

Pathogenesis of Diabetic Neuropathy and the Treatment Efforts for it

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Abstract

Neuropathy is the commonest complication in DM. Prolonged hyperglycemia is the cause of metabolic changes which leads to peripheral nerve injury through increased polyol influx, enhanced advanced glycation end products formation, oxidative stress and exaggerated release of inflammatory cytokines. In this article we will discuss these mechanisms and the treatment efforts targeting them.

Keywords: Neuropathy; Diabetic Neuropathy

Introduction

Peripheral neuropathy is the commonest complication of DM [1,2]. It involves sensory, motor and autonomic nerves. Multiple studies showed that autonomic cardiovascular neuropathy dramatically shortens the patients lifespan and increases mortality [3,4]. Without exploring the exact causative factors involved in diabetic neuropathy, it will not be possible to develop an effective treatment for it. Unfortunately, there is no current effective treatment for diabetic neuropathy at a global level.

Pathogenesis of peripheral neuropathy in diabetes mellitus

The polyol pathway

Increased polyol influx regulated by the enzyme Aldose Reductase has been studied extensively and it is considered one of the main mechanisms involved in peripheral neuropathy.

Multiple drugs have been developed targeting Aldose Reductase. However, they have serious adverse effects and or there was no significant improvement during clinical trials. Epalrestat is an Aldose Reductase Inhibitors (ARIs) which showed marked improvement only in patients with early neuropathy and modestly elevated levels of glycosylated haemoglobin [5].

Glycation and AGE products

Glycation has been involved in the pathogenesis of diabetic neuropathy [6-8]. Deposition of AGEs was shown in animal and human diabetic neurons; Stromal collagen, axoplasm of nerve fibers, schwann cells and endoneurial vessels [9] were affected by glycation and AGEs, schwann cells underwent apoptosis with release of TNF alpha and other inflammatory cytokines when ex-

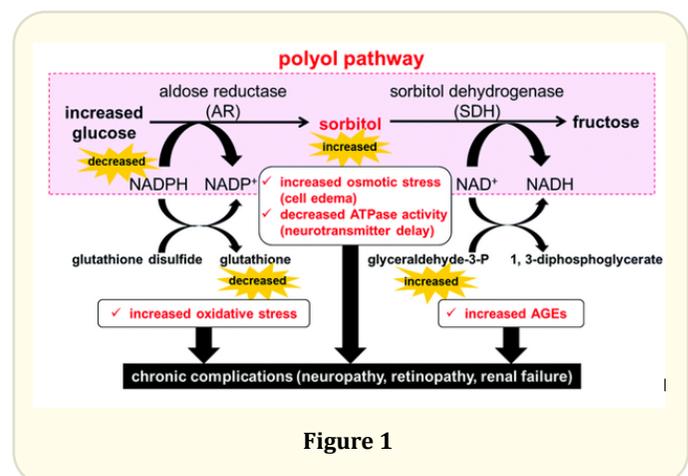


Figure 1

posed to a high AGEs environment [10]; axonal cytoskeleton of tubulin and neurofilaments caused stagnation of axonal transport leading to distal nerve fiber degeneration [6]; glycation of basement membrane collagen, laminin and fibronectin caused impairment of nerve fiber regeneration.

Currently, there are a few agents that can be administered acting on this mechanism such as: Atrovastatin which is found to reduce AGE formation through its anti-oxidative activity. Another agent is sRage which is found to completely inhibit the receptors for AGE known as RAGE inhibitors [11].

Oxidative stress

Generation of reactive oxygen species (ROS) is considered a major factor contributing to the development of diabetic neuropathy [12,13]; many experiments showed that oxidative stress can cause nerve fiber injury [14-17].

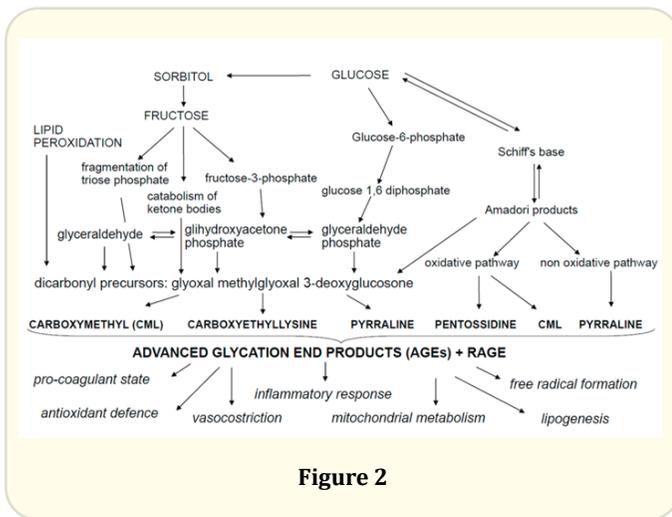


Figure 2

There are multiple attempts to inhibit diabetic neuropathy with using Antioxidants. One of these drugs is Alpha lipolic acid. In vivo it showed improvement in nerve conduction velocity delay, nerve blood flow and nerve structure [18,19].

Administration of Vitamin E resulted in reversal of defective nerve conduction in patients with mild to moderate diabetic Neuropathy [20].

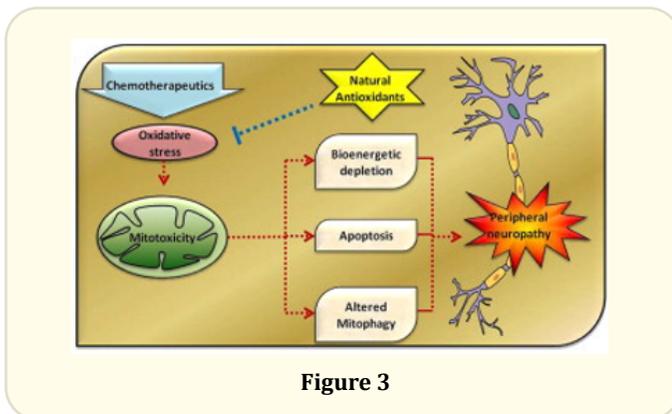


Figure 3

Exaggeration of proinflammatory cytokines release

Numerous studies showed that neurons undergo a proinflammatory process which cause symptoms and aggravates the development of neuropathy [21,22]; Diabetic neurons contain macrophages and there is increased release of TNF alpha and Interleukins(ILs) [21,23,24].

Currently, numerous studies are carried out targeting cytokines to overcome diabetic neuropathy; drugs as Pioglitazone and N-

acetyl cycteine showed improvement of nerve conduction velocity delay in STZ-diabetic rats [25,26]. Through inhibition of cytokines release or macrophages migration.

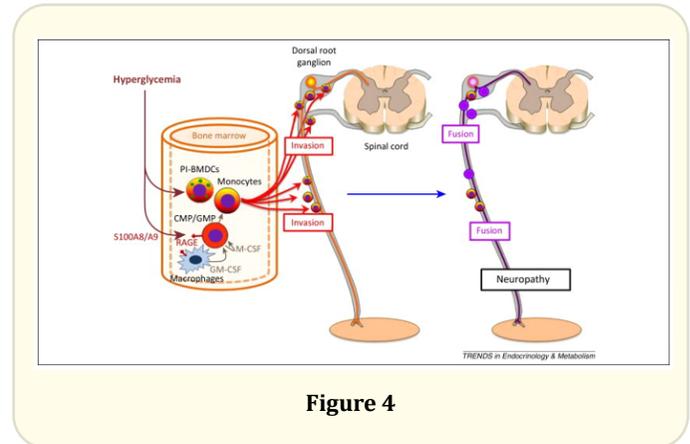


Figure 4

Conclusion

Diabetic neuropathy is a serious disorder and the mechanisms beyond it are complex. We have discussed four main mechanisms and the treatment efforts acting on them. More studies should be carried out to investigate deeply in the mechanisms beyond Diabetic Neuropathy to be able to develop more efficient drugs with less adverse effects.

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