

MONOAMINE OXIDASE INHIBITORS AND THEIR ROLE IN DEPRESSION

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Summary

The role of the monoamines, serotonin in mental illnesses including depression is well recognized. All antidepressant drugs in clinical use increase acutely the availability of these monoamines at the synapse either by inhibiting their neuronal reuptake, inhibiting their intraneuronal metabolism, or increasing their release by blocking the α_2 auto- and heteroreceptors on the monoaminergic neuron. This acute increase in the amount of the monoamines at the synapse has been found to induce long-term adaptive changes in the monoamine systems that end up in the desensitization of the inhibitory auto- and heteroreceptors including the presynaptic α_2 and 5-HT_{1B} receptors and the somatodendritic 5-HT_{1A} receptors located in certain brain regions. The desensitization of these inhibitory receptors would result in higher central monoaminergic activity that coincides with the appearance of the therapeutic response. Two types of MAO, i.e. type A (MAO-A) and type B (MAO-B). MAO-A oxidizes noradrenaline and serotonin; and MAO-B, mainly β -phenylethylamine. In the human brain, MAO-A exists in catecholaminergic neurons, but MAO-B is found in serotonergic neurons and glial cells. MAO-A and MAO-B may be closely related to various neuropsychiatric disorders such as depression and Parkinson's disease, and inhibitors of them are the subject of drug development for such diseases.

Keywords- monoamine oxidase inhibitors, depression, tyramine

Introduction

Monoamine Oxidase (MAO) is a flavinadenosine dinucleotide containing enzyme situated at the outer membranes of mitochondria in the brain, liver, intestinal mucosa, and various other organs. It catalyzes the various oxidative deaminations of biogenic amines such as neuroamines, vasoactive and exogenous amines, including dopamine, serotonin, norepinephrine, tyramine, and tryptamine. The end products are aldehydes and hydrogen peroxide that are involved in oxidative cellular processes [1]. MAO exists in two forms, i.e., MAO-A and MAO-B in human beings and both are 60 kDa outer-mitochondrial membrane-bound flavoenzymes that share 70% sequence identities [2].

Monoamine oxidase inhibitors have shown therapeutic value in a variety of neurodegenerative diseases [3]. In the 1950s the discovery of the antidepressant properties of MAO inhibitors (MAOIs) was the major finding that led to the monoamine theory of depression. Earlier MAO inhibitors introduced in clinical practice for the treatment of depression were abandoned due to adverse side-effects, such as hepatotoxicity, orthostatic hypotension called as 'cheese effect' characterized by hypertensive crises [4]. The overlapping specificities of MAO-A and MAO-B in the oxidative deamination of neurotransmitters and dietary amines, the development of specific reversible inhibitors has been a long sought goal. The expression levels of MAO-B in neuronal tissue increase 4-fold with age[5], that means increased level of dopamine metabolism and the production of high level of hydrogen peroxide, which are thought to play a role in the etiology of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases[6].

Monoamine Theory of Depression

The amine theory has suggested that the acute increase in the levels of the monoamines at the synapse ultimately results in antidepressant activity [7]. Increased amount of the monoamine at the synapse has been found to induce

desensitization of the inhibitory auto receptors and heteroreceptors located in certain brain regions. The desensitization of these receptors would result in higher level of central monoaminergic activity that coincides with the appearance of the therapeutic response. This change responsible for the therapeutic effect depends on the availability of the specific monoamine at the synapse. The depletion of this monoamine will either reverse the antidepressant effect or cause a relapse in the state of drug-free depressed patient previously treated with antidepressant drugs. Furthermore, blocking the somatodendritic and nerve terminal auto receptors indicates to increase the response rate in the treatment of major and treatment resistant depression, providing further support to the assumption that the antidepressant effect results from the long-term adaptive changes in the monoamine auto- and heteroregulatory receptors.

Monoamine Oxidase A and B

Johnston [8] discovered the monoamine oxidase inhibitor Clorgyline was able to distinguish two forms of MAO, i.e. MAO-A and MAO-B. Multiple forms of MAO were suggested in 1970 based on findings from Sandler's laboratory [9].

Clorgyline is a selective MAO-A inhibitor; whereas MAO-B prefers β -phenylethylamine as a substrate, and is inactivated by deprenyl [10] as a selective inhibitor. Tyramine, tryptamine and Dopamine, are oxidized by both MAO-A and MAO-B [11].

Both MAO-A and MAO-B regulate the concentrations in the brain of important neurotransmitters such as dopamine, nor adrenaline and adrenaline, which are related to movement, emotion, and cognition. Thus, it is thought that MAO-A and MAO-B are closely linked to various psychiatric and neurological disorders such as depression and Parkinson's disease [12]. Monoamine oxidase enzymes are responsible for the oxidative deamination of endogenous and xenobiotic amines, and have a different substrate preference, inhibitor

specificity, and tissue distribution. MAO inhibition allows endogenous and exogenous substrates to accumulate in brain and alter the dynamics of regular monoamine transmitters, such as noradrenaline, serotonin, or dopamine. MAO inhibitors (MAOIs) are mainly used in psychiatry for the treatment of depressive disorders and in neurology for the treatment of Parkinson's disease. More recently, MAOIs have been used to treat patients with anxiety disorders and Alzheimer's disease. The non-selective and irreversible MAOIs, such as phenelzine and tranylcypromine, are characterized by the risk of a hypertensive crisis when dietary tyramine is ingested, the selective MAO-B inhibitor selegiline and the selective and reversible inhibitor of MAO-A moclobemide, are free from this potential interaction.

Classification of Monoamine oxidase inhibitors

MAO-A selective	Clorgyline	Irreversible
MAO-A selective	Moclobemide	Reversible
MAO-A selective	brofaromine	Reversible
MAO-A Selective	Toloxatone	Reversible
MAO-A selective	Cimoxatone	Reversible
MAO-A selective	Befloxatone	Reversible
MAO-B Selective	Pargyline	Irreversible
MAO-B Selective	Selegiline	Irreversible
Non-selective	Tranylcypromine	Irreversible
Non-selective	Isocarboxazid	Irreversible

Clinical Implication

DEPRESSION

Depression is an abnormal mental condition associated with high medical morbidity and substantial mortality. The primary form of treatment for depression is pharmacotherapy. Recently the so-called tricyclic antidepressants were the drugs of choice for treatment. However, this has changed with the availability of newer, second-generation antidepressants that have more favorable side effect profiles and low toxicity with overdose.

Although MAOIs are not used as extensively as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, the classical clinical indication for the use of MAOIs is depression. After the discovery of the antidepressant effects of non-selective and irreversible MAOIs in the early 1950s, this class of compounds sparked a remarkable amount of interest. However, during the following years, fewer and fewer patients were treated with monoamine oxidase inhibitors because of fewer side effects. More recently, moclobemide has proven to be most effective in the wide spectrum treatment of major depression[13,14].

The antidepressive effect, taken together with moclobemide's absence of anticholinergic effects, lack of sedation, and similarity in pharmacokinetics in young and elderly individuals, makes moclobemide especially for use in treating the elderly depressed patient [15]. With normal aging, in the brain noradrenergic neurotransmission may decrease and also, MAO activity increases with aging[16]. These findings suggest that not only changes in pharmacokinetic variables, but also changes in the pharmacodynamics with aging, may be responsible for the different clinical profile in the treatment of depression in the elderly.

Mode of action

Monoamine oxidase inhibitors act by inhibiting the activity of monoamine oxidase, due to this prevent the breakdown of monoamine neurotransmitters and then increase their availability. There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine and norepinephrine and MAO-B preferentially deaminates phenylethylamine. Dopamine is equally deaminated by both inhibitors. Various formulations have forms of fluoride attached to assist in permeating the blood-brain barrier, which is suspected as a factor in pineal gland effects.

Pharmacokinetics of MAOIs

Phenelzine is rapidly absorbed, with maximum concentrations occurring 2–4 hrs after dosing [17]. The drug is mainly metabolized by acetylation; dosage adjustment in patients with renal failure and the elderly is not considered [18]. Phenelzine is a nonselective MAO inhibitor, and its metabolites are phenyl acetic acid, β -hydroxyphenylacetic acid. In addition, Phenelzine may also be ring-hydroxylated and *N*-methylated. Its plasma elimination half-life that is 1.5–4 hrs [19]. Tranylcypromine is rapidly absorbed and has a short plasma elimination half-life that is 2 hr [20]. The propargylamine selegiline is *N*-demethylated and *N*-depropargylated to yield arylalkylamines, and include amphetamine, *N*-methyl amphetamine, and *N*-propargylamphetamine [19]. These metabolites may undergo further metabolism, e.g. hydroxylation. *N*-Propargylamphetamine is reported to have neuroprotective effects [21]. The formation of these metabolites is mediated by cytochrome P450 (CYP) 2D6 (CYP2D6) and CYP3A4 [19] and [22]. The plasma elimination half-life of selegiline is 1.7 h [23].

Moclobemide is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism resulting in an increase in the systemic availability of moclobemide from 40% after a single dose to 85% after multiple doses; hepatotoxicity has not been reported. Moclobemide is biotransformed by C- and N-oxidation of the morpholine ring and by aromatic hydroxylation [19]. Approximately 95% of the drug clears via the renal system within 24 hrs [24]. Moclobemide is only about 50% protein bound. There are no important differences in moclobemide absorption and disposition between healthy young and elderly individuals [23, 25].

Brofaromine also has serotonin reuptake-inhibiting properties in addition to its MAO-inhibition property [26]. Total renal excretion accounts for 76% of an oral dose of brofaromine [27]. In elderly healthy volunteers the elimination half-life of brofaromine is comparable to that of

young healthy volunteers. However, mean plasma clearance is reduced by approximately 50% in the elderly [28].

Safety and Tolerability of MAOIs

Adverse drug reaction

First generation monoamino oxidase inhibitors (non-selective and irreversible MAOIs) have serious side-effects, including orthostatic hypotension, hepatotoxicity, and most importantly hypertensive crisis that occurs by the ingestion of foods containing tyramine (e.g. aged cheeses) [29]. When these non-selective and irreversible MAOIs are used, a strict tyramine-reduced diet must be observed. The pressor sensitivity of tyramine is normalized in 4 weeks after cessation of tranylcypromine therapy and more than 11 weeks after cessation of phenelzine therapy [30]. When levodopa is used in combination with selegiline, it can cause anorexia/nausea, dry mouth, dyskinesia, and orthostatic hypotension in patients with Parkinson's disease, the latter cause more serious problems. Moclobemide causes sleep disturbances, increased anxiety, restlessness, and headache regarding tolerability. Moclobemide overall showed good results comparatively less adverse effects were reported among moclobemide-treated patients, even better than selective serotonin reuptake Inhibitors [31]. Moclobemide has less potential to elicit this hypertensive crisis, because the pressor effect of tyramine from food is only marginally potentiated compared with tranylcypromine. The pressor effect of tyramine is normalized within 3 days after treatment with Moclobemide.

The combination of selective serotonin reuptake inhibitors and Moclobemide has good efficacy in cases of refractory depression, but may cause side effects, such as serotonergic syndrome result from this combination [32]. Hypertensive crisis occurs more frequently in elderly than in younger patients, because cardiovascular systems of the elderly are already compromised by age. The use of sympathomimetic drugs in combination with MAOIs causes increased blood pressure. In addition, compared with placebo, phenelzine was associated with a significantly higher incidence of

drowsiness, tremor, dyskinesia, diarrhoea, micturition difficulties, orthostatic effects, and various adverse dermatological effects. Although orthostatic hypotension occurs in most patients treated with traditional MAOIs [31]. Moclobemide is also characterized by good tolerability in the elderly.

Toxicity in Overdose

MAOIs are prescribed for depression because of the potential risk of suicide, adverse drug reactions and toxicity due to overdose are important factors to consider when choosing an antidepressant. When MAOIs are used in higher dosage, adverse cardiovascular effects are reported and because MAO selectivity is lost with such high doses, tyramine can induce potentially dangerous hypertensive reactions. Acute overdose with MAOI causes agitation, hallucinations, hyperpyrexia, hyperreflexia and convulsions abnormal increased blood pressure is also a toxic sign, so that gastric lavage and maintenance of cardiopulmonary function may be required. Overdose of traditional non-selective and irreversible MAOIs are dangerous and may be fatal [33].

Conclusion

Presently, monoamine oxidase inhibitors are used for the treatment of depressive disorders, anxiety disorders, Parkinson's disease, while the classical, non-selective and irreversible monoamine oxidase inhibitors are characterized by the risk of inducing hypertensive crisis when dietary tyramine is ingested, selective MAO-B inhibitors and moclobemide are free from this potential interaction. It seems obvious that a greater understanding of the pharmacodynamics and pharmacokinetics of MAOIs could result in improved treatment of the patients in the future. Another challenge for future basic and clinical research is to examine the possible preventive medications that slow the physiological, age-related activity decline of the catecholaminergic system in the healthy, but aged brain. It is reasonable to expect that MAOIs can slow the age-related decline of behavioral performance and decrease

susceptibility to various types of depression, Parkinson's disease, and Alzheimer's disease.

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