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Natural Monoamine oxidase inhibitors : A Review

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ABSTRACT

Monoamine oxidase (MAO) is an iron containing flavoenzyme that catalyzes the oxidative deamination of biogenic amines accompaned by the release of H_2O_2. Two subtypes, MAO-A and MAO-B, exist on the basis of their specificities to substrates and inhibitors. The regulation of MAO activity is important in the treatment of neurodegenerative diseases. These may therefore be candidates for use in delaying the progressive degeneration caused by neurological diseases. The aim of this paper is to summarize putative biological actions of some natural monoamine oxidase inhibitors to further understanding of the beneficial health effects of these substances against various neurodegenerative disorders and may also increase interest in the health benefits of herbal drugs suggesting that natural MAO inhibitors may be more widespread than had previously been suspected.

Keywords: MAO, Inhibitors, Plants, Harmala alkaloids.

INTRODUCTION

Monoamine oxidase (MAO) is an iron containing flavoenzyme that occurs within cells, bound to the surface membrane of mitochondria and involved in the degradation of biogenic amines. Two monoamine oxidase isoenzymes, MAO-A and MAO-B, are closely linked in opposite orientation on the X chromosome and are expressed in the outer mitochondrial membrane. MAO-A and MAO-B oxidize neurotransmitters and xenobiotic amines by oxidative deamination, the regulation of which is important in maintaining normal mental states.[1] MAO is abundant in noradrenergic nerve terminals but is also present in many other places, such as liver and intestinal epithelium.[2] MAO-A, the primary type in fibroblasts, preferentially degrades serotonin, norepinephrine and dopamine. MAO-B, the primary type found not only in platelets but also in the brain of man and other primates preferentially degrades phenylethylamine and benzylamine. MAO has been of particular interest to psychiatry and genetics because of the suggestion by Wyatt et al. (1973) that low activity is a 'genetic marker' for schizophrenia.[3] Low levels of MAO activity and mutations in the MAO-A gene have been associated with violent, criminal, or impulsive behavior.[1]

The activity of MAO helps to maintain neuron firing rates throughout the body within homeostatic limits. It does this by metabolizing in the liver bioactive amines absorbed into the bloodstream from food, by metabolizing in the endothelial cells of cerebral vascular microvessels, as part of the blood brain barrier, bioactive amines in the bloodstream, and by metabolizing in the cytoplasm of neurons, molecules of biogenic amine neurotransmitters that are not enclosed in vesicles. Part of the biochemical activity of MAO generates hydroxyl radicals, very toxic members of the oxygen free radical group that may be involved in neurodegenerative disorders such as Parkinson's disease. Inhibiting MAO with different drugs (e.g. selegiline) seems to have neuroprotective actions but this may be due to inducing the release of neuronal growth factors rather than by preventing the formation of free radicals. Other drugs that inhibit MAO are used to treat patients with atypical depression, panic attacks or post traumatic stress syndrome.[4] Attenuation of MAO-B activity may provide protection against oxidative neurodegeneration. For this reason, inhibition of MAO-B activity is used as part of the treatment of Parkinson's and Alzheimer's patients.[5]

Herbal products are often perceived as safe because they are "natural". In recent years, there is increased research on traditional ayurvedic herbal medicines on the basis of their known effectiveness in the treatment of ailments for which they have been traditionally applied. Herbal medicine is a major component in all traditional medicine systems, and a common element in Siddha, Ayurvedic, Homeopathic, Naturopathic, Traditional Chinese medicine, and Native American medicine

Plants with MAO-A and MAO-B inhibitory activity

The harmala alkaloids are psychoactive derivatives of beta carboline and have been identified as stimulants and short term MAO inhibitors, which would give antidepressant rather than sedative effects.[6]

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Recent epidemiological studies have consistently shown that "ready to drink" coffee brews exhibits inhibitory properties on recombinant human MAO-A and B isozymes catalyzing the oxidative deamination of kynuramine.MAO inhibition is reversible and competitive for MAO-A and B.The pyrido-indole (beta-carboline) alkaloids, norharman and harman, have been identified and isolated from MAO inhibiting coffee (*Coffea canephora* or *Coffea robusta* and *Coffea Arabica*) and are good inhibitors on MAO-A (harman and norharman) and MAO-B (norharman) isozymes.[7] The in vitro and ex vivo experiments suggest that there is a specific binding site for harman on MAO-A. However norharman (ß-carboline) is a much weaker displacing compound. [8]

Peganum harmala Pamphlet, the hallucinogenic herb of the American Southwest, contain a mixture of the harmala alkaloids, harmine and harmaline in the seeds, as well as the roots. They temporarily prevent biogenic amines from binding to the active site of the MAO molecule and undergoing oxydative deamination. For 3 to 6 hours, the harmala alkaloids interfere with the protective enzyme MAO, before their action is reversed and MAO activity restored.[9]

Passiflora incarnata (Passion flower), contains small amounts of harmala alkaloids, harmane (passaflorine), and possibly harmine (telepathine), harmaline, harmol, and harmalol. The presence of the last four in *Passiflora incarnata* is disputed. The importance of whatever harmala alkaloids are present to the therapeutic effect of passiflora is also questionable. They are contained in only very small amounts (0.01 percent or less).[10]

The methanol extract from the aerial parts of *Dictamnus albus* is found out to be active in inhibiting MAO from the mouse brain. Activity-guided fractionation led to the isolation of four known coumarins, 7-(6'*R*-hydroxy-3', 7'-dimethyl-2'*E*, 7'-octadienyloxy) coumarin, auraptene, umbelliferone, and xanthotoxin, as active compounds.[11]

The *Ginkgo biloba* leaf extract on rat brain produces in vitro inhibition of rat brain MAO-A and B. The *Ginkgo biloba* extract components responsible for the activity are kaempferol and isorhamnetin.[12]

A methanol extract of *Zanthoxylum schinifolium* stems show potent inhibitory activity against MAO in a mouse brain. Activity-guided separation and purification of the extract yielded lacinartin as an active coumarin compound.[13]

Hypericum perforatum (St.-John's-wort) has been studied for its MAO inhibitory activity. The MAO inhibition does occur with high concentrations of *Hypericum* constituents, it does not in the amounts found in commercial extracts. The influence of hypericin, hypericum total extract, and hypericum fractions on the activity of MAO, prepared in vitro from pork liver, have been investigated. The MAO inhibiting fraction contain hypericins (naphthodianthrone) as well as flavonols.[14] *Hypericum* species, *H. caprifoliatum, H. carinatum, H. connatum, H. cordatum, H. myrianthum, H. piriai, H. polyanthemum and H. brasiliense*, all native to South Brazil, have been assayed for MAO inhibitory activity in rat brain mitochondrial preparations. Three benzopyrans, HP1 (6-isobutyryl-5,7-dimethoxy-2,2-dimethylbenzopyran), HP2 (7-hydroxy-6-isobutyryl-5-methoxy-2,2-dimethylbenzopyran) and HP3 (5-hydroxy-6-isobutyryl-7-methoxy-2,2dimethylbenzopyran) isolated from *H. polyanthemum* are found out to be responsible for MAO inhibition.[15]

It is well established that tobacco smokers have reduced levels of MAO activities both in the brain and peripheral organs. The observation that inhibition of MAO-B protects against the Parkinsonian inducing effects of the nigrostriatal neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, have prompted studies to identify MAO inhibitors in the tobacco plant and tobacco cigarette smoke. The efforts on cured tobacco leaf extracts have led to the characterization of 2,3,6-trimethyl-1,4-naphthoquinone, a non-selective MAO inhibitor, and farnesylacetone, a MAO-B inhibitor. The studies have been extended to tobacco smoke constituents. Fractionation of the smoke extracts have confirmed and extended the qualitative results of an earlier report demonstrating the inhibitory activity of the terpene trans,trans-farnesol on rat brain MAO-B. Noteworthy is the absence of inhibitory effects on human placental MAO-A and beef liver MAO-B. A limited structure-activity relationship study of analogs of trans,trans-farnesol is reported. Although the health hazards associated with the use of tobacco products preclude any therapeutic opportunities linked to smoking, these results suggest the possibility of identifying novel structures of compounds that could lead to the development of neuroprotective agents.[16]

Six extracts of varying polarity of *Mentha aquatica* L. have been tested in a photometric peroxidase linked MAO bioassay. The 70% ethanol extract shows highest inhibitory activity. (*S*)-Naringenin has been isolated from the extract by bioassay guided fractionation on VLC and preparative TLC. The content of naringenin in *Mentha aquatica* might explain its use in traditional medicine for depression-like conditions.[17]

Three MAO inhibitors have been isolated from *Gentiana lutea*. Their structures were elucidated to be 3-3" linked-(2'-hydroxy-4-*O*-isoprenylchalcone)-(2"'-hydroxy-4"-*O*-isoprenyl dihydrochalcone),2-methoxy-3-(1,1'-dimethylallyl)-6a,10a-dihydrobenzo(1,2-*c*)chroman-6-one and 5-hydroxyflavanone. These compounds, and the hydrolysis product of 3-3" linked-(2'-hydroxy-4-*O*-isoprenyl chalcone)-(2"'-hydroxy-4"-*O*-isoprenyl dihydrochalcone), display competitive inhibitory properties against MAO-B which is more effective than MAO-A.[18]

Myristicin, 3-methoxy,4,5-methylendioxy-allylbenzene, is a natural organic compound present in the essential oil of *Myristica fragrans* (Nutmeg). Myristicin is a naturally occurring insecticide and acaricide with possible neurotoxic effects on dopaminergic neurons. Myristicin is a weak inhibitor of monoamine oxidase.[19]

The investigation of the effects of aqueous extract of *Glycyrrhiza glabra* L., popularly known as liquorice, on depression in mice models suggests that antidepressant-like effect of liquorice extract seems to be mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin. MAO inhibiting effect of liquorice may be contributing favorably to the antidepressant-like activity.[20]

The white and red varieties of ginseng, the root of *Panax ginseng*, have been investigated in rats and mice using a number of experimental paradigms of anxiety and compared with that of diazepam. Ginseng attenuates pentylenetetrazole-induced decrease in rat brain MAO activity, confirming its anxiolytic activity.[21]

The alkaloid yohimbine is not a MAO inhibitor, but the herb *Pausinystalia yohimbe* (Yohimbe), formerly known as *Corynanthe yohimbe* is. No cases of MAO inhibition in human have been reported, but yohimbine inhibits MAO in vitro.[22]

The study of biochemical and neurochemical indicators of mood in the animals (MAO enzyme inhibitory activity and neurotransmitter levels estimation) shows that curcumin derived from *Curcuma longa* (Turmeric) dose dependently inhibits the immobility period, increased serotonin as well as dopamine levels and inhibits both MAO-A and MAO-B in the mice.[23]

Plants with MAO-B inhibitory activity

Three varieties of methyl citrate and 1-methyl malate have been isolated from the fruits of *Opuntia ficus-indica* var. saboten Makino through in vitro bioassay-guided isolation for the inhibition on MAO. Their inhibition shows a significant activity on MAO-B. However, on MAO-A, their inhibitions show only marginal activity.[24]

Vinblastine and vincristine are alkaloids found in the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). Vinblastine and vincristine are inhibitors of MAO-B.[25]

Kava-kava, a psychoactive beverage is prepared from *Piper methysticum* Forster (kava-kava). Kava-kava extract is reversible inhibitor of MAO-B in intact platelets and disrupted platelet homogenates. Structural differences of kava pyrones results in a different potency of MAO-B inhibition. The two most potent kava pyrones, desmethoxyyangonin and (+/-)-methysticin display a competetive inhibition pattern.[26]

The hook of *Uncaria rhynchophylla* (Miq.) Jacks (Cat's claw) is a traditional Chinese herbal drug that is generally used to treat convulsive disorders. The fractionation and purification of *Uncaria rhynchophylla* extracts using a bioguided assay isolated two known compounds, (+)-catechin and (-)-epicatechin. The compounds inhibit MAO-B, as measured by an assay of rat brain MAO-B separated by electrophoresis on a 7.5% native polyacrylamide gel.[5]

Arisaema amurense, *Lilium brownii* var. colchesteri, *Lycium chinense*, and *Uncaria rhynchophylla*, are plants used in traditional Chinese medicines. The 50% aqueous methanol extracts of four active extracts, exhibits the inhibitory activity and selectivity towards MAO-B in rat brain homogenates.[27]

Scientific research with the dried extract of *Polygonum multiflorum* (Foti) has shown evidence it might increase the levels of superoxide dismutase (SOD), serotonin, norepinephrine, dopamine, and decrease levels of MAO-B.[28]

Plants with MAO-A inhibitory activity

Fifty-nine xanthones (=9*H*-xanthen-9-ones) of natural or synthetic origin have been investigated for their inhibitory activity toward MAO-A and B. Electron absorption spectroscopy,3D-QSAR studies and the Almond procedure confirmed that the compounds demonstrated reversible, time-independent activities, with selectivity toward MAO-A.[29]

The anxiogenic action of bradykinin has been investigated in rats and compared with that of yohimbine, a known anxiogenic agent. The experimental method consists of estimation of brain tribulin activity in terms of endogenous MAO-A and MAO-B inhibition. Bradykinin and yohimbine increase rat brain tribulin activity, the effect on the MAO-A inhibitor component being more marked than that on the MAO-B inhibitor component. The MAO A inhibitor component has been postulated to be the major anxiogenic moiety of tribulin.[30]

Animal source of MAO inhibitory activity

Velvet antler is a mainstay of traditional Chinese medicine, probably second only to ginseng in importance. Velvet antler does not refer to the velvety skin on growing antlers, but rather the whole cartilagious antler in a pre-calcified stage. Typically the antler is cut off near the base after it is about two-thirds of its potential full size, and before any significant calcification occurs. Supercritical fluid extraction of the MAO inhibitor from antler velvet with CO_2 has been explored. Evaluation of the inhibitory activity of extract on MAO indicates that the extracts have strong inhibitory effects on MAO-B, but have slight effects on MAO-A. The compositions of estradiol, uracil, hypoxanthine, *p*-hydroxybenzaldehyde and phospholipids in the supercritical fluid extraction extracts have been identified, which are reported to have the inhibitory effect on MAO.[31]

Equol, its methylated derivative, and a carbazole, all isolated from bovine urine, are relatively potent inhibitors of MAO suggests that natural MAO inhibitors may be more widespread than had previously been suspected.[32]

Fungal source of MAO inhibitory activity

Emericella navahoensis is a fungus with MAO inhibitory action. Norsolorinic acid, averufin and 6,7,8-trihydroxy-3-methylisocoumarin have been isolated from *Emericella navahoensis* as metabolites having MAO inhibitory action. Norsolorinic acid inhibits MAO in mouse liver non-competitively when kynuramine is used as a substrate.[33]

The compound tentatively named TL-1 has been isolated from *Talaromyces luteus* as a metabolite having MAO inhibitory potency. TL-1 show mixed type inhibition of MAO in mouse liver when kynuramine is used as a substrate. Despite the marked structural resemblance between TL-1 and 7-episclerotiorin, the latter compound has little inhibitory effect on MAO.[34]

In a screening study focusing on MAO activity on the ethyl ethanoate extract of an Ascomycete *Chaetomium qitadrangulatum*, 11 unique chromones (chaetoquadrins A-K) have been obtained. They show appreciable MAO inhibitory activity.[35]

Marine source of MAO inhibitory activity

Methylaplysinopsin is an indolyl-methylene derivative of creatinine which has been isolated from a sponge collected on the Great Barrier Reef. It is a reversible, short acting inhibitor of MAO-A.[36] An alkaloid aaptamine have been isolated from an unidentified

species of Indonesian marine sponge of the genus *Xestospongia*. It is a selective inhibitor of MAO-A.[37]

DISCUSSION

Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Roughly 50% of new chemical entities introduced during the past two decades are from natural products. Recent technological advances have renewed interest in natural products in drug discovery. Therefore, efforts should be directed towards isolation and characterization of the active principles and elucidation of the relationship between structure and activity. Furthermore, detailed analysis of the active constituents of natural drugs should be directed towards clinical relevance. Standardization is indispensable to maintain reproducible quality in biological evaluation. Although the clinical efficacy of various MAO inhibitors is reported by traditional practices, they have not been scientifically validated.

Ayurveda, the oldest medicinal system in the world, provides leads to find therapeutically useful compounds from plants. Therefore, ayurvedic knowledge supported by modern science is necessary to isolate, characterize, and standardize the active constituents from herbal source. This combination of traditional and modern knowledge can produce better MAO inhibitors with fewer side effects. Herbs are widely available in India and other countries. The wide spectrum makes them attractive candidates for further research.

CONCLUSION

The natural products, which have been considered, show promising role in acting as MAO inhibitors. The use of these drugs in formulating a multi component herbal formulation would surely help in treatment of various neurodegenerative disorders like Parkinson's and Alzheimer's disease. A detailed and planned research in this area would prove to be a new thrust in line of therapeutics.

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