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Role of Polyol Pathway in Pathophysiology of Diabetic Peripheral Neuropathy: An Updated Overview

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Abstract

The aim of this short communication article was to enlighten the role of polyol pathway in pathophysiology of diabetic peripheral neuropathy (DPN) through an evidence-informed overview of current literature. Findings from experimental models of DPN suggest that altered glutathione redox state, with exaggerated NA(+)-K(+)-ATPase activity, increased malondialdehyde content, decreased red blood cell 2,3-diphosphoglycerate concentration, reduced cyclic adenosine monophosphate, reduced myo-inositol and excessive sorbitol in peripheral nerves were indicative of polyol metabolic pathwayin producing pathophysiological changes of DPN, and treatments using aldose reductase inhibitors were found to reverse those changes.

Keywords: Polyol pathway; Myo-inositol; Sorbitol; Neurophysiology; Endocrinology.

The aim of this short communication article was to enlighten the role of polyol pathway in pathophysiology of diabetic peripheral neuropathy (DPN) through an evidence-informed overview of current literature.

Calcutt *et al*[1] measured motor nerve conduction velocity (MNCV), Na(+)-K(+)-ATPase activity, polyol-pathway metabolites, and myo-inositol in sciatic nerves from control mice, galactose-fed (20% wt/wt diet) mice, and galactose-fed mice given the aldose reductase inhibitor ponalrestat (300-mg/kg diet). Their data showed that exaggerated flux through the polyol pathway can cause an MNCV deficit that is unrelated to either myo-inositol levels or NA(+)-K(+)-ATPase activity.

Carroll *et al*[2] examined the effect of streptozocin (STZ) diabetes and aldose reductase inhibition on reduced (GSH) and oxidized (GSSG) glutathione levels in crude homogenates of rat sciatic nerve. The study concluded that altered glutathione redox state played no detectable role in the pathogenesis of this defect in diabetic peripheral nerve.

Finegold *et al*[3] studied the effect of polyol pathway blockade with sorbinil, a specific inhibitor of aldose reductase, on nerve myo-inositol content in acutely streptozotocin-diabetic ratswhich completely prevented the fall in nerve myo-inositol.

Mizuno *et al*[4] investigated the effects of three aldose reductase (AR) inhibitors, fidarestat, epalrestat and zenarestat, on the slowing of sensory nerve conduction velocity (SNCV), motor nerve conduction velocity (MNCV), and minimal F-wave latency prolongation in streptozotocin (STZ)-induced diabetic rats. “Fidarestat

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suppressed sorbitol accumulation remarkably and continuously until 24 h after administration. On the other hand, the inhibitory effect by zenarestat declined in a time-dependent manner, and epalrestat did not decrease sorbitol content."

Nakamura *et al*[5] compared the effect of a transition metal chelating agent, trientine (TRI), on diabetic neuropathy with that of an aldose reductase inhibitor, NZ-314 (NZ).Platelet hyperaggregation activities in diabetic rats were prevented by NZ, but not by TRI. Increased concentrations of malondialdehyde in diabetic rats were partially but significantly ameliorated by either TRI or NZ.

Nakamura *et al*[6] investigated the relationship between polyol pathway hyperactivity and altered carnitine metabolism in the pathogenesis of diabetic neuropathy, the effects of an aldose reductase inhibitor, [5-(3-thienyl) tetrazol-1-yl]acetic acid (TAT), and a carnitine analog, acetyl-L-carnitine (ALC), on neural functions and biochemistry and hemodynamic factors were compared in streptozotocin-diabetic rats. The observations suggested that there was a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy and that an aldose reductase inhibitor, TAT, and a carnitine analog, ALC, had therapeutic potential for the treatment of diabetic neuropathy.

Nakamura *et al*[7] studied relationship between the 2,3-diphosphoglycerate concentration in red blood cells as a biological indicator of tissue hypoxia and diabetic neuropathy, and the effect of a potent aldose reductase inhibitor, (2S,4S)-6-fluoro-2'5'-dioxospiro [chroman-4,4'-imidazolidine]-2-carboxamide (SNK-860),streptozotocin-induced diabetic rats. The study findingssuggested that a decrease in the red blood cell 2,3-diphosphoglycerate concentration was one of the factors contributing to tissue hypoxia, which resulted in diabetic neuropathy, and that this decrease was mediated through an aldose reductase inhibitor-sensitive pathway.

Oates[8] described the concept of the polyol pathway and its role inpathogenesis of diabetic peripheral neuropathy as follows:"metabolic flux through aldose reuctaseoccurred through the polyol pathway, rather than nerve concentration of sorbitol, acting as apathogeneic factor in diabetic peripheral nerve. Also, inhibition of metabolic flux through the polyol pathway should be a therapeutic goal in DPN..

Shindo *et al*[9] studied the effects of a stable prostacyclin analog, Iloprost, and aldose reductase inhibitors (ONO-2235 and isoliquiritigenin) to elucidate the role of cyclic Adenosine monophosphate (cAMP) in diabetic neuropathy in relation to polyol metabolism. The study findings suggested that polyol pathway activation resulted in cAMP reduction in sciatic nerves and that the reduction of cAMP in peripheral nerves might in turn be related to the pathogenesis of diabetic neuropathy.

Findings from experimental models of DPN suggest that altered glutathione redox state, with exaggerated NA(+)-K(+)-ATPase activity, increased malondialdehyde content, decreased red blood cell 2,3-diphosphoglycerate concentration, reduced cyclic adenosine monophosphate, reduced myo-inositol and excessive sorbitol in peripheral nerves were indicative of polyol metabolic pathway in producing pathophysiological changes of DPN, and treatments using aldose reductase inhibitors were found to reverse those changes.

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