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REVIEW ARTICLE

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ROLE OF PEROXYNITRITE IN DIABETIC NEUROPATHY: PEROXYNITRITE DECOMPOSITION CATALYSTS

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ABSTRACT

Diabetes is a major problem in the world. Diabetic complications, due to the persistent hyperglycemia, involves formation of reactive oxygen species (ROS) from various pathways like, increased flux of glucose to polyol pathway, aldose reductase activation, formation of advanced glycation end products(AGE), activation of protein kinase-C(PKC) and activation of poly(ADP-ribose) polymerase. Peroxynitrite is the most potent reactive oxygen species (ROS) and studies have shown that it is capable of oxidizing the proteins, non-proteins and nucleotides. It may lead to cell death and tissue injury. Peroxynitrite is implicated in sensory and motor nerve deficits in rodent models. Peroxynitrite reacts too slowly with endogenous reducing agents, but, very efficiently with synthetic metalloporphyrins. Peroxynitrite decomposition catalysts correct the sensory and motor nerve deficits in rodents. Present review focuses on the beneficial effects of peroxynitrite decomposition catalysts in experimental diabetic neuropathy.

KEY WORDS

Nitric oxide, superoxide, peroxynitrite, diabetic neuropathy, peroxynitrite decomposition catalysts.

INTRODUCTION

At present, Diabetes is a major problem in the humans and it's number may increase to 366 million in the world by year 2025[1,2]. Diabetes is a group of metabolic disorders, but sharing the hyperglycemia is a common feature. Persistent hyperglycemia in diabetes leads to complications like retinopathy, nephropathy, neuropathy and autonomic dysfunctions. It is estimated that more than 50% of the diabetic patients suffer from diabetic neuropathy.[1,2] Etiology of diabetic neuropathy is complex, multifactorial and partly unclear.[2,4,5] Diabetic neuropathy is characterized by known interwoven pathways, including increased flux of glucose to polyol pathway, increased hexosamine shunt, aldose reductase activation, decrease in nerve myoinositol content, formation of advanced glycation end products[AGE](non-enzymatic glycation), hypoxia/ischemia, impaired neurotropic support leads to impaired insulin/C-Peptide action, activation of protein kinase C(PKC),activation of poly(ADP-ribose)polymerase(PARP) etc.[5,6-8] The above factors result in the formation of reactive oxygen species(ROS) which are the main source for the diabetic complications.[8] Other cellular sources for reactive oxygen species(ROS), i.e., superoxide anion, are NAD(P)H oxidases, the mitochondrial respiratory chain[5,9],xanthine oxidase, the arachidonic acid cascade(lipoxygenase &cycloxygenase) and microsomal enzymes.[6,7] Diabetic neuropathy is a progressive disorder which mainly affects the nervous system. It initially causes the loss of sensation and progress to cause ataxia and autonomic failure due to sensory, motor and autonomic neuron loss respectively.[10]

Present review reveals the role of peroxynitrite and benefits of peroxynitrite decomposition catalysts in diabetic neuropathy.

Formation of peroxynitrite:

Peroxynitrite is a highly reactive molecule that plays a crucial role in the pathogenesis of diabetes and its complications[11] by the destruction of islets of pancreas.[8] Peroxynitrite is formed by the combination of nitric oxide (NO), is a free radical messenger molecule[12] and superoxide anion ($O_2^{-\cdot}$)[1-16, 20, 26, 27]. The formation is a diffusion limited reaction (k=6.7x10^9 $M^{-1}s^{-1}$) in gaseous phase[12,13] and rapid in aqueous phase.[14,15] Small amount of nitric oxide (NO) (released by endothelial nitric oxide synthase) and superoxide (a product of normal cellular metabolism) are synthesized from endothelial cells, macrophages and neutrophills.[14,16] Nitric oxide is involved in the regulation of blood pressure, platelet adhesion, neutrophil aggregation and synaptic plasticity. Under pathological conditions, large amount of nitric oxide and superoxide are synthesized. Ex:- inflammatory hyperoxia[14,16], circulatory shock[12], ischemia and xenobiotic metabolism[16]. Nitric oxide is not a potent oxidant, its reactivity is increased by the reaction with transition metals or reactive oxygen species. Nitric oxide toxicity intensity depends on the subsequent reaction with reactive oxygen species (ROS).[12] Nitric oxide synthesis is increased from epithelium by acetyl choline, adenine nucleotide, calcium ionophores and bradykinins etc.[16]

Detrimental effects of peroxynitrite:

Peroxynitrite is a potent oxidant that easily crosses the cell membrane and enters into the nucleus and breaks the DNA strand. Other reactive oxygen species does not have

enough half-life to enter into the cells and breakage of DNA.[9,13] It has been shown to capable of oxidizing the proteins and non protein sulfhydryl groups[14,16] i.e., cysteine, tyrosine, tryptophan, methionine[12], glutathione[16], carbohydrates[12] and lipid membranes[6,13,17], as well as hydroxylating and nitrating aromatic[8,14] residues of proteins and nucleotides[6,8,17], i.e., condition called oxidative or nitrosative stress.[18,19] Peroxynitrite may contribute to cell death and tissue injury in many human diseases i.e., arthritis, sepsis, inflammatory bowel diseases[14,20], stroke[8,14,17], CNS disorders[8], chronic rejection of renal allografts and acute respiratory disease syndrome.[21]

Peroxynitrite in diabetes & diabetic neuropathy:

Peroxynitrite is implicated in sensory and motor nerve conduction deficits[8,11], which are determined by thermal hyperalgesia and nitrergic innervations. These are known to contribute to the autonomic neuropathy in streptazotocin (STZ)-induced diabetic rats, mices and non obese diabetic(NOD) mices.[11] Peroxynitrite mainly produces a modified amino acid i.e., Nitrotyrosine, which was initially considered a specific marker for peroxynitrite generation[22,23], because of instability of protonated form of peroxynitrite at physiological pH.[24] But, other pathways can also induce tyrosine nitration. Thus, it is considered as collective index of reactive species rather than a specific indicator of peroxynitrite formation.[7] In recent studies, Accumulation of nitrotyrosine levels, in sciatic nerve[contribute to nerve dysfunction in experimental diabetic neuropathy][8], vascular endothelium, myocardium, kidneys and retinas of STZ-induced diabetes in rat and mice as well as cutaneous micro vascular endothelium and kidneys of diabetic patients[11], can be detected by Nitrotyrosine immunoreactivity.[8] Oxidative damage can be detected by increased levels of oxidized nucleoside 8-hydroxy deoxy guanosine[8-OHdG], which is a sensitive biomarker for the kidneys of diabetic rats and also tissues or body fluids of diabetic patients.[9]

Peroxynitrite decomposition catalysts:

The role of peroxynitrite is indirect and mainly based on the pharmacological and biochemical approaches in invivo studies.[20] Peroxynitrite reacts too slowly with endogenous reducing agents such as ascorbate and glutathione, to afford protection.[15,25] But, it reacts very efficiently with synthetic metalloporphyrins, compounds in this class, mainly several water soluble iron[14] and manganese porphyrins are having high reaction rates with peroxynitrite.[15,26,27] Thus, these compounds are considered as peroxynitrite decomposition catalysts.[15,25] These compounds acts by the mechanism, catalyzing the isomerization of peroxynitrite almost exclusively to nitrate at acidic pH. Catalysis is proposed to proceed via an oxo-Fe (IV) intermediate generated from the metal promoted cleavage of O-O bond. Subsequent recombination with NO_2 regenerates the Fe(III) state and produces nitrate. These catalysts thus dramatically increase the rate of peroxynitrite isomerization, preempting the formation of oxidizing radical species and generating the harmless nitrate anion. The catalysts manifest themselves by dramatic shifts in the resulting nitrite to nitrate ratio when compared with the proton catalyzed decomposition.[14,25]

The following drugs are the examples for peroxynitrite decomposition catalysts

1. 5,10,15,20-tetrakis(2,4,6-trimethyl-3,5-disulfonatophenyl)-porphyrinato iron (III) [FeTMPS]
2. 5,10,15,20-tetrakis(2,4,6-trimethyl-3,5-disulfonatophenyl)- porphyrin iron (III) [FeTMPyP][20]
3. 5,10,15,20-tetrakis(4-sulfonatophenyl)-porphyrinato iron(III) [FeTPPS][8]
4. Fe(III)-tetrakis-2-(N-triethylene glycol monomethyl ether) pyridyl porphyrin[FP15][11]

Peroxynitrite decomposition catalysts in diabetic neuropathy:

Till date, the data generated have been shown, after one week treatment with FP15, a peroxynitrite decomposition catalyst, corrected motor conduction velocity [MNCV], which is an important characteristic feature for diabetic neuropathy[8], and sensory nerve conduction velocity[SNCV] as well as hypoalgesia[6] and hyperalgesia[8], which is not prevented completely, in streptozotocin[STZ]-diabetic mice, but not affected in control mice.[6] Weight gain and blood glucose concentrations were not affected with FP15 treated diabetic NOD mices compared with corresponding non-diabetic control.[6,11] FP15 ameliorated the accumulation of poly(ADP-ribose) polymerase[PARP] in diabetic nerves.[6]

In vektor et al., studies have shown that FP15 treatment reduced diabetes-associated nitrosative stress and PARP activation in tissue sites of peripheral diabetic neuropathy. It also decreases the dysfunction and degeneration of small sensory fibers. FP15 treatment increase tactile response thresholds in STZ-diabetic mice, rats and *ob/ob* mice.[11]

Recent studies have shown an improvement in nerve blood flow, decrease in the peroxynitrite concentration in plasma and increase in the glutathione levels in sciatic nerve in after 2 weeks treatment of FeTPPS & FeTMPyP in experimental diabetic neuropathy.[8]

Peroxynitrite decomposition catalysts were found also to be effective both in vitro and in vivo, i.e., removing peroxynitrite and preventing its cytotoxic effects resulting in potent anti-inflammatory effects[20], and also effective in diabetes mellitus related endothelial and cardiac dysfunction, myocardial ischemia-reperfusion injury and doxorubicin-mediated myocardial dysfunction, arthritis and colitis.[28]

CONCLUSION

Taken together, multiple lines of evidence support the view that peroxynitrite – induced damage play a crucial role in the pathogenesis of diabetic neuropathy. Peroxynitrite decomposition catalysts may emerge as a novel approach for the experimental therapy of diabetic neuropathy.

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