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Comparison between Monoamine Oxidase A and B: role and effect in human diseases: A review

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Abstract

MAOs are isoenzymes that occur in two isoforms Monoamine oxidases A and B. They are flavoproteins found in mitochondria and their role is to catalyze the oxidative deamination of monoamine neurotransmitters to their corresponding aldehydes. Both MAOs play a major role in the human body as they contribute to many illnesses. MAO plays an essential role in both peripheral; and central nervous system through affecting the levels of MAO neurotransmitters. MAO-A is generally concentrated in dopaminergic and norepinephrinergic neurons. Contrary to MAO-B, which is predominantly concentrated in serotoninergic neurons. By-product of MAOs which are aldehyde, ammonia, and H_2O_2 (which is considered reactive oxygen species) that is toxic at high concentration or it may lead to the generation of free Radicals. Free radicals considered as a starting signal in the generation of cancers. Also, MAO inhibition showed to decrease pressure overload and heart failure. This action is mainly related to the prevention of oxidative stress mainly (H_2O_2) apoptosis in cardiac muscle and improved bioavailability of Norepinephrine. MAO-A plays a totally different role from MAO—B in renal carcinoma. Ranging from Alzheimer disease, depression to cardiac myopathy, diabetes, kidney diseases, and cancers, MAO-A participates differently from MAO-B in these diseases. Therefore it is necessary to study their separate effect in human diseases and the consequences of their inhibition. In this review, we compare between MAO-A and MAO-B effect from many aspects that includes heart failure, renal carcinoma, breast cancer, esophageal cancer, prostate cancer, bladder cancer, glioma and diabetes. And finally, the role of MAO inhibitors and their effects also have been discussed.

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INTRODUCTION

About a century ago Mary L.C Hare announced about monoamine oxidases (MAO) discovery specifically in 1928. First MAO was named tyramine oxidase. Tyramine oxidase opens the gate for scientists to study the potential effect of MAO as biological targets and in the discovery of drugs related to neurological diseases. Monoamine oxidases (MAO-A and MAO-B) are groups of mitochondrial-bound flavoproteins catalyzing the oxidative deamination of monoamine neurotransmitters to their correspond-

ing aldehydes. The binding of flavoenzyme (E–FAD) to monoamine neurotransmitter yield's the respective ammonia and aldehyde *by* reducing the flavin adenine dinucleotide (FAD) co-factor toward $FADH_2$. This step is proceeded by conversion of the aldehyde to either alcohol (glycol) by aldehyde reductase or carboxylic acid *through* aldehyde dehydrogenase. (Maggiorani *et al.*, 2017)

As a result, MAO plays a critical role in the (peripheral and central) nervous system through affecting the levels of monoamine neurotransmitters. Monoamine neurotransmitters include serotonin (5-hydroxytryptamine, 5HT), dopamine, norepinephrine, epinephrine, and a large number of trace amine such as tryptamine, tyramine, 2-phenylethylamine, etc. Even though both isoenzymes expressed in almost all body tissues but MAO-A specially expressed in placenta and fibroblast.

Where MAO-B is expressed in lymphocytes and platelets. All over both MAOs are present in almost all brain regions. MAO-A is generally concentrated in dopaminergic and norepinephrinergic neurons. Contrary to MAO-B, which predominantly concentrated in serotoninergic neurons. According to an extraordinary breakthrough in the pharmacotherapy of mental disorder, the unexpected discovery of the role of MAOs blockade in enhancing mood gave the first indication on the role of MAO in behavioural effects. Therefore, the antidepressant effects of MAO inhibitors is mostly related to blockade of MAO-A. (Fiedorowicz and Swartz, 2004)

Contrariwise, the other isoform (MAO-B) has found to play a major therapeutic effect in the treatment of Parkinson's disease. As Parkinson's disease principally linked to a reduction in dopamine neurotransmitter level. Upon clinical observations and pharmacological analysis, it's lead to concept development about the neuro-protection, slowing, reversing neuro-generation in Parkinson's and Alzheimer disease. All of the above-mentioned diseases are mainly related to the high level of oxidative stress in the brain. The high level of oxidative stress plays a central role in generation, initiation, and progression of neurodegeneration diseases. Therefore, inhibition of MAOs plays a significant therapeutic role in such diseases. (Uttara *et al.*, 2009)

MAOs Physiological Effects

Both MAOs share an imperative physiological role in the human body, whether in the peripheral, central nervous system or even in the degradation of any monoamines whether they were endogenous monoamine neurotransmitters or dietary amines. According to the central nervous system, both MAOs act through protecting neurons from exogenous amines, regulate the intracellular amines stores and finally terminate the actions of amines neurotransmitters. While for peripheral tissues, MAO prevents the entrance of dietary amines into the circulation by oxidative catabolism of these amines.

From different aspects, in a way to profoundly understand the physiological role of MAOs, Studies on the effect of MAOs gene deletion in mice was done in a way to improve the essential influence of MAO in the human body. It's found that MAOs gene knockout in mice has led to elevated serotonin, norepinephrine, and dopamine levels. All these effects generally attributed to MAO-A deficiency. Whereas MAO-B deficiency, associated with a high level of 2-phenylethylamine. An effect similar to the administration of non-selective MAO-inhibitor was observed, especially through high reactivity to stress. (Youdim *et al.*, 2006)

Impaired impulse control and mental retardation are the main consequences of MAO-A deficiency. For MAO-B deficiency, it tends to produce intermittent hypotonia and stereotypical hand movement. So it could be concluded that both MAOs are essential for neuronal development.

Another study on MAO-A knocks out have shown the essential effect of MAO-A on the neurons aggregation to form barrels and the development of normal thalamocortical axons. (Rebsam *et al.*, 2005). Studying the by-product of MAOs which are aldehyde, ammonia, and H_2O_2 (which is considered reactive oxygen species) that is toxic if present at high concentrations or the H_2O_2 will be converted to hydroxyl radical in the presence of free Fe^{+2}. Low levels of aldehyde dehydrogenase, which is important for the degradation of aldehyde intermediate, are also considered toxic to biological systems and also related to oxidative stress. (Singh *et al.*, 2013)

Role of MAO-A/ MAO-B in Cardiac Myopathy

Neuro-hormones (Norepinephrine and Dopamine) that is released by symptomatic fiber, and epinephrine that is released by the adrenal gland play a modulatory influence on the cardiac muscle. Heart failure mainly characterized by the augmented entry of catecholamine into the myocardium through up-regulation of monoamine transporter activity. All these promote the catalytic activity of MAO-isoenzymes. (Kaludercic *et al.*, 2014)

From observing the physiology of diabetic cardiomyopathy, it is noticed that it is mainly related to oxidative stress. One of the key sources of oxidative stress is the mitochondrial flavoenzyme MAO-A in the myocardium. Umbarkar *et al.* studied the role of

MAO-A in modulating diabetic cardiomyopathy. The study was done via inducing diabetes in Wistar rats by using streptozocin. The rats were treated with clorgyline. In order to understand the mechanism of apoptosis, certain markers were monitored such as superoxide dismutase activity, UCP3 protein expression and cardiac lipid peroxidation. All the markers approved that MAO-A participates in cell death apoptosis and raised up fibrosis through oxidative stress mechanism. At the same time, treatment with clorgyline prevents cardiac contractile dysfunction. So it is concluded that MAO-A is an essential source of oxidative stress in the heart and the resulting reactive oxygen species. (Umbarkar *et al.*, 2015)

Recent studies show that genetic and pharmacological inhibition of MAO-A leads to the prevention of heart failure in pressure overloaded mice. This action is mainly related to the prevention of oxidative stress mainly (H_2O_2) apoptosis in cardiac muscle and improved bioavailability of Norepinephrine. All these events lead to maintain proper left ventricular morphology and function. In spite of chronic cardiac stress conditions as a result of pressure overload. (Bianchi *et al.*, 2005; Santin *et al.*, 2016)

Parini's group research found that MAO-A considered as the most important source of myocardial reactive oxygen species. ROS can induce different signaling pathways. These signaling pathways may induce cell proliferation, apoptosis and hypertrophy (Mialet-Perez *et al.*, 2007). Bianchi *et al.* found that low levels of serotonin are able to prompt cardiac myocyte hypertrophy through ERK1/2 activation, which is an important signaling pathway that promotes cell growth (Figure 1). (Bianchi *et al.*, 2005)

The use of MAO-A inhibitors showed that serotonin-induced hypertrophy contains two main actions: the first one in vascular smooth muscle cells, where serotonin receptor stimulation-induced ERK phosphorylation. While the other action involves H_2O_2 formation by MAO, responsible for translocation of ERK into the nucleus. (Bianchi *et al.*, 2005)

In an *in vitro* study, MAO showed to play a role in norepinephrine-induced hypertrophy. Mainly via MAO-A generation of ROS. (Kaludercic *et al.*, 2010) The main mechanism thought to involve nuclear factors of activated T cells 3 and 4, and transcription factors contribute to maladaptive hypertrophic signaling. On the other hand, MAO-B is highly present in heart tissues. Kaludercic *et al.* showed that MAO-B is essential for proper catecholamine clearance and cardiac function. Under oxidative stress conditions, such as pressure overload, MAO-B activity participates in oxidative stress, structural and heart's functional derangements. (Nina Kaludercic et al., 2014)

A study reveals that both MAOs (A/B) expression in the myocardium increased in dogs upon aging that leads to congestive heart failure, which is mainly induced by tachy-pacing. (Ojaimi *et al.*, 2007)

Role of MAO A/B in many Renal Diseases

Development of ischemia/ reperfusion-induced acute kidney injury is mainly as a consequent effect of renal sympathetic nerve activity, essentially through Norepinephrine overflow from the nerve ending. Renal denervation and ganglionic blockade entrance during renal ischemia and post-ischemic acute kidney injury is accompanied by the low level of norepinephrine. That is usually high after reperfusion.

Isatin that is considered as endogenous MAO inhibitor found mainly in peripheral tissues. It is principally responsible for the regulation of Norepinephrine metabolism and blood pressure (Hamaue, 2000). Therefore, the cause and increase in norepinephrine concentration are strake-prone spontaneously in hypertensive rat brain. (Hamaue, 2000). The major contribution of MAO inhibitor is through an increase in catecholamine levels that lead to decrease production of reaction oxygen species and high norepinephrine level in renal venous plasma. Norepinephrine is generally metabolized by MAO in the kidney. A study showed that localized norepinephrine overflow in the kidney participates more to kidney pathogenesis and ischemia/reperfusion-induced acute kidney injury. Therefore, this effect is more dangerous than ROS effect on the kidney. (Tanaka *et al.*, 2013)

According to renal cancer, there is a major difference in expression of MAO-A and MAO-B in renal diseases. It is found that MAO-A is expressed in elevated levels in high-grade tumors of renal cell carcinoma. MAO-A percentage is raised from 9 to 45% in grade 2 and 3, respectively. (Hodorova *et al.*, 2012; Hodorová *et al.*, 2018). Also, it is noticed in normal renal tissues that MAO-A immune-reactivity present at high levels in epithelial cells of proximal tubules. On the other hand, MAO-A was almost absent in epithelial cells of distal tubules glomerular capsules, and in endothelial cells of renal vessels. (Hodorova *et al.*, 2012)

Hodorova *et al.* Studied the expression of MAO-B in both normal and carcinoma renal cells. It was found that MAO-B present in only 19% of kidney tumors, Concurrent with low protein expression. So it is concluded that MAO-B expression had no signif-

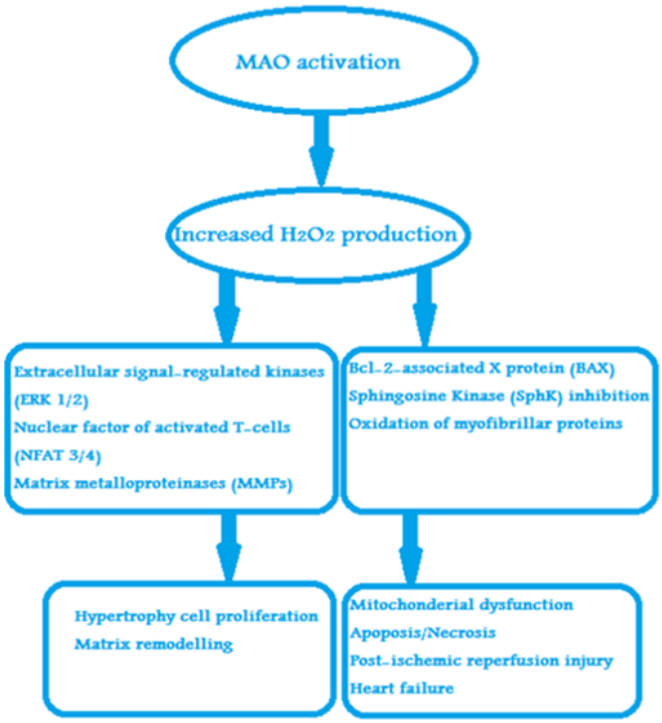

Figure 1: Cell survival pathway induced by a high level of H_2O_2. Generation of high H_2O_2 levels by MAO can trigger several signaling pathways in different types of cells

icant role in renal cancer development in contrast to MAO-A. (Hodorová *et al.*, 2018)

Role of MAOs in Diabetes

MAO plays a significant role in oxidative stress that mediated endothelial dysfunction in diabetes. A study on rats used steptozotocin induced diabetes; it is found a great enhancement in the regulation of both MAOs isoforms expression in aortas. Inhibition of both MAO-A and MAO-B using clorgyline and selegiline, respectively, showed a reduction in vascular contractility and improvement of endothelium-dependent relaxation. A 50% reduction in hydrogen peroxide was noticed after MAO inhibitor was used in diabetic aortic samples. (Sturza *et al.*, 2015). An experimental model of Zucker diabetic fatty rats, besides improvement in vascular reactivity, reduction in oxidative stress by more than 50% after using MAO inhibitors in type II diabetic models. (Sturza *et al.*, 2014)

Others studies demonstrated that incubating aortic samples from rats with high glucose caused a significant increase in MAO-A expression. While vitamin D incubation in aortic rings of diabetic rats showed a reduction in MAO expression and improvement in vascular reactivity. (Sturza *et al.*, 2019)

MAO-B is the major isoenzyme found in coronary heart disease patients, particularly in arteries, whether the patients are diabetic or not. In general, MAO inhibitors work through vascular relaxation improvement and oxidative stress diminishing. (Lighezan *et al.*, 2016)

Role of MAOs in Cancer

In 2018, cancer caused 9.6 million deaths, as cancer considered as the second prominent cause of death. Biological changes are one of the main goals in cancer research as it distinguishes between normal and cancerous tissues. A common method in detecting oncogenes is the evaluation of gene expression in each cancer type and link it to healthy tissue of the same organ. Comparison between cancer and non-cancer cells in a single type of cancer (breast cancer) or even a class have led to the potential development of an oncogenic mechanism that helped in developing therapeutic strategies in each type of cancer (Rybaczyk *et al.*, 2008). Bharti *et al.* studied breast cancer and the expression of MAO-A in it. Also, they studied IL-6/IL-6R expression. Particularly, in the hypoxic environment of the breast cancer model, they observed the co-relation between MAO-A and IL-6/IL-6R and tumor angiogenesis/invasion. In hypoxic cancer cells, activation of IL-6/IL-6R and it's downstream shown. As a consequence of IL-6/IL-6R elevation, MAO-A level showed inhibition in a hypoxic environment. While Inhibition of IL-6R signaling or IL-6R siRNA showed a high level of MAO-A activity. And this leads to inhibition of tumor angiogenesis and invasion. On the other hand, it was using 5-azacytidine (5-Aza) rais-

ing MAO-A level that leads to modulation IL-6 mediated invasive and angiogenesis signatures, including MMPs, VEGF, and EMT in hypoxic breast cancer. Also, High-grade invasive ductal carcinoma (IDC) clinical specimen shown to have depleted MAO-A expression and high level of IL-6R. Also, in high-grade IDC tissue specimen Shown to have unregulated expression of HIF-1α and VEGF and loss of E-Cadherin (Bharti *et al.*, 2018).

Breast tumor-initiating cells are the driven force for breast tumor growth and recurrence. It is noticed that breast tumor initiating cells occur in a magnitude order higher as breast tumor cells as they are propagated in vitro in comparison to adherent cells as clonal spheres. It is observed that serotonin antagonist were among the hits compounds. Expression of high levels of MAO-A transcripts and protein compared to adherent cells was showed by Tumorspheres derived from human breast cancer cell lines. Unexpectedly, MAO-A inhibition with selective inhibitors decreased tumorsphere-forming cells frequency. It is also noticed that one of the common features of human breast tumor cell lines is raised MAO-A expression. This effect is especially noticed with high-grade, ER-negative (ER^-) breast tumors. (Gwynne *et al.*, 2019)

According to prostate cancer, the determining factor for recurrence after radical prostatectomy is Gleason grade 4/5. Peehl *et al.* found that MAO-A is overexpressed in grade 4/5 in comparison to grade 3. Normal basal cells also express MAO-A. It is thought that it works through repression of secretory differentiation. Consequently, MAO-A, which is found in 4 and 5-grade cancer, might reveal de-differentiation to a basal cell-like phenotype. It is concluded that 4 and 5-grade cancer may be naturally found in basal cell-like from the expression levels of CD44 and MAO-A, even though the absence of additional typical biomarkers like p63 and cytokeratins 14 and 5. The association between prostate-specific antigen with MAO-A expression and the per cent of 4 and 5-grade cancer proposes that MAO-A may participate in the growth of a high-grade type of cancer. While antidepressant drugs may participate in treating prostate cancer. (Peehl *et al.*, 2008).

Goller et al. used [C-11] harmine. He used it in the characterization of expression of MAO-A in samples taken from patients with a urinary bladder tumor. Results of this study indicated that urinary bladder cancer specimens have a high expression of this enzyme. As the positron emission tomography and [C-11] harmine is available, it is obvious that detection of MAO-A in bladder cancer is reasonable and it is applicable either for treatment or diagnosis. (Goller *et al.*, 1995)

One of the common malignancies all over the world is esophageal cancer. It is associated with a high mortality rate as it is diagnosed late due to lack of diagnostic tools. Yang *et al.* analyzed 50 tumor tissues of primary esophageal cancer. The study showed decreased in MAO activity and expression in 48 (96%) and 44 (88%) patients, respectively. So it is concluded that MAO expression and activity can be employed as a diagnostic marker for esophageal cancer (Yang *et al.*, 2009). Chen *et al.* found that MAO-A is an important mediator of glycolysis and mitochondrial homeostasis in gastric tumor progression. Immunohistochemistry and Western blot analyses was used for examining MAO-A expression in both gastric cancer cell lines and tumor. In order to evaluate MAO-A effects on gastric cancer cell proliferation, FACS, CCK8 and bromodeoxyuridine incorporation assays were made. ATP generation, MitoSOX Red staining, and glycolysis assays were used to assess the MAO-A role in mitochondrial function. It is observed an upregulation of MAO-A in gastric cancer tissues and in AGS and MGC803 cell lines. It is also noticed decreased cell proliferation and cycle progression as MAO-A inhibited. In vitro, suppression invasion and migration of gastric tumor cells was noticed upon silencing MAO-A expression. Furthermore, lower mitochondrial damage in cell lines demonstrated by diminished mitochondrial ROS levels and improved ATP generation. Expression of the glycolysis rate-limiting enzymes pyruvate dehydrogenase and hexokinase 2 was regulated by MAO-A knockdown. Lastly, it is noticed that MAO-A blockade weakened the glycolysis effect in AGS and MGC803 cells. So it is concluded that MAO-A is mainly concerned with aerobic glycolysis and mitochondrial dysfunction, where human gastric tumor cells proliferation and metastasis occur as a consequence of this effect. (Chen *et al.*, 2020)

MAO Inhibitors

Starting as early as the fifties, isoniazid (anti-tuberculosis treatment) appeared to improve mood and constrain MAO activity. Nowadays, there are a large number of MAO inhibitors. Whether they are selective or not, they fall into categories of reversible and irreversible inhibitors. These inhibitors proved to be an effective medication in many illnesses such as affective disorders, neurodegenerative diseases, etc.

Phenelzine classified as non-selective, and irreversible MAO inhibitor that relates to hydrazine class. It is used in the treatment of many diseases such as panic disorder, post-traumatic stress

disorder, dysthymia, and bipolar depression. In March 2020, it is involved in phase II clinical trial in prostate cancer treatment. (Gross *et al.*, 2020)

MAO-A enzyme is significantly expressed in both normal basal cells of the human prostatic epithelium, in Gleason grades 4 and 5, and finally in aggressive prostate cancer. One of MAO-A inhibitors is Clorgyline, and it works through induction of secretory differentiation of normal prostate cells. It is found that many genes in the Polycomb Group repression signature that predicts aggressive prostate cancer outcome were upregulated by clorgyline, this leads to a conclusion that downregulation of EZH2 enzyme mediates the differentiation-promoting effect of clorgyline. It is known that MAO-A, previously in the clinical application used for the treatment of depression, may have possible application as therapeutic PCa drugs via promoting differentiation and inhibiting oncogenic pathway activity (Zhao *et al.*, 2009). Wang et al. studied the antiandrogen enzalutamide and MAO inhibitors in resistant prostate cancer patients. Enzalutamide has shown survival in cases with resistant prostate cancer, but many cases showed resistance to the antiandrogen drug. That may include inducing the androgen receptor (AR) splicing variant 7 (ARv7). It is informed that a high expression of MAO-A is linked with positive ARv7 detection in prostate cancer patients after taking enzalutamide. As it is known that FDA approved phenelzine and clorgyline for antidepression, in this study, it was shown that these drugs also act through resensitizing the enzalutamide resistant cells to enzalutamide treatment and more suppress enzalutamide resistant cell growth in vivo and in vitro. (Wang *et al.*, 2020)

Selegiline is an MAO-B irreversible inhibitor. That act primarily through raising dopamine levels in the brain. It is used mainly in Parkinson's disease and major depressive disorder treatment. MAO-B inhibitors have a synergistic effect when combined with choline esterase inhibitor for Alzheimer disease treatment. Selegiline showed a reduction in peripheral tissue damage as a consequence of cardiac failure and cerebral ischemia. On the other hand, pargyline (MAO-B inhibitor) proved to reduce heart rate, blood pressure and lastly amine oxidase activity. (Edmondson and Binda, 2018). MAO inhibitors also reported having anticonvulsant activity, especially the irreversible class. Tranylcypromine showed great anticonvulsant activity but not approved clinically because of the severe adverse effects. Loscher *et al.* studied the two types of MAO inhibitors, MAO-A and B respectively and their effect as an anticonvulsant. Esuprone showed to be the most effective anticonvulsant, so it could be considered as a promising approach in epilepsy treatment. (Löscher *et al.*, 1999). Glioblastoma is a public, greatest malignant brain tumor that is problematic to treat. Natural plant antimicrobial solution called PAMs that is considered a Chinese herbal medicine mixture. It contains an active constituent called Shikonia. It showed MAO-A inhibition. It was noticed that MAO-A enzyme participates in migration and progression of glioma. In addition, inhibitors of this enzyme participate in the reduction of glioma cell growth. One of the main therapy used for glioma is Temozolomide. Tumors develop resistance and reoccurrence usually happens. Moreover, we know that no effective treatment for this resistance is present. Testing three cell lines U251R, GL-26, U251S. PAMs showed inhibition to MAO-A catalytic activity, and as a consequence reduction of glioma growth. The effect of tumor growth reduction and MAO-A inhibition was almost similar to clorgyline effect. So it is concluded that MAO-A inhibition approved to reduce glioma drug resistance. (Li *et al.*, 2020)

CONCLUSION

MAO isoenzymes were discovered in the early decades of the last century. They work primarily through oxidative deamination of amines into their corresponding aldehydes and ketones. Both MAOs act by regulating MAO neurotransmitters in the human body. MAO isoenzymes produce oxidative stress through H_2O_2 production and this showed an apoptotic effect on the cardiac muscle. MAO-A appeared to be expressed in renal carcinoma cells more than MAO-B. Also, MAO-A appears to have an important role in prostate cancer, as inhibition of this enzyme showed a great effect on disease progression. MAO inhibitors produce a protective effect on the cardiac muscle. Finally, it is concluded that both MAOs have a principle role in many diseases and MAO inhibitors needed more investigations to explore their specific effect in a large number of human disease.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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