Chapter

Calcium Dyshomeostasis in Neuropathy Diabetes

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Abstract

Diabetes is a ceaseless ailment that is basic in practically all nations. Neuropathy is the most well-known constant difficulty of diabetes and is the underlying reason for ulceration in the legs of lower appendage removals. The predominance of diabetic polyneuropathy shifts from 23 to 29%. Incessant metabolic pressure incited by hyperglycemia, either low insulin creation in type 1 diabetes or diminished fringe affectability to insulin in type 2 diabetes influences cell homeostasis in practically all phone types. Changes in the sign Ca^{2+} have been recognized in different seclusion tissues from creatures initiated to diabetes just as patients with diabetes. Ca^{2+} homeostasis variations from the norm have likewise been found in an assortment of tissues, including bone, heart and smooth muscle, secretory cells, platelets, kidneys and osteoblasts. This variation from the norm by and large shows as an expanded resting centralization of intracellular Ca^{2+} ($[Ca^{2+}]I$), diminished Ca^{2+} transporter movement and diminished boost that produces Ca^{2+} signals. Ca^{2+} flagging issue are likewise found in neuron-sensory from trial creatures with diabetes.

Keywords: neuropathy, diabetes, calcium, intracellular, dyshomeostasis

1. Introduction

Diabetes is a chronic disease that is common in almost all countries. It is estimated that there were around 285 million adults with diabetes in 2010, this number will continue to increase globally due to population aging, population size growth, urbanization and high prevalence of obesity and lifestyle changes [1]. Estimated death rates from diabetes are 3.9 million sufferers worldwide in 2010 and remain a major problem in each country [2–6]. Whereas in Indonesia alone, it was estimated that 7 million people with diabetes mellitus in 2010 became number 9 in the world [7].

Neuropathy is the most common chronic complication of diabetes and is the initial cause of foot ulceration, Charcot type neuroarthropathy and lower limb amputation. Epidemiologically, a study based in Europe, the prevalence of diabetic polyneuropathy varies from 23 to 29%. One third of all diabetic patients have symptoms of neuropathy regardless of deficits or symptoms of neuropathic pain. Neuropathic pain due to diabetes is more common in patients with type 2 diabetes, women, and people from South Asia [7, 8].

Diabetes mellitus in people causes inconveniences in different tissues and organ frameworks, including the heart muscle, retina, secretory organs, kidneys, and fringe nerves. Ceaseless metabolic pressure instigated by hyperglycemia, either low insulin creation in type 1 diabetes or diminished fringe affectability to

insulin in type 2 diabetes influences cell homeostasis in practically all phone types. Hyperglycemia is generally viewed as the fundamental driver that triggers cell pathology variations from the norm and different downstream instruments, including metabolic worry, with the development of receptive oxygen species (ROS) that harm layers and other cell frameworks. Ongoing exploration uncovers an early decrease of the two intracellular frameworks associated, the Ca^{2+} signal homeostasis and the mitochondrial physiology. The event of these intracellular changes is comparative in each extraordinary cell type and can be viewed as a typical neurotic pathway [9, 10].

Diabetes mellitus in people causes entanglements that influence different tissues and organ frameworks, including the heart muscle, retina, glandular emissions, kidneys, and fringe nerves. Interminable metabolic pressure brought about by hyperglycemia coming about because of either low insulin creation in type 1 diabetes or diminished insulin affectability in type 2 diabetes influences cell homeostasis in practically all phone types. Hyperglycemia is generally viewed as the principle procedure that triggers cell pathology, and different downstream instruments, including metabolic pressure and the arrangement of receptive oxygen species (ROS) that harm cell layers and different frameworks [11].

Changes in the Ca^{2+} signal have been identified in different detachment tissues from creatures prompted into diabetes just as patients with diabetes. Ca^{2+} homeostasis variations from the norm have additionally been found in an assortment of tissues, including bone, heart and smooth muscle, secretory cells, platelets, kidneys and osteoblasts. This issue, for the most part, shows as an expanded resting convergence of intracellular $[Ca^{2+}]I$, diminished movement of the Ca^{2+} transporter (in spite of the fact that not generally) and diminished improvement that creates Ca^{2+} signals. Ca^{2+} flagging issue is likewise found in neuron-sensory from trial creatures with diabetes [11, 12].

Calcium (Ca^{2+}) homeostasis in nerve cells that is upset or irregular happens in different maladies of the sensory system. The most well-known issue of the fringe sensory system, neuropathic torment and diabetes polyneuropathy, were seen as related with weakened articulation and capacity of Ca^{2+}. Likewise found a connection between Ca^{2+} dyshomeostasis and mitochondrial brokenness in neuropathy because of diabetes. The primary impacts of changes in Ca^{2+} flagging happen in the plasma film and in intracellular Ca^{2+} in tactile neurons and are identified with irregularities in the endoplasmic reticulum. Impeded Ca^{2+} axonal motioning in diabetic neuropathy will incite axonal degeneration in fringe neuropathy. The nearness of Ca^{2+} dysregulation is influenced by varieties in waterway structure and Ca^{2+} siphon, this is seen in neuropathic and neuropathic structures, making the Ca^{2+} approach in neurons can be utilized for remedial mediations for neuropathic agony and fringe neuropathy. Neuropathic torment largely affects personal satisfaction and disarranges of physiology and Ca^{2+} waterway articulation have been embroiled in various torments. This investigation will likewise feature the most widely recognized type of fringe neuropathy, which is diabetes polyneuropathy. This issue can incorporate agony as a manifestation and in the long run form into degeneration of fringe nerve strands described by tangible misfortune [11, 13, 14].

Neural harm both horrible and models of harm with specific illnesses, will harm fringe tactile nerves and meddle with essential afferent action. As a rule interruption of essential afferent movement can likewise add to diligent neuropathic pain. The role of Ca^{2+} flux in the formation of axonal potential and release of neurotransmitters by primary sensory neurons will produce Ca^{2+} regulatory abnormalities which in turn contribute to neuropathic pain [15].

Late research has uncovered early aggravations from two intracellular integrative flagging frameworks, specifically Ca^{2+} signal homeostasis and mitochondrial

physiology. These progressions happen also in an assortment of totally different cell types, and can be considered as normal neurotic pathways [11, 16, 17].

2. Homeostasis of Ca^{2+} signals in cells

A portion of the systems for keeping up the centralization of Ca^{2+} in intracellularity are through the Ca^{2+} channel, Ca^{2+} transport and including the support. Various Ca^{2+}-sensors (spoke to by Ca^{2+}-controlled proteins) go about as effectors, which make an interpretation of Ca^{2+} signals into physiological reactions. What is significant is that the free Ca^{2+} resting focus in cells can change, going from 50 to 100 nM in the cytosol and near 0.5–1.0 mM in the lumen of the endoplasmic reticulum (ER). Any move from this fixation go, both the overabundance Ca^{2+} in the cytosol and Ca^{2+} exhaustion in the ER will make obsessive results, including activating different kinds of cell demise [11, 13].

2.1 Calcium channel

Transient changes in intracellular calcium levels can be caused by signals from intracellular calcium storage or from extracellular compartments through specific regulations. Electrophysiology of calcium channel sub type with kinetic opening and its conduct can be divided into [18–20]:

a. Type L, the conductance is strong, long lasting inward current, the antagonist is dihydropyridine.

b. Type T, transient inward current.

c. Type N, neither type L or T, many in neurons, are blocked by w-conotoxins GVIA

d. Type P, found mostly in cerebellar Purkinje cells, is blocked by IVA agatoxin.

e. Another type found is type Q and R in Purkinje cells.

Different classifications based on open or closed formations can be differentiated into:

a. VOC (voltage gate channel), the opening depends on the voltage that occurs.

b. ROC (receptor-operated channels), depending on the specific ligand bond.

c. SOC (store operated channels), the activation depends on the depletion of calcium in the ER with the CCE (capacitative calcium entry) mechanism.

The VOC contains four homologous units, each containing six transmembrane regions with conduction holes, voltage sensors, and places to open and regulatory channels, which can be passed by for example protein kinases, toxins and drugs. Dihydropyridine, phenylalanine, and benzodiasepin are attached to sub-unit a1. Three types of ROC canals are known, activated by glutamate and some agonists that can be attached such as KA, AMPA and NMDA, so they are also named as attached agonists. The location is in the synapses post. The canals formed by KA and AMPA receptors are permeable to Na^{+} and K^{+}, some AMPA are also to Ca^{2+},

whereas NMDA is permeable to Na^+ and Ca^{2+}. In neuroendocrine cells, activation by calcium passes through the SOC canal, this channel cannot be known in detail with protein levels but is homologous with transient potential receptors (trp or trp-like) from drosophila. The process of SOC through CCE, where the release of a small number of chemical factors will induce canal opening, and the second possibility is that the physical interaction between ER and plasma membrane stimulates CCE opening [18, 21, 22].

2.2 Calcium pumps

Plasma membranes control the exchange of calcium between intracellular and extracellular. Calcium in small and controlled amounts of calcium can enter cells through specific channels to stimulate intracellular events, including freeing calcium from its storage. An equal amount of calcium must also be excreted extracellularly. There are two known systems, i.e. mostly through the electrical exchange of NA^+ and Ca^{2+}. Another system is through ATPase (PMCA pump) with high affinity but low capacity to remove calcium, so it is also called fine-tuner cellular Ca^{2+}. Calcium also exchanges between the cytoplasm and internal organelles, dominated by mitochondria and ER which have SERCA pumps that have a mechanism similar to PMCA [23, 24].

The total calcium transported in the reticulum depends on the amount of pump available, which is high in the heart and skeletal muscles, but low in non-skeletal muscles. Calcium pumps are also found in low eukaryotes. In mushrooms there are two pumps namely PMR1 and PMC1 which are in the Golgi and Vacuole complex. 40–50% homologous with SERCA and PMCA, PMC1 does not have the calmodulin which is a characteristic of PMCA pumps [23, 24].

2.3 PMCA pumps

The PMCA pump was discovered since 1966 and functions to remove calcium from erythrocytes. It was purified in 1979 with a protein weight of 135 kDa. The architecture of this protein resembles that of the SERCA pump, having 10 transmembrane domains and three large hydrophilic units that protrude into the cytoplasm, what is different is the existence of a long C-terminal tail that contains a place to attach to calmodulin. Calmodulin is the main regulator for PMCA, although polyunsaturated fatty acids, phospholipids, protein kinases A or C also activate these pumps, with the result of reducing the concentration of calcium. After activation, it is dimerized by binding with calmodulin and proteolytic enzymes by removing C terminals. The calmodulin bond at rest will bind to both sides of the cytosol part of the pump, so that the pump will remain obstructed [23, 25].

A Ca^{2+} signalosome signal consists of many Ca^{2+} signal components. Duplication of components is the fact that there are many isoforms that increase the diversity of the Ca^{2+} signal system. Yellow arrows describe the ON reaction that enters Ca^{2+} into the cell, and the blue arrow represents the OFF reaction where Ca^{2+} will exit the cell or return to the endoplasmic reticulum (ER). During a trip through the cytoplasm, Ca^{2+} will temporarily stay in a buffer or inside the mitochondria. For the signal to occur, Ca^{2+} binds to sensors which then use various effectors to stimulate cellular processes. Different and suitable components will produce cell-specific signalosomes [26].

2.4 SERCA pumps

An enzyme that hydrolyzes ATP to transport Ca^{2+} across the SR membrane was discovered 40 years ago, then identified as a pump in the ER in non-muscle

cells. The ATPase was then called the SERCA pump as a protein weighing around 100 kDa. SERCA 1a is a major isoform in adult human muscle cells with rapid contraction, while SERCA1b in neonates. SERCA2a is found in heart muscle and muscle with slow contractions, while SERCA2b is found in smooth muscle and almost in non-muscle cells. SERCA3 is expressed only in non-lumen cells [27, 28].

The principle of action of enzymes in calcium pumps is actually almost the same. Calcium is bound to one side of the membrane and this reaction does not require ATP, then ATP attaches and splits into acyl phosphate as an aspartic residue, intermediate formation of phosphorylation is also called a P type pump. After phosphorylation, the pump transitions from E1 to E2 form, on E1 forms calcium-bound pumps with high affinity exposed to the cytosol side; in the E2 form calcium bound with low affinity is exposed to the ER/SR lumen or extracellular part, so that calcium can be released. After ATP and calcium released, enzymes slowly dephosphorylate and return to form E1. The SERCA and PMCA pumps are different in calcium-ATP transport [27, 28].

2.5 Calcium-sodium exchange

Sodium/calcium exchange (NCX, Na^+/Ca^{2+} exchangers) in the plasma membrane (PM, plasma membrane) is an important factor in homeostasis and calcium regulation in almost all cells. The NCX PM was discovered nearly 35 years ago in cardiac cells and neurons by using sodium electrochemical energy gradients, not directly from ATP for calcium transport. So the importance of calcium import or export depends on the NCX coupling ratio, membrane potential and sodium concentration gradient. Potential membranes and sodium gradients are maintained by sodium pumps (Na^+, K^+-ATPase) that are dependent on ATP. Sodium-calcium exchange in the mitochondria has also been identified and works similar to NCX [29–31]. Exchange in heart cells and neurons shows the coupling ratio is 3 Na^+:1 Ca^{2+}.

Sodium-calcium exchange is also present in photoreceptor cells, this cell is also dependent on K^+ and has a coupling ratio of $4Na^+$:($1Ca^{2+}+K^+$) so this exchange is also referred to as Na/(Ca,K) or NCKX exchange. The family of NCX is NCX2, NCX2 and NCX3, most of which are NCX1 with distribution on all networks. In the NCKX family, there are three sub-types namely NCKX1 in photoreceptors, NCKX2 in rods and neurons and NCKX3 expressed in the brain and smooth muscle. Topologically NCKX is almost similar to NKCX which both function on ion attachment and translocation [29–31].

NCX can facilitate the electronic exchange of sodium-sodium or calcium–calcium, also can be for sodium in-calcium exit or sodium in-calcium entry. For calcium- calcium exchange it is activated by nontransported alkaline metal ions. The sodium- calcium exchange reaction is consistent and sequential, where one calcium or three sodium binds to one side of the membrane, then translocates to the other side of the membrane, and dissociates before the other ions are bound to that side. In the exchange of sodium in and out of calcium and sodium in and out of calcium are both rheogenic (related to electric current/current flow) [29–31].

2.6 Calcium buffer

The principle of calcium buffer is that all groups that have negative potential can be a chelator for calcium. In this system many are dominated by small molecular carbosilic groups such as citrate or carbonyl protein groups. Included here are EF-hand protein, annexin and C2 protein. Most calcium buffers are included in the EF-hand protein group. To find out the buffer mechanism in calcium homeostasis,

there are several parameters that influence it, namely: cytosolic concentration, affinity for calcium ions or other metal ions, calcium kinetic for attachment and release as well as the mobility of calcium itself. In a simple way buffer works is that once calcium enters the buffer cells will bind calcium and reduce calcium levels. However, a fixed level of calcium concentration is obtained from the calcium balance across the cell membrane, not absolutely from the presence of the buffer itself [32, 33].

2.7 Mitochondria and calcium signaling

Mitochondria are no longer static organs as ATP producers, but also as a store of various lethal proteins which will be released in programmed cell death and this is an important intracellular calcium signal. Since the expression of the calcium transport membrane in the mitochondria has been found, the process of signaling calcium in the mitochondria has become clear [34–36]. Pension movements in the mitochondria are driven by several things such as:

a. Uniporter

b. VDAC (voltage dependent anion channel)

c. Exchange xNa^+/Ca^{2+}

Calcium is inserted into the membrane in the mitochondria by the uniporter. Uniporter activity is influenced by temperature and cation selectivity so that it can almost be called a channel rather than a career. Intake of calcium through uniporters is inhibited by red ruterium (RuR) which also blocks many cation channels including calcium plasmalemma canals, the ER channel which is sensitive to ryanodine to release calcium and vanilloid receptor channels, making it more convincing that the uniporter is a canal. Uniporters are regulated by cytosolic calcium levels and thus require higher levels to increase mitochondrial calcium levels [34–36].

The outer membrane of the mitochondria is permeable to small ions so it is not considered in calcium exchange. However, the outer membrane of the mitochondria has an important role in the modulation of calcium by the uniporter to pass the VDAC filter. VDAC is permeable to calcium and regulated both calcium levels and RuR levels. The most important way for calcium to exit the mitochondria is through the exchange of xNa^+/Ca^{2+}; initially thought to be the electronic exchange of $2Na^+/Ca^{2+}$. It will be doubted because this exchange requires twice as much energy as against the sodium gradient. The entry of calcium into the mitochondria is inhibited by mitochondrial depolarization [34–36].

A progression of proteins in MAMs (for example, PML, AKT, GRP-75, SIG-1R, Mfn-1/-2, BIP, AKT) controls the arrival of Ca^{2+} from ER and Ca^{2+} take-up by mitochondria, bringing about various useful outcomes. Cells produce Ca^{2+} flags through two instruments that utilization inside and outer Ca^{2+} sources. Calcium enters the cell through channels and siphons situated on the plasma layer, this is controlled by voltage (VOC) or outer ambassadors (ROCs). A progression of upgrades that follow up on receptors on the cell surface triggers enactment of the PLC which catalyzes the hydrolysis of 4.5-bisphosphate phosphatidylinositol to IP3 and DAG. IP3 official with IP3R receptors invigorates the arrival of Ca^{2+} ER and subsequently moves Ca^{2+} (red specks) from the ER to the mitochondria. The mitochondrial surface collaborates straightforwardly with the ER through the Ca^{2+} hotspot signal unit. Imports of mitochondrial Ca^{2+} happen through mitochondrial Ca^{2+} uniporters (MCU) and H^+/Ca^{2+} exchangers LETM1; on the other hand, NCLX, mitochondrial Na^+/Ca^{2+}

exchangers, together with PTP, send out Ca^{2+} from the lattice. Ca^{2+} levels come back to resting conditions through a progression of channels and siphons: PMCA and NCX bring about particle expulsion to the extracellular condition, SERCA (situated in the ER) and SPCA (in the Golgi mechanical assembly) make Ca^{2+} levels come back to basal levels in the capacity zone [17].

2.8 Endoplasmic reticulum (ER) and calcium signaling

ER as a widespread flagging organelle, ER works a ton, as a matter of first importance is a spot for protein amalgamation and development. Protein union is completed in harsh ER, though handling of protein after interpretation is orchestrated in escorts some portion of ER, which structures buildings with recently integrated proteins, collapsing them into the last tertiary structure and keep them from accumulating. In the event that the collapsing procedure falls flat, the escorts are still amassed with proteins that neglect to crease, therefore keeping them from continuing through the ER and out into the Golgi complex. Each time the collapsed protein fixation increments extremely high, ER builds up an exceptional response known as ER worry, subsequently, the signs that influence translation are sent to the core, which will control quality articulation as indicated by the earth. Other than blend protein, ER is a position of arrangement of phospholipids, glycosyl-phosphatidylinositols, and leukotrienes. ER can likewise work as a transfer site for different undesirable particles and toxic substances. Since ER has a constant lumen, as an expressway that permits transport of RNA, secretory items, different proteins and particles between enraptured cell parts. This ER is likewise firmly engaged with quick cell signals since it is a powerful stockpiling territory of Ca^{2+} which controls Ca^{2+} cytosol focus and creates Ca^{2+} transition between the cytosol and ER lumen because of extracellular incitement. At last, ER arranges all the different physiological procedures of cells. In this manner, ER is characterized as a multifunctional organelle fit for recognizing and incorporating approaching signs and creating yield flags because of natural changes [37, 38].

The definite system of ER combination is generally unfamiliar, including the focal job of Ca^{2+}. Ca^{2+} is the way in to the info and yield signals from the ER. An expansion in Ca^{2+} cytosol focus influences its fixation in ER, and thusly the exit and passage of Ca^{2+} in the ER influences the cytosolic Ca^{2+} focus. Various intra-ER escorts, for example, calreticulin, calnexin, grp78/BiP, endoplasmin (or glucose managed protein, grp94), are Ca^{2+} restricting proteins, and changes in free Ca^{2+} focuses in ER lumens extraordinarily influence their practical movement. In this manner, changes in Ca^{2+} content in the ER can give a connection between quick signals and moderate cell versatile reactions [38, 39]. The essential physiology of ER as calcium stockpiling is known in different volatile and non-sensitive cells. ER goes about as a powerful stockpiling of Ca^{2+} alongside the action of Ca^{2+} directs and transporters in the endomembranes, and intraluminal Ca^{2+} restricting protein, which works as a high limit Ca^{2+} cradle framework. Ca^{2+} that leaves the ER is controlled by two Ca^{2+} channels, Ca^{2+}-gated Ca^{2+} channels which are normally known as ryanodine receptors (RyRs) and InsP3-gated channels which are regularly known as InsP3 receptors (InsP3Rs). The aggregation of Ca^{2+} into the ER lumen is the consequence of Ca^{2+} siphon action from the sarco (endo) plasmic reticulum Ca^{2+}-ATPase (SERCA) [37, 38].

The Ca^{2+} flagging framework in certain cell types is regularly not single, yet comprises of various pathways, which are identified with produce cell-explicit frameworks in various cell types. A portion of the primary modules utilized by cells are [26]:

1. Agonists, for example, glutamate synapses and ATP act straightforwardly on channel-worked receptors (ROCs) in the plasma layer to permit outside Ca^{2+} to enter the cell.

2. Second couriers, for example, diacylglycerol (DAG), cyclic AMP, cyclic GMP and arachidonic corrosive work on the cytoplasmic side when opening SMOCs in the plasma layer.

3. Film depolarization (V) enacts VOC in the plasma layer for permits the passage of outside Ca^{2+} rapidly.

4. Film depolarization (V) enacts certain VOC isoforms, in particular, the L-type CaV1.1 channel, which actuates the receptor ryanodine 1 (RYR1) in the skeletal muscle through an immediate coupling compliance system.

5. The depolarizing film (V) enacts VOC in the plasma layer for permits the passage of outside Ca^{2+} to trigger Ca^{2+} enacting ryanodine 2 receptor (RyR2) to trigger the arrival of Ca^{2+} stores in the sarcoplasmic reticulum (SR) through the Ca^{2+} incited Ca^{2+} (CICR) discharge process. This component is found in the heart muscle and neurons.

6. Agonists following up on the outside of receptor cells produce 1,4,5-trisphosphate inositol, which at that point diffuses into the cell to enact the InsP3 (InsP3R) receptor to discharge Ca^{2+} from the ER.

CICR (calcium-induced calcium release) causes the release of Ca^{2+} from its storage site, the endoplasmic reticulum (ER). Canals that are sensitive to Ca^{2+} namely the ryanodine (R) receptor and the InsP3 (I) receptor are in the ER. CICR has two stages, namely the first is the transfer of signals from the plasma membrane to the channel receptors in the ER, starting from the opening of the VOC canal due to depolarization in the plasma membrane then Ca^{2+} will enter, diffuse then activate the R and I receptors, the second is with the Ca^{2+} process will be released from one canal to the next canal to release Ca^{2+} again so that the Ca^{2+} wave will arise which will increase the concentration of Ca^{2+} in the cytosol. Increasing the concentration of Ca^{2+} cytosol will activate the ON system thus activating intracellular signals [26, 39].

3. Dyshomeostasis Ca^{2+} in neurons

Signal unsettling influences and Ca^{2+} fixations have been recognized in different diabetic creature cell disengagement explores just as from diabetic patients. Ca^{2+} homeostasis variations from the norm have been found in most trial tissues, including bone, heart and smooth muscle, discharge cells, platelets, kidneys and osteoblasts. Diminished (in spite of the fact that not generally) and diminished upgrade evoked Ca^{2+} signals. Ca^{2+}-dealing with disarranges have additionally been found in tangible neurons from creatures with diabetes [11, 40, 41].

3.1 Increase in $[Ca^{2+}]I$ break

A huge increment in resting $[Ca^{2+}]$ in diabetic tangible neurons is a typical finding, despite the fact that there are a few contrasts between kinds of neurons. Research shows an expansion in resting $[Ca^{2+}]$ in dorsal root ganglion neurons

(DRG) of rodents with type 1 and type 2 diabetes. Centralization of $[Ca^{2+}]I$ breaks 30% higher in disconnection of DRG neurons in streptozotocin (STZ)-C57Bl/6, (type 1 diabetes model) contrasted with controls (205 ± 16 nM versus 156 ± 16 nM). The expansion in $[Ca^{2+}]I$ in little neurons is more noteworthy in db/db mice (type 2 diabetes model). There was no distinction in $[Ca^{2+}]I$ in huge neurons in the two mouse models. In another examination in Wistar-diabetic mice with STZ 8–14 weeks there was an expansion of 2- to 2.5-overlay resting $[Ca^{2+}]I$ in seclusion of enormous and little DRG neurons from L4-L6 lumbar, however expanded $[Ca^{2+}]$ I rest was not influenced in neurons from the ganglion in the more elevated levels of the spinal line (C3-L3). This distinction connects with the lumbar DRG tactile neuron vulnerability and the long axon of diabetic neuropathy. A portion of these distinctions are identified with contrasts in estimation of $[Ca^{2+}]I$ between considers with different models and term of diabetes, maybe likewise because of contrasts in different sub-populaces of neurons from the degree of DRG in the spine [11, 40].

3.2 Disruption of Ca^{2+} entry plasmalemma

The section of Ca^{2+} into the cytoplasm through the voltage-gated Ca^{2+} channel of plasmalemma is a significant part of the Ca^{2+} signal in sensitive cells. Tangible neurons have a few kinds of voltage-gated Ca^{2+} channels including low-edge (type T) and high-edge (type N and L), which vary in conductance, voltage-reliance and pharmacology. The measure of Ca^{2+} flows at both high and low edges is accounted for to increment in diabetic creatures by 40–100%. In any case, the adequacy of transient depolarization which is Ca^{2+} prompted in the separation of DRG neurons from diabetic and sound creatures is commonly not influenced, just discouraging in disengagement of little DRG neurons from L4-L6. This distinction can be clarified by an expansion in resting $[Ca^{2+}]$, though an increment in waterway Ca^{2+} flow might be redressed [42, 43].

3.3 Ca^{2+} homeostasis in ER

ER works as a dynamic Ca^{2+} stockpiling, fit for amassing, appropriating and discharging Ca^{2+} particles. Ca^{2+} ER homeostasis is accomplished within the sight of Ca^{2+} siphons spoke to by sarco (endo) plasmic reticulum Ca^{2+} ATP-ases (SERCAs) and Ca^{2+} trenches for discharge, including rianudin receptors (RyR), inositol triphosphate receptor (InsP3R) and Ca^{2+} adenine receptors for discharge, including rianudin receptors (RyR), inositol triphosphate receptors (InsP3R) and nicotinic adenic corrosive receptors. Dinucleotide phosphate (NAADP) in the endomembrane. The grouping of free Ca^{2+} in the ER lumen ($[Ca^{2+}]L$) is high, around 0.5–1.0 mM. The degree of $[Ca^{2+}]L$ is practically significant in light of the fact that it will control the speed of SERCA-subordinate Ca^{2+} take-up, actuation of the Ca^{2+} discharge channel, the Ca^{2+} sponsor and give tight power over different ER capersons for collapsing post-translational proteins. In this way, any long haul changes in $[Ca^{2+}]L$ will have significant sign, practical and adjustment results [44, 45].

ER additionally assumes a job in the quick reaction of neuronal Ca^{2+} through commencement (by means of metabotropically controlled InsP3-actuated Ca^{2+} discharge), enhancement (through Ca^{2+}-actuated Ca^{2+} discharge), engendering (by both regenerative initiation of Ca^{2+} and Ca^{2+} ER channels) and end (with SERCA-intervened Ca^{2+} uptake in the ER lumen. These procedures are directed by $[Ca^{2+}]$ I and $[Ca^{2+}]L$ fixations and second emissary digestion including InsP3, cyclic-ADP-ribose and NAADP. Diabetes will disturb Ca^{2+} ER homeostasis in tangible neurons by diminishing the measure of Ca^{2+} in the ER, in this way decreasing the plentifulness of the arrival of Ca^{2+}.The measure of Ca^{2+} discharged from ER is altogether

decreased in DRG neurons with diabetes. The evacuation of Ca^{2+} is prompted by low-portion ionomycin, caffeine (RyRs actuation) or by ATP (metabotropic initiation from diabetes). InsP3Rs), Ca^{2+} use diminishes essentially in the disconnection of tactile neurons from diabetic creatures after STZ administration. The decrease in the measure of Ca^{2+} ER is more prominent in DRG neurons and L1-L6 lumbar ri contrasted and cervical and cylinder DRG. Direct estimations of $[Ca^{2+}]L$ and $[Ca^{2+}]I$ indicated a huge reduction in cytosolic-instigated cytosolic Ca^{2+}. Decrease of $[Ca^{2+}]L$ and the pace of take-up of Ca^{2+} in diabetic neurons is related with diminished SERCA articulation in the homogenate of DRG L4-L5 from diabetic creatures [45, 46].

The focus of Ca^{2+} homeostasis regulation has shifted from pericarion/soma to axons. In sensory neuron culture from diabetic rats, axons appear to be far more susceptible to neurodegeneration because of high glucose levels. Adult sensory neurons isolated from diabetic rats after STZ administration for 3–5 months can grow in vitro 1–4 days. High-level glucose delivery triggers oxidative stress leading to an increase in 4-hydroxy-2-nonenal staining (ongoing lipid peroxidation measurement), axonal development to be suboptimal and the appearance of axonal structural abnormalities similar to axonal dystrophy/axonal degeneration in animal and human models with human diabetes. But pericarions/soma from neuron culture do not show clear signs of oxidative stress or degeneration. Axon toxicity due to glucose induced is only seen in neurons from diabetic animals and neurons that grow from control mice that match their age do not have sensitivity to high glucose levels [11, 45].

Research on Ca^{2+} homeostasis in axons utilizing continuous confocal imaging with Fluo4-AM under high amplification (X100) to investigate Ca^{2+} drifters in the seclusion of grown-up tactile neurons with diabetic rodents after STZ 4–5 months organization.

3.4 Ca^{2+} termination signal

End of the Ca^{2+} signal is activated during the time of cell action, this is finished by expelling Ca^{2+} in the plasmalemma (siphon Ca^{2+} ATP-ase plasmalemma, PMCA, Na^{+}/Ca^{2+} exchanger) or retention of Ca^{2+} to the ER and/or mitochondria. In the segregation of neurons from diabetic creatures, the practical limit of the expulsion framework has all the earmarks of being hindered as showed by the easing back down of the arrival of $[Ca^{2+}]I$ after incitement. This might be because of a lessening in PMCA siphon articulation. Simultaneously, prolongation/high Ca^{2+} levels are likewise connected with diminished Ca^{2+} take-up by intracellular organelles, for example, ER and mitochondria. Diminished SERCA articulation is likewise found in the core of diabetic creatures with STZ. In neurons, diminished SERCA action is showed by an abatement in the ingestion pace of Ca^{2+} after direct estimation of $[Ca^{2+}]L$. Moreover, mitochondrial buffering Ca^{2+} additionally debilitates in neurons with diabetes [47, 48].

3.5 Mitochondrial depolarization in diabetes

Endothelial cell culture shows that high intracellular glucose levels energize extreme electron gifts in the electron transport chain in the mitochondria which will result in mitochondrial hyperpolarization and expanded ROS creation. The procedure in the mitochondria is a focal arbiter of oxidative worry as a confusion of diabetes. This hypothesis recommends that high glucose focuses in the objective tissue as a type of diabetes confusions lead to an expansion in the inventory of NADH in the mitochondria which will additionally build the quantity of electrons and/or immersion, this can prompt a fractional decrease of oxygen and superoxide radicals

in the proximal piece of the electron transport chain. An expansion in ROS will at that point empower tissue degeneration. The capability of the inward mitochondrial layer depolarizes as opposed to hyperpolarization. Mitochondrial depolarization in STZ-diabetes can be forestalled by controlling low-portion insulin or NT-3 [49, 50].

Concentrates in the way of life of tactile neuron incipient organisms show that high glucose levels cause ceaseless mitochondrial depolarization followed by apoptosis. High glucose focuses do not execute neuronal incipient organisms from the passable portion for grown-ups in vitro or grown-up tangible neurons (for about a month at 50 mM glucose in vitro). Moreover there are no basic variations from the norm in mitochondrial neurons/axons or nerve cell passing in tangible ganglia in people with diabetes or autonomic neuropathy. In creature models of type 1 diabetes found unmyelinated little neuron cell misfortune however there is no data of apoptosis or variations from the norm in mitochondrial structure in DRG. Be that as it may, morphology and axonal development are upset by high glucose because of high oxidative pressure which brings about axonal degeneration [49, 50].

Adult sensory neurons from diabetic rodents with STZ 3–5 months were refined for 1 day, at that point given tetramethylrhodamine methyl ester (TMRM) and a color used to identify mitochondrial film depolarization. The outcomes demonstrated that axons from ordinary neurons encountered a pace of mitochondrial depolarization much sooner after expansion of uncoupler carbonylcyanide p-trifluoromethoxyphenylhydrazone (FCCP). Before the expansion of FCCP, mitochondrial axons were more energized than the diabetic neuron bunch [11].

3.6 Mitochondrial dysfunction and Ca^{2+} dyshomeostasis

Disarranges of Ca^{2+} homeostasis and mitochondrial film depolarization in grown-up tactile neurons happen prior (3–14 weeks) in test diabetes type 1 (STZ) and type 2 (db/db), this can be key in tangible neuropathy. The determinant factor for mitochondrial brokenness is not the nearness of hyperglycemia yet the nonattendance of insulin-subordinate neurotropic help, this is seen in vivo and in vitro. Insulin organization of 1 nM for 6–24 h of solid DRG societies essentially builds the capability of the mitochondrial layer and expands the degree of ATP generation contrasted with societies without insulin. Giving 50 mM glucose within the sight of insulin in culture has no impact on the layer potential in the mitochondria. Comparative outcomes were gotten in vivo, STZ-diabetic rodents given insulin focuses low which did not influence hyperglycemia. Insulin organization completely standardizes mitochondrial layer polarization, resting [Ca^{2+}] level and speed of tangible and engine nerve conductance [49, 51, 52].

Mitochondrial polarization and Ca^{2+} homeostasis in tangible neurons from diabetic creatures additionally become ordinary after organization of the neurotropic factor, NT-3. Giving neighborhood insulin to the spinal line at the degree of the lumbar (intrathecal) or fringe nerve (little osmotic siphon) or intranasally expands nerve conduction and epidermal nerve fiber thickness in STZ-diabetic rodents. Different investigations have indicated the job of phosphoinositide 3-kinase (PI3-kinase) and protein kinase B (Akt) in guideline of film potential in the mitochondria. This pathway is managed by insulin plasmalemma receptors (α and β subunit receptor insulin communicated in DRG neurons) and neurotrophin receptors. PI3/Akt association is checked whether DRG neurons are directed with a particular PI3-kinase inhibitor (LY294002), which will hinder insulin-subordinate and neurotrophin-subordinate, therefore repressing the guideline of mitochondrial and insulin-subordinate layer potential to build ATP levels [14, 16].

Several cell types are with specific Ca^{2+} signals. The four cells in **Table 1** are very different in spatial and temporal terms of the Ca^{2+} pathway, for example striped

	Skeletal muscle cell	Cardiac atrial cell	Ca1 Neuron	T cell
Receptors	—	ET-1R/α1R AngIIR	mGluR1 M1	TCR
PLC	—	PLCβ	PLCβ	PLCγ1
Entry channels	$Ca_v1.1$	$Ca_v1.2$	$Ca_v1.2$/$Ca_v2.1$ $Ca_v2.2$/NMDAR	ORAi1
Release channels	RYR1	RYR2 $InsP_3$ R2	RYR2 $InsP_3$ R2	$InsP_3$ R2
PMCAs	PMCA1a, 1c, 1d	PMCA1c, 1d, 2a	PMCA1a, 2a, 3a	PMCA4b
SERCAs	SERCA1a, 1b	SERCA2a	SERCA2b,3	SERC2b,3
Na^+/Ca^{2+} exchanger	NCX	NCX1	NCX1,3	—
Buffers	Parvalbumin	—	Parvalbumin Calbindin 28 K	—
Sensors	Troponin C Calmodulin	Troponin C Calmodulin	Calmodulin	Calmodulin

Table 1.
Ca^{2+} signals in various cells [1].

muscle cells use a specific pathway to deliver Ca^{2+} quickly for activation of muscle contraction, whereas T cell signals have a slower pathway component that is useful.

3.7 Dysregulation of Ca^{2+} and release of neurotransmitters

Signal contribution from the essential afferent into the spinal line includes the arrival of excitation synapses from the nerve terminal to the dorsal horn. Many mechanisms of neuropathic pain along with spinal cord sensitization in response to primary afferent activity in a state of persistent pain. The arrival of synapses from essential afferents is activated by potential activity, nearby film depolarization and enactment of high-voltage Ca^{2+} channels. The passage of Ca^{2+} will begin docking of vesicles containing excitation synapses and modulators, for example, glutamate, substance P and CGRP in the presynaptic layer and arrival of this particle into neural connections. Obstructing the passage of Ca^{2+} into the prespinal terminal forestalls the section of fringe contribution to the spinal rope, this piece of the sedative component hinders the impression of torment by restraining the passage of Ca^{2+} moderator into little tactile neurons through the actuation of narcotic receptors (sub-type) in the essential afferent terminal turns into an option in contrast to the objective of hindering the arrival of synapses from neurons. Peptides that are specific inhibitors of type N channels have been recognized in snails, conotoxins, which can square agony receptors in mice [8, 11].

4. Conclusion

In the fringe nerve, diabetes quite often influences the tactile nerve which brings about even tangible neuropathy. At first, diabetes will decrease the speed of nerve conduction and patients can likewise encounter an assortment of tactile manifestations going from torment to reflex issue. The cell and atomic pathophysiology of diabetes polyneuropathy stays dubious and a few pathways are related with hyperglycemia, including the polyol pathway, oxidative pressure, protein glycosylation

and impeded help from neurotropics. Elective components for starting the beginning of diabetic neuropathy are those identified with changes in mitochondrial work and cell Ca^{2+} homeostasis that are not legitimately brought about by hyperglycemia, however are activated by disabled sign falls identified with insulin receptors and neurotropic elements. The underlying pathogenesis of diabetes neuropathy is diminished insulin receptor incitement. This triggers mitochondrial brokenness and diminished ATP generation. The diminished ATP bolster will influence the component of Ca^{2+} homeostasis, the most evident aggravations are in the plasmalemma and the Ca^{2+} siphon in the ER. Diminishing Ca^{2+} take-up in the ER will decrease the Ca^{2+} focus in intra-ER, causing an ER stress condition. ER worry thus impacts union, post-translational alteration and protein transport, which thusly diminishes the stock of protein to the voltage-gated channel to the axon, bringing about an abatement in nerve conduction speed. These procedures can happen all the more effectively found in axons. This is exacerbated by constant hyperglycemia so degenerative neuropathy and extreme tactile nerve brokenness will happen.

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References

[1] Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, et al. Diabetes Research and Clinical Practice. 2010;**87**(3):293-301. DOI: 10.1016/j.diabres.2010.01.026

[2] Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Annals of Saudi Medicine. 2011;**31**(1):19-23. DOI: 10.4103/0256-4947.75773

[3] Metelko Ž, Pavlić-Renar I, Poljičanin T, Szirovitza L, Turek S. Prevalence of diabetes mellitus in Croatia. Diabetes Research and Clinical Practice. 2008;**81**(2):263-267. DOI: 10.1016/j.diabres.2008.04.016

[4] Gupta S, Singh Z, Purty A, Kar M, Vedapriya DR, Mahajan P, et al. Diabetes prevalence and its risk factors in rural area of Tamil Nadu. Indian Journal of Community Medicine. 2010;**35**(3):396. DOI: 10.4103/0970-0218.69262

[5] Chang CH, Shau WY, Jiang YD, Li HY, Chang TJ, Sheu WH-H, et al. Type 2 diabetes prevalence and incidence among adults in Taiwan during 1999-2004: A national health insurance data set study. Diabetic Medicine. 2010;**27**(6):636-643. DOI: 10.1111/j.1464-5491.2010.03007.x

[6] Aekplakorn W, Chariyalertsak S, Kessomboon P, Sangthong R, Inthawong R, Putwatana P, et al. Prevalence and management of diabetes and metabolic risk factors in Thai adults. Diabetes Care. 2011;**34**(9):1980-1985. DOI: 10.2337/dc11-0099

[7] Zhou B, Lu Y, Hajifathalian K, Bentham J, et al. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet. 2016;**387**(10027):1513-1530. DOI: 10.1016/S0140-6736(16)00618-8

[8] Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011;**34**(10):2220-2224. DOI: 10.2337/dc11-1108

[9] Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circulation Research. 2010;**107**(9):1058-1070. DOI: 10.1161/CIRCRESAHA.110.223545

[10] Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell Death & Disease. 2018;**9**(2):119. DOI: 10.1038/s41419-017-0135-z

[11] Fernyhough P, Calcutt NA. Abnormal calcium homeostasis in peripheral neuropathies. Cell Calcium. 2010;**47**(2):130-139. DOI: 10.1016/j.ceca.2009.11.008

[12] Lambert R, Srodulski S, Peng X, Margulies KB, Despa F, Despa S. Intracellular Na^+ concentration ($[Na^+]i$) is elevated in diabetic hearts due to enhanced Na^+-glucose cotransport. Journal of the American Heart Association. 2015;**4**(9):e002183. DOI: 10.1161/JAHA.115.002183

[13] Pinton P. Mitochondria-associated membranes (MAMs) and pathologies. Cell Death & Disease. 2018;**9**(4):413. DOI: 10.1038/s41419-018-0424-1

[14] Verkhratsky A, Fernyhough P. Mitochondrial malfunction and Ca^{2+} dyshomeostasis drive neuronal pathology in diabetes. Cell Calcium. 2008;**44**(1):112-122. DOI: 10.1016/j.ceca.2007.11.010

[15] Voitenko NV. Role of calcium signalling in the development of pain syndromes. Neurophysiology.

2005;**37**(2):166-171. DOI: 10.1007/s11062-005-0061-z

[16] Calì T, Ottolini D, Brini M. Mitochondrial Ca^{2+} and neurodegeneration. Cell Calcium. 2012;**52**(1):73. DOI: 10.1016/J.CECA.2012.04.015

[17] Patergnani S, Suski JM, Agnoletto C, Bononi A, Bonora M, De Marchi E, et al. Calcium signaling around mitochondria associated membranes (MAMs). Cell Communication and Signaling: CCS. 2011;**9**:19. DOI: 10.1186/1478-811X-9-19

[18] Kawamoto EM, Vivar C, Camandola S. Physiology and pathology of calcium signaling in the brain. Frontiers in Pharmacology. 2012;**3**:61. DOI: 10.3389/fphar.2012.00061

[19] Gardete-Correia L, Boavida JM, Raposo JF, Mesquita AC, Fona C, Carvalho R, et al. First diabetes prevalence study in Portugal: {PREVADIAB} study. Diabetic Medicine. 2010;**27**(8):879-881. DOI: 10.1111/j.1464-5491.2010.03017.x

[20] Prakriya M, Lewis RS. Store-operated calcium channels. Physiological Reviews. 2015;**95**(4):1383-1436. DOI: 10.1152/physrev.00020.2014

[21] Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harbor Perspectives in Biology. 2012;**4**:6. DOI: 10.1101/cshperspect.a005710

[22] Huettner JE. Glutamate receptor pores. The Journal of Physiology. 2015;**593**(1):49-59. DOI: 10.1113/jphysiol.2014.272724

[23] Brini M, Carafoli E. The plasma membrane Ca^{2+} ATPase and the plasma membrane sodium calcium exchanger cooperate in the regulation of cell calcium. Cold Spring Harbor Perspectives in Biology. 2011;**3**:2. DOI: 10.1101/cshperspect.a004168

[24] Carafoli E, Lim D. Plasma membrane calcium ATPase. In: Handbook of Neurochemistry and Molecular Neurobiology. Boston, MA: Springer US; 2009. pp. 581-596

[25] Niggli V, Carafoli E. The plasma membrane Ca^{2+} ATPase: Purification by calmodulin affinity chromatography, and reconstitution of the purified protein. Methods in Molecular Biology (Clifton, N.J.). 2016;**1377**:57-70

[26] Berridge MJ. Module 2: Cell signalling pathways. Cell Signalling Biology. 2014;**6**:csb0001002. DOI: 10.1042/csb0001002

[27] Sacchetto R, Bertipaglia I, Giannetti S, Cendron L, Mascarello F, Damiani E, et al. Crystal structure of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) from bovine muscle. Journal of Structural Biology. 2012;**178**(1):38-44. DOI: 10.1016/j.jsb.2012.02.008

[28] Vandecaetsbeek I, Vangheluwe P, Raeymaekers L, Wuytack F, Vanoevelen J. The Ca^{2+} pumps of the endoplasmic reticulum and Golgi apparatus. Cold Spring Harbor Perspectives in Biology. 2011;**3**:5. DOI: 10.1101/cshperspect.a004184

[29] Noble D, Herchuelz A. Role of Na/Ca exchange and the plasma membrane Ca^{2+}-ATPase in cell function. Conference on Na/Ca exchange. EMBO Reports. 2007;**8**(3):228-232. DOI: 10.1038/sj.embor.7400914

[30] Ottolia M, Torres N, Bridge JHB, Philipson KD, Goldhaber JI. Na/Ca exchange and contraction of the heart. Journal of Molecular and Cellular Cardiology. 2013;**61**:28-33. DOI: 10.1016/j.yjmcc.2013.06.001

[31] Wang Y-C, Chen Y-S, Cheng R-C, Huang R-C. Role of Na+/

Ca^{2+} exchanger in Ca^{2+} homeostasis in rat suprachiasmatic nucleus neurons. Journal of Neurophysiology. 2015;**113**(7):2114-2126. DOI: 10.1152/jn.00404.2014

[32] Schwaller B. Cytosolic Ca^{2+} buffers. Cold Spring Harbor Perspectives in Biology. 2010;**2**(11):a004051. DOI: 10.1101/cshperspect.a004051

[33] Kreutz MR, Naranjo JR, Koch K-W, Schwaller B. The neuronal functions of EF-hand Ca^{2+}-binding proteins. Frontiers in Molecular Neuroscience. 2012;**5**:92. DOI: 10.3389/fnmol.2012.00092

[34] Britti E, Delaspre F, Tamarit J, Ros J. Mitochondrial calcium signalling and neurodegenerative diseases. Neuronal Signaling. 2018;**2**:4. DOI: 10.1042/NS20180061

[35] Bradshaw RA, Dennis EA. Handbook of Cell Signaling. 2nd ed. Vol. 1. USA: Academic Press; 2010

[36] Supnet C, Bezprozvanny I. Neuronal calcium signaling, mitochondrial dysfunction, and Alzheimer's disease. Journal of Alzheimer's Disease. 2010;**20**(s2):S487-S498. DOI: 10.3233/JAD-2010-100306

[37] Verkhratsky A. Endoplasmic reticulum calcium signaling in nerve cells. Biological Research. 2004;**37**(4):693-699. DOI: 10.4067/s0716-97602004000400027

[38] Popugaeva E, Bezprozvanny I. Role of endoplasmic reticulum Ca^{2+} signaling in the pathogenesis of Alzheimer disease. Frontiers in Molecular Neuroscience. 2013;**6**:29. DOI: 10.3389/fnmol.2013.00029

[39] Kawano H, Mitchell SB, Koh J-Y, Goodman KM, Harata NC. Calcium-induced calcium release in noradrenergic neurons of the locus coeruleus. bioRxiv. 2019;**1729**:853283. DOI: 10.1101/853283

[40] Ghorbani ML, Nyborg NCB, Fjalland B, Sheykhzade M. Calcium activity of upper thoracic dorsal root ganglion neurons in Zucker diabetic fatty rats. International Journal of Endocrinology. 2013;**2013**:532850. DOI: 10.1155/2013/532850

[41] Shpakov AO, Derkach KV, Berstein LM. Brain signaling systems in the Type 2 diabetes and metabolic syndrome: Promising target to treat and prevent these diseases. Future Science OA. 2015;**1**(3):FSO25. DOI: 10.4155/fso.15.23

[42] Deleuze C, David F, Behuret S, Sadoc G, Shin H-S, Uebele VN, et al. T-type calcium channels consolidate tonic action potential output of thalamic neurons to neocortex. Journal of Neuroscience. 2012;**32**(35):12228-12236. DOI: 10.1523/jneurosci.1362-12.2012

[43] Gemes G, Bangaru MLY, Wu H-E, Tang Q, Weihrauch D, Koopmeiners AS, et al. Store-operated Ca^{2+} entry in sensory neurons: functional role and the effect of painful nerve injury. The Journal of Neuroscience. 2011;**31**(10):3536-3549. DOI: 10.1523/JNEUROSCI.5053-10.2011

[44] Burdakov D, Petersen OH, Verkhratsky A. Intraluminal calcium as a primary regulator of endoplasmic reticulum function. Cell Calcium. 2005;**38**(3-4):303-310. DOI: 10.1016/j.ceca.2005.06.010

[45] Zherebitskaya E, Schapansky J, Akude E, Smith DR, Van der Ploeg R, Solovyova N, et al. Sensory neurons derived from diabetic rats have diminished internal Ca^{2+} stores linked to impaired re-uptake by the endoplasmic reticulum. ASN Neuro. 2012;**4**:1. DOI: 10.1042/AN20110038

[46] Nedergaard M, Verkhratsky A. Calcium dyshomeostasis and pathological calcium signalling in neurological diseases. Cell Calcium. 2010;**47**(2):101-102. DOI: 10.1016/j.ceca.2009.12.011

[47] Gerbino A, Ruder WC, Curci S, Pozzan T, Zaccolo M, Hofer AM. Termination of cAMP signals by Ca^{2+} and Gαi via extracellular Ca^{2+} sensors: A link to intracellular Ca^{2+} oscillations. Journal of Cell Biology. 2005;**171**(2):303-312. DOI: 10.1083/jcb.200507054

[48] Boulware MJ, Marchant JS. Timing in cellular Ca^{2+} signaling. Current Biology. 2008;**18**:17. DOI: 10.1016/j.cub.2008.07.018

[49] Wang CH, Wei YH. Role of mitochondrial dysfunction and dysregulation of Ca^{2+} homeostasis in the pathophysiology of insulin resistance and type 2 diabetes. Journal of Biomedical Science. 2017;**24**(1):70. DOI: 10.1186/s12929-017-0375-3

[50] Haider SZ, Sadanandan NP, Joshi PG, Mehta B. Early diabetes induces changes in mitochondrial physiology of inner retinal neurons. Neuroscience. 2019;**406**:140-149. DOI: 10.1016/j.neuroscience.2019.02.026

[51] Farmer KL, Li C, Dobrowsky RT. Diabetic peripheral neuropathy: Should a chaperone accompany our therapeutic approach? Pharmacological Reviews. 2012;**64**(4):880-900. DOI: 10.1124/pr.111.005314

[52] Kann O, Kovács R. Mitochondria and neuronal activity. American Journal of Physiology. Cell Physiology. 2007;**292**(2):C641-C657. DOI: 10.1152/ajpcell.00222.2006