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Brief Communication

Recent advances in understanding the role of oxidative stress in diabetic neuropathy

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ABSTRACT

Diabetic neuropathy (DN) is one of the most common and severe manifestations of diabetes mellitus. The mechanisms underlying the structural, functional and metabolic changes in diabetic neuropathy have been under study for a long time. In this review the biochemistry and implications of the four pathways responsible for the development of DN, polyol pathway; increased AGEs (advanced glycation end-products) formation; activation of PKC (protein kinase C) and hexosamine pathway have been discussed. Experimental and clinical evidences suggest a close link between neurodegeneration and oxidative stress which serves as a unifying mechanism, thus linking the four pathways. Recent studies indicate that oxidative stress mediated DNA damage causes poly(ADP-ribose) polymerase (PARP) overactivation and reduced activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a factor common to all the four pathways. The exact mechanism of PARP mediated cell death in DN needs further investigation. Based on current studies neuroprotective and antioxidant therapy have been suggested as potential treatment and preventive solutions for DN.

1. Diabetic neuropathy

Diabetic neuropathies are a family of nerve disorders caused by diabetes. Diabetic neuropathy is the greatest source of non-traumatic amputations and mortality. It is solely responsible for more admissions to hospital than all other diabetic complications combined. Diabetic neuropathy has been defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes. A predisposition to the condition often exists in the form of hyperglycemia, and with time neuropathy is triggered by factors like age, degree of glycemic control, obesity, smoking etc. Nerve damage advances slowly with prolonged diabetes and the development of signs and symptoms is also gradual. The incidence directly depends on the duration of the disease. 10% patients have neuropathy when diagnosed with diabetes and within 25 years 50% patients are affected [1]. The overall prevalence of neuropathy in South Indian diabetic subjects is 19.1% [2] while it has been found to be 26.1% [3] in case of urban South Indian population.

2. Oxidative stress

Superoxide ion (O_2^-), hydrogen peroxide (H_2O_2), and nitric oxide (NO) are three free radical reactive oxygen species (ROS) that are essential for normal physiology but are also believed to accelerate the process of aging and to mediate cellular degeneration in disease states. To counteract these free radicals, the body produces an armory of antioxidants to defend itself. Compounds like flavonoids, uric acid, bilirubin, albumin, vitamin E, vitamin C, α-lipoic acid (ALA), thioredoxin (Trx) and glutathione (GSH); and enzymes like catalase, superoxide dismutase (SOD), peroxiredoxins glutathione peroxidase and have been described as antioxidants. Halliwell defined an antioxidant as 'any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or inhibits oxidation of this substrate' [4]. Oxidative stress occurs when the production of free radical moieties exceeds the antioxidant capacity of the system. This serious imbalance leads to increased ROS which further produce highly active singlet oxygen ($^1O_2$), hydroxyl radicals ($OH^\bullet$), and peroxynitrite ($ONOO^-$). Fig. 1 illustrates the chemistry of oxidative stress.

The agents formed as a result of reactive oxygen imbalance attack both proteins and DNA (nuclear and mitochondrial) by oxidation, nitrosylation and peroxidation reactions. The carbonyl content of proteins show stark elevation and DNA adducts are

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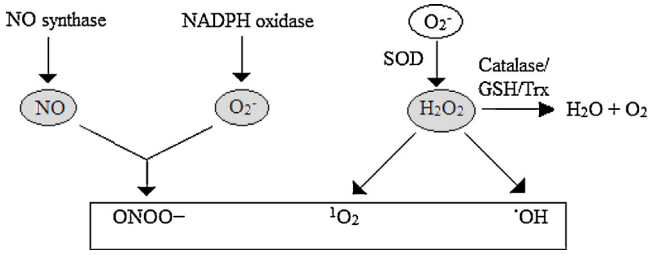

Fig. 1. Generation of Reactive Oxygen Species (ROS).

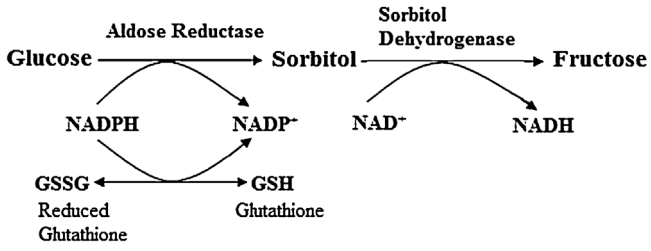

Fig. 2. Polyol pathway.

formed due to base modification and deoxyribose oxidation. Hydroxylation of guanosine yielding 8-oxo-7,8-dihydro-2′-deoxyguanosine is common and thus widely used as a marker [5]. During normal metabolism NO acts as a regulatory switch monitoring the transfer of electrons in electron transport chain (ETC) by competing with molecular oxygen for reversible binding to cytochrome c oxidase. Peroxynitrite competes with molecular oxygen for irreversible binding to cytochrome c oxidase thus inhibiting mitochondrial function and ATP synthesis [6]. Peroxynitrite is directly responsible for membrane lipid peroxidation as indicated by the formation of malondialdehyde in various models [7]. Oxidative stress also inhibits the mitochondrial import of preproteins and leads to their degradation [8]. One important factor is decrease in neurotrophic factors: nerve growth factor (NGF), neurotrophin-3 (NT-3) caused by oxidative stress induced mitochondrial damage [9]. Oxidative modification of transcription factors by superoxide ion and hydrogen peroxide leads to decreased expression of proteins needed for cell survival like bcl-2 and increased expression of pro-apoptotic proteins like PARP and JNK [10,11]. End products of the interactions between ROS and lipids, protein and nucleic acids accumulate due to inefficiency of the cell to recycle them. This induces deleterious events in the cell ultimately activating mechanisms of apoptosis. Thus oxidative stress represents a threat to the functional integrity of the cell which results in potential tissue damage. Experimental data suggests a close link between hyperglycemia and ROS production [12,13]. In dorsal root ganglion (DRG) neurons of diabetic rats the impairment of mitochondrial function and oxidative stress induced apoptosis via caspase-3 activation has been reported [14,15].

3. Pathogenesis of diabetic neuropathy

There are four established mechanisms regarding how chronic hyperglycemia causes diabetic neuropathy: increased polyol pathway flux; increased advanced glycation end-products (AGE) formation; activation of protein kinase C (PKC); increased hexosamine pathway flux.

4. The polyol pathway

Polyol pathway is extensively dependent upon the varied types of species, sites and tissues. Aldose reductase has a low affinity for glucose and normally only about 3% of glucose is metabolized by this pathway [16] (Fig. 2). But in hyperglycemic conditions up to 33% of total glucose utilization in some tissues can be through the polyol pathway [17]. Fig. 3 demonstrates the metabolism of glucose via polyol pathway.

The increased activity of aldose reductase results in reduced amounts of NADPH. Thus glutathione (GSH), the most abundant natural antioxidant is depleted. Sorbitol cannot cross membrane and accumulates producing osmotic stress in cells by drawing water into the insulin dependent cells (which is believed to lead to oxidative stress due to change in antioxidant potential) [18]. But experimental studies suggest that this increase in the sorbitol concentration within the diabetic vessels and nerves is too low for this change [19]. High sorbitol concentrations are observed to have depleted myo-inositol [20] which enters cells through phosphoinositides (phospholipid in membrane) and is responsible for intracellular signaling of neurons. Cellular levels of Ca^{2+} and phosphoinositol go down in addition to altered phosphatidylinositol synthesis due to activation of PKC. In turn Na^+/K^+ ATPase activity decreases leading to accumulation of Na^+ in nerves leading to slowed conduction in rat models [21,22].

The exact role of polyol pathway as a mechanism of diabetic neuropathy is not yet clear. Experimental studies and clinical trials to inhibit polyol pathway have been successful using aldose reductase inhibitor but have shown inconsistent results. However polyol pathway serves as a major link to other pathways. Increased cytosolic NADH:NAD^+ ratio (Fig. 3) in turn increases triose-phosphate concentrations, an intermediate in glycolysis by inhibiting glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Non enzymatic phosphate elimination from glyceraldehyde 3-phosphate (PGAL) and dihydroxyacetone phosphate (DHAP) leads to formation of methyglyoxal which is a precursor for AGE. While two acylations of DHAP and PGAL followed by non enzymatic phosphate elimination results in formation of diacylglycerol (DAG) which activates PKC.

5. Advanced glycation end products (AGEs)

AGEs are a complex and heterogenous group of compounds. Glycation can be detected at normal conditions but reactions are accelerated in hyperglycemic conditions. Reactive dicarbonyls are the precursor molecules and are synthesized through three pathways [23–25]:

1. Oxidation of glucose, which forms glyoxal by retroaldol condensation in which erythrose is removed from glucose to from glyoxal.
2. Irreversible degradation of fructose-lysine adducts (Amadori products): reducing sugars react non enzymatically with amino

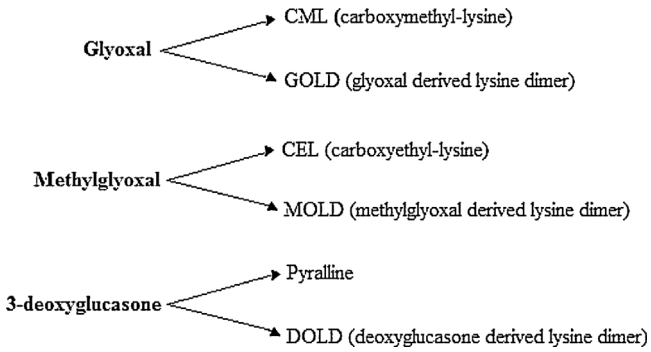

Fig. 3. Advanced Glycation End Products (AGEs) and their precursors.