, 135]. Although it remains to be determined whether non-catalytic properties of an off-target inhibition of MAO-A might be responsible for any Parkinson's disease-modifying effects of rasagiline or selegiline, our work on the catalytic-*dead* MAO-A(Asp 328Gln) variant and its ability to induce Bcl-2-related proteins [85] certainly support this possibility.

FIRST-GENERATION (IRREVERSIBLE) VERSUS NEWER REVERSIBLE INHIBITORS OF MAO

The substrate binding site is similar in MAO-A and MAO-B, suggesting that substrate and inhibitor specificities rely on additional influences, including the size of the recognition site itself, which is smaller in MAO-B [20]. The region contained within residues 120-220 and residues 50-400 determines substrate preference of rat liver MAO-A and MAO-B, respectively, while the region flanked by residues 220-400 appears to contribute to the relative catalytic activity towards their respective substrates [136]. Furthermore, crystal structures of the cavity-shaping loop at residues 210-216 in human MAO-A and 201-206 in human MAO-B [137] implicate these regions in substrate recognition, while residues 89-219 and 295-399 of human MAO-A may contribute to substrate/inhibitor-binding domains [137]. This is supported by the loss of catalytic activity associated with the deletion of carboxy-terminal amino acids in human MAO-A [138, 139] and explains why substitution of the carboxy-terminal amino acids of MAO-B with those of MAO-A imparts MAO-A activity and inhibitor specificity to the chimeric MAO-B/A protein [140].

The mechanism-based inhibition by irreversible 'suicide' inhibitors, such as clorgyline or selegiline, occurs following their binding to the FAD cofactor [141]. This binding triggers MAO to process clorgyline and selegiline as if they were substrates. As the catalytic reaction proceeds, a reactive intermediate covalently alkylates FAD, which effectively and irreversibly (hence 'suicide') blocks subsequent access by substrate(s). The so-called 'cheese effect' is a well-documented, noxious side-effect of irreversible inhibition of gut wall MAO-A, the resulting in the elevation in circulating levels of dietary sympathomimetic amines such as tyramine and, ultimately, tyramine-induced release of noradrenaline. Symptoms that can range from headache to a hypertensive crisis were first associated with MAO inhibitors and high tyramine content foods such as certain red wines and aged cheeses (hence 'cheese effect'). Concern about hypertensive crises led to the development of reversible inhibitors of MAO-A (RIMAs). Because tyramine still has competitive access to the active site on MAO-A and the 'cheese effect' is thus avoided, RIMAs such as moclobemide are better tolerated by at-risk populations, particularly the elderly, including those with cognitive deficits [142, 143]. RIMAs have a further advantage over irreversible inhibitors in that there is usually full recovery of brain MAO within 24 hours after cessation of treatment [144], which is an important consideration if transferring a patient onto a drug regimen that may be contraindicated with elevated levels of biogenic amines.

MAO-A expression could be a risk factor for AD [57, 93, 145, 146]. Depression, perhaps by virtue of its capacity to promote cognitive impairment, is now thought to represent a prodrome for AD-related dementia in certain patients [147-149]. This suggests that MAO inhibitors could be useful adjunctive drug therapies in AD. RIMAs are particularly efficacious in treating depression [142] and cognitive disorders [143] in the elderly, and are potential anti-apoptotic agents [150]. The selective MAO-A inhibitor clorgyline inhibits glutamate-induced excitotoxicity [151] as well as apoptosis induced by serum starvation [110, 150] and by the AD-related β-amyloid peptide *in vitro* [15], and protects against damage caused by the mitochondrial toxin malonate *in vivo* [152]. While selegiline is often used in Parkinson's disease [5], its benefit in AD patients remains a matter of debate [153, 154]. However, dual inhibitor drugs, i.e. those that target MAO and acetylcholinesterase simultaneously, have been proposed as therapeutics in AD [155], and ladostigil, which combines the activity of rasagiline and anticholinesterase activity, provides some benefit in the context of AD [156].

Depression is also a prodrome in Parkinson's disease [157] and appears to reflect reductions of noradrenaline in the locus coeruleus and of serotonin in the raphé nucleus [158]. While the combination of the older, irreversible MAO inhibitors, e.g. clorgyline and selegiline, with the Parkinson's therapeutic dopamine precursor, l-dopa, had raised some clinical concern [159, 160], the same does not hold for the newer generation MAO inhibitors. It is clear that the RIMAs moclobemide [161], brofaromine [162], and befloxatone [163], because they can be competitively displaced from the MAO-A enzyme by excess dopamine, also allow any excess dopamine (and other biogenic amine substrates) to be degraded [164]. Thus, Parkinson's patients tolerate moclobemide because of a limited 'cheese effect'[165]; because it improves motor functions [166]; and because it benefits the significant proportion of this patient population who suffer from depression [158, 167].

DO THE NEUROPROTECTIVE EFFECTS OF MAO INHIBITORS RELY SOLELY ON CATALYTIC INACTIVATION OF THE ENZYME?

While it is assumed that MAO inhibitors are usually quite selective and specific, in fact there are many reports that MAO inhibitors interact with other amine oxidases, various transaminases, decarboxylases, dehydrogenases, cytochromes, cytochrome P450s, biogenic amine receptors and transporters, imidazoline binding sites, and even sigma receptors (see reviews [168, 169]). All of these off-target interactions could certainly contribute to the therapeutic and/or adverse effect profiles of MAO inhibitors. Interestingly, the selective serotonin reuptake inhibitor (SSRI) antidepressants fluoxetine and its active metabolite nor-fluoxetine have been shown to have MAO-A inhibitory properties in the rat [170] and preliminary investigations (Mousseau, Holt and Baker, *unpublished data*) indicate that the same may hold true for human MAO-A, which could be part of the reason that the use of these SSRIs is contraindicated in patients already on an MAO inhibitor regimen.

Selegiline and rasagiline have been reported to prevent apoptotic phenotypes by up-regulating the anti-apoptotic

Bcl-2 and by down-regulating the pro-apoptotic Bad and Bax, and preventing nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase [44]. Selegiline also has been reported to inhibit the accumulation and fibrillar behaviour of β-amyloid [171] and can reverse age-related memory impairment [172]. Furthermore, pretreatment with selegiline or pargyline (also an irreversible inhibitor of MAO-B) protects dopaminergic neurons against MPTP-mediated neurotoxicity *in vivo* [173, 174] and *Mao-B* knock-out mice are resistant to MPTP-induced neurotoxicity [35]. Yet the effects of MAO-B inhibitors in some of the examples mentioned above might not rely specifically on MAO-B itself since neuroprotection was often associated with concentrations of the drug that were too low to inhibit the enzyme [175, 176]. Phenelzine, an irreversible inhibitor of MAO-A and MAO-B, also elevates brain levels of GABA, alanine and ornithine, sequesters toxic aldehydes such as 3-aminopropanal, acrolein and formaldehyde, and inhibits the enzyme primary amine oxidase [168, 177-180]); some of these actions could well be contributing to its reported neuroprotective effects [181]. Both tranylcypromine (also an irreversible inhibitor of MAO-A and MAO-B) [182] and phenelzine [183] have been shown to induce the expression of brain-derived neurotrophic factor in rat brain. Furthermore, the (S)-isomer of rasagiline (TVP1022), which possesses the N-propargyl moiety, but does not inhibit MAO-B, is neuroprotective [184], whereas rasagiline can induce both GDNF mRNA and protein expression, but an analogue devoid of the N-propargyl moiety cannot [185]. This suggests actions of these MAO inhibitors that could rely on an innate action of this moiety (as we had already discussed above), rather than on any catalytic-dependent mechanism. In addition, N-propargyl-containing compounds, such as selegiline and rasagiline, have been found to activate Bcl-2 family members, elevate superoxide dismutase and glutathione levels, up-regulate tyrosine hydroxylase and aromatic amino acid decarboxylase [134, 135, 186, 187], and interact with the mitochondrial pore complex and modulate amyloid precursor protein cleavage [44, 188, 189]. More recently, tranylcypromine has been shown to be a potent inhibitor of the histone demethylase, LSD1 [77], which implicates epigenetic regulation in its range of mechanism of action(s). Any of these mechanisms of action would certainly provide for elements of neuroprotection.

The use of the clorgyline in our recent characterization of the physical interaction between the AD-related PS-1 (M146V) protein and MAO-A revealed a surprising observation. It is known that AD-related mutations can exert changes in the PS-1 protein that, in turn, influence the conformation of the PS-1-substrate complex [190]. Perhaps by virtue of the direct interaction between PS-1(M146V) and MAO-A, a concomitant change in the structure of MAO-A could be occurring that could account for the increased potency of clorgyline we observed in the PS-1(M146V) mouse brain samples. Specific residues in MAO-A have been associated with conformational stability and access to the catalytic cleft [191]. It is therefore not unreasonable to posit that a PS-1-induced conformational change in the MAO-A protein could alter the accessibility of clorgyline to its binding site and would suggest partially interconvertible states of a single clorgyline binding site. Yet, perhaps more importantly, the increased potency of clorgyline, as a mechanism-based inhibitor, implies that the MAO-A protein in the PS-1M(146V) brain is in actual fact far more active, but is presumably being maintained in a latent, *inactive* state by the PS-1 protein. If cellular events could disrupt the physical interaction between PS-1 and this hyperactive MAO-A, then could a localized surge in MAO-A/H_2O_2-mediated oxidative stress ensue that could overwhelm free radical-scavenging coping mechanisms? Such a scenario could certainly contribute to the average increase in MAO-A activity per *surviving* neuron in vulnerable AD brain regions [95] and, as already suggested above, could certainly contribute to both the accumulation of toxic MAO-mediated metabolites in AD brains [102] as well as the loss of MAO-expressing neurons in the dorsal raphé nucleus, the locus coeruleus and the nucleus basalis of Meynert [98, 103-107].

MOLECULAR BIOLOGY HAS IDENTIFIED AMINO ACID RESIDUES AND DOMAINS THAT ARE CRITICAL FOR MAO FUNCTION

The study of the three-dimensional structure of MAO has advanced due, in large part, to investigations using selective irreversible inhibitors [192]. There is much similarity between human MAO-A and MAO-B, although a major difference is that human MAO-B is dimeric, whereas human MAO-A crystallizes as a monomer [193]. Also, the cavity-shaping loop is larger in human MAO-A than in human MAO-B or rat MAO-A (*note*: rat MAO-A crystallizes as a homodimer), suggesting that this cavity-shaping loop is involved in the process of dimerization [137]. A single amino acid residue, e.g. Ile335 in MAO-A and Tyr326 in MAO-B, dictates substrate specificity and sensitivity to selective inhibitors in the corresponding enzymes [84, 194]. Phe208 in rat MAO-A and Ile199 in rat MAO-B are also reported to contribute to substrate and inhibitor specificities [195], although mutations of these two corresponding residues in human MAOs do not alter substrate specificity [196]. Ser209 in human MAO-A also contributes to MAO-A function, but the same does not hold true for the analogous residue in MAO-B (i.e. Ser200) [197]. Other studies have identified specific lysine, tryptophan and tyrosine residues [198] and cysteine residues [199, 200] that may contribute either to FAD binding or to stabilizing the protein's conformation, access to the catalytic cleft and its substrate binding capacity [191, 198].

NON-MITOCHONDRIAL LOCALIZATIONS OF MAO PROTEINS HAVE BEEN OVERLOOKED

Recently, crystallography has revealed that the carboxy-terminal amino acids 463-506 in human MAO-A are responsible for membrane anchoring [137]. Studies on the membrane insertion region in rat liver MAO-B reveal that deletion of the 28 carboxy-terminal amino acids blocks the localization of MAO-B to mitochondria. The cytochrome b5 protein fused with the carboxy-terminal 28 amino acids of rat MAO-B is found expressed in mitochondria instead of remaining in cytoplasm [201], suggesting that the mitochondrial targeting signal of rat MAO-B is located within this region [201]. The identical region in human MAO-B appears to determine mitochondrial localization [138, 202]. It is quite

possible that these regions contain the ubiquitination site necessary for insertion of both MAO-A and MAO-B into the mitochondrial membrane [203, 204].

It is interesting that a catalytically active conformation of MAO-A is detected immediately upon interacting with the mitochondrial outer membranes, but prior to its ubiquitin-dependent insertion into the membrane [203], which suggests transient, but distinct pools of MAO-A and/or a conformational reconfiguration of the MAO-A by virtue of an interaction with a molecule already present on the outer membrane of the mitochondrion. The notion of pools of MAO-A is not novel; indeed, mitochondria are thought to contain approximately 70% of the total cellular MAO activity, whereas the microsomal fraction accounts for approximately 25% and the balance is thought to be present in a 'soluble' form [205, 206]. This distribution is not a consistent, however, as the heart seems to have a disproportionally high level of microsomal and 'soluble' MAO relative to that detected in mitochondria [207].

It should be noted that MAO activity in the lysosomal fraction was significantly lower under control conditions than when rats were treated with ^{14}C-pargyline, which indicated that the lysosomes rapidly accumulated labeled MAO [208]. These authors also noted that the rate of return of MAO was much more rapid in the microsomal fraction than in the corresponding mitochondrial fraction, suggesting that the lysosomal pool of MAO could be a 'precursor' for the mitochondrial pool, although this was never firmly established. These same authors observed that the yields of protein obtained in various fractions were not similar to the recoveries of enzyme activity or radioactivity. In retrospect, this mismatch of MAO protein and catalytic activity was perhaps the first indication of a possible post-translation regulation of MAO function.

An immunohistochemical study clearly showed that pargyline-sensitive pools of MAO could be detected in several subcellular compartments, including the rough endoplasmic reticular membranes, mitochondrial outer membranes, within the nuclear envelope and along parts of the plasma membranes in diverse tissues [209]. MAO activity has also been associated earlier with the nuclear membrane [210] and more recently the MAO-A protein, although having significantly lower catalytic activity, was found to re-locate to the nuclear fraction during pre-eclampsia/eclampsia [211]. The reduction in MAO-A activity in pre-eclampsia was confirmed, but the relocalization to the nucleus was not [212]. Pools of synaptic and extrasynaptic MAO have also been confirmed and, according to the authors, studies using total homogenates could provide misleading information because a substantial reduction of activity within a specific cellular location (e.g. in the synaptic terminals) could be masked by measurement of the total activity in tissue homogenates [213]. Although the evidence for expression of MAO proteins in diverse subcellular compartments exists, this simple, yet critical, fact is often overlooked in the interpretation of results. Indeed, MAO is now conveniently referred to as the 'mitochondrial enzyme' and this is such a commonly accepted fact that MAO is often used as a marker of mitochondrial fraction purity. While interpreting results based on a purely 'mitochondrial' localization is 'convenient', it certainly biases our understanding of the true role, and localization, of MAO in normal and pathological cell function.

POST-TRANSLATIONAL REGULATION OF MAO-A FUNCTION

This commentary would not be complete without an examination of post-translational regulation of MAO-A in disease. The induction of *MAO-A* mRNA and MAO-A protein and activity are known to correlate in the human encephalopathic brain [214]. This is not necessarily the case for the normal aging human brain [215] or for the AD brain, as mentioned above, and a discrepancy between *MAO* transcript levels in certain human and rodent cell lines has also been observed [216]. MAO-A, but not MAO-B, responds to manipulation of calcium (Ca^{2+}) either directly in rat brain homogenates [217] or by *in vivo* treatment with the Ca^{2+}-channel blocker nimodipine [218]. It is also known that Ca^{2+} selectively enhances MAO-A activity in mouse hippocampal HT-22 cells [15] and that the bacterial-derived toxin staurosporine can induce MAO-A-sensitive apoptosis in human neuronal SH-Sy5y cells [219], and that both of these latter effects occur independently of any change in *MAO-A* mRNA. This suggests the potential for post-translational regulation of MAO-A function. Although activation of the p38(MAPK) (p38 mitogen activated protein kinase) pathway has been associated with the induction of *Mao-A* mRNA and an MAO-A-sensitive apoptotic phenotype in PC12 and SK-N-BE(2)-C cells [110, 220], other studies [111, 216] clearly demonstrated that the effects of the p38(MAPK) protein itself on MAO-A-mediated events occur independently of changes in *MAO-A/Mao-A* transcript levels, respectively. We have identified Ser209 in overexpressed human MAO-A as a possible phosphorylation target for p38(MAPK) [197], although studies based on human MAO-A protein overexpressed in *Pichia pastoris* were not as conclusive [221]. It should be noted that human MAO-B has a homologous Serine residue (e.g. Ser200), but its cavity shaping loop is in a more compact conformation and there are no adjacent anionic groups near the hydroxyl of the Ser200 side chain to elicit a conformational change were it to be phosphorylated. These structural considerations might explain why p38(MAPK) could regulate MAO-A, but not MAO-B, *in vitro*. It remains to be seen if p38(MAPK) can be associated with the regulation of MAO proteins in human tissue preparations.

While any inhibitory effect of p38(MAPK) on MAO-A function would initially appear quite paradoxical, high basal activity of p38(MAPK) in healthy adult mouse brain has been observed, which suggests that this signalling protein, which is more often associated with a pro-apoptotic phenotype, might also contribute to normal brain cell physiology and survival [222, 223]. A pro-survival adaptive response to transient stress is suggested by the fact that H_2O_2, the by-product of MAO reactions, can actually activate p38(MAPK) [224] and inhibit MAO-A activity [225], apparently *via* a Ca^{2+}-dependent mechanism [226]. The PI3K/Akt pro-survival pathway might also be involved in regulating aspects of MAO-A function, but its effect does not include any influence on the Ca^{2+}-mediated regulation of MAO-A function [216]. Valproic acid was found to induce *MAO-A* promoter function as well as catalytic activity *via* an Akt-FoxO1

(transcription)-sensitive mechanism [227]. In addition, the Jun N-terminal kinase [228, 229], Ras/ERK (p44/42) [216, 230] and TGF-β/Smad3 [231] signalling cascades have been implicated in the regulation of MAO expression, function and/or inhibition. Given the acknowledged role of these cascades in regulating both transient (post-translational) and long-term (genetic/epigenetic) effects of cell signalling and responses to extracellular cues, a closer examination of the influence of signalling pathways on the regulation of the MAO-A and MAO-B systems is clearly needed.

As we draw this review to a close we acknowledge that our discussion on the therapeutic targeting of MAOs has focused primarily on pharmaceutical inhibitors. It is clear that there is a broad range of naturally occurring regulators of MAO function that have been omitted herein, including, but clearly not limited to, caffeine and analogues [232], kaempferol [233], and dietary components and associated metabolites [234, 235]. We do apologize *a priori* for not having expanded upon this very important topic.

CONCLUDING REMARKS

MAO is often described as an ubiquitous, membrane-bound enzyme that is expressed on the outer membrane of the mitochondria. Our current understanding of the contribution of MAO proteins to neurodegenerative processes is very often centered on the production of hydrogen peroxide as a byproduct of the reaction between MAO and biogenic substrates. The interpretation of results invariably attempts to satisfy a convenient model that is predicated on the assumptions (a) that MAO is a passive enzyme (i.e. it simply waits for a substrate to metabolize), (b) that only the expression of MAO protein dictates catalytic activity in a given tissue, and (c) that MAO proteins are *only* expressed in the outer mitochondrial membrane. Given that MAO is anchored to the membrane through a very short C-terminal trans-membrane helix, much of the protein is presumably left exposed for potential modification(s) by, and/or interactions with, other proteins (either circulating or juxtaposed on adjacent membranes). Fluctuations in MAO function might reflect protein levels that are influenced by both polymorphisms and epigenetic influences. Furthermore, the potential for effects of MAO that are not solely dependent on its catalytic activity might be a strategy that has evolved to satisfy different functional requirements for the MAO enzymes in a context- or cell-dependent manner. In other words, it is possible that MAO proteins display a behaviour that lies between catalytically active and inactive states, and that at any given time a cell's phenotype would be influenced by the dominating state. Thus, simply using an estimate of MAO activity as an outcome, without a concurrent evaluation of MAO expression levels and/or its localization within different cellular compartments, could bias the interpretation of the experimental outcomes. Although this might initially be viewed as an unnecessary increase in workload, in the long-term this would provide for more information and would surely help to clear up some, if not a substantial portion, of the ambiguity that surrounds the role(s) of MAO proteins in [patho]physiological contexts.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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