ROLE OF MAO INHIBITORS IN DIABETIC NEPHROPATHY

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ABSTRACT
Diabetic nephropathy is the leading cause of chronic kidney disease and is associated with increased cardiovascular mortality. Diabetic nephropathy has been classically defined by the presence of proteinuria >0.5 g/24 h. This stage has been referred to as overt nephropathy, clinical nephropathy, proteinuria, or macro albuminuria. It seems to occur as a result of an interaction between metabolic and hemodynamic factors. Hyperglycemia induces oxidative stress and leads to activation of multiple biochemical pathways which are the source of renal damage. Limited therapies are available as a symptomatic treatment which emphasize the need for more therapies to treat diabetic nephropathy. Monoamine oxidase (MAO) and its substrates are found in both the exocrine and endocrine parts of pancreatic beta cells. Many studies have showed that MAO-catalyzed reaction may cause structural damage to pancreatic beta cells resulting in disturbances in catecholamine’s metabolism and MAO also generate reactive oxygen species, which plays important role in pathogenesis of diabetic complications. Therefore inhibition of MAO can lead to the secretion of insulin. Thus the purpose of this review is to cover the role of MAO inhibitors as the new therapeutic approach in diabetic nephropathy.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both [1]. Development of diabetes involves several pathogenic processes like autoimmune destruction of the beta-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues [2]. There are two major forms of diabetes: type 1 and type 2 diabetes mellitus. Type-1 diabetes is primarily due to absolute deficiency of insulin resulting from autoimmune destruction of pancreatic β-cells and such individuals have tendency to develop ketosis. Type-2 diabetes is accompanied by insulin resistance and/or abnormal insulin secretion and increased glucose production [3]. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as β cell function declines [4]. In conventional therapy, type-1 diabetes is treated with exogenous insulin [5] and type-2 with oral hypoglycemic agents like sulfonylureas, meglitinides, and metformin etc [6].

In diabetes, hyperglycemia shows its injurious effects causing various complications which include micro vascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macro vascular complications (coronary artery disease, peripheral arterial disease, and stroke) [7]. These complications occur due to the hyperglycemia-induced tissue damage in capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves. This tissue damage apart from hyperglycemia is modified by both genetic determinants of individual susceptibility and by independent accelerating factors such as hypertension. Damage occurs only in the few cell types involved in diabetic complications as most cells are able to reduce the transport of glucose inside the cell when they are exposed to hyperglycemia, so that their internal glucose concentration stays constant. In contrast, the cells damaged by hyperglycemia are those that cannot do this efficiently. Thus, diabetes selectively damages cells, like endothelial cells or mesangial cells, whose glucose transport rate does not decline rapidly as a result of hyperglycemia, leading to high glucose inside the cell [8].

Mechanism of MAO in generation of free radical

In kidney, dopamine plays an important role in the regulation of different renal functions, like renin production, sodium excretion and glomerular filtration [9]. Most of the renal dopamine is produced by proximal tubule cells [10]. As shown for dopaminergic presynaptic endings, proximal tubule cells contain all the enzyme machinery necessary for dopamine synthesis. On the other hand, these cells are also one of the major targets of dopamine for regulation of tubule sodium reabsorption by a D1 and D2-like receptor stimulation [11]. The renal dopamine availability depends on the activity of the monoamine oxidases. Monoamine oxidases, catalyzes the oxidative deamination of biogenic amines such as serotonin, noradrenaline, tyramine, and dopamine, and is a potential source of reactive oxygen species. One of the reaction products generated by MAO during degradation of substrate is hydrogen peroxide. Studies have shown that H₂O₂ acts as a proliferative or apoptotic factor at low or high concentrations, respectively, some studies suggests that, at higher concentrations than those inducing proliferation of proximal tubule cells, H₂O₂ produced by MAO may have apoptotic properties [12, 13]. Furthermore, Due to generation of these free radicals oxidative stress is enhanced in kidneys which leads to activation of various pathways leading to Glomerular hypertrophy, Decline in glomerular filtration rate resulting in Nephropathy.

Diabetic nephropathy (D.N)

Diabetic nephropathy is serious secondary consequence of diabetes resulting in end stage renal disease caused by angiopathy of capillaries in the kidney glomeruli. It’s also known as Kimmelstiel-Wilson syndrome or intercapillary glomerulonephritis or may also be termed as nodular diabetic glomerulosclerosis [14]. British physician Clifford Wilson (1906-1997) and American physician Paul Kimmelstiel (1900-1970) were the first one who described the syndrome in 1936[15]. It is a clinical syndrome due to longstanding diabetes mellitus characterized by albuminuria (>300 mg/day or >200 mcg/min), irreversible and permanent decrease in glomerular filtration rate (GFR), and diffuse glomerulosclerosis and is a prime indication for dialysis [16].

Stages in the development of diabetic nephropathy are as follows:-

Stage-I:

This is termed as early hypertrophy-hyper function stage [17]. In this stage, Glomerular Filtration Rate (GFR) is increased due to glomerular hyper filtration. This occurs as a result of initial or ongoing injury due to hyperglycemia causing functioning nephrons loss. As to maintain kidney homeostasis each remaining nephron works harder, filtering more blood due to which the size of the kidneys is increased called kidney hypertrophy and renal plasma flow is also increased due to both low afferent and efferent arteriolar resistance, leading to increased glomerular capillary pressure and thus increased GFR. This situation, called hyper filtration, anticipates the eventual deterioration of renal function, damaging the glomerular capillary in ethereal ways, producing mesangial cell and glomerular basement membrane injury, and stimulating release of cytokines. All of these effects further produce rigorous injury and scarring of the remaining nephrons with further nephron loss [18, 19].

Unfortunately, in early stages of diabetic nephropathy there are no symptoms; however, stage I is reversible with early detection and proper glycemic control [20].

Stage-II:

It’s termed as Glomerular lesions without clinical disease stage. This silent stage develops over many years with structural lesions on biopsy but without clinical or laboratory signs of renal disease [17]. Its Characterized by basement membrane thickening which occurs as a consequence of extracellular matrix accumulation, with increased deposition of normal extracellular matrix.
components such as collagen types IV and VI, laminin, and fibronectin. Such accumulations result from increased production of these proteins, their decreased degradation, or a combination of the two. In this stage mesangial proliferation also occurs due to hyperfiltration. Mesangial expansion is defined as an increase in extracellular material in the mesangium such that the width of the interspace exceeds two mesangial cell nuclei in at least two glomerular lobules. The difference between mild and severe mesangial expansion is based on whether the expanded mesangial area is smaller or larger than the mean area of a capillary lumen. When the mesangium expands, it restricts and distorts glomerular capillaries and diminishes the capillary filtration surface. Thus, increasing GFR and stimulating release of cytokines, and resulting in kidney damage due to scarring of the remaining nephrons with further nephron loss. After certain duration GFR returns to normal values. Many patients remain in this stage until the end of their life [18, 21].

Stage III:
It’s known as the microalbuminuria stage (albumin 30-300 mg/dU) or initial/incipient nephropathy [17]. This is the first clinically detectable sign of glomerular damage. In this GFR begins to decrease as microalbuminuria appears. As albumin levels increase in the urine, levels in the blood are lowered allowing small amounts of albumin to be excreted in the urine by the damaged capillaries, resulting in noticeable edema. In addition, creatinine and blood urea nitrogen (BUN) levels also increase. These waste products accumulate in the blood which is termed as azotemia [20]. This leads to farther nephron loss, microalbuminaria, interstitial and glomerular scarring, and progressive renal failure [18]. Blood pressure may be increased or normal. Approximately 40% of patients reach this stage.

Stage IV:
It’s known as the overt diabetic nephropathy stage. Proteinuria develops (albumin > 300 mg/dU), GFR decreases below 60 mL/min/1.73 m2, and blood pressure increases above normal values [22]. Proteinuria is the hallmark of this stage; due to glomerular injury, permeability of the glomerular basement membrane increases and allows plasma proteins to escape into the urine, which results in proteinuria. Some of these proteins are absorbed by proximal tubular cells, triggering an inflammatory response that further contributes to interstitial scarring. The kidneys are no longer capable of excreting toxins and accordingly there is a progressive increase in Blood Urea Nitrogen and creatinine levels. Most people in this stage are hypertensive secondary to increased production of renin. Because hypertension accelerates the progression to End Stage Renal Disease, early detection is vital. If not treated at this stage, uremia and death will follow within 7 to 10 years [18, 20]

Stage V:
End-stage renal failure due to diabetic nephropathy, ESRD is when the kidneys fail to function, the GFR severely decreases, and hypertension continues to worsen. During this final stage, the kidneys cannot excrete toxins; maintain fluid, pH, and electrolyte balances; or secrete important hormones (renin, vitamin D, and erythropoietin). As a result, a multitude of symptoms become apparent that involve most major organ systems in the body [20]. Mostly patients with Terminal kidney failure need kidney replacement therapy like hemodialysis, peritoneal dialysis and kidney transplantation [23].

Risk factors for Diabetic Nephropathy
- Poor control of blood glucose: DN is more likely to develop in patients with lesser degree of glucose control, particularly if the Hemoglobin A1c concentration is above 11 percent [24].
- Long duration of diabetes [25]
- Hypertension is probably both a cause and an effect of diabetic nephropathy in the glomerulus, an early effect of systemic hypertension is dilatation of the afferent arteriole, contributing to intraglomerular hypertension, hyper filtration, and hemodynamically mediated damage. Renal responsiveness to the renin-angiotensin system may be abnormal in the diabetic kidney [26].
- Genetic factors like: insulin resistance:-The exact genetic model underlying DN susceptibility is uncertain, but theoretically few genes with a major contribution and some with minor interaction with the environment could cause DN [24]
- Smoking: Several lines of evidence have shown that smoking increases the risk and progression of diabetic nephropathy [26]

Pathogenesis of diabetic nephropathy
Diabetic nephropathy is caused by both metabolic alterations (hyperglycemia and possibly hyperlipidemia) and hemodynamic alterations (systemic and glomerular hypertension). Glucose dependent pathways are also activated within the diabetic kidney which result in increased oxidative stress, renal polylol formation and the accumulation of advanced glycation end products (AGEs). In combination, these pathways lead to enhanced renal albumin permeability and extracellular matrix accumulation, resulting in increasing proteinuria, glomerulosclerosis and ultimately tubulointerstitial fibrosis [27].

Haemodynamic pathways
Decreased resistance in efferent and afferent arterioles of the glomerulus leads to the early signs of Glomerular hyperfiltration and hyperperfusion. Various factors seem to be involved in this faulty autoregulation, inclusive of nitric oxide, vascular endothelial growth factor (VEGF), TGF-β1, and the rennin angiotensin system, particularly angiotensin II, due to these hemodynamic changes leakage of albumin increases from the glomerular capillaries, glomerular basement membrane thickens, increases harm to podocytes and also leads to overproduction of mesangial cell matrix. Moreover, enhanced mechanical exertion from these
hemodynamic changes induces localized release of certain growth factors and cytokines. Actions of angiotensin II and endothelin partly mediate these renal haemodynamic changes [28]. For example, exposing mesangial, glomerular endothelial or podocytes to shear stress induces specific cellular responses including activation of certain signal transduction systems, growth responses, enhanced synthesis of hormones and cytokines (e.g. ANG II, TGF-β1), and increased production of extracellular matrix proteins. These findings suggest that local haemodynamic stress contributes to the structural changes of diabetic nephropathy by the local activation of cytokines and growth factors [29].

**Renin-Angiotensin-Aldosterone System (RAAS)**

One of the best described and most researched vasoactive hormonal pathways in the pathophysiology of diabetic nephropathy is the RAAS. The RAAS is a major regulatory system involved in blood pressure control as well as in water and electrolyte homeostasis. An important role for the RAAS is regulating cell growth and differentiation, extracellular matrix (ECM) metabolism, and inflammation in chronic diseases, such as diabetic nephropathy. In addition, recent studies have suggested that metabolites of Ang II, including Ang (1-7) and Ang (1-9), may have important biological activities in diabetic nephropathy [30].

**Endothelin-1 and Thromboxane**

Vascular endothelium produces a potent vasoconstrictor peptide called Endothelin-1. It’s involved in diabetic renal growth. In the glomeruli and tubular epithelial cells diabetes mellitus induces the renal overflow of ET-1 which contributes to diabetic nephropathy, and also increases prostaglandin production like thromboxane contributing to early proliferation of mesangial cells [31].

**Metabolic pathway**

Diabetes has been classified as a disease of glucose overproduction by tissues, mainly liver and glucose underutilization by insulin requiring tissues like liver, adipose and muscle due to lack of insulin. There is, however, glucose over utilization in tissues not dependent on insulin for glucose transport like kidney, nerve and brain. There are serious complications due to this excess glucose in these tissues and their reversal is important for a good metabolic control and normalisation of other parameters. Almost complete reversal of the metabolic changes has been achieved in the activities of key enzymes of metabolic pathways in kidney and liver and an effective glucose control has been achieved suggesting a combination of therapies in the treatment of metabolic disturbance of the diabetic state [32].

**Advanced Glycation End Products (AGEs)**

Advanced Glycation pathway is of particular importance in diabetic nephropathy. These are chemical compounds of heterogeneous group which are formed when reducing sugars react with amine residues non-enzymatically, especially lysine and arginine, on proteins, nucleic acids and lipids and this process is termed as the “Maillard reaction”. The initial stage of the reaction is rapid and leads to the formation of Schiff bases i.e., reversible glycosylation proteins and over a period glucose dependent, a much slower reaction results in the formation of the Amadori product which is more stable [33]. These early glycosylation products gather principally on vessel wall collagen where they are subjected to a series of in vivo rearrangements and modifications leading to the generation of irreversible, complex compounds, called as AGEs. AGEs interact with specific receptors and best-characterized receptor is receptor for AGEs (RAGE) [34].

AGE receptors are present on various renal cell types including mesangial cells, podocytes, and proximal tubular cells. AGE promote activation and expression of IL-6 and TGFβ1 via NF-kB dependent pathways. The main site for reabsorption of filtered AGEs is the proximal tubule. TGF-β1 expression is closely linked to accumulation of AGEs in the kidney. AGEs are thought to lead to the transcriptional up-regulation of TGF-β1, possibly via PKC or oxidative stress. AGEs also enhance the formation of free radicals directly through catalytic sites in their molecular structure and also through the RAGE receptor by stimulation of membrane bound NADPH oxidase and exhaustion of cellular antioxidant systems, such as glutathione peroxidase. Mitochondrial dysfunction induced by AGEs and carbonyl intermediates may also contribute to the generation of superoxide. AGE contribute to the release of proinflammatory cytokine and expression of growth factor and adhesion molecule such as VEGF and CTGF, TGF-β1, IGF-1, PDGF, TNF-α, IL-1β, and IL-6 [35].

**Polyol pathway**

In cell, unused glucose in the cytosol is diverted to the polyol pathway, which involves two enzymatic reactions: the first is the reduction of glucose to sorbitol by the action of aldose reductase using NADPH, and the second oxidation of sorbitol to fructose by the action of sorbitol dehydrogenase (oxidation of sorbitol increases NADH) with a resultant rapid change in the cytoplasmic redox state and increased overflow of ROS. Decreased NADPH may compromise glutathione reduction in oxidatively stressed cells. However, chronic hyperglycemia enhances ROS generation and leads to excessive NADPH consumption in the polyol pathway, and inhibits decreased glutathione, which is the important substrate for glutathione-peroxidase mediated cellular antioxidant activity, thus ultimately resulting in disturbance of antioxidant property. Hence, polyol pathway is deliberated as a major source of ROS generation in the pathogenesis of diabetic nephropathy [36, 37].

**Protein kinase C pathway**

Activation of protein kinase C (PKC) isofoms has also been implicated in diabetic nephropathy. PKC is a family of serine-threonine kinases that are multifunctional isoenzymes involved in a range of cellular functions including expression of growth factors and regulation of basement membranes. PKC is activated by several mechanisms including enhanced DAG levels by De-novo

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synthesis or inhibition of DAG kinase. PKC α, β₁, β₂, δ, ε isoforms are observed in cultured mesangial cells, glomeruli, and tubules. Activation of PKC has effects on various intracellular signal transduction systems, including the enhancement of MAP kinase, cascades, and NADPH oxidases [38].

**Hexosamine Pathway**

It's activated when excessive metabolites of glycolysis accumulate. Intermediates in the pathway lead to changes in gene expression and protein function that contribute to the pathogenesis of diabetic complications [39]. Approximately 5% of glucose entering the cell is metabolized through the hexosamine biosynthetic pathway (HBSP), which converts glucose-6-phosphate into hexosamine-6-phosphate. Glutamine: fructose-6-phosphate-amidotransferase (GFAT) is the first and the rate-limiting enzyme of this pathway. In both mesangial cells and fibroblasts, GFAT overexpression, which increases the flux through the HBSP, leads to increased TGF-β and fibronectin expression. Very low level expression of GFAT is usually found in glomerular cells, but this is significantly enhanced in glomerular cells from patients with diabetic nephropathy, suggesting a potential in vivo relevance of the in vitro findings. Both high glucose and angiotensin II activate the GFAT promoter in mesangial cells, and this provides a potential molecular mechanism of GFAT overexpression in diabetic glomeruli [40].

**NADPH oxidase pathway**

In diabetes, NADPH oxidase is a major source of generation of ROS. It is located in plasma membrane of various renal cell types, including mesangial and proximal tubular cells, endothelial cells, vascular smooth muscle cells and interstitial fibroblasts. Due to activation of NADPH oxidase enzyme, it generates superoxides known as reactive free radicals. NADPH oxidase complex comprises several isoforms, which are the major source of ROS in the renal milieu and thus NADPH oxidase dependent overproduction of ROS play a key role in promoting hyperglycemia-induced oxidative stress. The NADPH oxidase increase oxidative stress and finally results in development of diabetic nephropathy.

The first step of the activation of NADPH oxidase is initiated following ligand: receptor interactions. The nature of ligands can vary from various cytokines (tumor necrosis factor-α and interleukin-1) to growth factors (platelet-derived growth factor, epidermal growth factor and transforming growth factor-β) to G protein-coupled receptor agonists (Angiotensin II, Ang II; serotonin, thrombin, bradykinin and endothelin); all these are amenable of activating NADPH oxidase followed by an increase of intracellular concentration of O₂⁻ and H₂O₂. In addition to the receptor-mediated activation, the mechanical forces, such as, stretch and shear stress, and metabolic factors like hyperglycemia, free fatty acids, and advanced glycation end products, are conceivably capable of modulating the activity of NADPH oxidase [36, 41].

**Reactive oxygen species (ROS)**

ROS are continuously generated in physiological condition and are effectively eliminated by several antioxidative systems. ROS includes mainly superoxide or hydroxyl radicals and other are alkoxyl, peroxyl, plus non-radical derivatives of oxygen, specifically hydrogen peroxide and ozone, which plays a major part in cell signaling, ageing and degenerative disease. The amount of ROS produced is finely balanced with the antioxidant activity and when it exceeds cellular defence power or diminishes the production of antioxidants can lead to increased oxidant-derived tissue injury or oxidative [42].

Reactive Oxygen Species are cytotoxic to renal cells and promote fibrogenic and inflammatory reactions in diabetic kidney. Hyperglycemia-induced enhanced mitochondrial ROS production plays a key role in the pathogenesis of DN [43]. In addition, it has been reported that ROS-mediated renal cell apoptosis is induced by hyperglycemia, angiotensin II, TGF-β and albumin. It has been noted that mitochondria-derived ROS constitute the major source of intracellular ROS that results in oxidative damage of lipids, proteins and DNA, ultimately leading to apoptosis and renal injury. Many renal cell types like mesangial cells, endothelial cells and tubular epithelial cells have been found to produce high levels of ROS under hyperglycemic conditions. ROS also activates several pro-inflammatory transcriptional factors which results in the production of vascular adhesion molecules, cytokines, and chemokines that subsequently lead to the influx of inflammatory cells into the kidney. This formation of ROS-mediated cell injury, apoptosis and kidney dysfunction. Moreover, the AGE-RAGE-mediated ROS generation stimulates production of pro-sclerotic growth factors such as TGF-β via mitogen-activated protein kinase and PKC pathways in both mesangial and renal tubulointerstitial cells. ROS-induced production of TGF-β1, the key regulator of Extra Cellular Matrix remodeling, causes mesangial expansion and tubular epithelial-mesenchymal transition leading to tubulointerstitial fibrosis, providing the proof of role of ROS in the progression of DN. Additionally, ROS has been noted to activate various transcription factors like NF-kB and activated protein-1 (AP-1) leading to upregulation of genes and proteins involved in the progression of DN [44].

Thus above evidence conveys that in the pathogenesis of diabetic nephropathy ROS plays a major role. Combination of strategies like glycemic control and/or inhibition of cytokines and growth factors prevent overproduction of ROS and conventional or catalytic antioxidants to increase the removal of preformed ROS may prove to be effective in preventing the development and progression of diabetic nephropathy [45].

**Carbonyl stress**

The accumulation of reactive di-carbonyl precursor or of glycoxidation or both and lipoxidation products is termed as carbonyl stress. That is the accumulation of carbonyl precursors whether they go on to form non-oxidative AGE or oxidative AGE derived from 3-deoxyglucosone-lysine dimer. This recently described phenomenon of carbonyl stress has been observed both in diabetes and uraemia and has been implicated in accelerated vascular damage observed in both conditions [46]. Carbonyl stress result from an increase in substrate stress and/or a decrease in the efficiency of detoxification of carbonyl compounds. The difference
between oxidative and carbonyl stress lies in the nature of carbonyl compounds, i.e., if the carbonyls are derived exclusively from oxidative reactions, then the condition would be described as oxidative stress. However, if the carbonyls are derived, in full or in part, from non-oxidative processes, then condition would be described as carbonyl stress [47].

Oxidative stress

In diabetes, increased production of ROS and sharp decrease in antioxidant defenses leads to oxidative stress and altered cellular redox status. Oxidative stress is a key component in the evolution of diabetic complications [48]. A no enzymatic source of oxidative stress includes glucose auto-oxidation, advanced glycation, the polyol pathway. The primary initiating event in the development of diabetic complications is $O_2^-$ formation by mitochondria. Engagement of RAGE with AGEs increases oxidative stress generation, thus participating in diabetic nephropathy. For example, oxidative stress may facilitate both the formation of intracellular AGEs and cross-linking in diabetes. In renal tubular epithelial cells hyperglycemia induced oxidative stress leads to an increased Bax protein expression accompanied by a reduced Bcl-2 expression leading to the apoptosis of renal tubular cells. Chronic hyperglycemia essentially facilitates a state of chronic oxidative stress in the renal milieu, the long-term consequence of which is progressive loss of glomerular and tubular cells. In diabetes, chronic hyperglycemia sustains the oxidative stress by excessive generation of ROS in glomerular and tubular cells, via overexpression of NADPH oxidase and contributes to renal tissue injury. The activation of glomerular sterol regulating element binding protein-1c (SREBP-1c) plays an important role in the progression of diabetic nephropathy by inducing NADPH oxidase-mediated oxidative stress in glomeruli. Diabetes-induced PKC-activation significantly contributes to renal accumulation of type IV collagen, laminin, and fibronectin by increasing the expression of TGF-β in the glomeruli of diabetic rats. The oxidative damage progresses concomitant with worsening glucose metabolism, vascular dysfunction, and kidney disease [49, 50].

Nephrin

For the maintenance of the dynamic functions Podocytes (specialized visceral epithelial cells) are important. Nephrin, a protein found in these cells, is important for maintaining the integrity of the intact filtration barrier. In diabetic nephropathy the renal expression of nephrin might be impaired. According to studies Patients with diabetic nephropathy have markedly diminished renal nephrin expression as compared with patients without diabetes. Furthermore, nephrin excretion is increased 17-30% in patients with diabetes (with and without albuminuria) as compared with that in individuals without diabetes. Thus, nephrin excretion could be an early finding of podocyte injury, even before the onset of albuminuria [51, 52].

MAO (Monoamine oxidase)

It is a flavoenzyme which is tightly associated with the outer membrane of mitochondria [53]. MAO catalyzes the oxidative deamination of biogenic and xenobiotic amines. It inactivates such biogenic amines such as serotonin, dopamine, noradrenaline, adrenaline and various trace amines, thus regulating their levels [54]. Furthermore, it’s a ubiquitous enzyme, which is found in all vertebrate and invertebrate tissues. Depending on their substrates and sensitivity to their inhibitors Monoamine oxidase are divided into two subtypes (MAO-A and MAO-B) [55].

Under normal physiological conditions MAO-A oxidizes norepinephrine and serotonin, and MAO-B oxidizes phenyl ethylamine preferentially substrates dopamine and tyramine for both isoenzymes irrespective of concentration [53].

At the subcellular level, MAO is located in the outer membrane of mitochondria. According to study reports MAO has been shown to be present in the islets of Langerhans of golden hamsters, rats and rabbits. It’s also present in a majority of pancreatic islet cells which indicates that MAO is apparently present in pancreatic beta cells. In islet of Langerhans MAO are sensitive to MAO inhibitors like deprenyl, clorglyline, pargyline, harmine, and tranylcypromine. Recent studies have showed that in both the exocrine and endocrine parts of human pancreas MAO-A and MAO-B are present. In the exocrine pancreas MAO-A is widely distributed. In contrast, MAO-B is shown in pancreatic ducts and centroacinar cells.

From rabbit pancreatic islets Hydrazine-type MAO inhibitors like phenelzine, potentiateins glucose-stimulated insulin release. Whereas some non-hydrazine MAO inhibitors such as harmine, induces insulin secretion. Studies have reported that MAO inhibitors enhances insulin secretion by reducing beta cell MAO degradation and these MAO-catalyzed reactions release the by-products like hydrogen peroxide, ammonia which cause structural damage to pancreatic beta cells and leads to the disturbances in catecholamine metabolism which plays an important role in the pathogenesis of the acute and chronic complications of diabetes mellitus [55].

In kidney, MAO represents one of the major DA metabolic pathways as kidneys contain one of the highest MAO activities, and one of the reaction products generated by MAOs during substrate degradation is Hydrogen peroxide ($H_2O_2$) [56].

Monoamine oxidase (MAO-A and B), result in formation of reactive oxygen species which might cause diabetic nephropathy (DN) contributing to reduced dopamine levels and to unbalanced kidney redox state. Evidences have suggested that MAO activity might have a role in many other chronic pathological conditions, characterized by tissue redox unbalance, with concurrence of diabetic nephropathy (DN), a long-term micro vascular complication and leading cause of morbidity and mortality of diabetic patients.

Experimental evidence has shown that, in the central nervous system, as well as in the kidney of rodents, angiotensin-II, by activating AT1, increases MAO activity thus increasing DA metabolism. These results designate MAO activity as a crossover of an intriguing relationship between dopamine and angiotensin-II, above all in those pathological conditions characterized by increased levels of angiotensin-II as in diabetes. In fact, in the diabetic kidney, angiotensin-II mediates the constriction of the efferent artery, enhances glomerular pressures, induces hypertrophy and increases tissue oxidative stress. Based on the above remarks, MAO levels might be found increased in DN. This increase might contribute to reduce the natriuretic effect of dopamine and to unbalanced cell redox state [57].
Studies have showed that in the Diabetic rat kidney, MAO-A activity correlated with gamma-GGT (gamma-glutamyl transpeptidase), suggesting a sort of causal relationship between MAO-A and ROS-dependent tubular damage participating to proteinuria. MAO (A+ B) is the main enzyme involved in dopamine degradation in the proximal tubule, the site where dopamine is also synthetized. Once synthesized, dopamine is transported outside the cell to activate tubular dopamine receptors thus exerting its natriuretic effect. Enhanced MAO activity in this site may reduce dopamine availability at the receptor site by contributing to reduce glomerular filtration efficiency. Dopamine is a common substrate for MAO-A and B, meaning that each isoform participates in its degradation depending upon isoform relative tissue expression. In normoglycemic kidney (N), where MAO-A and B showed almost similar levels of activity, dopamine is plausibly equally degraded by both isoforms. Thus, as a result of AT1 activation, the increase of MAO activity, might contribute to reduce dopamine levels, its natriuretic effect and, not less importantly, its receptor-independent hypertrophy effects [57].

MOH inhibitors bind to and inhibit MAO A and B, preventing dopamine degradation. This results in greater stores of dopamine available for release and reduced hepatic gluconeogenesis. Moreover, MAO inhibitors have been reported to suppress free radical formation, up-regulation of the antioxidant enzyme (superoxide dismutase and catalase) activities not only in the brain dopaminergic tissues but also in systemic organs like heart and kidney [58]. Studies have also reported that MAO inhibitors protect dopamine cells from apoptosis[59]. It has been demonstrated that the treatment with selegiline may be accompanied by hypoglycemic effects in both human and animals and this adverse property appears to be common for various MAO. These affect glucose synthesis in renal tubules due to its direct actions and inhibit renal gluconeogenesis [60].

Therefore due to reduced hepatic and renal gluconeogenesis and nephroprotective actions of MAO inhibitors they can be much useful in the treatment of diabetic nephropathy.

CONCLUSION

In the last several years, there has been enormous progress made not only in our understanding of the risk factors and mechanism of the development of diabetic nephropathy, but also in the treatment possibilities aimed at preventing the progression of diabetic nephropathy. MAO is found in pancreatic beta cells where it is co-localized with insulin in secretory granules. It’s reported that MAO inhibits insulin secretion. However, some of its substrates including, serotonin, adrenaline and noradrenaline have been shown to stimulate insulin secretion. MAO may play a key role in pancreatic beta cell function and in production of reactive oxygen species that leads to oxidative stress, hence in the pathogenesis of diabetes mellitus and its complications. Thus we may use MAO inhibitors in the treatment of diabetic nephropathy as some positive results have been reported but more studies are required for the stronger evidences.

Author’s Statements

Competing Interests
The authors declare no conflict of interest.

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