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Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: Focus on modulation of CNS monoamine neurotransmitter release

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ABSTRACT

Inhibitors of monoamine oxidase (MAO) were initially used in medicine following the discovery of their antidepressant action. Subsequently their ability to potentiate the effects of an indirectly-acting sympathomimetic amine such as tyramine was discovered, leading to their limitation in clinical use, except for cases of treatment-resistant depression. More recently, the understanding that: a) potentiation of indirectly-acting sympathomimetic amines is caused by inhibitors of MAO-A but not by inhibitors of MAO-B, and b) that reversible inhibitors of MAO-A cause minimal tyramine potentiation, has led to their re-introduction to clinical use for treatment of depression (reversible MAO-A inhibitors and new dose form MAO-B inhibitor) and treatment of Parkinson's disease (MAO-B inhibitors). The profound neuroprotective properties of propargyl-based inhibitors of MAO-B in preclinical experiments have drawn attention to the possibility of employing these drugs for their neuroprotective effect in neurodegenerative diseases, and have raised the question of the involvement of the MAO-mediated reaction as a source of reactive free radicals. Despite the long-standing history of MAO inhibitors in medicine, the way in which they affect neuronal release of monoamine neurotransmitters is still poorly understood. In recent years, the detailed chemical structure of MAO-B and MAO-A has become available, providing new possibilities for synthesis of mechanism-based inhibitors. This review describes the latest advances in understanding the way in which MAO inhibitors affect the release of the monoamine neurotransmitters dopamine, noradrenaline and serotonin (5-HT) in the CNS, with an accent on the importance of these effects for the clinical actions of the drugs.

Contents

Abbreviations: MAO, monoamine oxidase; MAO-A, monoamine oxidase isoform A; MAO-B, monoamine oxidase isoform B; COMT, catechol-O-methyltransferase; AAADC, aromatic amino-acid decarboxylase; PrAO, primary amine oxidase; VAP-1, vascular adhesion protein 1; LSD-1, lysine-specific histone demethylase type 1; CB-1, cannabinoid receptor type 1; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; CNS, central nervous system; BDNF, brain-derived neurotrophic factor; GDNF, glial cell-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; PKC, protein kinase C; MAO-I, monoamine oxidase inhibitor; MFB, medial forebrain bundle; RIMA, reversible monoamine oxidase type A inhibitor; MNT, monoamine neurotransmitter; DA, dopamine; NA, noradrenaline (norepinephrine); 5-HT, serotonin (5-hydroxytryptamine); PE, 2-Phenylethylamine; BZ, benzylamine; L-dopa, L-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid; DHPG, dihydroxyphenylglycol; MHPG, methoxyhydroxyphenylglycol; 5-HIAA, 5-hydroxindole acetic acid; DAT, dopamine transporter; NET, norepinephrine transporter; SERT, serotonin transporter; VMAT, vesicular monoamine transporter 2; OCT, organic cation transporter; PMAT, plasma-membrane amine transporter; PD, Parkinson's disease; SOD, superoxide dismutase; MDD, major depressive disorder; LID, L-dopa-induced dyskinesia; Tcp, tranylcypromine; MDMA, 3,4-Methylenedioxy-N-methylamphetamine; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

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1. Introduction

Although the use of monoamine oxidase inhibitors (MAO-I) for treatment of major depressive disorder (MDD) declined sharply after the realization that MAO inhibition can result in serious cardiovascular reaction following ingestion of certain foodstuffs containing tyramine ("cheese effect"), yet two major developments, (a) the fact that selective inhibition of MAO-B does not cause cheese effect, and (b) the development of reversible MAO-A inhibitors with low tyramine-potentiation property, have facilitated their re-introduction for treatment of neurological and psychiatric disorders. The use of older, non-selective inhibitors is still available for treatment of specific types of depression in patients with good treatment compliance, who can be expected to adhere to certain dietary constraints, although the strong pharmacological actions of these drugs make them a possible choice for suicide. In recent years skillful manipulation of pharmacokinetics and new drug development has in addition introduced the possibility of selective inhibition of brain MAO over that in the periphery, thus further advancing the clinical potential of these drugs. Two selective inhibitors of MAO-B, selegiline and rasagiline, are currently in use for symptomatic treatment of Parkinson's disease (PD) and affective disorders (selegiline transdermal system), and the potent neuroprotective properties of propargyl-derivative MAO-B inhibitors have projected these drugs to the forefront of discussion about drug therapy of PD. In addition, this group of drugs may have potential in the treatment of other neurodegenerative disorders. The present review deals with the recent advances in the biochemical aspects of the enzyme MAO and pharmacological aspects of its inhibition on monoamine neurotransmitter (MNT) release, as well as reviewing the background and current status of the most important MAO-I which are currently in use in medicine. The major purpose of this review is to summarize information on the ways in which MAO-I affect release of the monoamine neurotransmitters, dopamine (DA), noradrenaline (NA) and 5-hydroxtryptamine (5-HT). Additional effects of the inhibitors are also described, where these may impact the final action of the drugs on MNT. This review is also intended as an update, and most of the references quoted are post 2000; older research has been included where this is important for describing the key developments in the topic. For other recent reviews on MAO-I, see (Youdim et al., 2006; Binda et al., 2011; Riederer & Laux, 2011). The number of chemical compounds with inhibitory effect on MAO is truly vast, and the present review is limited to a few of the most important compounds which have been extensively studied for their actions on MNT release and metabolism, and/or have relevance to clinical medicine.

1.1. Monoamine oxidase: the enzyme

Oxidative deamination of a variety of monoamines by animal tissue was described by Schmiedeberg (Schmiedeberg, 1877). The biochemical characteristics of the enzyme now known as monoamine oxidase (MAO; EC 1.4.3.4.) were first described by Mary Hare (Hare, 1928) who referred to it as tyramine oxidase. Subsequent studies showed that the enzyme studied metabolizes a wide range of primary, secondary and tertiary monoamines, but has much lower affinity for diamines (e.g. histamine). The enzyme is localized to the mitochondrial outer membrane (Denney & Denney, 1985; Edmondson et al., 2009) and is expressed in most tissues of the body, with high levels in liver. Monoamine oxidase exists in two isoforms, MAO-A and MAO-B, encoded by two separate genes, localized to the X-chromosome (Xp11.23). The two proteins have similar structures and molecular weights (70% amino acid sequence identity), but differ in their selectivity for substrates and inhibitors (see Table 1). The overall reaction of substrate oxidation can be expressed as:

$$\text{R-CH}_2\text{–NH}_2 + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{MAO}} \text{R-CHO} + \text{NH}_3 + \text{H}_2\text{O}_2$$

The initial reaction products include an aldehyde and H_2O_2, which have potential toxicities. In the case of primary amines, ammonia is released as a product, but metabolism of secondary or tertiary amines will yield other nitrogenous products. The immediate aldehyde products are rapidly metabolized by aldehyde metabolizing enzymes, and reactive oxidizing free radicals which can be produced from H_2O_2 are neutralized by radical scavengers such as superoxide dismutase (SOD), catalase and endogenous anti-oxidants such as glutathione. The possibility that the enzymes which normally neutralize the toxic products may themselves be dysfunctional in pathological conditions such as PD has given rise to the concept that excessive or even normal MAO activity can be a potential cause of oxidative stress in these conditions (Jenner, 2003; Vaya et al., 2012).

The realization that MAO exists as two isoforms (isozymes) initially arose from the discovery (Johnston, 1968) that the propargyl inhibitor clorgyline shows selectivity for inhibition of the deamination of NA and 5-HT at concentrations which only slightly impair deamination of benzylamine (BZ) and 2-phenylethylamine (PE). Subsequently, another propargyl inhibitor, selegiline [R(-)-deprenyl], was shown by Knoll and associates (Knoll & Magyar, 1972) to inhibit the deamination of BZ and PE at concentrations which only slightly impaired the deamination of NA and 5-HT. The isoform which showed greatest activity towards 5-HT and NA was termed MAO-A, while the isoform showing greatest activity towards BZ and PE was termed MAO-B. Kinetic experiments showed that the Km of MAO-A for deamination of 5-HT is about 10-fold less than that of MAO-B, while the reverse is true for PE [see (Youdim et al., 1988)]. Some substrates, e.g. DA, have similar Km values for both enzyme forms (O'Carroll et al., 1983), although when expressed in yeast cells, recombinant human MAO-B showed a higher Kcat and a lower Km for deamination of DA than did human MAO-A (Edmondson et al., 2009). In keeping with their effectiveness to reduce the metabolism of NA and 5-HT, selective inhibitors of MAO-A are effective as antidepressants whereas selective MAO-B inhibitors are not (Murphy et al., 1979; Youdim & Finberg, 1983), unless given in high doses sufficient to inhibit both enzyme forms. However, because MAO-A is the major enzyme form associated with sympathetic neurons, selective inhibition of MAO-A causes potentiation of the sympathomimetic effects of tyramine ("cheese effect"), whereas selective inhibition of MAO-B does not (Finberg & Tenne, 1982; Finberg & Gillman, 2011). The fact that selective MAO-B inhibitors are effective in the treatment of PD gives impact to their postulated ability to potentiate the effects of endogenous DA in PD brain.

A major development in understanding the structural requirements for selective substrates and inhibitors was the crystallization of human MAO-B by Edmondson, Mattevi and coworkers (Binda et al., 2002), human MAO-A (De Colibus et al., 2005) and rat MAO-A (Ma et al., 2004) following expression of the two recombinant human enzymes in the yeast *Picchia pastoris* (Edmondson group), or recombinant rat MAO-A in *Saccharomyces cerevisiae* (Ma et al., 2004) and the subsequent determination of the two enzymes' molecular and subunit structures.

1.2. The two isoforms of MAO

1.2.1. Molecular structure

Elucidation of the detailed structure of MAO-A and -B has enabled further understanding of the mechanism of substrate binding and catalysis, as well as the structural requirements for inhibitor binding and inhibitory effect. Human and rat MAO-A and MAO-B exist in the outer mitochondrial membrane as dimers, on the basis of recent data using EPR (Electron Paramagnetic Resonance) (Upadhyay et al., 2008). MAO is a flavoenzyme, and substrates and inhibitors bind to a cavity in the molecule in which flavin forms one flat face. Substrates bind to N-5 of flavin leading initially to formation of an unstable adduct, which breaks down in the case of substrates, or enables covalent binding in the case of irreversible inhibitors. Details of the MAO-A and

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