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Endoplasmic reticulum–mitochondria interplay in chronic pain: The calcium connection

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Abstract

Chronic pain is a debilitating condition that affects roughly a third to a half of the world's population. Despite its substantial effect on society, treatment for chronic pain is modest, at best, notwithstanding its side effects. Hence, novel therapeutics are direly needed. Emerging evidence suggests that calcium plays an integral role in mediating neuronal plasticity that underlies sensitization observed in chronic pain states. The endoplasmic reticulum and the mitochondria are the largest calcium repositories in a cell. Here, we review how stressors, like accumulation of misfolded proteins and oxidative stress, influence endoplasmic reticulum and mitochondria function and contribute to chronic pain. We further examine the shuttling of calcium across the mitochondrial-associated membrane as a mechanism of cross-talk between the endoplasmic reticulum and the mitochondria. In addition, we discuss how endoplasmic reticulum stress, mitochondrial impairment, and calcium dyshomeostasis are implicated in various models of neuropathic pain. We propose a novel framework of endoplasmic reticulum–mitochondria signaling in mediating pain hypersensitivity. These observations require further investigation in order to develop novel therapies for chronic pain.

Keywords

Endoplasmic reticulum stress, mitochondria, mitochondrial-associated membrane, calcium, pain

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Introduction

Pain is an adaptive response to noxious stimuli that cause tissue injury or have the potential to cause an injury.[1] It is the most common symptom across a wide variety of medical conditions ranging from autoimmune disorders like rheumatoid arthritis and multiple sclerosis, to traumatic nerve injury[2,3] and is a major reason for seeking consultation with a physician.[4,5] When pain loses its adaptive value and becomes persistent, even after the initial injury has healed, it becomes a disease in its own right.[1]

Studying pain in a laboratory setting is particularly difficult due to the subjective nature of pain perception. To overcome this obstacle, researchers carefully control the extent of the injury or disease and closely monitor nocifensive behaviors in animals. Models of neuropathic pain, such as spinal nerve ligation (SNL) and spared nerve injury (SNI), typically induce traumatic damage to the nerve resulting in evoked and spontaneous pain behaviours.[6,7] Other disease-oriented pain models, like diabetic neuropathy and chemotherapy-induced pain, affect the molecular integrity of nerves and typically induce a more global, complex injury response involving inflammation, immune activation, and gliosis as well as

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changes in the neurovasculature.[8,9] The underlying pathology responsible for pain hypersensitivity across these conditions remains enigmatic. It is clear, however, that pain is a common feature of many medical conditions, regardless of their aetiologies. Whether these pain states share common or divergent mechanisms is being actively investigated.

Chronic neuropathic pain results from a lesion or disease of the somatosensory nervous system comprising of peripheral sensory neurons as well as the spinal cord and the brain.[10] Enhanced excitability, or sensitization, throughout this pain axis is thought to mediate neuropathic pain. In the central nervous system (CNS), changes in the response properties of complex neuronal and glial networks, such as disinhibition, contribute to persistent evoked and spontaneous pain.[11,12] In the periphery, however, specialized cells, known as nociceptors, are responsible for transducing painful stimuli. These cells typically have a high stimulation threshold allowing them to fire action potentials when exposed to noxious heat, chemicals, and mechanical stimulation.[13,14] In concert with other sensory neurons, nociceptors inform the CNS about the nature, location, and intensity of the painful stimulus.[15] Enhancement of the response properties of sensory neurons, known as peripheral sensitization, can arise and is response to neuropathy caused by tissue injury and inflammation or lesions to the nerve fibers.[16,17] Sensitization leads to hyperalgesia (increased sensitivity to painful stimulus) and allodynia (pain from a previously non-noxious stimulus).[18]

Major efforts have been made to understand the mechanisms that underlie the sensitization of nociceptors.[15,18,19] Some molecules that might be held responsible include reactive oxygen species (ROS), adenosine triphosphate (ATP), and calcium (Ca^{2+}).[20] Besides providing energy for many cellular processes, ATP acts as a nociceptive transmitter via the purinergic receptors, sensitizing nociceptors to further stimulation.[21] ROS such as superoxide (SO) are chemically reactive molecules that are produced as a by-product of the chemical processes in the mitochondria, lysosomes, and the endoplasmic reticulum (ER). High levels of ROS during times of stress lead to oxidation of nucleic acids, lipids, and proteins in a process known as oxidative stress.[22] SO and its descendant peroxynitrite have been linked to alterations in protein kinases, glutamatergic signaling, and ion channel modulation in the development of hypersensitivity.[23] Ca^{2+} is a multifunctional ion that is involved in neuronal plasticity by regulating neurotransmitter release, action potential propagation, and changes in gene expression.[24] The role of plasmalemmal Ca^{2+} signaling through voltage-gated Ca^{2+} channels and transient receptor potential (TRP) channels is well-documented in pain pathophysiology.[25] Ca^{2+}-signaling also results in increased production of both ROS and ATP by mitochondria, and thus may serve as a master regulator between these molecules and the development of nociceptor sensitization. However, the precise mechanisms that regulate intracellular Ca^{2+} (iCa^{2+}) stores to mediate pain remain to be fully elucidated.

In this regard, the ER and mitochondria are two organelles that act together as an important Ca^{2+} signaling hub and as such, they may represent a fundamental regulator of iCa^{2+}, excitability and neuronal plasticity.[26] Indeed, emerging evidence is beginning to shed light on the critical role these two organelles play in nociceptor sensitization and chronic pain. Given their important position within the cell for Ca^{2+} regulation, this review will discuss the complex relationship between the ER and mitochondria and explore how dysregulation within and between these organelles can impact on nociceptor sensitization and the implications this has for chronic pain.

The endoplasmic reticulum

The ER is perhaps the largest tubular organelle in the cell.[27] In neurons, the ER is continuous throughout the cell, extending from the dendritic arbors to the cell soma, across the axon and into the presynaptic terminals.[28] The ER has classically been subdivided into the rough ER (containing ribosomes), the smooth ER (without ribosomes) and the nuclear envelope.[27] The ER performs a variety of functions. Most notably, a host of luminal and transmembrane chaperones and foldases help synthesize and mature proteins in the ER.[29] In addition, the ER is also important for lipid synthesis. As such, the smooth ER synthesizes phospholipids, glycolipids, and cholesterol which are used for various functions such as synthesizing steroid hormones from cholesterol.[30] The ER also contains many detoxifying enzymes that metabolize lipid soluble molecules by converting them into polar, water-soluble compounds that are then secreted from the cell and the body.[31] In addition, the ER is the cell's largest dynamic repository of Ca^{2+}.[26] Many of the ER's chaperones (e.g., BiP, calreticulin, calnexin) are low-affinity, high-capacity Ca^{2+} binding proteins (CBPs).[26] Their function as chaperones also heavily depends on the luminal concentration of Ca^{2+}.[32]

Since the ER extends throughout the cell, it also serves as a highway for RNAs, proteins, lipids, and ions.[27] Changes in the intraluminal environment of the ER, such as increased protein synthesis and altered Ca^{2+} homeostasis, may lead to ER stress which is initially protective but detrimental in the long-term.[33]

The unfolded protein response

Stressful conditions such as amino acid deprivation, viral infection, heme deficiency, and accumulation of

unfolded proteins lead to the induction of a larger translational regulation pathway known as the integrated stress response (ISR). The ISR is mediated by the stimulation of four kinases, general control nonderepressible 2 kinase (GCN2), protein kinase R (PKR), heme-regulated eIF2α kinase (HRI), and protein kinase RNA-like ER kinase (PERK), respectively.[34] These kinases converge onto the phosphorylation of eukaryotic initiation factor 2 α (eIF2α) regulating its translational capacity and allowing the cell to aptly react to the stressor.[34]

Protein synthesis, folding, and quality control are canonical functions of the ER. Upon increased protein demand, the ER responds to an accumulation of unfolded or misfolded proteins by initiating a series of cellular processes collectively known as the unfolded protein response (UPR) (Figure 1).[34] The goal of the UPR is to reduce translation of proteins, increase the expression of chaperones, and degrade misfolded proteins. This response is mediated by three downstream transducers: PERK, inositol-requiring enzyme 1α (IRElα), and activating transcription factor 6 (ATF6).[34] Each of these ER resident proteins contains a single transmembrane domain and a single luminal domain.[35] Under stressed conditions, binding immunoglobulin protein (BiP; also known as heat shock protein A 5, HSPA5, and glucose response protein 78, GRP78) dissociates from ATF6, PERK, and IRE1α activating their respective arm of the UPR.[34] BiP, then, actively folds unfolded proteins using its allosteric ATPase activity and prevents the formation of protein aggregates by binding and restraining unfolded proteins.[36]

Once BiP is sequestered from PERK's luminal domain, PERK autophosphorylates and oligomerizes as either a dimer or a transient tetramer.[37] The extent of oligomerization of PERK may represent the degree of unfolded proteins in the ER since the tetramer configuration is a more potent kinase than the dimer.[34] Upon activation, PERK phosphorylates eukaryotic initiation factor 2 α (eIF2α) reducing the general translation of proteins while enhancing translation of select mRNAs. In particular, PERK-eIF2α signaling increases translation of those transcripts that encode an upstream open reading frame (uORF).[38] eIF2α phosphorylation enhances the expression of activating transcription factor 4 (ATF4) which in turn increases the expression of the proapoptotic transcription factor C/EBP homologous protein (CHOP).[39] ER stress and the UPR have been linked to several neuropathic pain states, including peripheral nerve injury (PNI), diabetic neuropathy,

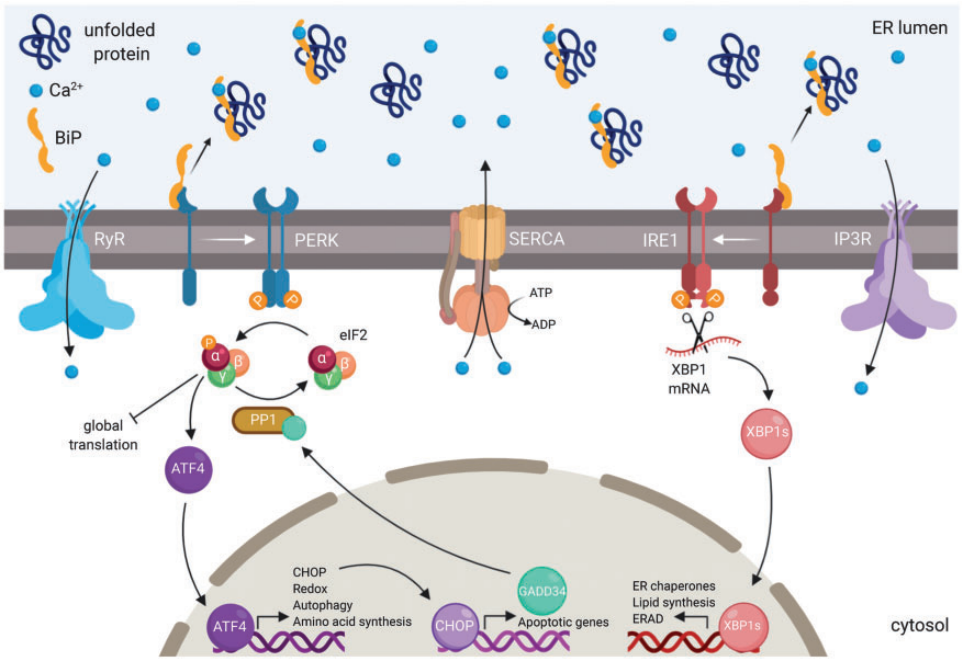

Figure 1. The unfolded protein response of the ER. The dissociation of BiP from PERK and IRE1 induces oligomerization and autophosphorylation of these kinases, initiating the unfolded protein response. Activated IRE1 acts as an endoribonuclease and splices XBP1 mRNA (XBP1s) generating a potent transcription factor that enhances the production of ER chaperones and genes associated with ER-associated degradation. PERK activation enhances phosphorylation of eIF2α as part of the integrated stress response. This results in the suppression of global translation, and expression of stress-induced genes like ATF4, CHOP, and GADD34. In concert with protein phosphatase 1, GADD34 functions to reverse eIF2α phosphorylation and resume global translation. Many of ER's chaperones, including BiP, require Ca^{2+} for proper functioning. SERCA actively pumps Ca^{2+} into the ER while the activation of IP3Rs and RyRs releases Ca^{2+} into the cytosol. Stressors, like inflammation, may modulate the activity of ER Ca^{2+} transporters and thus influence ER functioning.

chemotherapy-induce neuropathic pain. Furthermore, inhibiting certain arms of the ER stress pathway attenuates pain hypersensitivity.[40,41] Mechanisms supporting these observations will be discussed below.

Mitochondria

Mitochondria are unique organelles thought to have originated from bacteria that were endocytosed by an early eukaryote. They have their own DNA (mtDNA) that encodes for proteins which allow for efficient aerobic energy production.[42] They are composed of both an outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM). The IMM encloses the matrix, and has many folds, referred to as cristae. Cristae increase the surface area available to harbor the five transmembrane proteins involved in energy production by oxidative phosphorylation (Complex I–V).[43] These transmembrane proteins pump hydrogen ions into the intermembrane space, creating a potential difference across the IMM ($\Delta\Psi m$) that is used by the protein ATP synthase (Complex V) to make ATP. The $\Delta\Psi m$ also provides an electrochemical driving force for the movement of ions such as Ca^{2+} across the IMM.[44] An important byproduct of mitochondria metabolism is the generation of ROS, which are important signaling molecules, but under pathological conditions can lead to oxidative stress and exacerbated damage.[45]

Mitochondria form dynamic and integrated tubular networks, regulated by proteins such as MFN1 and MFN2, which promote mitochondrial fusion, and by Fis1 and Drp1 which regulate fission.[46,47] These networks not only allow for the coordination of ATP production spatially and temporally but also play a role in regulating mitochondria–cell communication involved in metabolism, the cell cycle, stress responses, and cell death cascades.[46] Although the mechanism of how mitochondrial networks could mediate these processes is still under investigation, there are numerous hypotheses. For example, mitochondrial networks may control energy production through Ca^{2+} signaling. In a fused mitochondrial network, Ca^{2+} can diffuse throughout the network thus allowing small changes in Ca^{2+} to have a greater affect and reach more sites of energy production.[48,49]

Mitochondrial-associated membrane

Mitochondria interact with the ER through a specialized domain called the mitochondria-associated ER membrane (MAM). The MAM is composed of contact sites tethered by protein complexes, which facilitate ER–mitochondria crosstalk and juxtaposition (as reviewed by Veeresh et al.[50] and Vance[51]). The ER–mitochondria encounter structures (ERMES) complex regulates phospholipid transfer as well as mitochondrial dynamics and mitophagy.[52] Phosphofurin acidic sorting cluster 2 (PACS2) regulates communication between the ER and mitochondria, ER homeostasis, and apoptosis.[53] Presenilin 2 (PS2) in the presence of mitochondrial fusion protein mitofusin (MFN2) promotes ER–mitochondrial tethering.[54] The IP3R-S1R-GRP75-VDAC complex is crucial for Ca^{2+} transfer from the ER to mitochondria. The inositol triphosphate receptor (IP3) receptor in the ER is stabilized by the sigma1 receptor (S1R) to allow Ca^{2+} efflux. This complex is tethered by the chaperone glucose response protein 75 (GRP75) to the voltage-dependent anion channel (VDAC) to facilitate mitochondrial uptake of Ca^{2+}.[50,55] In addition, vesicle-associated membrane protein-associated protein B (VAPB) in the ER associates with protein tyrosine phosphatase-interacting protein 51 (PTPIP51) in the mitochondria to help facilitate Ca^{2+} transfer.[56]

In neurons, ER–mitochondrial interactions through the MAM can significantly influence many key processes relevant to nociceptor function such as mitochondrial bioenergetics, Ca^{2+} homeostasis, and action potential generation.[55,57,58] For example, Ca^{2+} regulates activity-dependent signaling and neuronal excitability, and in nociceptors this regulation is important to prevent aberrant signaling and pain.[59] Thus, Ca^{2+} modulation at the MAM can play a role in pain control through nociceptor excitability.

ER stress results in various functional and structural changes at the MAM.[60] ER stress can lead to increased MAM contacts and strengthened Ca^{2+} transfer to mitochondria, which boosts energy production.[61] Interestingly, some proteins known to be involved in the UPR, IRE1, and PERK perform noncanonical functions at the MAM.[62,63] IRE1 localized at the MAM regulates IP3 receptors and maintains mitochondrial bioenergetics.[62] Whereas PERK at the MAM regulates juxtaposition between the ER and mitochondria and promotes apoptosis by conveying ROS signals and maintaining high levels of CHOP.[63]

Sigma1 receptors (S1Rs) are also important in the development of neuropathic pain. In models of neuropathic pain, hypersensitivity can be reduced using S1R knockouts and pharmacological S1R antagonists.[64–66] In addition to their role at the MAM, S1Rs can translocate to both the plasma membrane and nucleus to modulate voltage-gated channel activity.[67] These diverse functions present multiple pathways through which S1Rs are be involved in neuropathic pain. The S1R antagonist MR309 reduced chemotherapy-induced neuropathic pain in clinical trials, demonstrating its promise as a therapeutic target in pain.[68]

ER Ca^{2+} regulation and the impact on pain

Voltage gated Ca^{2+} channels, TRP channels, glutamatergic channels, and purinergic receptors on the plasma

membrane regulate the influx of extracellular Ca^{2+} in sensory neurons and are heavily involved in pain pathogenesis following disease, injury, and inflammation (for an extensive review, see Bourinet et al.[25]). Plasma membrane Ca^{2+}-ATPase (PMCA) and Na^{+}/Ca^{2+} exchanger (NCX) are primarily responsible for extruding cytosolic Ca^{2+}.[69] The bulk of the intracellular Ca^{2+} is stored in the ER.[27] Since Ca^{2+} is a multifunctional ion involved in a variety cellular processes, the ER can directly impact gene expression, bioenergetics, ion channel physiology, and enzyme function.[27] With the presence of Ca^{2+} transporters on the ER membrane, the ER can be excited to release or sequester Ca^{2+}, tightly regulating the concentration of available cytosolic Ca^{2+}. In the ER, Ca^{2+} is stored as bound to CBPs, many of which are chaperones, like calnexin, calreticulin, and BiP.[26,27] By and large, each CBP binds to many Ca^{2+} molecules in a low-affinity, high-capacity manner such that the opening of a Ca^{2+} exporters allows for the immediate dissociation of Ca^{2+} from the CBPs.[26] The ER also maintains a concentration of free Ca^{2+} unbound to CBPs. Free Ca^{2+} determines the driving force of Ca^{2+} release, while Ca^{2+} bound to CBPs determines the total amount of Ca^{2+} that can be released.[70,71] Ca^{2+} efflux from the ER is mediated by Ca^{2+}-sensitive ryanodine receptors (RyRs) and inositol triphosphate receptors (IP3Rs), while the influx of Ca^{2+} into the ER is mediated by sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pumps in concert with store-operated Ca^{2+} entry (SOCE) (Figure 1).

Ryanodine receptors and pain

RyRs are named after their antagonist, ryanodine, which was originally used as an insecticide. RyRs are one of the largest membrane proteins consisting of four-identical subunits arranged in a four-leaf clover-shaped structure.[72,73] There are three variants of RyRs (RyR1, RyR2, and RyR3) all of which can be activated by free Ca^{2+} in the cytosol in a process known as Ca^{2+}-induced Ca^{2+} release or CICR.[27] RyR1 is the most sensitive to cytosolic Ca^{2+} followed by RyR2 and then RyR3[74,75] RyR3s were classically known as the "brain" isoform; however, all three isoforms can be detected in the nervous system spanning across different cell types and being expressed in virtually every cellular compartment.[26,76,77] RyRs are not exclusively selective for Ca^{2+}. Instead, they also counter-conduct other cations such as Mg^{2+}, Li^{+}, Na^{+}, and K^{+}.[78] This allows the channel to release Ca^{2+} without largely affecting the membrane potential.[78] RyRs can associate with other proteins to further enhance a cellular Ca^{2+} response.[79]Voltage-gated calcium channels and Ca^{2+}-sensitive large-conductance K^{+} (BK) channels are functionally coupled to RyRs.[80,81] As a result, cytosolic Ca^{2+} increase due to neuronal activity can enhance Ca^{2+} release from the ER which in turn readily affects action potential dynamics via Ca^{2+} sensitive channels.[81]

A growing number of diseases and conditions are linked to impaired RyR function such as genetic RyR mutations in malignant hyperthermia, central core disease, and catecholaminergic polymorphic ventricular tachycardia.[82] Aberrant RyR function has also been implicated in neurodegenerative disorders like Alzheimer's disease.[83] Recently, pain and *hyperalgesic priming* have been linked to RyR sensitization in rats. A single dose of a priming stimulus, like ryanodine, induces long-lasting changes in the nervous system such that a second pain-inducing stimulus, like prostaglandin E2, provokes a much more profound algesic response than would be observed without the primer. In female mice, a low dose (1 pg) of ryanodine is sufficient to induce priming compared to a much higher dose of 100 ng in males.[84] This heightened sensitivity to ryanodine in females is mediated by estrogen receptor α (ERα) such that antagonizing the ERα using antisense oligonucleotides abolishes the priming phenotype. Activating ERα using an agonist, propyl pyrazole triol, promotes priming in the absence of ryanodine.[84]

IP3Rs and pain

IP3Rs are another class of ER Ca^{2+} release channel. IP3Rs respond to inositol triphosphate (IP3) which is catalyzed by phospholipase C (PLC) typically after the activation of plasmalemmal G-protein coupled receptors (GPCRs) such as metabotropic glutamate receptors (Figure 3).[26] Like the RyRs, there are three types of IP3Rs: IP3R1, IP3R2, and IP3R3. The channel may form as homo- or hetero-tetramers.[26] IP3Rs can be further modulated by (de)phosphorylation by various kinases, like protein kinase A, B, and C, and phosphatases like calcineurin.[85] Further splice variations in the IP3R genes allow for even more functional diversity of the channel despite 60%–80% shared homology among IP3R isotypes.[26] IP3Rs open when both IP3 and Ca^{2+} bind to the receptor.[86] It is believed that IP3 primes the receptor to cytosolic Ca^{2+} which allows for the opening of the channel in a Ca^{2+}-dependent manner.[86] IP3R1s are maximally activated around 300–400 nM of Ca^{2+} beyond which they lose their sensitivity to intracellular Ca^{2+}.[87] In contrast, IP3R2s and IP3R3s are not inhibited by high Ca^{2+} concentration.[88] Activation of the IP3Rs may lead to widespread Ca^{2+} waves or be confined to microdomains depending on the sensitivity of IP3Rs to IP3, the density of IP3Rs, degradation of IP3, and the cell's buffering capacity for IP3.[27] Since IP3Rs are co-activated by intracellular Ca^{2+}, RyR-mediated CICR enhances Ca^{2+} release from IP3Rs

(and vice versa) possibly contributing to widespread Ca^{2+} waves in the ER.[27,86]

The coupling of IP3 production with stimulation of GPCRs allows the cell to regulate intracellular Ca^{2+} release in response to the external environment (Figure 3). As such, the binding of bradykinin, an inflammatory mediator, to its B2 receptor induces IP3 production, enhances Ca^{2+} release from the ER, activates Ca^{2+}-sensitive calmodulin, and contributes to neuronal sensitization.[89,90] The link between bradykinin and inflammatory pain has been well-documented.[90,91]Fractalkine-induced inflammation and subsequent hyperalgesia was recently shown to be mediated by IP3-induced Ca^{2+} transients in microglia.[92] Like ryanodine, a low dose (1–3 pg) of IP3 induces hyperalgesic priming in female, but not male, rats in a ERα dependent manner.[93] Interestingly, both ryanodine-induced and IP3-induced hyperalgesic priming can be blocked by inhibiting either IP3Rs or RyRs, respectively.[93] This observation in females implies that Ca^{2+} release from the ER intricately links RyRs and IP3Rs, possibly in a CICR manner that is sex specific.

SERCA pumps and pain

Cytosolic Ca^{2+} concentrations are tightly regulated by SERCA pumps. These channels belong to a class of P-type Ca^{2+} ATPases that respond to increases in intracellular Ca^{2+} levels by actively sequestering the ion from the cytosol into the ER (Figure 1).[26] Like other ER Ca^{2+} transporters, there are three paralogs of SERCA: SERCA1, SERCA2, and SERCA3. SERCA2 is further differentiated by its spliced isoforms, SERCA2a and SERCA2b. Of particular interest is SERCA2b which is ubiquitously expressed in nervous tissue.[27] SERCA2b activity is modulated by Ca^{2+}-sensitive calreticulin and ER resident protein 57 (ERp57), both of which also function as chaperones.[94,95] When Ca^{2+} decreases in the ER lumen, calreticulin binds to SERCA2b increasing its activity, while ERp57 functions as a thiol oxidoreductase, catalyzing disulfide bridges on the SERCA channel and consequently enhancing Ca^{2+} uptake. Hence, luminal Ca^{2+} concentration inversely determines the rate of Ca^{2+} uptake by SERCA such that channel activity peaks at low luminal Ca^{2+} concentrations and wanes at higher concentrations.[27] With a drastic increase in cytosolic Ca^{2+} (e.g., during an action potential), other transporters with a greater capacity for Ca^{2+}, such as mitochondrial calcium uniporter (MCU) and Na^{+}/Ca^{2+} exchanger (NCX), can further support Ca^{2+} homeostasis.[26]

A loss of SERCA function has been linked to neuropathic pain after PNI. Reduced SERCA function in response to PNI leads to a slower recovery of Ca^{2+} transients in small diameter nociceptors.[96] The inability of the ER to buffer increases in cytosolic Ca^{2+} after injury leads to Ca^{2+}-signaling-induced hyperexcitability of these afferents and neuropathic pain.[20,97] This is further exemplified in axons of sensory neurons obtained from diabetic rats where a loss of SERCA activity contributes to diminished Ca^{2+} levels in intracellular stores.[98]Thrombospondin-4, an extracellular matrix glycoprotein commonly elevated after nerve injury, was shown to suppress SERCA activity, enhance PMCA activity, drain ER Ca^{2+}, and stimulate store-operated Ca^{2+}-entry[99] (Figure 3). The net result of this is a loss of intracellular Ca^{2+} levels. Similar observations have been made following axotomy.[100]

Store-operated Ca^{2+} entry and pain

During a Ca^{2+} transient, Ca^{2+} enters the cell through the plasma membrane and is also released from the ER. To replenish this loss of ER Ca^{2+} pool, store operated Ca^{2+} channels (SOCCs), particularly the Orai channels, pump extracellular Ca^{2+} into the cytosol and into the ER via the SERCA channels.[101,102] The function of these SOCCs is dependent on the intraluminal ER Ca^{2+} concentration.[103] Stromal interaction molecule (STIM) proteins were identified as Ca^{2+} sensors in the ER.[104] There are two homologs of STIM proteins, STIM1 and STIM2 in vertebrates that are expressed in a variety of tissues and organs including nervous tissue.[105] These single-pass transmembrane ER proteins are localized diffusely throughout the ER under resting conditions.[106] Upon emptying of the Ca^{2+} store, STIM proteins redistribute and cluster on the ER membrane nearest to the plasma membrane where their CRAC activation domain (CAD; also known as STIM-Orai activation region or SOAR) binds and activates Orai channels on the plasma membrane.[104,107] Orai channels also redistribute and cluster to ER–plasma membrane junction sites creating microdomains of store mediated Ca^{2+} entry (SOCE).[106,108] There are three human homologs of Orai channels, Orai1-3, each of which share considerable homology (~62% overall identity) with each other but have very little overlap with other ion channels.[107] Orai channels are found ubiquitously in various tissues.[109–111] Of note, high Orai1 expression in the brain implicates its role in the nervous system.[112] Various mechanisms, such as glycosylation and pH sensing, and proteins, including golli proteins and septins, can further regulate SOCE.[103] Through the formation of ER:plasma membrane microdomains, the ER—an intracellular Ca^{2+} store—becomes functionally linked to the extracellular supply of Ca^{2+}. An extensive review of SOCE and its regulatory mechanisms can be found elsewhere.[103,107]

The role of SOCE in mediating disease and injury has only recently come to light primarily because the Orai channels were only identified and cloned at the turn of

the century.[113–115] Since then, SOCCs have been implicated in various disease states including autoimmunity,[116] neurodegeneration,[117] arthritis,[118] and tumorigenesis.[119] Only recently has the role of SOCCs been established in pain pathophysiology. It was noticed that intraplantar, intraperitoneal, and intrathecal administration of YM-58483, an inhibitor of SOCE, prevented both acute and chronic mechanical and thermal hypersensitivity in a dose-dependent manner following a SNI and CFA-administration as well as reducing both phases of the formalin response.[120] Similarly, YM-58483 administration in a model of rheumatoid arthritis was found to reduce cytokine production in the periphery and ERK and CaMKIIα expression in the spinal cord, resulting in attenuated pain hypersensitivity.[118] Although these reports demonstrate the analgesic effects of inhibiting SOCE, the molecular underpinning of this phenotype remained unknown until recently. In a series of experiments employing Orai1 knock-out animals, Dou et al.[121] showed that Orai1 contributed to neuronal hyperexcitability in the spinal cord and pain behaviors following formalin and carrageenan administration. In the periphery, knockdown of STIM1, STIM2, Orai1, and Orai3 were found to diminish SOCE in DRG neurons.[122] Thapsigargin, a SERCA blocker that depletes ER Ca^{2+} and thereby induces SOCE, promoted hyperexcitability of sensory neurons in vitro. This phenotype was abolished with Orai1 and Orai3 double knockdown.[122] These observations clearly implicate SOCE in regulating pain pathophysiology. The sequence of events that lead to the imbalance of intracellular Ca^{2+}, however, remains unclear. Is the ER Ca^{2+} dysregulated first and that is followed by increased SOCE or is the SOCE impaired that then induces ER Ca^{2+} release? The answer is probably dependent on the disease or injury. In either case, a vicious cycle of Ca^{2+} dyshomeostasis becomes detrimental to the cell.

Mitochondrial Ca^{2+} regulation and the impact on pain

Mitochondria were not considered to be major Ca^{2+} regulators under physiological conditions until fluorescent Ca^{2+} dyes made it possible to measure Ca^{2+} in organelles of live cells.[123,124] Although they store less Ca^{2+} than the ER, mitochondria are nonetheless important buffers of intracellular Ca^{2+}.[125,126] Ca^{2+} influx into the mitochondrial matrix occurs through the MCU located on the IMM, which has high Ca^{2+} selectivity, but low affinity.[127] The MAM overcomes this barrier by creating microdomains of high Ca^{2+} at the IP3R-S1R-GRP75-VDAC complex (Figure 2).[50,128] In this complex, VDACs on the OMM of mitochondria are tethered by the chaperone GRP75 to IP3Rs in the ER. Thus, when IP3Rs open, and are stabilized by S1Rs, there can be efficient transport of Ca^{2+} into the mitochondrial matrix by the MCU.[50,127,128] The VAPB-PTPIP51 complex also facilitates Ca^{2+} uptake by tethering the MAM.[56,129]

Ca^{2+} regulates various mitochondrial processes (Figure 3) including ATP and ROS production, fission and fusion, opening of the mitochondrial permeability transition pore (mPTP), and mitochondria-mediated apoptosis.[24,130] For example, Ca^{2+} can stimulate ATP production via activation of Krebs cycle dehydrogenases.[131] ROS and Ca^{2+} have a complex relationship. Ca^{2+} signaling can stimulate of ROS-generating enzymes and upregulate ROS production during mitochondrial respiration.[132] In addition, ROS can influence Ca^{2+}-dependent processes. Oxidation of BK channels leads to a loss of Ca^{2+}-sensing ability and thus a loss of activation.[133] Since BK channels prevent repetitive firing, loss of their function can lead to nociceptor hyperexcitability and pain.[134]

Normally, mitochondrial Ca^{2+} concentration is maintained steadily by a balance between influx through MCUs and efflux through the mitochondrial sodium-calcium exchanger (NCLX).[126,135,136] However, mitochondria can also buffer Ca^{2+} elevations in the cytosol by uptake and precipitation as Ca^{2+}-phosphate.[24,137] In DRG neurons, both the MCU and NCLX are critical to this process.[138] Knocking down the NCLX can reduce both MCU Ca^{2+} uptake, and TRPV1 receptor-mediated Ca^{2+} currents in nociceptors. Thus, mitochondrial Ca^{2+} buffering is important for regulating intracellular Ca^{2+} homeostasis. This capacity to buffer intracellular Ca^{2+} can significantly influence Ca^{2+} transients in nociceptors, the overall level of nociceptor excitability, and ultimately, pain.[139]

Pathophysiology impacting the ER and mitochondria

ER stress in PNI

Along with various other homeostatic processes, ER stress has also been implicated in the pathophysiology of PNIs (Table 1). Damage to peripheral nerves induces a robust UPR in axons and soma of sensory neurons in the DRG (reviewed by Valenzuela et al.[140]) Interestingly, ER chaperones, like BiP, and transcription factors, like CHOP, are elevated at the site of injury following sciatic nerve crush and are retrogradely transported back to the soma as markers of injury.[141] It is unlikely that UPR by-products from injured axons are the only source of ER stress markers observed in the DRG considering that ER stress markers are elevated in the DRG as early as one day after injury.[142] Regardless, axonal ER stress is proposed to be beneficial and essential for nerve

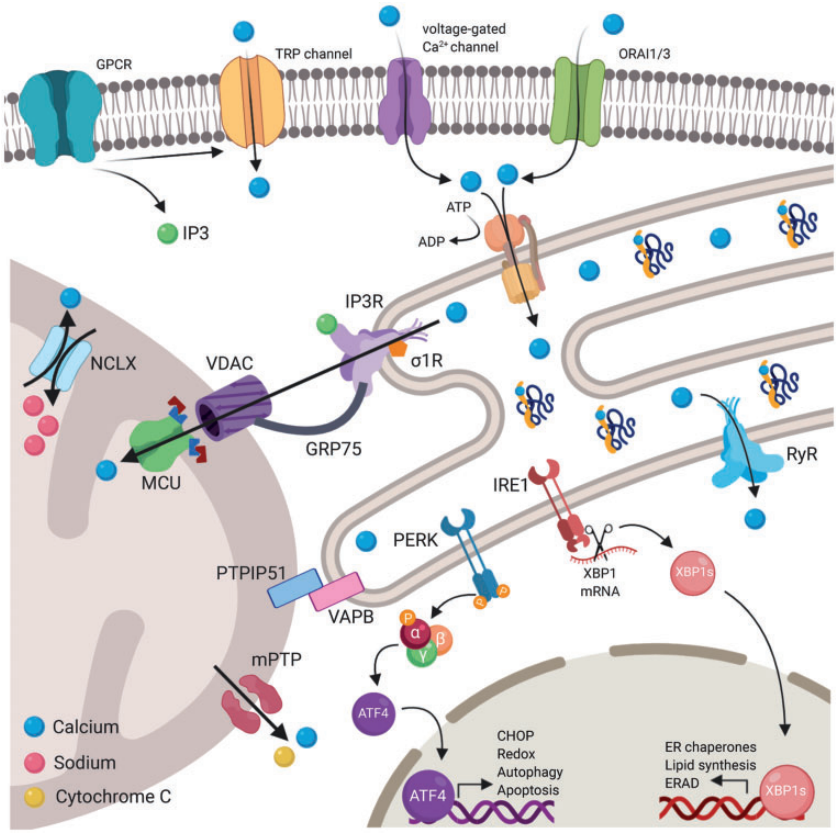

Figure 2. The ER and the mitochondria are connected by Ca^{2+}. Extracellular Ca^{2+} commonly enters sensory neurons via voltage-gated Ca^{2+} channels, store-operated Ca^{2+} channels (ORAI1/3), and transient receptor potential channels upon stimulation. This increase in cytosolic Ca^{2+} is rapidly neutralized by the SERCA pump and stored in the ER. Various CBPs including chaperones, like BiP, buffer ER Ca^{2+} levels. The ER and mitochondria are connected by the MAM, which facilitates Ca^{2+} transfer from the ER through IP3 receptors, to the mitochondria through the VDAC in a complex tethered by the chaperone GRP75. This exchange is regulated by the MAM complex VAPB-PTPIP51. Ca^{2+} subsequently enters the mitochondrial matrix through the MCU and is extruded by the NCLX. Ca^{2+} can also exit the mitochondria through the mPTP under pathological conditions. Ca^{2+} dyshomeostasis along this axis can not only disrupt ER and mitochondrial function but also affect iCa^{2+} and cell excitability, contributing to pain hypersensitivity.

regeneration and locomotor recovery possibly by addressing the high demand of protein synthesis required for axonal outgrowth. In this respect, the upregulation of ERp57, an ER resident disulfide isomerase, was found to improve axonal regeneration and locomotion following sciatic nerve injury.[143] Furthermore, regeneration and recovery after sciatic nerve crush depended on the activation of the more protective IRE1α-XBP1 axis as opposed to the more detrimental PERK-ATF4 pathway.[41] Moreover, axotomy-induced Ca^{2+} release from the ER promotes IRE1 and PERK phosphorylation.[144] Inhibiting PERK and IRE1 signaling using GSK2606414 and 4μ8c, respectively, collapses the growth cone, fragments axonal ER, and impairs axonal regeneration. Interestingly, axotomy-induced PERK activation does not increase CHOP levels in the axon, although increased phosphorylation of eIF2α is observed.[144] Combined with increased splicing of XBP1 and BiP expression in the axons following axotomy, this observation further suggests that enhancing the ER folding capacity and reducing ER load after a PNI enhances the regenerative capacity of the nerve. However, which cytoprotective proteins are specifically folded following nerve injury remains to be investigated and will require high-throughput translatomic and proteomic screening.

Only recently has ER stress been linked to pain in PNI models. Melemedjian et al.[145] was one of the first studies to correlate increases in eIF2α phosphorylation in injured nerves of rodents following SNL; however, no mechanistic role of the ISR in inducing mechanical pain was investigated. Another study found elevated BiP, XBP1, p-eIF2α, and ATF6 expression in the dorsal horn of the spinal cord two weeks after SNL surgery which correlated with microglial activation and mechanical hypersensitivity in these animals.[146] Furthermore, knockdown of ATF6 using an intrathecal siRNA reduced neuronal BiP expression and partially reversed

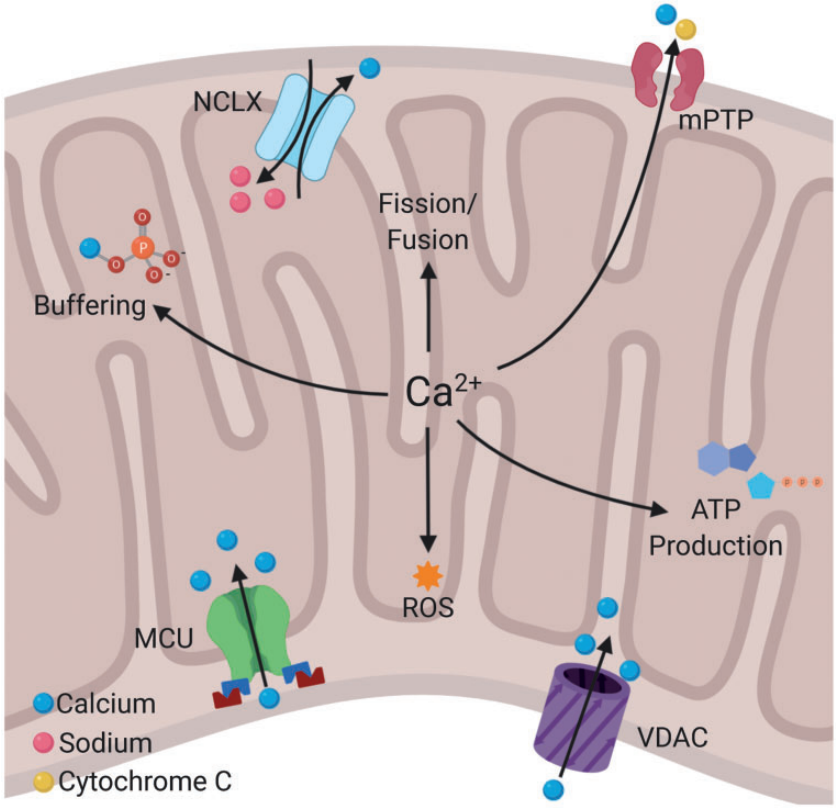

Figure 3. Mitochondria both regulate, and are regulated by Ca^{2+}. Ca^{2+} enters the outer mitochondrial membrane through the VDAC, then subsequently is transported into the mitochondial matrix via the MCU. Ca^{2+} homeostasis within the mitochondrial matrix is maintained by extrusion via the NCLX, which exchanges three Na^{+} for one Ca^{2+}. However, mitochondria can also buffer excess Ca^{2+} by precipitating it as calcium-phosphate. Ca^{2+} can also regulate various mitochondrial processes such as fission and fusion, ATP production, ROS production, and mPTP opening. Reducing ATP and increasing ROS can cause widespread dysfunctions within the cell. Opening of the mPTP depolarizes the mitochondrial membrane potential as it allows Ca^{2+} efflux, and it can also trigger apoptosis by release of cytochrome C.

mechanical hypersensitivity. Intrathecal treatment of chemical chaperones, 4-PBA and tauroursodeoxycholic acid (TUDCA), was also found to partially reverse nociceptive behaviours after SNL.[147,148] In the periphery, Yamaguchi et al.[142] found that BiP, XBP1, and CHOP expression was elevated in the sensory neurons as early as one day post-SNL only to recover within a week. Interestingly, treatment with salubrinal, an eIF2α phosphatase inhibitor, reduced mechanical, thermal, and cold hypersensitivity[142] suggesting that induction of the ISR may ameliorate pain possibly by reducing global translation, enhancing ER folding capacity, and thereby dampening ER load.

As an oxidoreductase and a chaperone, protein disulfide isomerase (PDI) reduces disulfide bonds and produces H2O2 as a by-product. Along with other chaperones, SNL induces PDI expression in the spinal cord. Inhibiting PDI using bacitracin, an antibiotic, reduces ER stress, mitochondrial SOD levels, and mechanical hypersensitivity associated with nerve injury.[148] This suggests that SNL-induced pain may be a result of ER–mitochondria cross-talk.

Mitochondria in PNI

Mitochondrial dysfunction is evident in both peripheral and central tissues in PNI models (Table 2). Mitochondria after PNI exhibit fragmentation, depolarized membrane potentials, reduced ATP synthesis, and oxidative stress.[149] Mitochondrial dysfunctions can trigger apoptosis and axonal degeneration in the periphery and spinal cord, leading to pain.[149–152] However, neuropathic pain in PNI is not exclusively caused by degeneration. Both peripheral and central sensitization contribute to pain maintenance.[153] Elevated Ca^{2+} signaling underlies nociceptor hyperexcitability in other neuropathic pain conditions.[97] Interestingly, mitochondrial dysfunction observed in PNI models may also contribute to iCa^{2+} dyshomeostasis, but the relationship is likely complicated. Mitochondria both regulate and are

Table 1. Overview of ER pathologies.

Disease	Reference	Findings
Peripheral nerve injury pain	Castillo et al.[143]	Overexpressing ERp57 improved nerve regeneration and locomotion after sciatic nerve crush.
	Ge et al.[148]	Inhibiting PDI, a chaperone, in SDH after SNL reduced ER stress and mechanical pain.
	Liu et al.[147]	Intrathecal 4-PBA administration alleviated mechanical and thermal hypersensitivity in SNL rats.
	Melemedjian et al.[145]	SNL induced phosphorylation of eIF2α in the sciatic nerve
	Ohtake et al.[144]	Nerve regeneration following axotomy requires Ca^{2+}-dependent activation of IRE1 and PERK signaling.
	Onate et al.[41]	Nerve regeneration and motor recovery was associated with IRE1-XBP1 signaling, but not PERK-ATF4 pathway, in a nerve crush model.
	Yamaguchi et al.[142]	ER stress markers are elevated following SNL. Salubrinal, an eIF2α phosphatase inhibitor, reduced pain hypersensitivity.
	Ying et al.[141]	Mild ER stress enhanced nerve regeneration after crush injury. UPR by-products are retrogradely transported from the nerve to the DRG.
	Zhang et al.[146]	SNL induced BiP and ATF6 in SDH neurons and PERK signaling in astrocytes. ATF6 knockdown in the SDH reduced BiP levels and pain behaviours in SNL rats.
Diabetic neuropathy	Barragan-Iglesias et al.[165]	MGO triggers ISR in IB4+ sensory neurons and produces mechanical hypersensitivity. Treatment with ISRIB resolves eIF2α phosphorylation and pain in MGO administered and diabetic mice. MGO enhanced Ca^{2+} responses of sensory neurons.
	Griggs et al.[163,164]	MGO sensitizes lamina II SDH neurons of *db*/*db* mice via the TRPA1-AC1-Epac pathway. Spinal neurons demonstrate enhanced Ca^{2+} responses upon stimulation.
	Inceoglu et al.[160]	STZ-induced diabetes robustly generates ER stress in the sciatic nerve and glabrous skin. 4-PBA treatment attenuated mechanical hypersensitivity in a time- and dose-dependent manner.
	Lupachyk et al.[159]	4-PBA and TMAO attenuated diabetes-induced ER stress, nerve dysfunction, fiber loss, and oxidative stress in the sciatic nerve and the spinal cord. $CHOP^{-/-}$ mice were less susceptible to diabetic peripheral neuropathy.
	Zherebitskaya et al.[98]	Hypoalgesia associated with chronic STZ-induced diabetes is a result of reduced ER Ca^{2+} loading.
Chemotherapy-induced neuropathic pain	Andoh et al.[40,185]	Ptx treatment promoted CHOP expression in the sciatic nerve, enhanced excitability of SDH neurons, and produced tactile hypersensitivity.
	Megat et al.[182]	Ptx enhances excitability of sensory neurons
	Resham and Sharma[184]	Wnt signaling inhibitors normalized sciatic nerve function, reduced axonal BiP expression, and attenuated pain hypersensitivity in Ptx treated rats.
	Tanimukai et al.[186,187]	In vitro, Ptx induced CHOP and caspase 3 expression in SK-N-SH neuroblastoma cells. Inducing sigma 1 receptor and BiP reduced ER stress and was cytoprotective.

regulated by Ca^{2+},[24] so, while Ca^{2+} elevations can overwhelm mitochondrial buffering and lead to dysfunction, mitochondrial dysfunction can also be a starting point for pathological iCa^{2+} elevation. This complex association presents a significant target for future study to probe into how mitochondrial dysfunction might contribute to PNI-induced neuropathic pain.

ER stress in diabetic neuropathy

Diabetes mellitus (DM) is a metabolic disorder characterized by abnormally high blood glucose levels. The cause of DM is linked to either reduced insulin production (type 1) or a resistance to insulin (type 2).[154,155] Peripheral neuropathy and subsequent neuropathic pain is a common phenomenon in DM (Table 1).[156] Initially, patients with DM and preclinical rodent models of DM typically present with mechanical and thermal hypersensitivity.[157] Later disease stages are associated with hyposensitivity as a result of sensory fiber retractions from the skin.[158] Pain in DM follows a "glove and stocking" pattern in which distal limbs are affected first, followed by more proximal areas of the body.[156] This section will highlight mechanisms involved in neuropathic pain associated with DM, rather than loss of sensation, that have been linked to impaired ER function, Ca^{2+} dyshomeostasis, and mitochondrial damage.

Several studies have directly investigated the role of ER stress in mediating diabetes-induced pain (Table 1). ER stress in the streptozotocin (STZ) model of type 1 DM is characterized by increased phosphorylation of PERK, eIF2α, and IRE1α, as well as the cleavage of ATF6 in the sciatic nerve and the glabrous skin of the

Table 2. Overview of mitochondrial pathologies.

Disease	Study	Finding
Peripheral nerve injury	Bae et al.[197]	Mitochondrial superoxide in the spinal dorsal horn of mice after PNI contributes to sensitization.
	Englezou et al.[152]	DRG neurons exposed to H_2O_2 in vitro display mitochondrial fission and eventual mitochondria-mediated apoptosis, which may give insight into how peripheral neurons are lost after PNI.
	Graham et al.[198]	PNI in mice results in increased mitochondrial fission and mitophagic protein expression in whole muscle tissue.
	Kim et al.[151]	Inhibiting mPTP opening in PNI with cyclosporin A attenuates allodynia and spinal cord cytochrome c release.
	Wang et al.[150]	Pro-BDNF induces mitochondria-mediated apoptosis of neurons and satellite glia in vitro
Diabetic neuropathy	Hall et al.[199]	DRG neurons from diabetic rats showed increased voltage-dependent Ca^{2+} currents.
	Kostyuk et al.[175]	Prolonged cytosolic Ca transients in cells from diabetic mice are dependent on mitochondrial dysfunction, and may contribute to neuropathic pain.
	Russell et al.[200]	Hyperglycemia induces ROS production and mitochondrial-mediated apoptosis in vitro.
	Srinivasan et al.[168]	DRG neurons from diabetic rats in vitro have increased apoptosis due to mitochondrial dysfunction.
	Vincent et al.[170]	An imbalance in mitochondrial biogenesis and fission results from hyperglycemia in DRG neurons in vitro and may contribute to diabetic neuropathy via neuronal injury.
Chemotherapy-induced neuropathic pain	Duggett et al.[188]	Rats treated with paclitaxel display energy dysfunction in the DRG that correlates with pain.
	Flatters and Bennett et al.[176]	In rats, paclitaxel-induced mitochondrial abnormalities may be responsible for pain, as their timelines correlate.
	Jia et al.[189]	Paclitaxel treatment in rats induces mitochondrial damage and production of reaction oxygen species that may activate the NLRP3 inflammasome and contribute to pain.
	Kidd et al.[193]	Paclitaxel-induced intracellular Ca^{2+} elevations can be inhibited with cyclosporin A, suggesting that paclitaxel may cause pain by inducing mPTP-opening and aberrant Ca release.
	Xiao and Bennett[194]	Spontaneous discharge of sensory neurons in rats treated with paclitaxel is likely a factor in paclitaxel-induced peripheral neuropathy.

paw.[159,160] Other markers of ER stress such as BiP and spliced XBP1 are also known to be upregulated with DM.[160] The spinal cord is also known to increase CHOP and BiP expression in diabetic rats.[159] Alleviating UPR/ER stress using chemical chaperones, 4-phenylbutyric acid (4-PBA) and trimethylamine oxide (TMAO), reverses tactile allodynia and heat hypoalgesia in rats.[159,160] Denervation associated with late-stage DM is also reversed in rodents administered with 4-PBA and TMAO.[159]STZ-induced DM in transgenic CHOP-deficient mice have reduced nerve fiber loss from the glabrous skin as compared to STZ-induced DM in wild-type mice.[159]CHOP-knockout mice experience minimal thermal hypoalgesia as compared to wild-types in response to STZ-induced diabetes. However, $CHOP^{-/-}$ does not confer protection against mechanical and tactile hypersensitivity.[159] Collectively, these studies suggest that diabetes-induced ER stress contributes to neuropathic pain.

Methylglyoxal (MGO), a common metabolite present in high concentrations (up to 5 μM) in the plasma of diabetic patients, is known to induce heat, mechanical, and affective pain in DM by activating peripheral and spinal TRPA1 channels.[161–166] Recently, the involvement of the UPR in MGO-induced pain hypersensitivity was postulated.[165] Intraplantar injection of MGO induces rapid and transient mechanical hypersensitivity in rats and mice that is associated with increased phosphorylation of PERK and eIF2α, particularly in the IB4+ nociceptors.[165] Preventing the phosphorylation of eIF2α using the ISR inhibitor, ISRIB, attenuated mechanical pain in both MGO-induced neuropathy and STZ-induced DM.[165] Systemic 4-PBA treatment was also able to ameliorate MGO-induced mechanical hypersensitivity.[165] Hence, MGO-associated ER stress and ISR in IB4+ nonpeptidergic nociceptors, may contribute to mechanical hypersensitivity observed in type 1 DM. Furthermore, acute MGO treatment in vitro

enhances KCl-induced cytosolic Ca^{2+} transients in dissociated mouse DRG neurons.[165] These studies propose that rises in MGO in diabetes can enhance intracellular Ca^{2+} signaling in painful diabetic neuropathy.

In contrast, axons of sensory neurons from hypoalgesic type 1 STZ-induced diabetic rats have dampened Ca^{2+} responses to KCl and caffeine stimulation.[98] This suggests that Ca^{2+} stores in the ER are likely depleted in DM as a result of reduced SERCA-mediated Ca^{2+} uptake.[98] The discrepancy between these studies may stem predominantly from the differences in their experimental paradigms (acute vs. chronic), disease model (type 1 vs. type 2 DM), and the presence of hyperalgesia. Perhaps, increased Ca^{2+} signaling contributes to the initial hyperalgesia in DM-induced neuropathy, while at later stages, diabetic neuropathy is characterized by reduced intracellular and intra-ER Ca^{2+}. Both, the increase in and the loss of intracellular Ca^{2+} contribute to detrimental processes within the cell including excitotoxicity,[69] ER stress,[26] mitochondrial dysfunction (see below), and cell death.[69]

Mitochondria in diabetic neuropathy

Numerous studies have revealed mitochondrial dysfunction in models of DM (Table 2). This includes increased fission, $\Delta\Psi m$ depolarization, reduced ATP production, disrupted calcium homeostasis, and oxidative stress.[97,167–170] While mitochondria dysfunction plays a role in diabetic neuropathy, both the pathways that lead to this dysfunction, and the mechanism by which it induces neuropathy are contested. The two hallmark factors of type 1 DM and its relevant models are a lack of insulin, and resultant hyperglycemia. Whether only one or both of these factors is responsible for mitochondrial dysfunction in DM is questioned in the literature.[171–173] Several competing theories have been put forward to explain how mitochondrial dysfunction may be implicated in diabetic neuropathy. Hyperglycemia may increase mitochondrial fission, ROS production, and mitochondrial DNA damage, leading to neuropathy through apoptosis.[171,174] Although these mechanisms would explain sensory fiber retraction, this model does not link mitochondrial dysfunction to nociceptor hyperexcitability. Alternatively, impaired mitochondrial ATP production and reduced mitochondrial membrane potential could arise in response to reduced insulin receptor stimulation. This would significantly effect Ca^{2+} homeostasis and trigger ER stress, leading to changes in transcriptional and translational programs of the cell.[172] Considering that increased intracellular Ca^{2+} has been linked to nociceptor hyper-excitability and neuropathic pain in diabetic neuropathy, impaired ER–mitochondrial Ca^{2+} homeostasis in diabetic neuropathy is a promising potential mechanism to explain the aberrant nociceptor activity and pain associated with the disease.[97,175]

ER stress in chemotherapy-induced peripheral neuropathy

Neuropathy associated with chemotherapy agents is the single largest reason for reducing and halting treatment of cancer.[176] Approximately 68% of patients receiving chemotherapy will develop chemotherapy-induced peripheral neuropathy (CIPN) in their first month of treatment.[177] CIPN affects the nerves in a "glove and stocking" pattern where the longest axons are affected first, similar to DM-induced neuropathy.[178] Unlike DM-induced neuropathy, however, CIPN symptoms appear suddenly, affect multiple areas simultaneously, and progresses rapidly.[178] As a result of the CIPN, patients can experience acute and chronic sensory, motor, and autonomic dysfunction.[179] Sensory impairments typically involve mechanical, thermal, and cold pain hypersensitivity as well as paresthesias and dysesthesias.[179] Chronic use of chemotherapeutic agents may lead to permanent damage of the nerves, resulting in a loss of sensation.[178] Platinum derivatives (e.g., oxaliplatin), vinca alkaloids (e.g., vincristine), and taxanes (e.g., paclitaxel, Ptx) are commonly used chemotherapy agents known to cause CIPN and the associated pain phenotype.[178,180]

Treatment with Ptx and oxaliplatin usually accompanies an acute pain syndrome three to four days after the start of the treatment as well as chronic neuropathic pain even after treatment has stopped.[181] It is well established that chemotherapeutics contribute to neuronal injury and inflammation, especially in the peripheral nervous system (Table 1).[181] Sensory neurons of the DRG from mice treated with paclitaxel fire spontaneously and become hyperexcitable, both of which are evidence of painful neuropathy.[182] The protective and detrimental effects of ER stress and the ISR have previously been described in various cancer models (reviewed by Nam and Jeon[183]) However, the effects of ER dysfunction in the context of pain in CIPN are not well understood. A recent report found that intraperitoneal Ptx (2 mg/kg) administration reduced sensory nerve conduction velocity and increased pain behaviors in rats.[184] Resham and Sharma[184] further observed that heat, cold, and mechanical hypersensitivity was correlated with increased expression of BiP in the sciatic nerves of Ptx treated animals.[184] Another study found that a single intraperitoneal injection of Ptx (5 mg/kg) was sufficient to induce CHOP expression in the sciatic nerve, increase the excitability of spinal dorsal horn neurons, and lead to mechanical allodynia in C57BL/6 NCr mice.[40,185] In vitro, Ptx treatment of SK-N-SH neuroblastoma cells increased the phosphorylation of eIF2α and induced the expression of CHOP as well as the pro-apoptotic

caspase 3[186,187] Furthermore, pretreatment with fluvoxamine, a Sigma 1 receptor inducer, and BiP-inducer X (BIX) attenuated ER stress and protected the SK-N-SH cells from paclitaxel-associated cytotoxicity.[187] However, whether these drugs can mitigate pain in CIPN remains to be investigated.

Mitochondria in chemotherapy-induced peripheral neuropathy

Mitochondrial dysfunction is a well-characterized feature of chemotherapy-induced peripheral neuropathy (Table 2). The drug paclitaxel, for example, affects both mitochondrial structure and function in sensory neurons. Some mitochondrial changes linked to Ptx include swelling, vacuolation, decreased respiration, reduced ATP production, loss of $\Delta\Psi m$, mitochondrial permeability transition pore (mPTP) formation, ROS production, and Ca^{2+} release.[176,188–190] These dysfunctions can be accounted for by the theory that Ptx interacts with the mitochondrial membrane to induce mPTP-opening.[191] Opening of the mPTP allows for aberrant passage of molecules into and out of the mitochondria, which can alter oxidative phosphorylation and ATP production, as well as trigger cell death cascades.[192] In addition, in a nerve-injury model, treatment with the mPTP blocker cyclosporin A not only prevented mitochondrial dysfunction, but also reduced pain.[151,193] Taken together, this evidence suggests that Ptx-induced mPTP-opening and subsequent Ca^{2+} release may underlie nociceptor hyperexcitability and neuropathic pain.[176,194]

Conclusions and future directions

There is a new appreciation for the roles of the ER and mitochondria in mediating chronic pain. What is emerging from these studies is a recognition of the complex interplay between these two organelles and the impact that disturbances in this interplay may have on Ca^{2+} signaling and ultimately, nociceptor excitability. Although the examples discussed here generally involve some form of axonal injury or trauma, emerging research also suggests that chronic pain associated with inflammatory diseases such as Multiple Sclerosis and rheumatoid arthritis may also be linked to ER and mitochondria dysfunction.[195,196] In all of these pathologies, it is clear that pain is a major overlapping symptom. A common thread linking pain to these conditions is stress at the ER and the ensuing mitochondrial dysfunction and Ca^{2+} dyshomeostasis. This has opened an exciting new avenue for research that is leading toward a more comprehensive understanding of the underlying mechanisms driving chronic, neuropathic pain in these states. A better understanding of how disturbed ER–mitochondrial interactions can lead to nociceptor hyperexcitability may provide insight into novel, therapeutic targets that can be manipulated to reverse the changes that have sensitized the system and thus restore the homeostatic state.

Declaration of Conflicting Interests

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