The primary biochemical mechanisms of Diabetic Peripheral Neuropathy (DPN)


Diabetic Peripheral Neuropathy (DPN) is an extraordinary common complication of diabetes accounting for substantial suffering by predisposing the foot to ulceration and lower extremity amputation. Besides, it has also become a huge economic burden for patients and for the world. However, primary treatment trials have not yet provided appropriate therapies due to a poor understanding of the mechanisms underlying the disease.

The currently well-accepted cause of the disease is hyperglycemia, while insulin resistance and dyslipidemia may also have impacts on it. Hyperglycemia contributes to oxidative stress in neurons and thus activates various biochemical pathways to damage the neural tissues. This review focuses on the 8 primary biochemical mechanisms of DNP, namely polyol pathway, advanced glycation end-products pathway, PKC pathway, PolyADP-ribose polymerase pathway, hexosamine pathway, oxidative stress and mitochondrial dysfunction, inflammation and growth factors, and dyslipidemia and insulin resistance, intending to provide a systemic mind for seeking the therapeutic targets for DPN.

Key Words: Diabetic Peripheral Neuropathy (DPN); Hyperglycemia; Insulin resistance; Oxidative stress; Inflammation

INTRODUCTION

According to statistics, the number of people with diabetes was 6.4% of the total population in 2010 (about 285 million) around the world and still continued to rise. It was estimated that the number would reach up to 7.7% in 2030 (about 439 million) (1). As the most common chronic complication of diabetes, DPN seriously affects people’s life quality. What’s more, its disability rate and death rate have been increasing in recent years (2). More than one half of the patients with type 1 or type 2 diabetes are suffering from DPN (3). Among them, 15%-30% complain of pain (4) and the others develop anaesthesia and numbness. The general manifestations of DPN are numbness, acmesthesia, burning sensation, itching and thermalgia. The symptoms may diffuse from toes to soles, and then spread upward to legs, and finally fingers and palms are affected. Its clinical symptoms are relevant to imbalance of large sensory fiber and both cold and heat sensibility affected small sensory fiber disease usually brings out pain and temperature sensation disorder. The common manifestations of diabetes-induced chronic pain are hyperalgia, allodynia, cæthesia and spontaneous pain (6,7).

DCCT (Diabetes Control and Complication Trial) holds that DPN is mainly caused by hyperglycemia (8). However, more data have suggested that DPN is induced not only by abnormal blood glucose concentration but also by insulin resistance (9) and dyslipidemia (10) in recent years. At present, the number would reach up to 7.7% in 2030 (about 439 million) (1). As the most common chronic complication of diabetes, DPN seriously affects people’s life quality. What’s more, its disability rate and death rate have been increasing in recent years (2). More than one half of the patients with type 1 or type 2 diabetes are suffering from DPN (3). Among them, 15%-30% complain of pain (4) and the others develop anaesthesia and numbness. The general manifestations of DPN are numbness, acmesthesia, burning sensation, itching and thermalgia. The symptoms may diffuse from toes to soles, and then spread upward to legs, and finally fingers and palms are affected. Its clinical symptoms are relevant to imbalance of large sensory fiber and both cold and heat sensibility induced by small sensory fiber (5). Large sensory fiber disease has effects on the feeling and reaction of ankles, and may result in falling and loss of equilibrium sense. Small sensory fiber disease usually brings out pain and affects temperature sensation. The common manifestations of diabetes-induced chronic pain are hyperalgia, allodynia, cæthesia and spontaneous pain (6,7).

DCCT (Diabetes Control and Complication Trial) holds that DPN is mainly caused by hyperglycemia (8). However, more data have suggested that DPN is induced not only by abnormal blood glucose concentration but also by insulin resistance (9) and dyslipidemia (10) in recent years. At present, the study on mechanisms of DPN focuses on glycometabolism. Extensive animal and in vitro experiments indicated that biochemical pathways played more important roles in the development of diabetes-induced complications. The relevant biochemical pathways include polyol pathway, advanced glycation end-products, protein kinase C (PKC), poly (ADP-ribose) polymerase pathway, hexosamine pathway, inflammation, expression of nerve factors and etc. Most of them can cause increased oxidative stress and disorder of mitochondrial function, and serve as important targets for the prevention and treatment of DPN. This review mainly discusses the research progresses of DPN’s biochemical pathway in terms of its mechanisms.

MECHANISMS

Polyol pathway

In general, the activation of polyol pathway is the reduction of glucose to sorbitol. Normally, glucose is metabolized through glycolytic pathway, tricarboxylic acid cycle and oxidative phosphorylation (11). Under hyperglycemia state, excessive glucose in cells is metabolized through the polyol pathway, which may induce the increased concentrations of sorbitol and fructose and decreased expression and uptake of inositol. As a result, the activity of Na+/K+-ATPase decreases (12) and nerve conduction velocity slows down. Finally, peripheral nerve is damaged. In general, the activation of polyol pathway is the reduction of glucose to sorbitol. Normally, glucose is metabolized through glycolytic pathway, tricarboxylic acid cycle and oxidative phosphorylation (11). Under hyperglycemia state, excessive glucose in cells is metabolized through the polyol pathway, which may induce the increased concentrations of sorbitol and fructose and decreased expression and uptake of inositol. As a result, the activity of Na+/K+-ATPase decreases (12) and nerve conduction velocity slows down. Finally, peripheral nerve is damaged.

Advanced glycation end-products pathway

Advanced Glycation End-Products (AGEs) are a binding product of excessive glucose and protein. It can be synthesized in vivo and ingested by food intake. Current researches show that AGEs can accelerate the aging of human body and induce a lot of chronic degenerative diseases by attacking the tissue cells (13). There are three mechanisms through which AGEs damage the cells. The first is to promote cell apoptosis by modifying the biochemical function of intracellular proteins (16,17). The second is to modify substance like laminin and fibronectin in the cell matrix, and promote the sprouting of poor collateral and regeneration of DPN-associated axons (18). The third is to modify plasma protein by producing ligands which can bind to RAGE (AGEs receptor) in macrophages, smooth muscle, vascular endothelial cells and Schwann cells (19). The combination of AGE and RAGE will increase the production of ROS and the activation of NF-κB, resulting in multiple changes in gene expression and inducing the enhancement of endothelial

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permeability, proliferation of smooth muscle cells and fibroblasts, and degradation of extracellular matrix. As a result, the secretion of cytokines will be carried out, which leads to apoptosis ultimately. These changes will accelerate atherosclerosis and cause the occurrence of arteriosclerosis, thrombosis and microvascular complications (20). Berhas found the changes of biochemical function and morphological structural modification in diabetic state, while in RAGE-silenced mice, abnormal symptoms like hyperplasia, nerve conduction disturbance and axonal atrophy were relieved (21). This implies that the activation of RAGE may induce the development of DPN.

PKC pathway

The PKC family consists of many enzymes that can phosphorylate target proteins, and the activities of most members are determined by Ca²⁺ and serine phosphate and diacylglycerol. The long-term hyperglycemia may increase the levels of diacylglycerol and activate the PKC pathway, and then induce inflammation and lead to the development of DPN. In general, abnormal activation of PKC affects neural blood flow and decreases nerve conduction velocity. In vitro, activation of PKC can induce the activation of NFκB, expression of vascular endothelial growth factor and overexpression of plasminogen activator inhibitor-1 (22). Above pathological changes have effects on vascular contraction and capillary permeability. PKC is also involved in the mechanism by decreasing the activity of Na⁺/K⁺-ATPase, which slows down nerve conduction velocity and induces nerve regeneration.

Poly(ADP-ribose) polymerase pathway

Polymerase (PARP) is a common nuclear DNA repair enzyme that generates protein-binding ADP-Ribose by splicing NAD⁺. It has been demonstrated that PARP can cause oxidative stress (23). The activity enhancement of PARP will excessively consume NAD⁺, which causes energy insufficiency and induces oxidative stress (24). PARP is associated with many symptoms like decreased nerve conduction velocity, disorders of nerve and blood vessel, mechanical allodynia and thermal hyperalgesia, and loss of myelin sheath (23-25). Additionally, it has been certified that the content of ADP increased in polymyoskeletal nerves and Schwann cells of rats that had suffered from diabetes for four weeks (23). Although the specific detection of ADP ribosomal protein and its effects on DPN still remain unknown, it showed that neuropathy did not occurred at the end of small nerve fiber in PARP-1 knockout mice, which indicated that the activation of PARP played a certain role in the development of DPN (26).

Hexosamine pathway

The hexosamine pathway is also a pathway for glucose metabolism. In the processes of glucose metabolism, nearly 3% of total sugar gets involved in the hexosamine pathway by means of fructose-6-phosphate, which will be converted into glucosamine-6-phosphate under the action of glutamine-6-phosphate aminotransferase which is the rate limiting enzyme in hexosamine pathway. It is the initial sign for the formation of UDP-N-acetyl glucosamine (23). Additionally, it has been found that O-glucosamine transferase and phosphorylation provides a new pathway. It is the initial sign for the formation of UDP-N-acetyl glucosamine. O-glucosamine transferase takes UDPGlcNAc as substrate to modify serine and threonine residues.

Increased protein modification caused by O-glucosamine transferase may induce diabetic vascular complications via inhibiting transcription factor Sp1. Sp1 can activate glucose-induced housekeeping gene, plasminogen activator inhibitor-1 and transforming growth factor β. Activation of these specific genes may induce mitosis of vascular smooth muscle cells and vascular endothelial fibrosis, promote the formation of collagen matrix, reduce the proliferation of mesangial cells and play an important role in atherosclerosis as well (27). At the same time, the interaction between O-glucosamine transferase and phosphorylation provides a new level of regulation (28). Due to the changes in gene expression and protein function, hyperglycemia-induced hexosamine pathway can lead to neuronal degeneration and necrosis, and diabetic neuropathy occurred as a result.

Oxidative stress and mitochondrial dysfunction

Oxidative stress is the common basis of insulin resistance, diabetes and cardiovascular diseases. Hyperglycemia can lead to reduced glycolysis and overload of tricarboxylic acid cycle, thus resulting in the occurrence of oxidative stress. In endothelial cells under hyperglycemic state, excessive glucose gets involved in glycolysis and tricarboxylic acid cycle, leading to the obvious increase of NADH and FADH₂, which can induce excessive protein expression in the mitochondrial membrane and hyperpolarized membrane potential is produced as a result. It decreases the electron transfer rates and increases the superoxide produced by complex I and complex III. Superoxides produced by complex I mainly act on mitochondrial matrix directly, while that produced by complex III are more evenly distributed in mitochondrial matrix (29). Therefore, superoxides generated in above two sites may cause damage to mitochondrial proteins and result in apoptosis and necrosis.

It is well known that superoxides produced by mitochondrial electron transport chain tend to induce various pathogenesis under hyperglycemic state (30). Superoxides may cause damage to mitochondrial DNA, and thus PARP pathway can be activated to inhibit the activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (31). The inhibitory effect of GAPDH may result in the accumulation of glycolysis intermediate products in the mitochondria, and thus lead to oxidative stress and mitochondrial dysfunction. In the upstream, thereby turning to other cellular pathways and activating the four classic pathways in downstream, namely generation of AGEs, PKC pathway, hexosamine pathway and poylorn pathway. Many experiments took mature sensory nerves or dorsal root ganglia of diabetic rats to verify that long-term diabetes could decrease mitochondrial membrane potential and respiratory chain activity (32). Activation of PKC and its effects on DPN were found that there was a decline of mitochondrial respiratory intensity in DRG of diabetic rats, which is related to oxidative phosphorylation, biosynthesis of ubiquinone, TCA cycle and decrease in oxidation associated proteins (32,33). Although we cannot explain in detail how diabetes acts on mitochondrial respiration directly, the results of quantitative proteomic analysis showed that stress under hyperglycemic state might inhibit synthesis of most mitochondrial proteins in culture of embryonic sensory neurons (34).

Inflammation and growth factors

Diabetic neuropathy presents chronic subclinical signs of inflammation, and proinflammatory factors contribute to the occurrence and maintenance of neuropathic pain (35). Proinflammatory factors, like TNF-α, IL-1, IL-6, IL-8, MCP-1 and C-RP, play key roles in amplifying inflammatory reactions. Experiments in recent years have indicated the relationship between TNF-α and diabetic neuropathy. An obvious increase of TNF-α could be found in the blood of patients with type 1 or type 2 diabetes (36), while DPN did not occur in TNF-α gene knockout diabetic mice (37). Most of the proinflammatory cytokines are produced due to stimulation of immune cells, and some are produced by macrophages and adipose cells. Infected or injured tissues will release chemokines that can activate endothelium and enhance the expression of adhesion molecules. It has been proved that Intercellular Adhesive Molecule-1 (ICAM-1), Vascular Adhesive Molecule-1 (VCAM-1) and E-selectin are all associated with diabetic complications (38).

Neurotrophic factors contribute to the development and maintenance of nervous system by promoting the growth and survival of neurons. Nerve nutrition family of growth factors includes Nerve Growth Factors (NGF), Brain Derived Neurotrophic Factors (BDNF), neurotrophins-3 (NT-3) and Neurotrophins-5 (NT-5). Each neurotrophic factor can regulate the nerve function and support the growth and survival of different neurons. Each member in the neural regulatory protein family of growth factors is essential for the survival of Schwann cells and can regulate the formation and degeneration of myelin sheath (39). The contents of NGF and NT-3 decrease in DPN tissue and serum, and diabetes can reduce the transport of NGF and NT-3 in the peripheral nerve (40). Intrathecal transport of NGF and NT-3 can increase the distribution of myelin fibers in the foot skin of diabetic mice, so lack of neurotrophic factors may affect the formation of nerve fibers (41).

Growth factors secreted by Schwann cells also have an impact on diabetic neuropathy. Neuregulin-1 forms a family consisting of glia derived neurotrophic factor and they will bind to B2 Erb receptors of Schwann cells (42). Neuregulin plays a complex role in the regulation of myelin formation, because all of them can promote the formation of myelin and induce the concentration-dependent demyelination (39). The experiment of Guertin et al. showed that increase in neuregulin level could induce ErbB2 receptor-activated Wallerian degradation after the axonal damage (43). It was found that hyperglycemia may induce transcriptional activated Erb B2 receptors and increase the uptake of thymidine (44). In diabetic mice, increase of Erb B2 receptor phosphorylation in sciatic nerve helped to decrease motor nerve conduction velocity and relieve hyperalgesia (45). In summary, nerve regulation factors secreted by myelinated Schwann cells neurons can induce the occurrence of demyelination in the hyperglycemic state (46). However, it remains to be further studied that whether diabetes can affect the expression of different subtypes of neural regulation factors and whether they can induce attenuation of peripheral nerve myelin sheath.

Desipramine and insulin resistance

Recent studies on patients with T1DM have found that controlling blood glucose is significant in preventing neuropathy, but that does not work
in patients with T2DM (47). So there must be other factors that induce neuropathy in T2DM. It is noted that the incidence of dyslipidemia in T2DM is high and lipid homeostasis has been found to be associated with diabetic neuropathy (48). High-fat diet fed mice still developed DPN after the hyperglycemic state had disappeared (49). The normally fed mice showed relieved mechanical pain, while high-fat diet fed mice showed hyperalgesia (51). Therefore, we should not be limited to the study on the pathological mechanism of glucose metabolism but study the effect of dyslipidemia on DPN further.

Although long-term chronic hyperglycemia is regarded as the main cause of DPN, patients with impaired glucose tolerance or prediabetes also developed DPN (52). When the insulin levels in the blood of STZ-induced diabetic rats decreased to 2 ng/ml, their sensitivity to mechanical pain changed before hyperglycemia occurred, and when hyperglycemia-induced DPN occurred, their insulin levels had dropped below 0.5 ng/ml (53). So impaired insulin signaling or insulin deficiency in peripheral neurons may induce DPN. The expression of neuronal insulin receptor will decrease when peripheral nerves are physically hurt or under diabetic state (54). Insulin is essential to the function of most neurons, while insulin receptors abundantly expressed in dorsal root ganglion neurons and peripheral nerve axons. When drug therapy didn’t work in relieving hyperglycemia, foot injection of insulin in diabetic mice could improve the nerve fiber density and the mechanical pain sensitivity (55). Dependent on the phosphatidylcholine kinase, insulin can improve the respiratory function and mitochondrial membrane potential. So insulin deficiency may affect the function of diabetic sensory neurons by inhibiting mitochondrial respiration.

PROSPECT

In recent years, diabetic neuropathy animal model was established by the injection of STZ to induce diabetes. Most of which were T1DM and people generally focused on glycometabolism. Intervention therapy for T1DM is mainly through the control of blood glucose to protect nerve functions. T2DM is often combined with other risk factors like coronary heart disease, dyslipidemia, obesity and hypertension, and patient presenting multiple symptoms usually to be considered with metabolism syndrome. The incidence of dyslipidemia in T2DM is high. Research suggested that dyslipidemia might be the main cause of type 2 diabetic neuropathy (49). So we can try to find new therapeutic targets from metabolism syndrome like dyslipidemia, obesity and hypertension in the study of type 2 diabetic neuropathy. There are extensive researches on the relationship between blood brain barrier and diabetes complications, while the blood nerve barrier, which is similarly characterized, is rarely studied. Pericyte, as a microvascular component, is the structural support of the blood nerve barrier. Kanda et al. thought that the study on pericyte was vital for the treatment of diabetic peripheral neuropathy and even some intractable neuropathic pain (56). Therefore, pericyte and the blood nerve barrier may become new targets for the future study of DPN.

Generally, there have been increasing studies on mechanisms of diabetic peripheral neuropathy, but little substantial progress is made, which indicates obviously insufficient of the interdisciplinary study on endocrinology and pain (57). Hence it is significant for us to broaden our horizon, jump out of the traditional thinking mode and look for new target points.

REFERENCES


