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OVERVIEW

Role of Oxidative Stress and Ca^{2+} Signaling on Molecular Pathways of Neuropathic Pain in Diabetes: Focus on TRP Channels

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Abstract Diabetes mellitus, a debilitating chronic disease, affects ~100 million people. Peripheral neuropathy is one of the most common early complications of diabetes in ~66 % of these patients. Altered Ca^{2+} handling and Ca^{2+} signaling were detected in a huge variety of preparations isolated from animals with experimentally induced type 1 and 2 diabetes as well as patients suffering from the disease. We reviewed the role of Ca^{2+} signaling through cation channels and oxidative stress on diabetic neuropathic pain in sensory neurons. The pathogenesis of diabetic neuropathy involves the polyol pathway, advanced glycation end products, oxidative stress, protein kinase C activation, neurotrophism, and hypoxia. Experimental studies with respect to oxidative stress and Ca^{2+} signaling, inhibitor roles of antioxidants in diabetic neuropathic pain are also summarized in the review. We hypothesize that deficits in insulin, triggers alterations of sensory neurone phenotype that are critical for the development of abnormal Ca^{2+} homeostasis and oxidative stress and associated mitochondrial dysfunction. The transient receptor potential channels are a large family of proteins with six main subfamilies. The sheer number of different TRPs with distinct functions supports the statement that these channels are involved in a wide range of processes ranging in diabetic neuropathic pain and it seems that the TRPC, TRPM and TRPV groups are mostly responsible from diabetic neuropathic pain. In conclusion, the accumulating evidence implicating Ca^{2+} dysregulation and over production of oxidative stress products in diabetic neuropathic pains, along with recent advances in understanding of genetic variations in cation channels such as TRP channels, makes modulation of neuronal Ca^{2+} handling an increasingly viable approach for therapeutic interventions against the painful and degenerative aspects of many diabetic neuropathies.

Keywords Calcium ion · Diabetes · Sensory neurons · Pain · Oxidative stress · Transient receptor potential channels · Mitochondria

Abbreviations

2-APB	Aminoethoxydiphenylborane
HEK	Human embryonic kidney
IGF	Insulin growth factor
NGF	Nerve growth factor
NMDA	*N*-methyl-D-asparate
NO	Nitric oxide
PKA	Protein kinase A
PKC	Protein kinase C
RAGE	Advanced glycation end-products
ROS	Reactive oxygen species
SERCA	Sarcoendoplasmic reticulum Ca^{2+}-ATPase
STZ	Streptozotocin
TCA	Tricarboxylic acid
TRP	Transient receptor potential
TRPV1	Transient receptor potential vanilloid 1
VDCC	Voltage-dependent Ca^{2+} channels

Introduction

Diabetic neuropathy in Type 1 and 2 diabetes in both humans and animals models is associated with reduction of motor and sensory nerve conduction velocity and structural changes in peripheral nerve including endoneural

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microangiopathy, abnormal Schwann cell pathology, axonal degeneration, paranodal demyelination and loss of myelinated and unmyelinated fibers- the alter [1].

Peripheral neuropathy is one of the most serious complications of diabetes. Peripheral neuropathy is one of the most common early complications of diabetes in ~66 % of these patients. Diabetic neuropathy is frequently painful that typically involves the extremities occurring as an exaggerated response to either a painful stimulus (hyperalgesia) or a mild and normally non-painful stimulus (allodynia) [2, 3]. Existing therapies for this devastating complication of diabetes are largely inadequate.

Neuropathic pain manifesting itself as allodynia and hyperalgesia continues to be a significant problem in clinical medicine. Increasing the local Ca^{2+} concentration at the site of injury or in the spinal cord may contribute to the development or neuropathic pain [4]. The main routes of extracellular Ca^{2+} influx to the cells are voltage-dependent Ca^{2+} channels. Current arising from voltage-dependent Ca^{2+} channels are subdivided into 2 major classes based on the membrane potential at which they become activated: high-voltage activated or sustained currents which are further divided into I, P, O, N and R subtypes and low-voltage activated or transient (T-type) Ca^{2+} currents which are further divided into Cav 3.1, Cav 3.2, Cav 3.3 [5].

When pain messages are transmitted from the periphery to the central nervous system, the nociceptive transmitters such as substance P are released via exocytosis from the primary sensory terminals in the spinal dorsal horn, which is regulated by high threshold voltage-dependent Ca^{2+} channels such as N-and P/Q-types located in presynaptic nerve terminals [5]. So far, several studies including our previous report have demonstrated that voltage-dependent Ca^{2+} channels may contribute to the streptozotocin (STZ)-induced diabetic neuropathic pain [6]. The increased responsiveness of the spinal pain transmission is likely due to the increased responsiveness of the primary afferent neurons, which could results in enhanced neurotransmitter exocytosis via the opening of voltage-dependent Ca^{2+} channels or due to the postsynaptic hyperexcitability in dorsal horn projection neurons, which possible to be induced by enhanced Ca^{2+}-influx through voltage-dependent Ca^{2+} channels. There are 6 subfamilies of transient receptor potential (TRP) channels and oxidative stress-dependent Ca^{2+} over influxes through the TRP channels have also important role in diabetes and diabetic neuropathic pain. Such changes in transmission within the spinal cord may contribute to diabetic neuropathic pain [6].

The human body is equipped with a complete arsenal of defenses against external and internal aggressions. Those against the so-called reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical and hydrogen peroxide are crucial in inflammatory responses where they participate in physiological processes such as the arachidonic acid cascade and phagocytosis [7]. It is generally believed that oxidative stress is the key pathological process inducing nerve damage in diabetes [8]. The following pathways, triggered by hyperglycaemia and/or lack of insulin, contribute to oxidative stress in diabetic neuropathy:

1. poly pathway-excess glucose drives increased aldose reductase activity resulting in elevated flux through the poly pathway and build up damaging levels of polyols and associated pro-oxidants [9]. High intracellular glucose concentration also directly elevates ROS through raised Ca^{2+} influx and mitochondrial activity [10];
2. protein glycation-hyperglycaemia induced these proteins and/or activation of the receptor for advanced glycation end-products (RAGE) which induces cellular stress, in part, through activation of inflammatory pathways [9], and
3. reduced neurotrophic support-maintenance of normal phenotype of sensory neurons is impaired due to diabetes-induced loss of neurotrophic support by insulin and the insulin-like growth factors (IGF-1, IGF-2), nerve growth factor (NGF) and neurotrophin-3 (NT-3) [11].

Mitochondria are main intracellular source of ATP production. They also involved many other cellular functions including Ca^{2+} signaling and apoptosis. Mitochondria are also major sites for reactive oxygen species (ROS) and reactive nitrogen species productions [5]. In β-cells it has been reported that ROS, and probably hydrogen peroxide in particular, are one of the metabolic coupling factors in diabetes [12]. Moreover exposure of β-cells to low glucose activates 5′ AMP-activated protein kinase (AMPK) in a superoxide-dependent, AMP-independent way [13]. Hence, ROS may contribute to physiological and pathophysiological control of β-cell functions.

In the review papers, we reviewed last development of mitochondria, endoplasmic reticulum and TRP channels dependent-Ca^{2+} signaling and oxidative damage in neuropathic pain.

Diabetic Neuropathic Pain and Ca^{2+} Signaling

Diabetes mellitus, a debilitating chronic disease, affects ~100 million people [8]. Therapies for this devastating complication of diabetes are largely inadequate, partly attributable to lack of insight into the pathophysiological mechanisms of this disease [9]. One of the most prominent features of diabetic peripheral neuropathy is the development of pain that typical involves the extremities, occurring as an exaggerated response to either a painful stimulus (hyperalgesia) or a mild and normally nonpainful stimulus

(allodynia). The precise cellular mechanisms of hyperalgesia and allodynia neuropathic pain remain poorly understood, but the remodeling of voltage-and ligand-gated ion channels that can increase excitability of the sensory neurons may play a critical role [9, 10].

Glucose entry into β-cell promotes glycolysis, generating pyruvate that is imported into mitochondria, where it feeds the tricarboxylic acid (TCA) cycle. TCA cycle activation induced transfer of electrons from TCA cycle intermediates to the respiratory chain reactions via NADH and FADH2 and then the chain reactions induce production of ROS in mitochondria. The mitochondrial electron transport chain is an important site of ROS production within the cell. Electrons from sugar, fatty acids, and amino acids catabolism accumulate in the electron carriers of the respiratory chain reactions. ROS formation is coupled to electron transport as byproducts of normal mitochondrial respiration through the one-electron reduction of molecular oxygen [14]. In addition, mitochondria are not the only contributes ROS generation in pancreatic islets. Indeed, β-cells express phagocyte like NADPH oxidases, negatively modulating the secretary response by reducing cAMP secondary to ROS generation [15]. Moreover, NADPH oxidases have been reported to be responsible from Rac1-Nox-ROS-JNK1/2 signaling pathway in the islet β-cell leading to the onset of mitochondrial dysregulation in the T2D zucker diabetic fatty rats.

In diabetes, alterations in neuronal Ca^{2+} signaling may contribute to the development of distal symmetrical sensorimotor polyneuropathy and pain [11] (Table 1). Diabetes increases the current amplitude of multiple voltage-dependent Ca^{2+} currents [1], and Ca^{2+} influx activates nitric oxide (NO) cGMP/protein kinase G pathways; blockade of this pathways decreases experimentally induced pain [40]. In diabetic rats, protein kinase A (PKA), protein kinase C (PKC), and NO second messenger systems contribute to hyperalgesia, whereas *N*-methyl-D-asparate (NMDA) receptor-mediated events are not thought to be involved [16] (Fig. 1). Additionally, persistent elevations of cytosolic Ca^{2+} have been implicated in neuronal degeneration [17] and apoptosis [18]. Therefore, attenuation of oxidative stress and amelioration of abnormal Ca^{2+} signaling have emerged as important therapeutic targets in sensorimotor polyneuropathy [19].

A great body of evidence has been gathered about diabetes-induced changes of calcium signaling in different cell types. It has been reported that current densities of L- type Ca^{2+} channels were increased in diabetic beta cells [4]. Diabetes mellitus can affect both the peripheral and central nervous system. It has been shown that depolarization-induced Ca^{2+} transients in small, but not in large, dorsal root ganglion (DRG) neurons became substantially prolonged during STZ-induced and spontaneously occurring diabetes [5]. High-threshold, voltage-dependent calcium currents were enhanced in acutely dissociated, capsaicin-sensitive DRG neurons from diabetic rats, compared with non-diabetic controls [20]. Diabetes-induced alterations in neuronal Ca^{2+} homeostasis might explain the observed differential effects of diabetes on long-term potentiation and long-term depression in rat hippocampus.

Umeda et al. [6] investigated the gene and protein expression levels of α1 subunits in the dorsal root ganglia and the spinal cord from STZ-induced diabetic mice using real-time polymerase chain reaction and immunohistochemistry. They found that the STZ-induced diabetic hyperalgesia may be caused by a selection alteration in expression of P/Q-type voltage-dependent Ca^{2+} channels in mouse DRG neurons especially in small C-fibers and

Table 1 Roles of different chemicals on Ca^{2+} channels and molecular pathways of diabetic neuropathic pain in dorsal root ganglion (DRG) and sensory neurons

Channel or molecular ways	Chemicals	Effects	Reference
PKC	PKCβ selective inhibitor LY333531 and Taurine	Modulator	Tahara et al. [23]
L-type calcium channels	Nifedipine/ω-conotoxin	Inhibitor	Voitenko et al. [1]
VDCC: α1A and α1B neuron subunits	Genetic expression study	α1A (P/Q type): increased α1B (N-type): not change	Umeda et al. [6]
T-type Ca^{2+} channels	Genetic expression study	Cav3.2 and 3.3 are present but not Cav3.1	Wen et al. [21]
NO/cGMP/protein kinase G pathways	Taurine	Blockage	Li et al. [81]
T-type calcium channels	Nickel and L-cysteine	Regulator	Jagodic et al. [82]
SERCA2	Insulin, IGF-I, IGF-II, NGF, NT-3	Impaired	Verkhratsky and Fernyhough [5]

IGF insulin growth factor, *NGF* nerve growth factor, *NO* nitric oxide, *SERCA* sarcoendoplasmic reticulum Ca^{2+}-ATPase, *VDCC* voltage dependent Ca^{2+} channels

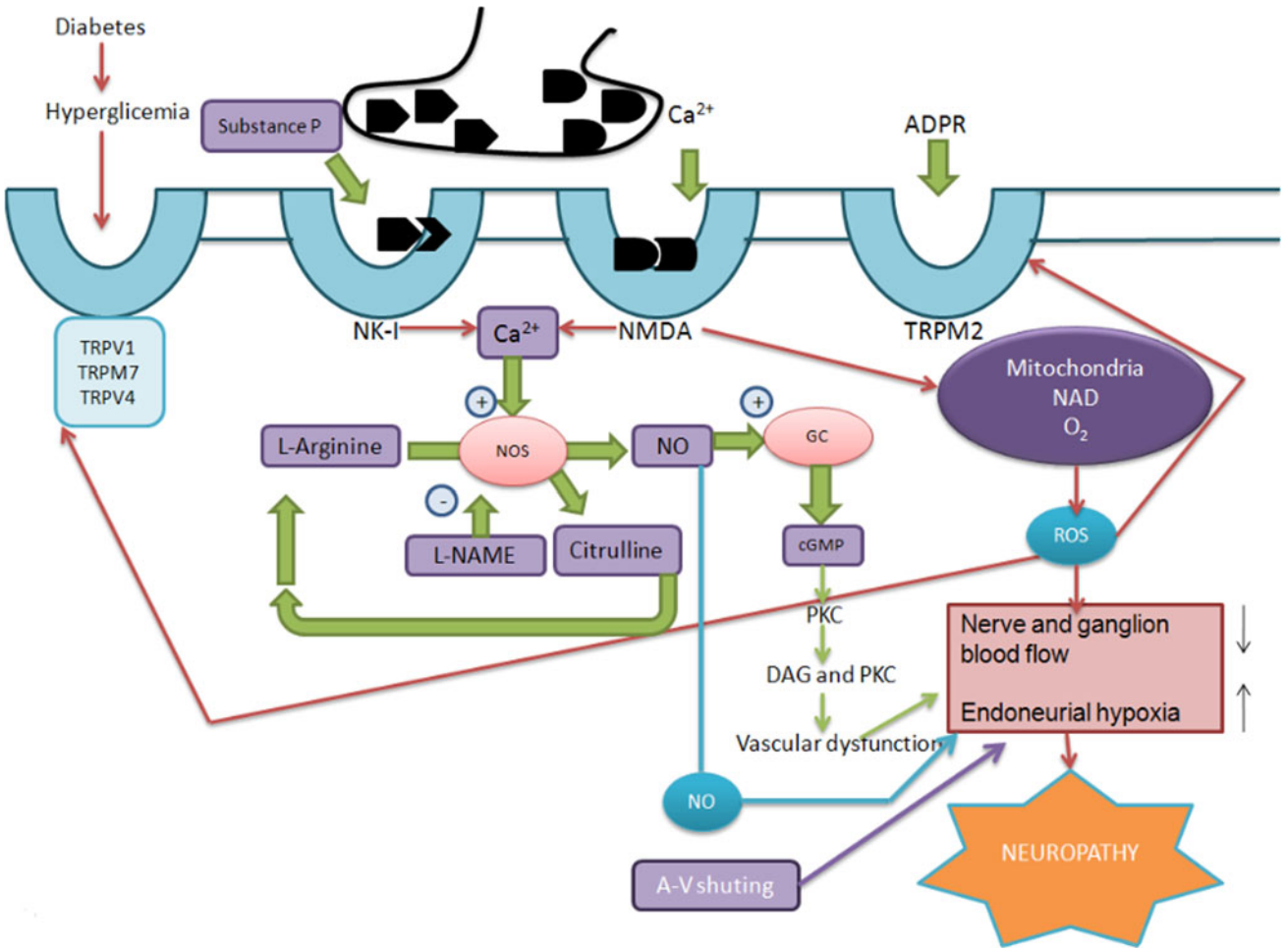

Fig. 1 Cells regulate intracellular Ca^{2+} levels lightly and excessive Ca^{2+} loads can lead to inappropriate activation of process that are normally operate at low levels, causing metabolic derangements and eventual cell death. Excessive Ca^{2+} load, in particular via *N*-methyl-D-aspartate (NMDA) receptors (NMDAR), is toxic to neurons in neurodegenerative diseases. NMDAR-mediated Ca^{2+} entry triggers a neurotoxic signal cascade involving the activation of neuronal nitric oxide (NO) synthase (nNOS), formation of the toxic ROS and NO and activation of the pro-apoptotic proteins poly(ADP-ribose) polymerase (PARP-1). Diabetes and hyperglycelima stimulate Ca^{2+} influx into cytosol through TRP channels by activation of ROS production. Sustained depolarization of mitochondrial membranes and enhanced ROS production activates transient receptor potential (TRP) channels such as TRP melastatin 2 (TRPM2), TRP vanilloid (TRPV) and voltage gated Ca^{2+} channels (VGCC) and Ca^{2+} influx increases by activation of TRP via ROS. The molecular pathway may be a cause of neurological symptoms and represents a fruitful subject for further study

medium. They concluded that an enhanced expression of P\Q-type channels results in an increased transmitter release at the primary afferent neurons, which may lead to nociceptive abnormality.

Mibefradil, a benzimidazolyl-substituted tetraline derivative, is a novel Ca^{2+} channel blocker with several interesting pharmacological properties. Previous research has indicated that mibefradil may act on peripheral T-type Ca^{2+} channels in antinociceptive effects in neuropathic pain. Recently, Wen et al. [21] reported that there were T-type Ca^{2+} channels (Cav3.2 and Cav3.3, not Cav3.1) in the lumbar spinal cord of rats, and under the neuropathic pain conditions, the mRNA expression of T-type Ca^{2+} channels increased. They concluded that T-type Ca^{2+} channels may play an important role to the development of the neuropathic pain following chronic compression of DRG neuron operation.

Li and Chen [22] PKCβ is a serine/threonine kinase that is activated by intracellular Ca^{2+} and may, in turn, modify Ca^{2+} signaling. The Ca^{2+} homeostasis in excitable cells such as neurons is tightly regulated because intracellular Ca^{2+} is a pivotal second in many signaling cascades and is linked to such physiological phenomena as neurotransmitter release, cell survival, and axonal growth and maintenance. Its disturbance is a critical issue in neurodegenerative diseases. Similarly, the abnormality of Ca^{2+} homeostasis in diabetic DRG neurons has been shown to be an early molecular marker of diabetic

neuropathy. The enhanced voltage-dependent Ca^{2+} current and impaired inhibitory G-protein function, and derangement of intracellular organelles with a Ca^{2+} buffering effect, such as endoplasmic reticulum and mitochondria have been shown to contribute to disturbed calcium signaling in diabetic neuropathy.

The pathogenesis of diabetic neuropathy involves the polyol pathway, advanced glycation end products, oxidative stress, PKC activation, neurotrophism, and hypoxia. These factors may contribute to the development of nerve dysfunction and degeneration [4–7, 10]. Among them, the activity of PKC, especially its β isoform, may play a major role. On the basis of its pathogenic mechanism, PKCβ selective inhibitor LY333531 is currently under investigation in clinical trials. Tahara et al. [23] investigated the possible direct action of LY333531 on DRG neurons to intracellular Ca^{2+} homeostasis. They demonstrated that the PKCβ selective inhibitor LY ameliorates disturbed Ca^{2+} homeostasis via decreased mitochondrial Ca^{2+} buffering in small DRG neurons of diabetic rats.

Kostyuk et al. [24] in 1999 published work showing elevated resting $[Ca^{2+}]_i$ in small neurons of the DRG of type 1 and type 2 diabetic mice, however, observed no changes in large neurons and in a follow-up study found no change in cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) concentrations in any DRG cell type of STZ-diabetic rodents. Specifically, Kostyuk et al. [24] also demonstrated in small DRG neurons isolated from STZ-treated C57Blac6 mice, a model of type 1 diabetes, the resting $[Ca^{2+}]_i$ was $\sim$30 % higher than in control (250 $\pm$ 16 nm vs. 156 $\pm$ nm); the elevation in $[Ca^{2+}]_i$ in small neurons was even greater in type 2 diabetic db/db mice. In their study, there were no differences in $[Ca^{2+}]_i$ concentrations in large neurons, however, in either mouse model. It has to be noted though, that the same group, almost at the same time, reported the absence of any changes in resting $[Ca^{2+}]_i$ in DRG neurons isolated from type 1 STZ-diabetic rodents; the reason for such a discrepancy remain unknown but may relate to differences in severity and/or length of STZ-diabetes within these studies.

In study of Drel et al. [25] it appears that the db/db mice the (type 2 diabetes) may have been maintained for 2–3 months. In STZ-diabetic Wistar rats of 8–14 weeks duration resting $[Ca^{2+}]_i$ concentrations was substantially increased by 2–2.5 fold in both large and small DRG neurons isolated from lumbar L4–L5 DRG; the $[Ca^{2+}]_i$ concentrations increase correlated with the progression of the disease. Conversely, resting $[Ca^{2+}]_i$ was not affected by 8–14 weeks of experimental diabetes in neurons from ganglia located at higher levels of the spinal cord (C3–C4).

Jagodic et al. [9] found that T-type channels in medium-size DRG neurons in STZ-induced diabetic neuropathy show prominent changes in voltage-dependent in activation, allowing a greater fraction of the channels to be available for activation during both short and prolonged periods of depolarization.

Voitenko et al. [1] investigated effects of STZ-induced diabetes on neuronal. They measured the $[Ca^{2+}]_i$ concentrations via Fura-2AM Ca^{2+} signaling method in dorsal horn neurons from acutely isolated spinal slices. They found that the K^+-induced $[Ca^{2+}]_i$ elevation was inhibited to a different extent by nickel ions, nifedipine and ω-conotoxin suggesting the co-expression of different subtypes of plasmalemmal voltage-gated Ca^{2+} channels. In their study, the suppression of $[Ca^{2+}]_i$ transients by Ni^{2+} (50 μM) was the same in control and diabetic neurons. On the other hand, inhibition of $[Ca^{2+}]_i$ transients by nifedipine (50 μM) and ω-conotoxin (1 μM) was much greater in diabetic neurons compared with normal animals.

The endoplasmic reticulum plays an important role in multiple programmed cell death pathways. Apoptosis caused by endoplasmic reticulum-induced oxidative stress has been also related with diabetes [26, 27] and can be caused by the accumulation of unfolded proteins resulting from disrupted Ca^{2+}-dependent changes in the endoplasmic reticulum [28]. Both thapsigargin, a potent and specific inhibitor of sarco-endoplasmic reticulum ATPase (SERCA), and endogenous factors that downregulate SERCA, evoke endoplasmic reticulum-induced oxidative stress and apoptosis in β-cells [29, 30].

In addition to multiple isoforms of SERCA, the endoplasmic reticulum of β-cells express several classes of cytosolic Ca^{2+}-releasing channels including the inositol triphosphatase receptors (IP_3Rs) and ryanodine receptors [31, 32]. In the oxidative stress-induced diabetic state, the expressions of these receptors are known to be modulated in several cell types including pancreatic β-cells [33]. It was recently reported that ryanodine receptors inhibition reduced the ratio of ATP to ADP in MIN6 β-cells, an event that could conceivability activate endoplasmic reticulum oxidative stress [34]. Furthermore, studies of other cells have indicated that endoplasmic reticulum oxidative stress-related damage can be affected by inhibitors of IP_3Rs and ryanodine receptors [35].

Neuropathic Pain, Ca^{2+} Signaling, Oxidative Stress and Mitochondria

The human body is equipped with a complete arsenal of defenses against external and internal aggressions. Those against the so-called reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical and hydrogen peroxide are crucial in inflammatory responses where they participate in physiological processes such as the arachidonic acid cascade and phagocytosis [7]. Mitochondria are the major sources of ROS production since unpaired

electrons are generated in the process of oxidative phosphorylation. Partial reduction of molecular oxygen by the unpaired electrons leads to the production of superoxide radicals which are one of the ROS and readily converted to hydrogen peroxide by superoxide dismutase enzymes [36]. There are three types of superoxide dismutase enzymes and magnesium superoxide dismutase enzyme is present in mitochondria matrix [28]. Unlike hydrogen peroxide, superoxide anion does not pass that readily across the membrane and thus for superoxide radicals produced in the matrix, the activity of manganese dependent superoxide dismutase enzyme is critical to prevent the mitochondrial matrix components for oxidative stress.

Tricarboxylic acid (TCA) cycle and electron transport chain contribute to key enzymatic components of mitochondria. During the process of braking down carbon substrates into acetyl CoA, reducing equivalents are produced, which are then fed to the electron transport chain consisting Complex I (NADH dehydrogenase), Complex II (succinate dehydrogenase), Complex III (ubiquinol cytochrome c reductase), and Complex IV (cytochrome c oxidase). Complex V is ATP synthase or proton-translocating ATP synthase [37]. Complexes I-IV involve ubiquinone (Coenzyme Q10). On the other world, they contain flavins, which contain riboflavin, iron-sulfur clusters, copper centers, or iron-containing heme moieties. Complex I is the main site for mitochondrial ROS production, where superoxide radicals are produced on the matrix side and rapidly dismutated to hydrogen peroxide [25, 39]. In addition, Complex III has also been reported as a site of superoxide radical production [25]. Complex III has important role on ischemic and apoptotic superoxide radical production.

The concentrations of ROS are kept under strict control by the activity of a complex defense system including enzymes and non-enzymatic species such as vitamin C, vitamin E, vitamin A or β-carotene [8]. Vitamin E, α-tocopherol, is the most important antioxidant in the lipid phase of cells. Vitamin E acts to protect cells against the effects of free radicals, which are potentially damaging byproducts of the body's metabolism [38]. Vitamin C, as well as being a free radical scavenger, also transforms vitamin E to its active form. These enzymatic and non enzymatic antioxidants are also essential for inhibition of phagocytic activity related to ROS production [7, 8, 38]. Hydrogen peroxide is converted to water by glutathione peroxidase and it is one of the body's major antioxidants [7].

Complex I is especially susceptible to NO damage, and animals administrated natural and synthetic complex I antagonists have undergone death of neurons [39, 40]. Increased oxidative and nitrosative stresses [41] have also emerged as leading candidates in the pathogenesis of distal symetrical sensorimotor polyneuropathy. A direct relationship has emerged between measures of oxidative stress and the development of nerve blood flow and nerve conduction deficits [42–45] as well as impaired neurotrophism [46, 47]. Oxidative stress has also recently been invoked as a contributing factor to painful symmetrical sensorimotor polyneuropathy [48]. However attenuation of oxidative stress alone may be insufficient to completely alleviate neuropathic pain complicating diabetes, emphasizing the need to impact additional metabolic pathways implicated in pain pathogenesis [49].

Taurine (2-aminoethanesulfonic acid) functions as in important endogenous antioxidant [50] and it is well known that Ca^{2+} modulator and neurotransmitter could promote chronic cytotoxicity in diabetes. They aimed to explore this hypothesis by assessing the potential of taurine replacement to ameliorate hyperalgesia and abnormal Ca^{2+} signaling in sensory neurons of STZ-induced diabetic rats and they found that taurine replacement may provide a novel mechanistically based approach to the treatment or prevention of distal symmetrical sensorimotor polyneuropathy [18].

Role of Transient Receptor Potential (TRP) Channels in Diabetes

The *trp* gene was identified through genetic studies of a mutation in the *Drosophilia* visual transduction system. The term of "TRP" is derived from "transient receptor potential", because photoreceptors with the *trp* gene mutant fail to generate the Ca^{2+}-dependent "sustained" phase of receptor potential and therefore fail to show subsequent Ca^{2+}-dependent adaptation to light. There are 30 mammalian TRP channels, grouped into six subfamilies. Members of the TRP channels superfamily include TRP canonical (TRPC) subfamily consisting of 7, TRP vanilloid (TRPV) subfamily consisting of 6, TRP melastatin (TRPM) subfamily consisting of 8, TRP polycystein (TRPP) subfamily consisting of 3, TRP mucolipin (ML) subfamily consisting of 3, and TRP ankyrin (TRPA) subfamily consisting of only one member [51, 52].

TRPM2 Channels

TRPM2 may be a new target for diabetes therapy (Table 2). In study of Uchida and Tominaga [53], they observed impaired glucose tolerance and impaired insulin secretion in TRPM2 knockout mice. In addition, insulin secretion via TRPM2 occurs through control of intracellular Ca^{2+} concentrations and Ca^{2+} influx-independent mechanisms. It was recently observed that basal blood glucose levels increased in TRPM2-KO mice as compared to wild-type mice without any difference in plasma insulin

Table 2 Roles of TRP channels on diabetic neuropathic pain in different cells

Channel	Cells	Effects	Reference
TRPM2	Pancreatic β-cells	Impaired glucose tolerance insulin secretion	Uchida and Tominaga [53]
TRPM2	Human blood	HOMA-%B was negatively associated with three TRPM2 variants	Romero et al. [55]
TRPM2	Pancreatic β-cells	TRPM2 is also expressed in human islets	Qian et al. [56]
TRPV1	Diabetic hearts	Protective effects of pretreatment with capsaicin	Wei et al. [57]
TRPV1	Central neurons	Protein expression in the vagal complex unaltered	Zsombok et al. [60]
TRPV1	DRG	TRPV1 expression	Pabbidi et al. [59]
TRPV1	Sensory neurons	Enhanced expression	Pabbidi et al. [59]
TRPV1	Intraepidermal TRPV1 nerve	TRPV1 expression was significantly increased by distal small nerve fibre diabetic neuropathy	Wilder-Smith et al. [61]
TRPV1 TRPV3 TRPV4 TRPM8	Human diabetic neuropathy skin biophys	TRPV1 represented a more selective therapeutic target than other TRPs for pain and hypersensitivity	Facer et al. [70]
TRPM6 TRPM7	Human Blood	No association of any single nucleotide polymorphisms	Romero et al. [72]
TRPM7	Diabetic human monocytes	Important role in the pathogenesis of atherosclerosis	Wuensch et al. [71]
TRPM7	Diabetic men blood	No evidence of a role for the TRPM7 gene in risk of incident ischemic stroke	Romero et al. [72]
TRPM6 TRPM7	Diabetic women blood	Association of TRPM6 of single nucleotide polymorphisms	Song et al. [73]
TRPM7	Familial Alzheimer's disease mutant cells	Role of phosphatidylinositol 4,5-bisphosphate (PIP2) and TRPM7	Landman et al. [74]
TRPC	Human saphenous vein	Entry and expression of TRPC channels	Chung et al. [78]
TRPC1	Human diabetic nephropathy	Dysregulation of HNF 4 alpha and TRPC1	Niehof and Borlak [80]
TRPC1 TRPC2 TRPC3 TRPC6	Caudal artery smooth muscle of diabetic rats	The channels are responsible for the dysfunction of receptor-mediated Ca^{2+} influx in the cells	Mita et al. [75]
TRPC6	Diabetic human platelets	Channel protein expression	Liu et al. [79]
TRPC6	Glomerular mesangial cells	TRPC6 protein is decreased	Graham et al. [76]
TRPC3	Type 2 diabetes mellitus patients	Enhanced expression in platelets	Zbidi et al. [77]
TRPC1	Human diabetic nephropathy	Dysregulation of HNF 4 alpha and TRPC1	Niehof and Borlak [80]

TRP Transient receptor potential, *TRPC* TRP cononcial, *TRPV* TRP vanilloid, *TRPM* TRP melastatin

levels. In isolated β-cells, smaller intracellular Ca^{2+} increase was observed in response to high concentrations of glucose in TRPM2-KO cells than in wild-type cells. Moreover, insulin secretion from the islets of TRPM2-KO mice in response to glucose treatment was impaired, whereas the response to tolbutamide, an ATP-sensitive potassium channel inhibitor, was not different between the two groups. They concluded that TRPM2 is involved in insulin secretion stimulated by glucose [54]. Romero et al. [55] investigated gene variation of TRPM2 in the pathophysiology of type 2 diabetes mellitus and they observed no evidence for an association of the variants tested with T2DM, although HOMA-%B was negatively associated with three TRPM2 variants (rs2838553, rs2838554 and rs4818917). Qian et al. [56] found that a current in βTC3 insulinoma cells and provided a mechanism for oscillatory calcium responses in the presence of glucose.

TRPV1 Channels

In study of Wei et al. [57] reported that in the sensory nerve fibers, could modulate the cardiac function, be impaired by diabetes and could contribute the further severe postischemic heart injury. Bishnoi et al. [58] found that STZ induced a direct effect on neurons trough expression and

function of the TRP vanilloid 1 (TRPV1) channel in sensory neurons resulting in thermal hyperalgesia, even in non-diabetic STZ-treated mice. In the present study, they investigated the role of expression and function of TRPV1 in the central sensory nerve terminals in the spinal cord in STZ-induced hyperalgesia in rats. It was reported that both STZ-and transgene-mediated T1D are associated with two distinct phases of thermal pain sensitivity that parallel changes in TRPV1 as determined by paw withdrawal latency [59]. To understand the mechanism underlying this phenomenon, DRG neurons and stably TRPV1 expressing human embryonic kidney (HEK)293 cells, Pabbidi et al. [59] investigated the expression and function of TRPV1. They found that STZ has a direct action on neurons and modulates the expression and function of TRPV1, a nociceptive ion channel that is responsible for inflammatory thermal pain. Zsombok et al. [60] tested the hypothesis that synaptic modulation by TRPV1 receptors is reduced in the DMV in slices from a murine model of type 1 diabetes. The TRPV1 agonist capsaicin robustly enhanced glutamaterelease onto DMV neurons by acting at pre-terminal receptors in slices from intact mice, but failed to do so in slices from diabetic mice [60]. A recent study of Wilder-Smith et al. [61] suggested that in human painful neuropathies, epidermal TRPV1 expression is mainly in keratinocytes. Ohanyan et al. [62] subjected mice lacking TRPV1 [TRPV1(-/-)], db/db, and control C57BLKS/J mice to in vivo infusion of the TRPV1 agonist capsaicin or the α-adrenergic agonist phenylephrine to examine the integrated circulatory actions of TRPV1. TRPV1(-/-) mice exhibited no changes in MAP in response to capsaicin, suggesting the actions of this agonist are specific to TRPV1 activation [62]. Manni et al. [63] their results point to the potential of electro-acupuncture as a supportive therapy for the treatment of diabetic neuropathies. The efficacy of electro-acupuncture might depend on its actions on spinal/peripheral NGF synthesis/utilization and normalization of the levels of several sensory neuromodulators. Hyperglycemia and hypoxia are two main phenomena in diabetes associated with several complications [63] and Ristoiu et al. [64] found that hypoxia is a new sensitization mechanism for TRPV1, which might be relevant to diabetes-related complications, and also for other diseases that are associated with acute hypoxia.

Tanaka et al. [65] their study is the first to show the antidiabetic pharmacological effects of the TRPV1 signal inhibitor *N*-(4-tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropyrazine-1(2H)- carbox-amide (BCTC). These findings suggest that TRPV1 antagonists may represent a new class of drugs effective in treating type 2 diabetes mellitus because of their dual effects as insulin sensitizers and secretagogues [65]. Liu et al. [66] examined whether cardiac nociception was altered in the STZ-induced diabetic rat model by assessing intrapericardial capsaicin-evoked electromyography responses in the spinotrapezius muscle. Their results suggested that STZ-induced diabetic rats develop somatic mechanical allodynia, but reduced cardiac nociception. They concluded that decreased TRPV1 function may contribute to the reduction of cardiac nociception in the diabetic rat [66]. The up regulation of kinin B1R in spinal dorsal horn microglia by pro-inflammatory cytokines is proposed as a crucial mechanism in early pain neuropathy in STZ-diabetic rats [67]. Mohammadi-Farani et al. [68] aimed to see if diabetic hyperalgesia is related to changes in TRPV1 or Cannabinoid CB1 receptors of periaqueductal gray. Kang et al. [69] investigated whether dietary capsaicin can reduce obesity-induced inflammation and metabolic disorders such as insulin resistance and hepatic steatosis. Facer et al. [70] reported that human DRG sensory neurons co-expressed TRPV1 and TRPV3, and that these were increased in injured human DRG. Related receptors TRPV4, activated by warmth and eicosanoids, and TRPM8, activated by cool and menthol, have been characterized in pre-clinical models [52, 70]. However, the role of TRPs in common clinical sensory neuropathies needs to be established.

TRPM6 and TRPM7 Channels

Romero et al. [55] hypothesized that gene variation of TRPM6 and TRPM7 may play a role in type 2 diabetes mellitus. Using a case–control population sample of the Boston metropolitan area (all whites, 455 controls and 467 cases), they assessed the relationship of 29 TRPM6 and 11 TRPM7 tag-single nucleotide polymorphisms (SNPs) with (1) several diabetes-related intermediate phenotypes (fasting insulin levels, fasting glucose levels, hemoglobin A1c, and homeostatic model assessment) and (2) the presence of T2DM. Wuensch et al. [71] investigated the effects of high glucose-induced oxidative stress on TRP channel expression in human monocytes and they were observed that Increased TRPC3 and TRPC6 protein expression was accompanied by increased 1-oleoyl-2-acetyl-sn-glycerol-induced calcium influx, which was blocked by the TRPC inhibitor 2-aminoethoxydiphenylborane (2-APB). Romero et al. [72] reported that TRPM7 gene variation might play a role in the risk of ischemic stroke. Results of Song et al. [73] provided suggestive evidence that two common non-synonymous TRPM6 coding region variants, Ile1393Val and Lys1584Glu polymorphisms, might confer susceptibility to type 2 diabetic women with low magnesium intake. Landman et al. [74] found that the TRPM7-associated Mg^{2+}-inhibited cation (MIC) channel underlies ion channel dysfunction in presenilin FAD mutant cells, and

the observed channel deficits are restored by the addition of PIP2, a known regulator of the MIC/TRPM7 channel.

TRPC Channels

Mita et al. [75] reported that Ca^{2+} entry from the extracellular space via alpha (1)—adrenoceptor-activated, Ca^{2+}-permeable channels, but not voltage-gated Ca^{2+} channels, is impaired in endothelium–denuded caudal artery smooth muscle from type 2 diabetic Goto-kakizaki rats. Hence, TRPC channel expression may be responsible in part, for the dysfunction of receptor-mediated Ca^{2+} entry in caudal artery smooth muscle of Goto-Kakizaki rats. Recently a study was performed to investigate the underlying mechanism, particularly the roles of ROS and protein kinase C, in the diabetes induced TRPC6 down regulation [76] and it was found that high glucose significantly reduced TRPC6 protein expression in cultured mesangial cells [76]. Zbidi et al. [77] reported that expression of TRPC3, Orail and STIM1 is enhanced in DM2 subjects as compared to controls. Their findings provide an explanation to the enhanced Ca^{2+} entry induced by physiological agonists in platelets from diabetes mellitus patients with type 2 [77]. Chung et al. [78] reported that diabetes would modulate the capacitative calcium entry likely through the store-operated calcium channel specifically via the regulation of TRPC. In a study of Liu et al. [79], high glucose increases TRPC6 channel protein expression on the platelet surface which is mediated by a phosphatidylinositol 3-kinase-dependent pathway. Niehof and Borlak [61] reported dysregulation of HNF4 alpha and TRPC1 as a possible molecular rationale in diabetic nephropathy.

Conclusions

Diabetes induces a distal symmetrical polyneuropathy in which sensory dysfunction is an early and frequent feature. A number of pathogenic pathways secondary to hyperglycaemia, namely polyol pathway flux, oxidative stress, impaired neurotrophic factos and advanced glycation end-products have been proposed for the molecular basis of diabetic neuropathy and pain. Based on the results discussed above, we suggest that hyperglycaemia-dependent alterations of Ca^{2+} influx through cation channels, mitochondrial function and oxidative stress induced parallel pathophysiological mechanism in diabetic neuropathy. In this mechanism, impaired insulin signaling and Ca^{2+} influx through TRP and voltage gated Ca^{2+} channel activations triggers sensory neuron mitochondrial depolarization. The consequent increase in mitochondrial depolarization induces further ROS production and disrupts Ca^{2+} homeostatic mechanisms, particularly voltage gated Ca^{2+} channels.

Mutations in TRPs are linked to pathophysiology of diabetic neuropathy. Progression from mutations in TRPs to pathophysiology and diabetes will cause understanding of etiology of neuropathic neuropathy. In this review, we also focused on two distinct aspects of TRP channel physiology, the role of TRP channels in intracellular Ca^{2+} homeostasis, and their role in the transduction of diabetic pain in sensory neurons and it seems that the TRPC, TRPV and TRPM groups are mostly responsible from diabetic neuropathic pain. There are scarce reports some TRP channels such as TRPM2 channels in diabetic neuropathic pain. In future, role of other TRP channels such as TRPM2 on diabetic DRG neurons should have investigated in animal and human models.

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