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The Role Of Transcription Factor in Painful Diabetic Neuropathy

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ABSTRACT Painful Diabetic Neuropathy is a condition that manifests as a painful sensation that affects most of the patient with diabetes. This condition is caused by prolonging hyperglycaemic condition, which later causing damage to nerve cell through some classical hyperglycaemic pathway. This will result in the formation of oxidative stress and AGE/ROS which is responsible for the ischaemic condition that causes the damage to nerve cells. There are transcription factors that have been studied responsible for Painful Diabetic Neuropathy, such as NF-κB, PAI-1, Nrf2, and TGF-β.

KEYWORDS Painful Diabetic Neuropathy, transcription factors, NF-κB, PAI-1, Nrf2, and TGF-β

Introduction

Painful Diabetic Neuropathy (PDN) is one of the micro-vascular complications that affects most of the patient with uncontrolled blood sugar, this condition characterized by numbness, burning, stabbing, pain, or electric shock sensation that worsens at night in the extremities [1]. This sensation often appears in the distal part of the extremities which will slowly spread proximally, this is called "stocking-glove" sign, this appears due to an increasingly severe state of diabetes — this situation affecting a patient's quality of life because it interferes with daily activities [2].

Pathophysiology

Studies have been conducted to understand the pathogenesis of PDN. Many theories explained the causes of pain in diabetic neuropathy are caused by Reactive Oxygen Species (ROS) which are produced in a state of chronic hyperglycemia. Oxidative damage that causes various damage to the vascular starts from classical hyperglycemic pathways such as Polyol Pathway, Protein Kinase C Pathway (PKC), a formation of the Advanced Glycation End Product (AGE Pathway) and Hexosamine Pathway [1–4].

The pathophysiological factors responsible for PDN that have been studied are Oxidative-Nitrosative stress and Neuro-Inflammation. Molecular studies found the involvement of several transcriptional regulators such as NF-κB, Plasminogen Activator Inhibitor (PAI-1), Nrf2, and Tumor Growth Factor-β (TGF-β in the pathophysiology of DPN [5].

There are several mechanisms responsible for Painful Diabetic Neuropathy. People with uncontrolled blood sugar will have AGE formation, protein glycation, antioxidant deficits, all of this resulting in oxidative stress. This oxidative stress affects Na-K-ATPase activity, causing ischemic in nerve cells [6]. In diabetic people, there's an increase in Reactive Oxygen Species (ROS) and the accumulation of oxidative stress that can cause damage to nerve cells, hence reducing nerve cells conduction [5].

1.NF-κB

NF-$\kappa\beta$ is a DNA binding protein factor that influences the transcription of various inflammatory molecules such as cytokines, chemokines, Cell Adhesion Molecules (CAM) and others. The inflammatory molecule was responsible in the pathophysiology of diabetes and its complications both macro and microvascular via the NF-$\kappa\beta$ pathway [5]. Uncontrolled blood sugar and insulin resistance affect the incidence of diabetic vascular complications. Hyperglycemic conditions cause the formation of AGE and excessive ROS production. The main pathway that influences the formation of AGEs and ROS: polyol fluxes, activa-

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tion of PKC, accumulation of AGEs and increased hexosamine flux. Thus, ROS and AGEs cause the initiation of the proinflammatory process and endothelial damage through activation of NF-$\kappa\beta$ [4–6].

People with uncontrolled blood sugar and insulin resistance, trigger conditions such as the formation of AGE / RAGE, the production of oxidative stress and hypoxia. This condition activates NF-$\kappa\beta$, where NF-$\kappa\beta$ is a protein that activates molecules that cause inflammation in nerve cells such as iNOS, IL-6, COX-2, and TNF-α, hence this will contribute to damaged nerve cell [5,7].

The activation of NF-$\kappa\beta$ is essential for cell proliferation and cell migration. NF-$\kappa\beta$ also plays a role in a variety of actions such as free radicals, stress, cytokines, UV radiation and bacterial antigens [8].

2.PAI-1

The idea of Plasminogen Activator and PAI-1 is based on the finding that fibrinolysis disorders in small blood vessels cause ischemia in nerve cells, resulting in oxidative stress and symptoms of painful diabetic neuropathy. This idea arose from research that has been done to humans. The number of plasminogen activators decreased 4-6 times in microvascular epineural and endoneurial sural nerves in patients with diabetic neuropathy compared to control nerve biopsies. The decreased number of Plasminogen Activator caused thrombosis and ischemia of the nerves[8].

PAI-1 is an inhibitor of plasminogen activators, such as tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) and the primary regulator of the fibrinolysis system. The effects of PAI-1 are significant in the incidence of thrombosis, including cancer, a fibrotic disease, atherosclerosis, renal and pulmonary fibrosis, and type 2 DM. Through regulations from T-PA and U-PA, PAI-1 plays a role in the physiological processes of wound healing and the formation of new tissues [9]

PAI-1 stimulates the mitosis process in smooth muscle cells which plays a role in the occurrence of atherosclerosis. The PAI-1 regulation is not only regulated through a hexosamine pathway, but also the PKC pathway. Therefore, neuropathic diabetic pain occurs through a similar injury mechanism [2].

3.NRF2

Nuclear Factor-2 Erythroid Related Factor is a transcription factor that regulates cell resistance to oxidants [2,4]. NRF2 controls and regulates the production of a series of genes to be responsible for exposure to the oxidation process [4,10]. Nrf2 together with NF-κB work together to maintain a state of homeostasis, but due to excess production from ROS, there is an imbalance between Nrf2 and NF-κB resulting in nerve cell damage [2].

Activation of Nrf2 increases defence against antioxidants and prevents oxidation stress. The study shows that NRF2 plays an essential role in protecting against various types of diabetes complications such as nephropathy, retinopathy, muscle atrophy, cardiomyopathy, and neuropathy. Various activators of NRF2 have been tested in diabetic patients for protection against various types of diabetes complications If there are deficiencies or inhibition to Nrf2, an oxidation process will occur which will cause damage and various abnormalities [11].

4.TGF-β1

The cause of PDN is very complex and involves various pathophysiology such as hyperglycemia and dyslipidemia which are responsible for the formation of oxidative stress and the formation of AGE products. As an inflammatory mediator, TGFβ1 will activate NF-κB. As a result, the genes regulated by TGFβ1 are often associated with oxidation stress and implicated in the production and maintenance of glutathione [12].

TGFβ1 has an essential function in the process of macrophages and chemotaxis fibroblasts, suppression of lymphocyte function, collagen synthesis, and stimulation of the extracellular matrix. This process is characterized by increased TGFβ1 expression in humans with atherosclerosis plaques. Diabetic patients often present with acute myocardial infarction showing a decrease in smooth muscle cells and an increase in macrophage cells and TGFβ1 in lesions. TGFβ1 could be used for DPN diagnosis because TGFβ1 appears as a key effector in diabetic foot neuropathy and showing significant independent correlations with diabetic neuropathy. However, still, further studies and research are needed [12,13].

Conclusion

A prolonged hyperglycaemic condition causes painful diabetic neuropathy (PDN). Hyperglycaemia induces the formation of AGEs and overproduction of reactive oxygen species (ROS) The pathophysiology of DNP involves these transcription factors such as NF-κB, Plasminogen Activator Inhibitor (PAI-1), Nrf2, and Tumor Growth Factor-β(TGF-β. These transcription factors are involved in the process of micro-vascular and macro-vascular complication via a different glycemic pathway. Understanding the role of these transcription factors will be beneficial for the future to help the clinicians making a diagnosis and therapy plan for patients with DPN.

Competing Interests

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