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Review

The Possible Role of The Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency in The Polyneuropathies

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ABSTRACT

Glucose is the main energy source of the various types of cells and largely metabolized by either glycolysis or pentose phosphate pathway (PPP). Glucose-6-phosphate dehydrogenase (G6PD, glucose 6-phosphate (G6P): NADP (+) oxidoreductase, EC 1.1.1.49) is the first and rate limiting enzyme of the oxidative branch of the PPP. This enzyme found in many species from bacteria to humans and is found in all cell types. G6PD deficiency is the most common enzyme deficiency affecting 400 million people worldwide. However, moderate G6PD deficiency may not give symptoms but can lead to various neurological and neurodegenerative disorders including polyneuropathies. Both inflammation and oxidative stress play a major role in the formation of the neurological disorders, however, G6PD gives advantage to brain and nerve cells to fight against oxidative stress, neurodegeneration, neuronal survival and aging. In conclusion, G6PD plays vital role to maintain homeostasis of lipid, redox and energy metabolisms. Thus, impairment in the G6PD activity may cause elevated levels of oxidative stress involved in the formation of the neurodegeneration and may involve in the primary cause of idiopathic sensory-motor polyneuropathy.

Keywords: Glucose-6-phosphate dehydrogenase; oxidative stress; brain, glucose metabolism

INTRODUCTION

Cells, mainly neurons utilize glucose as the main energy source for instance brain is consuming 20% of glucose-derived energy in the body. Glucose metabolism provides energy for ATP production, neurotransmitter synthesis, maintenance of ion balance, generation of action potential, neuronal and non-neuronal cellular function, that all maintain together physiological and pathological functions of the brain (1–3). Metabolization of glucose occurs via either glycolysis or pentose phosphate pathway (PPP) depends on the requirement and the favor of the metabolic pathways in the brain. Major cellular ATP production occurs via glycolysis, where glucose is converted into pyruvate to produce ATP and provides a substrate for oxidative phosphorylation (OXPHOS). On the other hand, glucose is degraded into NADPH and 5-carbon sugars via glucose 6-phosphate dehydrogenase (G6PD) (D-glucose-6-phosphate: $NADP^+$ oxidoreductase, EC 1.1.1.49) in PPP, which has both oxidative and non-oxidative branches. PPP activity increases in cells with high rate of proliferation or in need of NADPH, thus PPP play vital role to maintain cellular redox balance in the all cells including nerve cells (2, 4–6) (Figure 1). Different cell types have different pathways to metabolize glucose, for instance neurons use mainly glycolysis to produce ATP, where oligodendrocytes and astrocytes metabolize glucose via PPP to maintain NADPH to produce cholesterol which is necessary in the myelin sheath (7–9).

G6PD enzyme is found in many species from bacteria to humans in all cell types (10). Also, G6PD deficiency is the most common enzyme deficiency affecting 400 million people worldwide (11, 12). Since G6PD enzyme is the centre of the metabolism, its activity must be very tightly regulated. Previously, it is thought that NADPH/NADP ratio regulate G6PD, however according to many studies over past 25 years, G6PD is regulated at the transcription, translation, post-translation, and intracellular location levels. Positive regulators of G6PD can be categorized as Platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin, vitamin D, phosphoinositide 3-kinase (PI3K), phospholipase C-γ, RAS-GTPase, (cyclic guanosine monophosphate) cGMP-dependent protein kinase G (PKG), mTOR, S6 kinase, Src, TP53-inducible glycolysis and apoptosis regulator (TIGAR), heat shock protein 27 (Hsp27), ATM, SREBP, Nrf2, where negative regulators are aldosterone, cAMP, cAMP-dependent PKA, CREM, arachidonic acid, p38 MAP kinase,

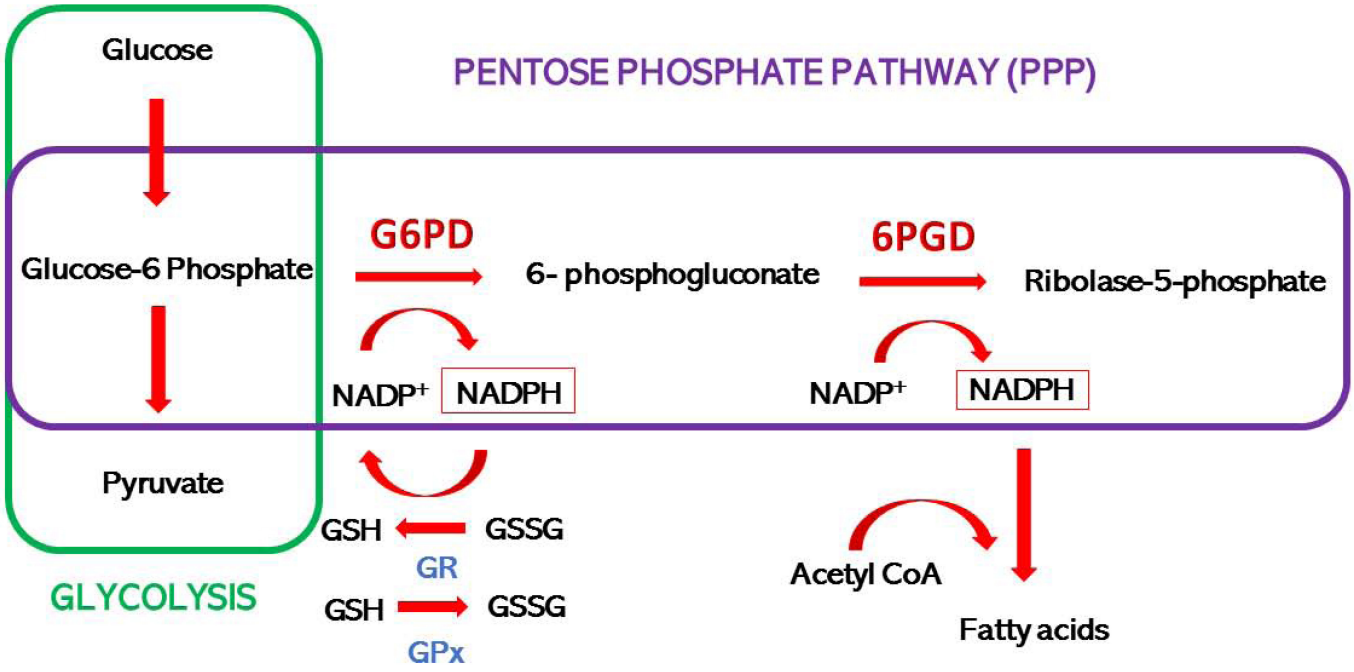

Figure 1. The role of glucose-6-phosphate dehydrogenase on the oxidative stress metabolism via pentose phosphate pathway.

p53, TNF-α, AMP kinase. Thus there are multiple proteins and pathways involving in the regulation of G6PD activity, expression, location, interaction with other proteins from gene expression to its activity (13–20).

Since supplying metabolic energy to the nerve cells and metabolic activity in the brain must be constant at all times to maintain homeostasis, energy metabolism must be tightly controlled (4). In this concept, we aimed to explain the role of the G6PD in nervous system metabolism in relation with oxidative stress, energy and lipid metabolisms in our review.

Glucose-6-phosphate dehydrogenase and anti-oxidant defence

Glucose-6-phosphate dehydrogenase is the rate limiting enzyme in the PPP involved in the production of the reduced nicotinamide adenine dinucleotide phosphate (20, 21). Glucose 6-phosphate (G6P) is converted to ribulose-5-phosphate (R5P), where $NADP^+$ is reduced to NADPH through G6PD and 6-phosphogluconate dehydrogenase (6PGD) enzymes. NADPH is major cellular reductant involving in the balance between oxidized glutathione (GSSG) and reduced glutathione (GSH) as redox couple system (Figure 1). GSH is a major antioxidant molecule involving in the various cellular processes such as detoxification, anti-oxidant defence mechanism and cell proliferation through maintaining the intracellular redox homeostasis. Detoxification of xenobiotics, drugs, toxins or heavy metals occurs via glutathione metabolism. GSH is oxidized to GSSG under oxidative stress conditions via glutathione peroxidase (GPx) enzyme and reduced back to GSH by glutathione reductase (GR) enzyme to maintain GSH/GSSG balance by NADPH-dependent mechanism in both cytosol and mitochondria (22–28). Intracellular GSH concentration and GSH/GSSG ratio play a major role in the defence mechanism against oxidative stress that is regulated by glutathione dependent enzymes including GR and GPx (26–30). NADPH is the limiting substrate for GR activity catalysing the reaction of converting GSSG to GSH, therefore cells exposed to elevated levels of oxidative stress need high PPP activity (2, 26, 31–35).

In this concept, impairment in the G6PD metabolism disrupts the balance between the reduced and oxidized forms of nicotinamide adenine dinucleotide phosphate ratio leading to the imbalance in the redox homeostasis. That causes dysfunctional cell growth and signalling, abnormal embryonic development, and altered susceptibility to various types of infection (28, 36–38). On the other hand, G6PD has a neuroprotective role in the brain ischemia through promoting pentose phosphate pathway and G6PD protects brain against neurodegeneration and oxidative stress-induced DNA damage (39, 40). Abnormal G6PD activity in the brain leads to elevated levels of oxidative stress which may impair calcium mobilization, apoptosis in neurons, astrocytes and microglia, ion transport and excitotoxicity, thus brain homeostasis. Neuronal death occurs via either apoptosis or excitotoxicity and imbalance in both pathways is mainly contributed to diseases including Alzheimer, Parkinson, Huntington and amyotrophic lateral sclerosis (ALS) (41–43).

Role of G6PD in the brain disorders and nervous system

G6PD is the rate limiting enzyme in the PPP responsible for NADPH production that is involved in both lipid and oxidative stress metabolisms. Glucose is metabolized by either glycolysis or PPP in the cells dependent on the requirement and favour of the metabolic processes. So, G6PD is main enzyme responsible

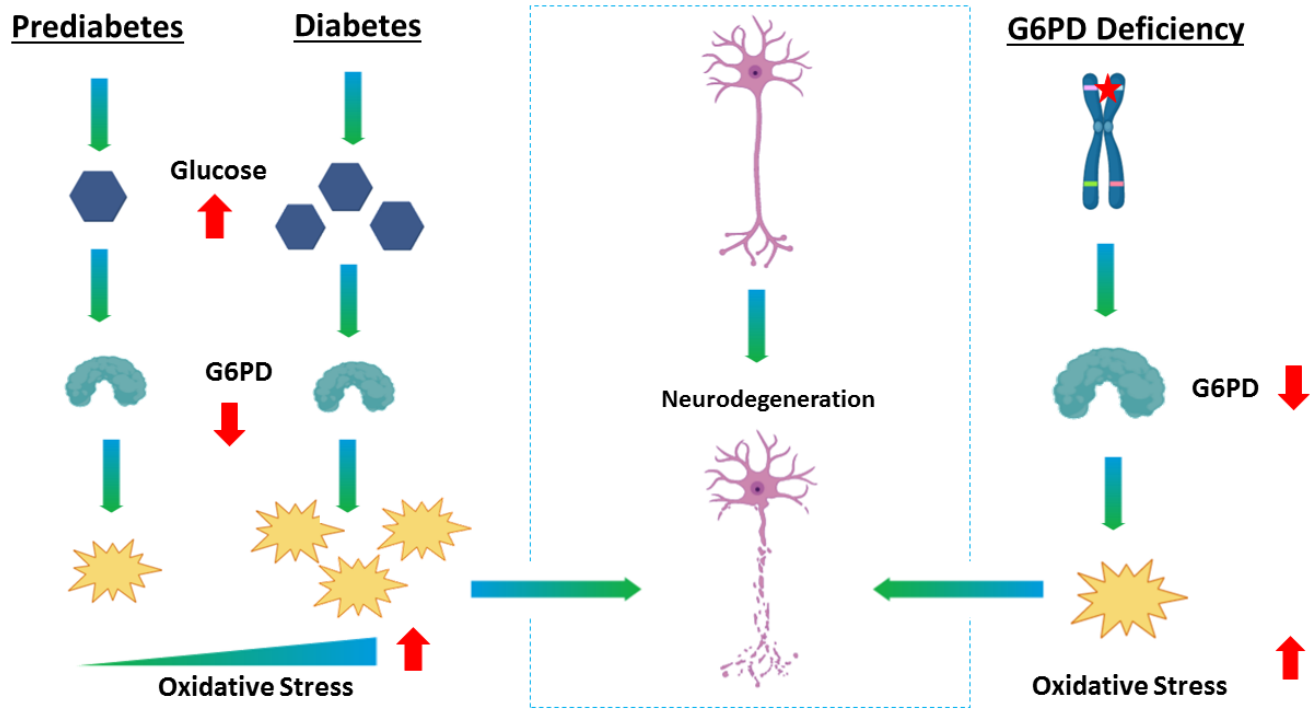

Figure 2. Possible contribution of pre-diabetes, diabetes and G6PD deficiency on the neurodegeneration via elevated levels of oxidative stress.

for cellular redox homeostasis, NADPH/NADP balance, inflammation, oxidative stress, lipid and fatty acid metabolism. On the other hand, glucose metabolism involved in the cell death pathways by glucose-metabolizing enzymes, thus responsible for the regulation of the cell death as well (20, 12, 43).

Both inflammation and oxidative stress play a major role in the formation of the neurological disorders, however PPP pathway gives advantage to brain to fight against oxidative stress, neurodegeneration, neuronal survival and aging. For instance, decreased glucose consumption in the brain is tightly associated with the aging and neurodegeneration (12, 20, 43). Oxidative stress can be described as the imbalance between antioxidant defences and reactive oxygen species (ROS) also known as free radicals as well. Compared to the other organs, brain is the most susceptible one against oxidative stress, since high oxygen consumption, higher levels of iron in some brain areas, PUFA as target for lipid peroxidation and low activity of antioxidant enzyme activities compared to the other organs including liver and kidney (44–46). Also, it is suggested, that neuron loss in neurological disorders are mainly resulted from ROS-induced neuron loss including ALS, Parkinson Disease, ischemia and Alzheimer's Diseases (47–50).

Glutathione is a major redox agent in the cell and involved in the balance between GSSG and GSH as redox couple system. GSH metabolism is responsible for the various cellular processes such as detoxification, antioxidant defence mechanism and cell proliferation through maintaining the intracellular redox homeostasis. Xenobiotics, drugs, toxins or heavy metals are detoxicated by glutathione metabolism enzymes. GSH is oxidized to GSSG during oxidative stress metabolism via GPx enzyme and reduced to back GSH by GR enzyme to maintain GSH/GSSG balance by NADPH-dependent mechanism in both cytosol and mitochondria (22–28, 30). Both Intracellular GSH levels and GSH/GSSG ratio are key players of the defence mechanism against oxidative stress regulated by glutathione dependent enzymes including GR, GPx and glutathione S– transferase (GST) (28–30). NADPH is produced by G6PD via PPP and the limiting substrate for glutathione reductase activity catalysing the reaction of converting GSSG to GSH, therefore cells exposed to elevated levels of oxidative stress need high PPP activity (2, 26). Mitochondria is the organelle where oxidative phosphorylation takes place resulting in the ROS formation, therefore both mitochondrial dysfunction and oxidative stress contribute to the formation of various neurological disorders including schizophrenia, anxiety related disorders, Huntington, Alzheimer, Parkinson, depression and multiple sclerosis (MS) (45, 51–55).

Overall, G6PD plays vital in the NADPH production, redox homeostasis, lipid and glucose metabolism, thus it maintains homeostasis and defence mechanism against diseases in the brain. Thus, impairment in the G6PD activity is directly involved in the imbalance of oxidative stress metabolism that leads to neurodegeneration, since the brain is the most vulnerable organ against oxidative stress compared to the other organs including liver and kidney.

G6PD deficiency and Polyneuropathies

There may be several disorders that the main causative is unknown cause or mechanism but G6PD deficiency may have a key role in these idiopathic diseases. Neuropathy is not caused by a single disease and there may be lot underlying reasons such as diabetes, autoimmune disorders, medications, xenobiotics, poisons and no known cause (56). G6PD is the most common enzymopathy and the severe form the best described red blood cell worldwide if the patient has acute haemolysis from G6PD deficiency. However, moderate form of G6PD deficient persons are asymptomatic (57). Combination of two diseases, diabetes and G6PD deficiency potential causes idiopathic sensory-motor polyneuropathy because both of these diseases are directly increase oxidative stress and change the redox potential of glutathione (26, 58, 59). G6PD enzyme deficiency contributes to the elevated levels of oxidative stress as a result of decreased G6PD activity that may cause neuron degeneration. On the other hand, high glucose concentrations inhibit G6PD that, leading to increased oxidative stress and β-cell apoptosis leading to the nerve damage. As a result, both increased levels of glucose and decreased G6PD activity contribute to the elevated levels of oxidative stress leading to the neurodegeneration causing even different types polyneuropathies (Figure 2) (6, 58, 60, 61).

Contribution of oxidative stress on the different types of polyneuropathies have been reported previously, for instance chronic idiopathic axonal polyneuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP) and familial amyloid polyneuropathy (62). On the other hand, G6PD deficiency is tightly associated with nonarteritic anterior ischemic optic neuropathy in (63, 64). Although G6PD deficiency may be tightly associated with different types of neuropathies, there are no published data explaining possible mechanisms and correlation between G6PD deficiency and polyneuropathies.

CONCLUSION

Since G6PD enzyme is the centre of the many dynamic motions, different biological and pathophysiological processes, it is regulated at transcriptional, translational and post-translational levels. This enzyme has enormous roles in all types of cells, especially important in the nervous system. The brain is highly susceptible to oxidative injury, changes in total brain lipids, energy depletion. The protective effect of G6PD deficiency against malaria is well known, but the mechanism(s) of protection from various multifactorial disorders and NCS diseases such as cancer, AD and PD remain unclear. Understanding the molecular properties and G6PD activity of brain tissue metabolism, can provide new insights into the pathophysiology of various diseases and may lead to the discovery of new diagnostic biomarkers and therapeutic molecules for decreasing the rate of damage then slowing aging and improving health span.

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