In Diabetes, the chronic hyperglycemia and associated complications affecting peripheral nerves are one of the most commonly occurring microvascular complications with an overall prevalence of 50–60%. Among the vascular complications of diabetes, diabetic neuropathy is the most painful and disabling, fatal complication affecting the quality of life in patients. Several theories of etiologies surfaced down the lane, amongst which the oxidative stress mediated damage in neurons and surrounding glial cell has gained attention as one of the vital mechanisms in the pathogenesis of neuropathy. Mitochondria induced ROS and other oxidants are responsible for altering the balance between oxidants and innate antioxidant defence of the body. Oxidative-nitrosative stress not only activates the major pathways namely, polyol pathway flux, advanced glycation end products formation, activation of protein kinase C, and overactivity of the hexosamine pathway, but also initiates and amplifies neuroinflammation. The crosstalk between oxidative stress and inflammation is due to the activation of NF-κB and AP-1 and inhibition of Nrf2, peroxynitrite mediates endothelial dysfunction, altered NO levels, and macrophage migration. These all culminate in the production of proinflammatory cytokines which are responsible for nerve tissue damage and debilitating neuropathies. This review focuses on the relationship between oxidative stress and neuroinflammation in the development and progression of diabetic neuropathy.

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia associated with symptoms like polydipsia, polyphagia, polyuria, blindness, weight loss or gain, sore heals, burning and tingling sensation, and so forth. Diabetic population of the world in 2013 was 382 million and it has been projected to rise to 592 million by the year 2035 [1]. Diabetes has become a challenging health problem affecting the global population and the prevalence is higher in developing countries. Among the top 10 countries having highest number of people with diabetes, 8 are middle-income rapidly developing countries. There will be a 42% increase in the developed countries and a 170% increase in the developing countries in diabetic cases by 2030 [2].

Diabetes is associated with both macrovascular and microvascular complications, in which the major microvascular complication is diabetic neuropathy (DN) with a prevalence of 50–60% [3]. The neuropathy progresses with decreasing nerve functionality and nerve blood perfusion which may result in malnourished nerve and leads to permanent nerve damage. The clinical manifestations of diabetic neuropathy include numbness, burning and tingling sensation, and intractable pain [4].

Although hyperglycemia is considered to be a major pathophysiological factor in the development of diabetic neuropathy, the associated mechanisms are not fully understood yet. Some of the major pathways like polyol pathway [5], advanced glycation end products [6], hexosamine flux [7], mitogen-activated protein kinases [8], altered activity of Na+/K+-ATPase [9], poly-ADP ribose polymerase (PARP) over activation [10], and cyclooxygenase-2 (COX-2) activation [11] have been reported to play a crucial role in development and progression of diabetic neuropathy (Figure 1). Nerve cells are prone to hyperglycemic injury as the neuronal glucose uptake is based on external glucose concentration...
which is 4-5-fold higher in diabetic subjects. It has been noted in experimental diabetes that the levels of neurotrophic support, including nerve growth factor and insulin like growth factor are reduced [12], which also contribute to malnourishment of nerves. All these pathways form a common platform with end result as neuronal dysfunction and nerve damage and this translates in the development of various clinical deficits seen in patients suffering from diabetic neuropathy. 

Treatement of painful diabetic neuropathy presents a great challenge to clinicians due to poor diagnostic criteria and the limited treatment options available. Currently, drugs in clinical use for diabetic neuropathic pain include tricyclic antidepressants, selective serotonin and noradrenaline reuptake inhibitors, anticonvulsants, and opioids [13]. Although there is a range of pharmacological agents available for treating the pain associated with diabetic neuropathy, only duloxetine and pregabalin are approved by US Food and Drug Administration (US FDA) for the treatment of diabetic neuropathic pain. However, as single agents, they are limited by incomplete efficacy, high cost, and dose limiting adverse effects [14–16].

In spite of the voluminous research done in the field of diabetic neuropathy, clear understanding of the pathophysiology and the interwoven mechanisms are still lacking. There is a need to investigate futuristic, combinational, and other nonpharmacological approaches for alleviating DN and associated neuronal deficits.

2. Classical Pathways of Hyperglycemic Vascular Damage

Diabetic neuropathy is a syndrome which can affect both the somatic and autonomic divisions of the peripheral nervous system. In severe diabetic conditions, longer nerve fibres show an earlier loss of nerve conduction velocity with loss of their nerve terminals. The damaged nerve terminals are the reason for tingling and loss of sensation and reflexes.
are often first observed in the feet and then they ascend to affect other areas [4]. One of the major causes for all these complications is reactive oxygen species (ROS) produced from processes initiated and amplified under chronic hyperglycemic conditions. Further, classical hyperglycemic pathways like polyol pathway, protein kinase C (PKC) pathway, formation of advanced glycation end products (AGE pathway), and hexosamine pathway activation leads to aggravation of oxidative damage leading to vascular complications [17]. In polyol pathway, aldose reductase enzyme converts glucose into sorbitol, which is then oxidized into fructose by sorbitol dehydrogenase (SDH) with NAD⁺ as a cofactor. In case of hyperglycemic conditions, increase in oxidative stress directly results from the accumulation of sorbitol and indirectly through consumption of NADPH, a cofactor for the regeneration of reduced glutathione (GSH) [18]. Increased flux through polyol pathway can decrease (Na⁺/K⁺) ATPase activity and studies suggested that decreased activity of this enzyme may activate PKC pathway [19]. Activation of PKC increases cytolic phospholipase A₂ activity and produces arachidonate and prostaglandin E₂ (PGE₂) which effectively inhibits cellular (Na⁺/K⁺) ATPase [20]. Persistent and excessive activation of several PKC isoforms initiates tissue injury by diabetes-induced ROS [21], which leads to enhanced de novo synthesis of DAG from glucose via triose phosphate. Increased levels of triose phosphate concentrations can increase the formation of both methylglyoxal, a precursor of AGEs, and diacylglycerol (DAG), an activator of PKC [22]. Evidence suggests that the enhanced activity of PKC isoforms results in activation of various signalling mechanisms like mitogen-activated protein kinases (MAPK), nuclear factor kappa light chain enhancer of B cells (NF-κB), and thus leads to initiation of inflammation as depicted in Figure 1. Overactivation of PKC has been also implicated in the decreased nitric oxide (NO) production in smooth muscle cells and increased expression of fibronectin factor, plasminogen activator inhibitor (PAI-1), tumor growth factor-β (TGF-β), and NF-κB activation in cultured endothelial cells and in case of vascular smooth muscle cells [23]. AGE pathway activation results in production of many advanced glycation end products, which act on specific receptors like receptor for advance glycation end products (RAGE) present on monocytes and endothelial cells to increase the production of cytokines and adhesion molecules and also causes the alteration of protein structure. AGEs have been shown to have an effect on matrix metalloproteinases, which might damage nerve fibres [24]. AGE receptor ligation can activate transcription of pleiotropic factor NF-κB and thus enhances the production of various proinflammatory mediators (Figure 1) [25]. Hyperglycemia and insulin resistance induced excess fatty acid oxidation also appears to be reason for pathogenesis of diabetic complications [26]. In hexosamine pathway, fructose-6-phosphate converts to glucosamine-6-phosphate by glutamine fructose-6-phosphate amidotransferase (GFAT). Glucosamine-6-phosphate then converts into UDP-N acetyl glucosamine with the help of specific O-GlcNAc transferases. Evidence suggest that inhibition of GFAT blocks hyperglycemia-induced transcription of both TGF-α and TGF-β1 [27].

The mechanism behind the hyperglycemia-induced expression of genes such as PAI-1, tumor growth factor-α (TGF-α), and TGF-β1 is not clear. However, it has been observed that hyperglycemia causes a fourfold increase in O-GlcN acylation of the transcription factor specificity protein 1 (Sp1), which mediates hyperglycemia-induced activation of the plasminogen activator inhibitor-1 (PAI-1) promoter in vascular smooth muscle cells and of TGF-β1 and PAI-1 in arterial endothelial cells (Figure 1) [28]. Activation of PAI-1, TGF-α, and TGF-β1 causes accumulation of extracellular matrix which may lead to neuroinflammation associated with diabetic neuropathy [29].

3. Oxidative Stress and Mitotoxicity: Role in Neuronal Dysfunction

Hyperglycemia induces activation of classical pathways like AGE, PKC, hexosamine, and polyol pathways to mediate cellular damage [17]. However, the hyperglycemic cell injury is the result of cumulative occurrence of this cascade of pathways discussed in the previous section [22].

Generation of superoxide from mitochondrial electron transport chain is known to contribute towards hyperglycemia initiated various etiological pathways. Hyperglycemia enhances the reducing equivalents to electron transport chain (ETC) and the electrochemical potential across the inner mitochondrial membrane and hence increases superoxide production [22]. Superoxide inhibits glyceraldehyde phosphate dehydrogenase (GAPDH) either directly or indirectly through PARP mediated NADH⁺ depletion [30, 31]. Inhibition of GAPDH by ROS leads to accumulation of glycolytic intermediates upstream of this enzyme and redirected to initiate cellular pathways like AGE formation. Once the AGEs are formed, they bind to RAGE and activate many other crucial pathways like NF-κB and PARP. PKC pathway is activated through dihydroxy acetone phosphate mediated diacylglycerol (DAG) activation. Hexosamine pathway which is activated through enhanced flux of fructose-6-phosphate and polyol pathway by elevated glucose levels [17]. This, in turn, leads to osmotic stress in the cells which further takes the cell towards necrotic cell death. Enhanced activity of Mn-SOD, a mitochondrial form of superoxide dismutase (SOD) or overexpression of uncoupling proteins (UCP-1) in experimental diabetic animals, prevents the development of vascular complications in the animals and also reduced oxidative stress mediated neuronal damage [31, 32]. The mechanism for this neuroprotective effect can be the reduction of mitochondrial ROS generation and the clearance of the notorious ROS from the cells.

In addition to the above theory, mitochondrial abnormalities and mitochondria associated oxidative stress stands at a central position in the pathogenesis of diabetic neuropathy [33]. It has been noticed that defects in functioning of ETC chain components compromises ATP production and enhances the generation of free radicals. The free radicals generated causes damage to mitochondrial DNA (mt DNA) and nuclear DNA (n DNA) which in turn aggravates mitochondrial damage [34]. This vicious cycle developed inside mitochondria produces intense oxidative stress and drives the
cell towards apoptotic/necrotic death [35]. It is an established fact that diabetes is known to affect the respiratory capacity of ETC functional complexes and thus alters ATP production (Figure 1). Mainly complex I and complex III are known to be affected, which turn out to be electron leakage centres and thus inflates ROS production [34].

In addition to disturbed mitochondrial functionality, its dynamics (size, shape, and number) is also known to be affected in diabetic neuropathy [36]. Changes in mitochondrial morphology, movement characteristics can affect the transfer in axons which can lead to various sensorimotor changes. The glove and stocking pattern of thermal sensitivity is due to impairment in the anterograde axonal transport in sensory neurons [37]. Dysfunctional mitochondria can also mediate cell death through execution of apoptotic pathways, by releasing pro apoptotic factors from mitochondria into the cytosol [35]. Various experimental observations point towards the critical role of mitotoxicity in the pathophysiology of diabetic neuropathy.

4. Neuroinflammation and Role in Peripheral Nerve Damage

Diabetic peripheral neuropathy is characterized by debilitating pain and sensory loss which leads to diminished quality of life. Persistent hyperglycemia is believed to be underpinning for the neuroinflammation and nerve damage leading to the neuropathic pain. All the characterized classical pathways like polyol pathway, PKC pathway, MAPK pathway, and increased production of AGEs could directly or indirectly initiate and progress the production of inflammatory mediators [13]. Especially the accumulation of AGE products of proteins and lipids stimulate the generation of inflammatory mediators and activation of transcription factor NF-κB, a potent inducer of inflammatory processes [38]. These AGEs act on various receptors present on microglia and macrophages stimulate production of cytokines like IL-1, IL-6, IL-17, TNF-α, chemo attractant protein-1, C-reactive protein and chemokines like CCL-2, CXC, and so forth (Figure 1) [39, 40]. Activation of RAGE can induce inflammatory cascade through the activation of NF-κB pathway. NF-κB is a transcription factor that upregulates the gene expression of proinflammatory cytokines and also is responsible for the induction of neuronal apoptosis. Activation of NF-κB also suppresses the expression of antioxidant genes by downregulating Nrf-2 pathway and thus indirectly weakening the innate antioxidant defense (Figure 2) [41]. Persistent hyperglycemia induced inflammation also affects the structural features of neuron as the glycosylation of myelin protein alters its antigenicity causing infiltration of monocytes, macrophages, neutrophils from the blood circulation, and activation of glial cells of the nervous system [24, 42]. These immune cells in turn secrete inflammatory cytokines which further damages myelin sheath and increases nerve excitability, thus leading to edema and neuroinflammation. The stimulated monocytes and immune cells have a vicious positive feedback loop for increasing the production of inflammatory mediators thus potentiating nerve catastrophe. The cytokines like IL-1, IL-6, and IL-17 can sensitize the peripheral receptors causing neuropathic pain [43]. Additionally, neuroinflammation leads to nerve damage due to apoptosis induced by MAPK signalling [44]. TNF-α also promotes the expression of cell adhesion molecules which are capable of decreasing the blood perfusion rate and thus decreases neurotrophic support [42]. The released chemokines have been shown to produce hyperalgesia through the activation of chemokines receptors present on the nerves. Hypoxia and ischemia created in diabetes also aggravate the neuroinflammation through the induction of inducible nitric oxide synthase (iNOS), which releases NO, a physiological mediator of inflammation [45]. In large, activation of inflammatory cascade, proinflammatory cytokine upregulation, and neuroimmune communication pathways plays vital role in structural and functional damage of the peripheral nerves leading to the diabetic peripheral neuropathy.

5. Cross Talk between Inflammation and Oxidative Stress

Hyperglycemic condition is known to activate both oxidative stress and inflammatory pathways. The interaction of these two pathways complicates the hyperglycemia mediated neuronal damage. The oxidative stress induced ROS and various constitutional inflammatory pathways are known to interact at multiple levels to produce plethora of pathophysiological outcomes (Figure 2) [46].

Hyperglycemia is known to increase metabolic flux through mitochondrial electron transport chain, leading to inefficient electron transfer through redox centres and hence generating superoxide anion [22]. Excessive superoxide generation leads to production of other ROS such as H2O2, OH−. Superoxide can also combine with nitric oxide (NO) to produce peroxynitrite (ONOO−), a potent reactant which causes nitration of several important proteins and leads to structural and functional damage [47]. Peroxynitrite mediated DNA damage leads to activation of PARP, a nuclear enzyme which causes transfer of poly-ADP ribose units to DNA by utilising NADH energy pool. Depletion of NADH leads to bioenergetic crisis and thus drives the cell towards necrosis [48]. Necrotic cell death is known to release cellular debris, which further drives the inflammatory cells to the damaged spot and hence activates a local inflammatory episode (Figure 2).

Hyperglycemia mediated oxidative stress also activates other cellular pathways like Nrf2 and NF-κB. Activation of Nrf2 pathway enhances the production of several antioxidant and cytotoxic protective enzymes through transcriptional facilitation of antioxidant response element (ARE) of genome. These enzymes include SOD, GSH, HO-1, and glutathione s-transferase (GST) [49]. Activation of this Nrf2 pathway stands as one of the cellular homeostatic mechanisms to protect cells from enhanced oxidative stress. However, persistent Nrf2 activation is subdued through hyperglycemia mediated ERK activation, and hence redox homeostasis is failed in diabetic state as depicted in Figure 2 [50].

Oxidative stress mediated inflammation is known to execute NF-κB, activator protein-1 (AP-1), and MAPK pathways. ROS are known to activate inhibitory kappa –B kinase
Hyperglycemia mediated oxidative stress and inflammatory pathways are known to interact with each other at various levels. ROS activates nuclear factor (erythroid-1) related factor (Nrf2) by directly oxidising the thiol residues on kelch-like ECF associated protein (Keap-1). Nrf2 then migrates into the nucleus to activate antioxidant response elements (ARE) of genome. However, this Nrf2 activation by hyperglycemia is inhibited through extracellular related kinase activation (ERK). ROS also activates inhibitory kappa B kinase (IKK), which then phosphorylates the inhibitory kappa B protein (I\(\kappa B\)); the latter combines with cytosolic NF-\(\kappa B\) complex ant thus preventing its transcription. Phosphorylation of I\(\kappa B\) labels it for ubiquitination and proteasomal degradation and, hence, releases NF-\(\kappa B\) complex to enter into nucleus, which then expresses several proinflammatory mediators. Similarly, oxidative stress mediated c-JUN N terminal kinases (JNK) activation mediates the c-JUN component of activator protein-1 (AP-1) activation, which then combines with c-FOS subunit. The resulting AP-1 heterodimer binds with genome and increases production of various vascular inflammatory mediators. Oxidative stress mediated PARP activation also leads to inflammation through necrotic cell death. Nrf2 inhibits I\(\kappa B\) degradation and thus prevents NF-\(\kappa B\) mediated inflammation. NF-\(\kappa B\) also prevents the Nrf2 signalling through histone deacetylases (HDAC3) recruitment (ASK-1-apoptosis signalling related kinase-1 and MCP-1-monocyte chemoattractant protein-1).

Among the above mentioned pathways, the crosstalk between Nrf2 and NF-\(\kappa B\) is critical both physiologically and pharmacologically [41]. Activation of Nrf2 pathway is known to inhibit NF-\(\kappa B\) activation through reduced ROS mediated IKK activation and by inhibiting the degradation of I\(\kappa B\). Further activation of NF-\(\kappa B\) competes with Nrf2 N-terminal kinases (JNK), which further activates JUN subunit of AP-1 and hence facilitate AP-1 mediated collagenase, TGF-1\(\beta\), and other cytokines production (Figure 2) [53]. Although AP-1 involvement in the pathogenesis of DN needs to be explored, its activation can produce a local sequela of vascular inflammation and thus support the rationale for its participation in neuroinflammation.

Among the above mentioned pathways, the crosstalk between Nrf2 and NF-\(\kappa B\) is critical both physiologically and pharmacologically [41]. Activation of Nrf2 pathway is known to inhibit NF-\(\kappa B\) activation through reduced ROS mediated IKK activation and by inhibiting the degradation of I\(\kappa B\). Further activation of NF-\(\kappa B\) competes with Nrf2 N-terminal kinases (JNK), which further activates JUN subunit of AP-1 and hence facilitate AP-1 mediated collagenase, TGF-1\(\beta\), and other cytokines production (Figure 2) [53]. Although AP-1 involvement in the pathogenesis of DN needs to be explored, its activation can produce a local sequela of vascular inflammation and thus support the rationale for its participation in neuroinflammation.
for binding to antioxidant response element (ARE), either
directly or indirectly through recruiting histone deacetylase
3 (HDAC3) to the ARE region (represented in Figure 2)
[54]. Interaction between these two pathways maintains
the cellular homeostasis. However, diseases associated with
excessive oxidative stress generation can cause imbalance in
Nrf2-NF-κB axis and thus produce damaging consequences
[41].

There is much scientific evidence supporting the involve-
ment of inflammatory pathways in direct peripheral nerve
damage and neuroinflammation. However, a growing body
of researchers suggests that neuroglial cells act as connecting
link between oxidative stress and neuroinflammation [55].
According to this theory, oxidative damage to glia produces
excessive proinflammatory cytokines, which in turn acts on
membrane receptors of neuronal cells and thus activates
inflammatory pathways, causing neuroinflammation [56].
There is also evidence supporting the role of vascular inflam-
mation in the pathogenesis of diabetic neuropathy. Accumu-
lation of all these evidence suggests that neuroinflammation
is not the sole episode underlying peripheral nerve dam-
age but it is accompanied by inflammation and oxidative,
nitrosative stress in the vasa nervorum and neuroglial cells.

6. Futuristic Strategies for
Diabetic Neuropathy

Identification of pathomechanisms underlying disease patho-
genesis is important to not only devise new treatment
strategies but also be useful in discovering new disease
biomarkers. Biomarker identification can be useful to identify
the extent of disease progression and thus can amplify the
scope of better drug targeting. Currently available diagnostic
methods for DN include assessment of vibration perception
threshold (VPT) and calculation of neuropathy disability
score (NDS) based on ankle reflexes and perception changes
to variety of stimuli [57]. Newer techniques with minimal
invasion or noninvasive operation include corneal confo-
cal microscopy (CCM) and skin biopsy techniques. CCM
allows the identification of corneal nerve fibre length and
nerve density and thus can be used as diagnostic aid to
quantify peripheral neuropathy [58]. Skin biopsy and con-
sequent immunohistochemistry allow the quantification of
the number of nerve fibres per unit area [59]. However, these
diagnostic procedures can be combined with examination
of biochemical changes to accurately monitor the disease
progression and response to treatment.

Based on the compelling evidence put forth by many
research groups, it is being clear that oxidative stress medi-
ated neurodegeneration and the accompanied inflamma-
tory reactions play a prominent role in the pathogenesis
of diabetic neuropathy [13]. Modulation of these pathways
by pharmacological agents can prevent the functional and
pathophysiologicial disturbances associated with peripheral
neuropathy and can accelerate the discovery of new treatment
strategies for diabetic neuropathy. Some of the important
categories of drugs which have potential to affect the oxidative
stress and inflammatory pathways in relevance to peripheral
neuropathy will be discussed in the following section.

Oxidative stress is also known to enhance the endo-
plasmic stress through accumulation of misfolded proteins.
Recently, the role of ER stress in the pathogenesis of diabetic
neuropathy has been well observed. ER plays an important
role in the proper folding and processing of proteins. Oxida-
tive damage to the ER causes dysfunctional protein process-
ing system and enhances the accumulation of nonfunctional
proteins [60]. Chaperons are the ER proteins which help
in processing newly synthesized proteins. Administration of
chemical chaperons such as trimethylamine oxide and 4-
phenyl butyric acid was found to inhibit the diabetes associ-
ated oxidative stress in spinal cord and dorsal horn, reduce
intraepidermal nerve fibre loss, and ameliorate peripheral
nerve damage and thus it can be used as a therapeutic strategy
for diabetic neuropathy [61].

Nitrosative stress is also considered to be equally con-
tributing in the pathogenesis of diabetic neuropathy as
similar to oxidative stress [62]. Primarily, peroxynitrite is the
toxicant of this pathway which causes biomolecular damage
and PARP activation. PARP activation further depletes cel-
ular energy pool and causes necrotic cell death [47]. Use of
peroxynitrite decomposition catalysts and PARP inhibitors
prevent the neuronal damage associated with diabetic neu-
ropathy. Several trails done with these agents could alleviate
the biochemical and functional impairment produced due to
diabetes in sciatic nerves and dorsal root ganglion (DRG)
neurons [63, 64].

Due to massive involvement of oxidative stress in
the pathogenesis of diabetic neuropathy, several antioxidants
have been tried in patients with diabetic neuropathy. Alpha-
lipoic acid, vitamin E, and acetyl-L-carnitine were studied
clinically in several controlled prospective clinical trials [65–
67]. Among them alpha-lipoic acid was shown to relieve
sensory and functional deficits of DN and has been approved
by FDA for therapeutic use [68].

Impaired synthesis of vasoactive prostanoids and associ-
ated endothelial dysfunction is one of the pathological factors
contributing to DN, which is initiated by both oxidative
stress and inflammation. Diabetic neuropathy is associated
with compromised blood flow which results in lack of
endovascular blood supply to neurons which may be directly
or indirectly related to oxidative stress directed endothelial
damage in vasa nervorum [69]. Several vasodilators like
angiotensin receptor antagonists, endothelin antagonists,
phosphodiesterase inhibitors, calcium channel antagonists,
nitrovasodilators, and prostanoid analogues have been tested
in animal models of diabetes and among them angiotensin II
receptor antagonists (e.g., ZD7155) and ETβ receptor antag-
onists (e.g., BMS 182874) found to alleviate neurovascular
deficits in STZ induced diabetes model [70, 71]. However,
their clinical success needs to be explored to evaluate their
therapeutic use in diabetic neuropathy. Enhanced oxygen
delivery to peripheral nerves result in increased nerve
regeneration through counteraction of ischemic, hypoxic,
inflammatory, and necrotic episodes associated with diabetic
neuropathy [72].

Neuroinflammation occurs when there is a persistent
release of proinflammatory mediators and the pathways are
activated through corresponding cytokines in neuronal cells.
The proinflammatory mediators include TNF-α, IL-6, IL-1β, COX-2, and iNOS as well as several chemokines [44]. Antibodies or chemical agents against these cytokines and chemokines could alleviate the proinflammatory episode associated with diabetic neuropathy [42, 73]. These agents are known to inhibit the consequences of inflammatory changes associated with neuroglial activation. Transcriptional modulators of NF-κB and MAPK can provide a two-tier targeting approach for the prevention of neuroinflammatory changes in DN.

NF-κB and Nrf2 pathways are two important pathways mediating cellular homeostasis through controlling oxidative stress and inflammation. As discussed in the above section, deregulation in the balance of Nrf2–NF-κB axis may lead to several pathophysiological consequences and hence modulators of these pathways could be used to prevent such results [41]. NF-κB pathway involvement in the pathogenesis of diabetic neuropathy was well documented. Several natural inhibitors of NF-κB like curcumin, resveratrol, and melatonin and small molecule modulators of this pathway (BAY 117082, JSH23) were used in experimental diabetic animals [41, 74–76]. These drugs were shown to be promising by modifying the sensorimotor functional and proteomic changes associated with neuropathy. The use of NF-κB inhibitors can prevent the AGE mediated proinflammatory cytokine production and thus halts the events associated with neuroinflammation. Similarly, it is being observed that overt oxidative stress in neuronal cells is a pivotal pathogenetic mechanism in nerve damage, which can be prevented by enhancing Nrf2 mediated ARE gene expression. Nrf2 enhances the production of antioxidant and cytoprotective enzymes which counteract oxidative stress. Several pharmacological antioxidants have been known to enhance Nrf2 mediated antioxidant expression in experimental models of diabetic neuropathy and found to improve behavioural, functional, and biochemical characteristics associated with diabetes [77, 78]. Rather than individually targeting Nrf2 and NF-κB, pharmacological modulators of both transcription factors can produce a better therapeutic response by simultaneously enhancing Nrf2 and inhibiting NF-κB [41].

Since mitochondria are the primary source of superoxide, mitochondria targeted antioxidants can reduce the corresponding oxidative damage. Several antioxidants like α-lipoic acid and N-acetyl cysteine are shown to have therapeutic efficacy in animal and human diabetic neuropathy [68, 79]. However, targeting the antioxidant molecules directly to the mitochondria not only reduces oxidative stress but also inhibits the other pathophysiological pathways associated with mitochondrial dysfunction. Antioxidant molecules can be effectively conjugated to lipophilic cationic molecules like triphenyl phosphonium (TPP+) and hence accumulate in the mitochondria based on the large negative potential inside the mitochondrial membrane [80]. Mito Q, Mito vitamin E, Mito PBN, and so forth are the examples of drugs that were delivered to mitochondria in various experimental setups. Other strategies like Szeto-schiller (SS) peptides can also be conjugated to antioxidants to attain maximum concentration of drug inside the mitochondrial matrix. These peptides comprise four alternative aromatic/basic amino acid backbones and direct the targeted antioxidants to inner mitochondrial membrane. These SS peptides scavenge hydrogen peroxide and peroxynitrite radicals and are known to inhibit lipid peroxidation reactions effectively [81]. These drugs have shown beneficial effect in the preclinical models of diabetic neuropathy and need to be further assessed clinically [82]. Along with mitochondrial antioxidants, drugs which can increase the mitochondrial function can alleviate bioenergetic crisis and ETC dysfunction associated with DN. One such example of drugs includes PGC-1α modulators, which can rescue the mitochondrial dysfunction by enhancing the production of mitochondrial enzymes and mtDNA transcription through nuclear respiratory factor 1 (Nrf1) activation [83]. PGC-1α activation is also known to reduce the oxidative damage through enhanced Nrf2 activation [84].

7. Summary

Oxidative stress and neuroinflammation are identified to be pivotal pathophysiological triggers in various diabetes associated microvascular complications including diabetic neuropathy. The use of drugs targeting oxidative stress-inflammatory pathways was found to improve the sensorimotor and functional deficits associated with diabetic neuropathy. But their clinical success remained inferior due to complexity in cellular redox signalling pathways and its further interaction with cellular kinome, genome, and epigenome. Since, redox imbalance produced in one pathway can elicit another pathway, combinational use of several strategies mentioned above could produce more beneficial effects than monotherapy. Mitochondrial dysfunction is known to initiate the hyperglycemic cellular injury; the use of drugs targeting mitochondria will find greater attention in the near future for the treatment of diabetic neuropathy. Still, a lot of work is warranted to further elucidate the cross talk of oxidative stress, mitochondrial dysfunction, and inflammation in the pathophysiology of diabetic neuropathy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The authors are grateful for the support of NIPER-Hyd and IICT-Hyderabad, AP, India, in the preparation of this paper.

References


[38] S. D. Yan, A. M. Schmidt, G. M. Anderson et al., "Enhanced cellular oxidant stress by the interaction of advanced glycation


