International Journal of Research and Review
www.ijrrjournal.com E-ISSN: 2349-9788; P-ISSN: 2454-2237

Review Article

Role of Glutathione Peroxidase [GPx] in Peripheral Neuropathy: A Critical Update on Clinical and Experimental Studies

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ABSTRACT

Glutathione peroxidase, a Selenium containing enzyme, protects the cells by acting as an antioxidant and neutralizing free radicals. The present review highlights the role of Glutathione Peroxidase in Diabetic Peripheral Neuropathy as well as some of the Neurodegenerative disorders like Alzheimer's Disease and Parkinson's disease which contributes to increase mortality and effecting quality of life in many individuals throughout the World. However, the role of Glutathione peroxidase is found important even in animals. Various studies showed that Gpx1gene knockout experiment in mice leads to Diabetic Peripheral Neuropathy. The mice found deficient in cellular GPx show no increased sensitivity to Hyperoxia and apart from this deficiency of Gpx1 accelerates the progression of Atherosclerosis in Apolipoproteins E-deficient mice.

Keywords: Glutathione peroxidase, Diabetic Peripheral Neuropathy.

INTRODUCTION

Diabetes Mellitus is a group of chronic multifactorial disorder characterized by hyperglycemia which is associated with increased morbidity and mortality. The complications associated with Diabetes Mellitus are more in macro and micro vascular.

DIABETIC PERIPHERAL NEUROPATHY: One of the frequently observed microvascular complication is the Diabetic Peripheral Neuropathy [DPN]. DPN is a condition caused due to progressive elevation of high blood glucose levels which leads to nerve damage. [1]

EPIDEMIOLOGY: The incidence of DPN in Diabetic Population was found to be 50%, the world Diabetic population in 2013 was found to be 382 million and it has been estimated that it may rise to 592 million by 2035. [2] Therefore, understanding pathogenesis, progression and management of DPN assumes great significance.

CHARACTERISTIC FEATURES OF DPN: DPN is characterized by abnormal nerve conduction and thermal perception, another important feature is Axonal atrophy, demyelination blunted regenerated potential and loss of nerve fibers. [3] It is intricated with inflammation and degeneration of

peripheral nerves which is accompanied by pain, paresthesia and loss of sensation. [4]

PROGRESSION OF DISEASE: The neuropathic pain progresses by waning in nerve functionality and blood perfusion rooting to nerve malnourishment leading to permanent damage. [5] The development of disease results in replication of pain with complete numbness along with the serious foot problems often leading to ulceration and foot amputation[3].

DIAGNOSIS OF DPN: the diagnostic method involved in DPN is Nerve Conduction Studies (NCS). [6] Electromyography is used to record electrical activity in nerve cells which detects the nerve damage. A probe is used which sends electrical signals to the nerve and an electrode is placed along the nerves pathway to record the response of nerves to the signal. Apart from NCs, techniques like monofilament and tuning fork are also used. The Toronto clinical score is used to categorize the type of Neuropathy. [6]

EXPERIMENTALMODELS: A new model with spontaneous onset of T2DM is the Obese BB/Zdr rat [7, 8] which showed mild deficits in NCV and progressive mild axonal atrophy but there is no loss of nerve fiber even aftre14 months of DM. Instead, it showed strong segmental demyelination and Waller ion degeneration with T1 BB/W rat. This conclude that all of the type II rodent animal model, fails to show paranodal changes or axoglial dysfunction which is in keeping with the lack of this structural abnormality in T2DM Human neuropathy. [9]

Another study was carried out by Esposito *et al.*, in "Mitochondrial oxidative stress in mice lacking the glutathione peroxidase -1 gene concluded that genetic inactivation of GPx1 resulted in growth retardation, presumably due in part to reduced mitochondrial energy production as a result of increased oxidative stress. [10]

PATHOPHYSIOLOGICAL TRIGGERS INVOLVED IN DPN: According to the work done by various researches it is exposed that high glucose (Hyperglycemia) is characterized with elevated systemic and cellular oxidative stress which is regarded as an important pathway of cellular damage resulting in Diabetic Complication. Humans have evolved a highly sophisticated and complex anti-oxidant protection system to protect the body's cell and oxygen system against Reactive Oxygen Species (ROS). [11]

OXIDATIVE STRESS: Oxidative Stress reflects an imbalance between the systemic manifestation of Reactive Oxygen Species and Biological system's ability to neutralize Reactive intermediates. [3]

ANTI-OXIDANTS: Anti –Oxidant are the substances which get oxidized by scavenging ROS to prevent oxidative damage of sub cellular proteins, carbohydrates and lipids. Anti-Oxidant enzymes such as Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GPX) reduces the oxidative process. [12]

GLUTATHIONE PEROXIDASE AND ITS SUPERIORITY: SOD is considered as a first line defense against ROS which converts Superoxide in (O2) to hydrogen peroxide (H2O2) which may still react with other ROS CAT and GPX, detoxify H2O2 to water, therefore they are also requisite along with SOD when it is active. Various studies recommended that treatment with anti-oxidant inhibits or lowers progression of Neuropathy in animal models of Diabetes, highlighting the ROS as a leading cause of DPN. Glutathione Peroxidase (GPX1) is a tripeptide which has the capability to diminish the Hydrogen Peroxide H2O2 and lipid peroxide. [11] Hence, it plays a vital role in prevention of tissue damage by ROS. In view of anti-oxidant role of GPx enriched with neutralizing free radicals the present review aimed at investigating the prescribed role of GSH in DPN. The process of reduction of oxidized glutathione to glutathione is NADPH dependent. In Hyperglycemia,

NADPHis consumed as an effect/result of increased polyol pathway activity causing GSH deficiency and secondarily enhance oxidative stress in Diabetes (Fig.1)

Recent review of literature revealed that significance of anti-oxidant enzymes in Human body in scavenging ROS of particular interest in GPX in view of a vital GSH. In lungs, the glutathione peroxidase activity is enclosed due to exposure of ozone. Further, increased activity of this enzymes is observed in Erythrocytes and lymphoid cells. In brain of individual suffering from Parkinson's disease, there is a significant reduction of GPX, in substantia nigra and many other areas. [12] GPX, which is a most common isoform of GPS family is a selenium dependent enzyme encoded by GPX, gene that is located on chromosomes 3p21 with two axons. [4] Oxidative damage of neuronal components forms the basis of Neurodegeneration and brain aging. [13] It has been evident from various studies that pathogenesis of major neurodegenerative disorder including Alzheimer's disease, Parkinson's disease, Huntington's disease, Friedreich's ataxia and amyotrophic lateral Sclerosis involves the generation of Reactive Oxygen Species and Mitochondrial dysfunction. These diseases may progress due to disturbance of Glutathione peroxidase homeostasis which may directly lead to disease or in direct results from Oxidative Stress in such disorder. [14]

PEROXYNITRITES: peroxynitrites are unstable structural isomer of nitrate, which is formed by reaction of Hydrogen Peroxide H2O2 with nitrite NO2. It is an oxidant and nitrating agent causes damage to wide array of molecules in cells including GNA and proteins. They are responsible for nitrasiative stress whose by component nitrotyrosine NT has numerous cytotoxic effects, as a result NT and Nitrasiative stress attenuated as Biomarker for DPN progression. [14]

ADVANCED GLYCATION END (AGE) PRODUCTS: on long exposure of hyperglycemia, formation of covalent abducts occurs involving glucose and plasma protein by a phenomenon call glycation, therefore protein glycation and AGE plays a vital role in generation of DPN. [14]

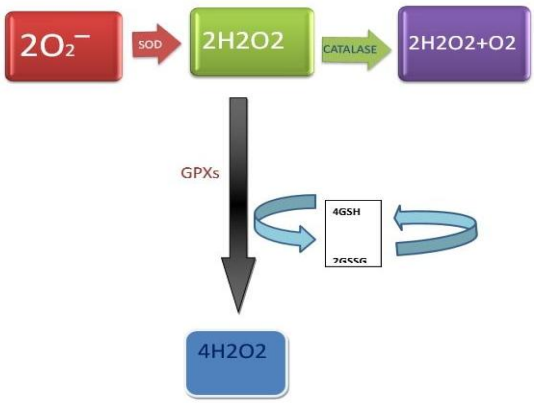

Figure 1. Role of Glutathione peroxidase in oxidative stress

Glutathione peroxidase plays a major role in neurodegenerative diseases such as -

PARKINSON'S DISEASE: The important mediators of neuronal death in PD are excitotoxicity, production of ROS and inhibition of Oxidative phosphorylation. Auto oxidation of Dopamine is responsible for the formation of neuromelanin which generates Quinone and semi quinine species and various ROS. [15] In patients with PD, reduced immunostaining of GSH is seen Dopaminergic neurons. However, in the brain most of the GSH concentration in substantia nigra pars compacta, GSH is decreased in dopaminergic neurons which make up 1-2% of total cell population, also in glial cells. [16, 17] There is increase in activity of gamma- glutamythronspeptidase (gamaGT)in PD which is an membranous ectoenzyme which catalyzes transfer of gamma-glutamyl moiety from GSH or a glutathione conjugate onto an acceptor molecule. [18,19]

ALZHIEMERS DISEASE: transcription of GSH peroxidase and GSSG reductase was increased in inferior parietal lobule and hippocampus, but not in the cerebellum of patients with AD, reflecting the protective gene responsible for increased peroxidation in the brain contributing in the severe

pathogenesis of AD. [20] However, it is hypothesized that oxidative stress is a pathogenic mediator involved in progression of AD but alteration in glutathione system are secondary events responsible for neurodegeneration. DM is involved in production of numerous free radicals causing damage of cell components due to oxidation. This ROS potentiates various molecular mechanisms to oxidative damage resulting in hyperglycemia, Beta cell apoptosis is caused by stress signaling pathway. [20]

CONCLUSION

Glutathione peroxidase has a variety of pivotal functions in cells. Genetic ailments of glutathione related enzymes are les, but its depletion is involved in the pathogenesis of significant neurodegenerative diseases. On the basis of recent studies indicating Glutathione depletion causes neurodegeneration, neuronal GSH depletion would be a primary cause of neurodegenerative disorders. The development of drugs that goals neuronal Glutathione production would be a propitious approach as a therapeutic strategy for neurodegenerative diseases.

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How to cite this article: Zoheb M, Parveen Z, Afreen A et.al. Role of glutathione peroxidase [GPx] in peripheral neuropathy: a critical update on clinical and experimental studies. International Journal of Research and Review. 2019; 6(12):360-364.

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