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REVIEW ARTICLE

Selenium and Neurological Diseases: Focus on Peripheral Pain and TRP Channels

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Abstract: Pain is a complex physiological process that includes many components. Growing evidence supports the idea that oxidative stress and Ca^{2+} signaling pathways participate in pain detection by neurons. The main source of endogenous reactive oxygen species (ROS) is mitochondrial dysfunction induced by membrane depolarization, which is in turn caused by Ca^{2+} influx into the cytosol of neurons. ROS are controlled by antioxidants, including selenium. Selenium plays an important role in the nervous system, including the brain, where it acts as a cofactor for glutathione peroxidase and is incorporated into selenoproteins involved in antioxidant defenses. It has neuroprotective effects through modulation of excessive ROS production, inflammation, and Ca^{2+} overload in several diseases, including inflammatory pain, hypersensitivity, allodynia, diabetic neuropathic pain, and nociceptive pain. Ca^{2+} entry across membranes is mediated by different channels, including transient receptor potential (TRP) channels, some of which (*e.g.*, TRPA1, TRPM2, TRPV1, and TRPV4) can be activated by oxidative stress and have a role in the induction of peripheral pain. The results of recent studies indicate the modulator roles of selenium in peripheral pain through inhibition of TRP channels in the dorsal root ganglia of experimental animals. This review summarizes the protective role of selenium in TRP channel regulation, Ca^{2+} signaling, apoptosis, and mitochondrial oxidative stress in peripheral pain induction.

Keywords: Calcium ion, neurological diseases, oxidative stress, peripheral pain, TRP channels, selenium.

1. INTRODUCTION

Pain can be induced by the excessive production of ROS or RNS species [1], and several kinds of cation channels act as sensors of oxidative stress and join the pain perception and transduction pathway [2, 3]. Yabe-Nishimura *et al*. [4] suggested that NADPH oxidase-generated ROS increases TRPV1 channel activity and enhances the translocation of protein kinase C (PKC), causing inflammatory pain in mice DRG neurons. An experimentally thermal hyperalgesia model can be induced by peroxynitrite, which occurs by directly combining subplantar superoxide radical injection and endogenous nitric oxide (NO). In a study, a powerful antioxidant, melatonin, has been found to be responsible for hyperalgesia healing because of its anti-inflammatory activity [5]. Khattab showed that TEMPOL is a superoxide dismutase mimetic radical scavenger that promotes carrageenan-induced hyperalgesia *via* its analgesic and anti-inflammatory activity [6]. In another study, researchers evaluated the role of a strong protein antioxidant, sestrin 2, in neuropathic pain after peripheral nerve injury induction. They found that sestrin 2 protein expression decreases ROS levels and that it may help in achieving oxidant/antioxidant balance after injury and in suppressing ROS-dependent neuropathic pain in mice [7].

Different stages of the afferent pain pathway, including the detection of environmental stimuli, generation of action potentials, and propagation of signal transduction through the release of neuropeptides, are related to calcium-permeable cation channels [2]. Calcium channel blockers can be useful for reducing nociception [8]. However, there is a positive feedback mechanism among intracellular calcium concentrations, and mitochondrial membrane depolarization results in ROS production that is linked to calcium ion-permeable transient receptor potential (TRP) channels. Deciding where the feedback loop can be cut is therefore important in the development of new strategies for the treatment of painful sensation.

Pain is as old as human history, and everyone experiences it in one or more stages of life [9]. Although it can be unpleasant, pain is nonetheless an essential part of human survival and adaptation mechanisms [10]. It is often classi-

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fied into two main categories—nociceptive and neuropathic pain. Nociceptive pain is a subjective experience that leads to tissue injury, and is often described as a sharp, aching, and pulsating pain. Nociceptors are activated by extreme temperature, high pressure, tissue damage-induced inflammation, and chemicals, such as substance P, serotonin, acetylcholine, low-pH solutions, ATP, and lactic acid [11], and they can be induced by alcoholism, chemotherapy, and diabetes [12]. Anticonvulsant and antidepressant drugs have been used for the treatment of neuropathic pain with limited success. Although the etiology of neuropathic pain is not fully understood, recent data suggest the important roles of excessive oxidative stress and calcium ion (Ca^{2+}) overload in neurons [13, 14].

Oxidative stress results from an imbalance between the increased production of reactive oxygen species (ROS) and oxidative stress regulation by antioxidant systems. Lipid peroxidation-mediated oxidative tissue damage occurs during neurological disease and peripheral pain. In addition to the exogenous overproduction of ROS, in general, ROS accumulation results from mitochondrial respiratory chain pathways [13]. Enzymatic and non-enzymatic antioxidants have important roles in scavenging the ROS produced by the mitochondria [15]. For this reason, glutathione peroxidase (GPx) plays a critical role in protecting neurons from the harmful effects of ROS. Selenium is a co-factor for GPx enzymatic activity, and mitochondrial respiratory chain reactions are also modulated by selenium [16]. Excessive ROS production and increased Ca^{2+} influx are implicated in several diseases, including inflammatory pain, hypersensitivity, allodynia, diabetic neuropathic pain, and nociceptive pain [14, 17, 18]. Selenium may exert neuroprotective effects through modulation of ROS overproduction and Ca^{2+} entry in several neuronal diseases by supporting GPx activity and inhibiting cationic movements into the cytosol [19].

Increases in Ca^{2+} entry in peripheral pain and neuropathy occur through the activation of Ca^{2+} channels, such as voltage-gated calcium channels (VGCCs), and other channels, such as TRP channels. The mammalian TRP superfamily consists of 28 channels with 6 different subgroups. Some TRP channels are expressed in peripheral neurons and also in the central nervous system (CNS) and dorsal root ganglion (DRG), with the members of TRP sub-families (TRPA1, TRPM8, TRPV1, and TRPV2) being grouped as nociceptive TRP channels [20]. Neuronal TRP channels are activated by nociceptive stimuli, resulting in the neuronal depolarization and generation of action potentials [11]. After perception of the peripheral stimuli, nociceptive neurons initiate a series of action potentials in primary afferent fibers of the DRG neurons to stimulate postsynaptic neurons *via* pain mediators, including the calcitonin gene-related peptide (CGRP), substance P, and other excitatory neurotransmitters, such as glutamate. Peripheral pain signals are directed by nociceptive neurons through Aδ and C fibers to pain-related locations of the brain and the cerebellum, so the peripheral and CNS are connected to each other through pain mediators in the transmission of painful stimuli [21]. Moreover, previous studies have shown that distinct TRP channels are functionally expressed in primary nociceptors and in Aδ and C fibers [22-24], although the molecular mechanisms involved in peripheral pain have not yet been clarified.

Some clues on neuropathic pain have been found in recent data, and they show the roles of TRP channels in the etiology of neuropathic pain in experimental animal research. For example, Klein *et al*. [25] investigated the role of TRPA1, TRPC5, TRPM3, TRPM8, TRPV1, TRPV2, TRPV3, and TRPV4 in somatosensory function by using the von Frey test, and suggested the role of the TRPV3 channel in response to temperature, touch, and chemicals as a part of avoidance behavior. Other data from Salat *et al*. [26] reported the anti-nociceptive activities of TRPA1, TRPM8, and TRPV1 antagonists in neurogenic and neuropathic pain in a mouse model. Collectively, these behavioral and pharmacological studies show that TRP channels are directly involved in pain pathways. In some experiments, essential peripheral pain mediator neuropeptide release in sensory nerves has been attributed to TRP channels. Kirkwood *et al*. [27] investigated the role of TRPV1 channels in CGRP and substance P release in acute pancreatic pain. They suggest that the activation of TRPV1 promotes substance P release from pancreatic sensory nerves. The effects of TRPA1, CGRP, and substance P on colitis in a mice model were investigated, and TRPA1 channel activation by the induction of colitis was increased *via* Ca^{2+} signaling and substance P release [28]. In an experimental animal study, the involvement of TRPA1, but not TRPV1 channels has been reported to be related to CGRP release [29]. The report was confirmed by De Col *et al*. [30], who demonstrated that TRPA1 agonists induce CGRP release through the dura mater of rodents. Several studies report that antioxidant treatments, including those with selenium, can regulate the harmful effects of oxidative stress and irregular Ca^{2+} accumulation in neuronal cells. Several ROS-sensitive TRP channels may be responsible for cytosolic Ca^{2+} overload and cause neurological diseases and neuropathic pain; these are discussed below.

Inflammation occurs as a result of a pathological condition that produces pain, and it is sensed by the peripheral nervous system and CNS. Inflammatory cytokines, such as TNF-α, IL-6, and IL-1β are released from activated macrophages when neural or other tissues are damaged in pathological pain [31]. Some studies suggest that inflammation is related to the numbers and types of ion channels at nerve endings [32, 33].

TRP channels constitute the largest group of activator chemicals and are involved in the generation of pain sensation in mammals [34]. The expression level of pain-related TRP channels, such as TRPA1 and TRPV1, has been reported to increase the risk of pain induction in animal models [5, 6, 14]. Recently, interest in the role of TRP channels in neurological diseases, including neurodegenerative diseases (Table **1**), and peripheral pain (Table **2**) has increased. Although the results of previous data on TRPA1, TRPC5, and TRPV1 in neurons indicated that the oxidation of cysteine groups is very important for the activation of these channels [35, 36], novel studies point to modulator role of selenium treatments in neuronal channels [37]. Selenoproteins are selenocysteine-containing proteins, and they are mainly expressed in the human brain and DRG; they are most likely involved in antioxidant processes, which are the key factors in preventing the onset and progression of peripheral pain [38]. In addition, some newly synthesized selenoproteins and

Table 1. Effects of antioxidants and selenium treatments on possible therapeutic targets in different experimental neurological disease models of rodents (TBI, traumatic brain injury; SCI, spinal cord injury).

Channel	Agent	Material	Value/Effect	Refs.
TRPA1	NAC	Mice	Ischemia and oxidative stress induced peripheral postischemic dysesthesia treatment	[24, 87]
TRPA1	Resveratrol	Rat DRG and HEK-293 cells	TRPA1 inhibition	[83]
TRPA1-TRPV1	NAC	Rats	Cigarette smoke induced superior laryngeal irritation treatment	[192]
TRPA1-TRPV1	17-β estradiol, tamoxifen and raloxifene	Rat DRG	Inhibition of peripheral pain, TRPA1 and TRPV1	[88]
TRPM3	Flavones	Rats	Inhibition of TRPM3 mediated thermal hyperalgesia	[193]
TRPV1	*Hypericum perforatum* extract	Rat DRG	SCI-induced pain and neuronal death reduction	[194]
TRPV1	NAC and GSH	Mice DRG	TRPV1 Inhibition	[72]
TRPV1	Selenium and NAC	Rat hippocampus	Treatment of TBI induced rats	[118]
TRPV1	Dexmedetomidine	Rat hippocampus and DRG	Neuroprotective effects on cerebral ischemia induced-oxidative stress	[195]
TRPV1	Vitamin C, E and NAC	Rats	Treatment of cortical neuronal death *via* TRPV1	[196]
TRPV1	Curcumin	Rats	Inhibits TRPV1 mediated pain hypersensitivity	[197]
TRPV1	Selenium	Rats	Inhibits memory impairments	[117]
TRPV1	*Hypericum perforatum*	Rats	Inhibiting SCI	[198]
TRPV1	Melatonin and selenium	Rat hippocampus and DRG	Neuroprotection in diabetic rats	[19]
TRPV1	Melatonin and selenium	MCF-7 cells	Inhibiting TRPV1 and enhanced chemotherapeutic action	[115, 116]
TRPV4	Trolox and MitoE	Rats	Oxidative stress-induced neuronal and astrocytic damage attenuated in hippocampal slices	[186]
TRPV4	Trolox	Rat hippocampal slices	Amyloid β induced neuronal and astrocytic damage attenuated	[143]

selenium products have been found to possess remarkable physiological properties [39, 40]. Despite accumulating evidence to implicate the involvement of several TRP channels in a wide range of neurological diseases, including peripheral pain, only 4 of the 28 mammalian TRP channel subunits, namely TRPA1, TRPM8, TRPV1, and TRPV3, have been exploited thus far to reach the clinical stage of drug development [34]. Because of the high potency of TRP channel inhibitors, selenium might serve as an alternative to conventional therapeutic drugs through inhibition of the TRP channel for the treatment of neurological diseases, including peripheral pain.

This review summarizes two main topics: (1) the role of TRP channels expressed by primary sensory neurons in the development of pain associated with peripheral pathologies and the possible approaches to translate preclinical data to the development of effective new analgesics and (2) the potential role of selenium as a novel inhibitor of TRP cation channels and its potential for treating neurological diseases and peripheral neuropathic pain.

2. ROLE OF CALCIUM AND OXIDATIVE STRESS IN PAIN PERCEPTION

Anions or cations intervene in various cellular metabolic processes either directly or indirectly as co-factors of enzymes. The electrical activity of excitable cells leads to cationic mobilization, including that of Ca^{2+}. The cellular microenvironment of neurons is also well organized for cationic mobilization because the difference in Ca^{2+} concentrations in the extracellular ($[Ca^{2+}]_e$ = ~1.2–3.0 mM) and intracellular milieu ($[Ca^{2+}]_c$ = ~100 nM) is more than 10,000 fold. Transient increases in $[Ca^{2+}]_c$ from 100 nM to µM initiate the physiological pathways of neuronal response. The main sources of Ca^{2+} are extracellular fluid and Ca^{2+} storage organelle, such as the endoplasmic reticulum and the mitochondria [41]. There are many types of calcium-permeable channels/pumps in the plasma membrane and intracellular organelle receptors that regulate intracellular Ca^{2+} signals within microseconds to mediate physiological reactions. Ca^{2+} entry from the extracellular space is mediated by several kinds of channels, such as VGCCs, store-operated calcium

Table 2. Effects of different forms of selenium on possible therapeutic targets in different animal and human experimental pain model studies.

Model	Form of Se	Effect	Pathway	Refs.
Human	Selenium	Antioxidant	Inflammatory state	[160]
Human	Selenium	Antioxidant	Reduce pain in patients suffering from chronic pancreatitis.	[162]
Mice	1,2-bis-(4-methoxyphenylselanyl) styrene	Anti-nociceptive and anti-inflammatory	Regulation of serotoninergic system	[154]
Mice	3-(4-chlorophenylselanyl)-1-methyl-1H-indole	Anti-nociceptive and anti-inflammatory	Involvement of neurotransmitters systems	[155]
Mice	$(OMePhSe)_2$	Anti-nociceptive action and incorporation	Restored the changes in inflammatory and apoptotic protein contents	[156]
Mice	$(OMePhSe)_2$	Anti-nociceptive action	Thermal stability and the anti-nociceptive action	[157]
Mice	$(m\text{-}CF_3\text{-}PhSe)_2$	Anti-nociceptive and anti-depressant-like actions	Inflammation-induced depression and chronic pain	[161]
Rat	Selenium nanoparticles	Anti-inflammatory	Radioprotective effect by increasing antioxidant activity	[153]
Rat	Selenium	Anti-nociceptive and anti-inflammatory	Pharmacological targets in the treatment of FM-induced apoptosis and peripheral pain	[37]
Rat	$(OMePhSe)_2$	Antioxidant	Supplemented diet for antidepressants and analgesics	[158]

entry channels, ionotropic N-methyl-D-aspartate (NMDA) receptors, ligand-gated calcium channels, and TRP channels. Ca^{2+} release from intracellular stores mainly occurs by stimulation of ryanodine receptors (RyR) and inositol triphosphate receptors (IP_3R). However, prolonged high levels of $[Ca^{2+}]_c$ threaten cellular integrity by activation of cysteine-dependent aspartate proteases (caspases) [42-44]. Thus, Ca^{2+} store organelle also sequesters Ca^{2+} to restore cytosolic Ca^{2+} levels to the normal cytosolic values. However, Ca^{2+} overloading in the mitochondria disturbs their normal function by depolarizing the intermembrane space and inducing apoptotic cascades *via* the release of cytochrome c and by generating ROS from the respiratory chain [45, 46].

Neuronal cells are sensitive to abnormal ROS production because of the nervous system's lipid-rich environment. ROS and reactive nitrogen species (RNS) indirectly trigger IP_3R activation *via* phospholipase C (PLC)-mediated IP_3 production, causing Ca^{2+} release [47]. ROS also directly induce Ca^{2+} influx into the cytosol by activation of ROS-sensitive Ca^{2+} permeable channels in the cell membrane. This positive feedback mechanism, therefore, creates a cycle that gradually increases Ca^{2+} concentration, leading to cell death [48]. Moreover, aged neurons have much concentrated resting Ca^{2+} levels [49].

Intracellular Ca^{2+} levels are regulated by several Ca^{2+} channels in the cell membrane and by Ca^{2+} release from the intracellular organelle. Two major intracellular stores of Ca^{2+} are present, the endoplasmic reticulum and the mitochondria. VGCCs are localized in the outer membrane of the mitochondria, allowing the diffusion of Ca^{2+} from the cytosol to the intermembrane space. The mitochondrial Ca^{2+} uniporter is an essential channel for the transport of Ca^{2+} through the inner membrane into the matrix by using an electrochemical gradient. The sodium-calcium exchanger transports one Ca^{2+} and three Na^+ from the matrix to the intermembrane space. To accumulate large amounts of Ca^{2+} for prolonged durations, calcium phosphate precipitations form near the cristae and then migrate to free zones in the matrix of the mitochondria. However, excessive deposition of Ca^{2+} causes mitochondrial depolarization, an increase in ROS production, mitochondrial cytochrome c and nucleic acid release, cellular swelling, and, finally, apoptotic cell death. The mitochondria not only have a role in Ca^{2+} homeostasis, but they also need Ca^{2+} for intrinsic functions, including ATP synthesis, tricarboxylate cycle function, and generation of reducing agents, such as NADH and $FADH_2$ [50, 51].

The mitochondria generate endogenous ROS following mitochondrial depolarization that is triggered by Ca^{2+} overload. The ROS-related activation of PLC pathways can lead to IP_3R-mediated Ca^{2+} release from the endoplasmic reticulum. Therefore, the mitochondria and the endoplasmic reticulum modulate intracellular calcium signaling [52].

Interestingly, mitochondrial functions and Ca^{2+} signaling are closely related processes, as Ca^{2+} in one store acts as a messenger between the cytosol and its mitochondrial units to regulate the energy requirements of neurons.

Ca^{2+} has also been presented as a key regulator of cell survival, but it can cause apoptosis in response to a number of pathological conditions. In addition, the mitochondria act as Ca^{2+} buffers by sequestering excess Ca^{2+} from the cytosol [53]. Blockade of Ca^{2+} influx into the intracellular organelle, such as the endoplasmic reticulum, the mitochondria, and the cytosol, can effectively produce a rapid, simultaneous, and reversible cessation of movements. Ca^{2+} overloading in the mitochondria induces an apoptotic program by stimulating

the release of apoptosis-promoting factors, such as cytochrome c, and by generating ROS as a result of respiratory chain damage. Mitochondrial function is also essential for neuronal survival because neurons critically depend on ATP synthesis generated by mitochondrial oxidative phosphorylation [53]. In fact, the release of Ca^{2+} from endoplasmic reticulum stores by IP_3 receptors and the entry of Ca^{2+} through TRP channels in neurons have been implicated in multiple models of apoptosis as being directly responsible for mitochondrial Ca^{2+} overload [33]. An increase in apoptotic death through an increase in mitochondrial membrane potential, as well as a decrease in ATP synthesis and mitochondrial Bcl-2 protein production through activation of the TRPV1 channel, was reported in pancreatic neuroendocrine tumor cells by capsaicin [54]. However, a decrease in mitochondrial membrane depolarization through inhibition of Ca^{2+} entry was reported in SH-SY5Y neuroblastoma cells by antioxidant (curcumin) treatment [55].

3. SELENIUM

An essential trace element for vertebrates, selenium was first reported in 1817 by Berzelius [56]. It exists in two natural forms in nature either inorganic (selenite, selenide, and selenate) or organic (selenocysteine, selenomethionine, and Se-methylselenocristeine) [57]. The molecules of selenium act as co-factors for different enzymes, such as GPx, thioredoxin reductase (TrxRs), and iodothyronine deiodinases [38, 58]. It attracted much attention because of its role in preventing various diseases [59]. The useful properties of selenium are attributed to its ability to be incorporated into various proteins, with 25 selenoproteins formed by selenocysteines. Although high concentrations of selenium have cytotoxic effects, low-dose selenium can scavenge ROS and reduce pain [60, 61].

Selenium forms several allotropes (red, black, and gray) that interconvert with temperature changes. It has two opposite physiological features. Concentration-dependent selenium can exert *therapeutic* or *toxic* effects. High doses of selenium promote the proliferation of cancer cells and have neurotoxic effects, although low and intermediate doses inhibit cancer cell proliferation and have therapeutic effects on neurological diseases [60, 61]. There are several antioxidant nanoparticles, such as selenium nanoparticles. The metabolism of selenium nanoparticles through the up-regulation of antioxidant enzymes but down-regulation of ROS products in cells and neurons has been summarized in recent papers [60, 61].

4. TRP CHANNELS

As mentioned above, intracellular Ca^{2+} signals are controlled by ion pumps and cation channels, including the superfamily members of TRP channels that are responsible for non-specific cationic influx into the cytosol. The trp gene was first identified in the eye cells of Drosophila and has since been also found in vertebrates. There are six subfamilies (*Ankyrin:* TRPA, *Canonical:* TRPC, *Melastatin:* TRPM, *Mucolipin:* TRPML, *Polycystin:* TRPP, and *Vanilloid:* TRPV) and 28 subtypes of these channels in mammals, with 27 of these being functionally expressed in humans, except for the TRPC2 pseudogene. The TRP channels have six transmembrane segments with a binding loop S5 to S6 and have a tetrameric structure. The majority of TRP channel subtypes, excluding TRPM4 and TRPM5, are permeable to Ca^{2+} and are widely expressed in the brain and sensorial tissues, such as those in the hippocampus, cerebral cortex, DRG, and trigeminal ganglion (TG) neurons [62-64]. Several reports have proposed that TRP channel-mediated Ca^{2+} signaling mediates pain sensation. For example, Kahya *et al*. [19] suggested the role of TRP channels in diabetic neuropathic pain *via* overloading of cytosolic Ca^{2+} levels, in which hyperglycemia and diabetes stimulate Ca^{2+} influx into the cytosol through TRP channels by elevation of ROS levels. Because of the disruption of intracellular Ca^{2+} homeostasis, depolarization of mitochondrial membranes and enhanced ROS production result in the activation of oxidative stress-sensitive TRP channels and play an important role in the pathophysiology of diabetic neuropathy. We also emphasized the role of TRP channels in the transduction of diabetic pain *via* sensory neurons that may be mediated by the TRPC, TRPV, and TRPM subfamilies [34].

TRP channel expression levels were increased in DRG and TG neurons by chemotherapeutic agents, such as cisplatin, oxaliplatin, and paclitaxel [65]. Moreover, the antagonists of these TRP channels attenuated chemotherapeutic-induced mitochondrial oxidative stress, inflammation, cold allodynia, and hyperalgesia. There are high expression levels of seven TRP superfamily members in pain-related neurons (*e.g*., DRG and TG), and these are TRPA1, TRPM3, TRPM8, TRPV1, TRPV2, TRPV3, and TRPV4. Moreover, Mori *et al*. [35] reported that most of these channels are activated by oxidative stress. The neuroprotective effects of several antioxidants, including selenium, on different neurological diseases are well understood because of their ROS scavenging activity and antioxidant capacity [66-69]. Furthermore, oxidative stress-sensitive TRP channels can be inhibited by antioxidant treatment, and this contributes to cell survival; mitochondrial functions likewise reduce apoptotic cascades [70-76]. To understand the role of these seven types of TRP channels in the neurobiology of pain, understanding first their structural and functional differences, as well as their activation and inactivation mechanisms, is necessary.

5. ANTIOXIDANTS AND TRP CHANNELS IN PAIN

5.1. TRPA1

The TRPA1 channel is a member of the ankyrin subfamily and is localized mainly in DRG and TG neurons, nodose ganglia, cerebral cortex, hippocampus, and non-excitable tissues. A unique feature of the ankyrin subfamily is that repeats of cysteine-rich ankyrin regions are located close to the N-terminal domain of TRPA1 channels, suggesting the sensor role of environmental irritants and pungent stimuli [77, 78]. TRPA1 channels are gated by cool temperatures (<18°C) and some environmental irritants, such as cinnamaldehyde, mustard oil, allicin, icilin, carvacrol, eugenol, and gingerol [79]. Oxidative stressors can also activate TRPA1 channels [80], and the inhibition of TRPA1 channels can be by antagonists (for example, by high concentrations of camphor, mecamylamine, AP-18, HC-030031, and *compound 31* from Novartis), as well as by antioxidants (such as resveratrol) [81].

TRPA1 channels are activated by neuropathic pain, nociception, allodynia, and cold hyperalgesia [82, 83]. The role of TRPA1 in the induction of pain is well known, for example, in diabetic neuropathic pain [83], inflammatory pain [84], mechanical allodynia [85], and chemotherapeutic agent-induced pain [86]. However, reports on the role of antioxidants in the inhibition or activation of TRPA1 channels in pain are limited, with no reports on selenium and TRPA1 activity. A recent study by Stenger *et al*. [87] found that N-acetyl-cysteine (NAC, but not GSH) inhibits TRPA1-dependent calcium influx in transfected HEK-293 cells, whereas Yu *et al*. [83] demonstrated that the antioxidant resveratrol (and other stilbenoids) inhibits TRPA1-related currents and reduces pain-related behaviors in rats [83]. In addition, Yazgan and Nazıroğlu [88] reported that 17-β estradiol, tamoxifen, and raloxifene also cause the inhibition of TRPA1 and pain [88].

5.2. TRPM8

The TRPM8 channel is another member of the melastatin subfamily and is widely expressed in primary nociceptive fiber (Aδ and C) sensory neurons in the skin and mucosa, urogenital system, lung epithelial cells, and myocytes [89]. TRPM8 cationic currents can be induced by low temperatures (T<22°C –26°C) and by agonists, such as menthol, eucalyptol, geraniol, icilin, and linalool [90]. Non-selective TRPM8 cationic currents can be inhibited by capsazepine, clotrimazole, econazole, AMG2850, and *N*-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1(2*H*)-carbox-amide (BCTC). It is important to note that capsazepine and BCTC were first described as antagonists of TRPV1 channels and later as inhibitors of TRPM8 [91]. TRPM8 channels respond to cold temperatures, and inhibition of these channel currents may provide cold hyperalgesia and allodynia [92, 93], with reports of cold activation of TRPM8 channels in DRG neurons [94]. The role of TRPM8 in the transduction of pain has been known for a long time, for example, in cold hyperalgesia [95, 96], chemotherapeutic-induced hypersensitivity [97, 98], inflammatory pain [99], migraine [100], and mechanical allodynia [101]. However, studies on the role of antioxidants in the inhibition or activation of TRPM8 channels in pain and on the effects of selenium on TRPM8 activity are limited.

5.3. TRPV1

TRPV1 cation channels are abundantly expressed in the TG, DRG, hypothalamus, cerebellum, cerebral cortex, hippocampus, thalamus, substantia nigra, and peptidergic neurons which are responsible for painful sensation and neurogenic pain [63]. Similar to TRPA1, TRPV1 channels also contain short ankyrin repeats in their structures [102]. TRPV1 channels are activated by higher temperatures (T>43°C), chemicals, such as capsaicin and resiniferatoxin (a vanilloid), fatty acid derives, including anandamide, N-acylethanolamines, and N-arachidonoyl dopamine, the environmental irritants camphor and allicin, and oxidative stress [103, 104]. TRPV1 channels can be gated by an intracellular acidic pH (<6.5) and some lipid derivatives [105]. TRPV1 cationic currents are inhibited by antagonists, such as capsazepine, 5′-iodoresiniferatoxin, ruthenium red, and antioxidant administration [19, 106]. The relationship between TRPV1 channels and nociception or neuropathic pain was confirmed in knock-out animal studies [107]. Another study on pain concluded that eriodictyol reduces nociception by inhibiting TRPV1 channels and protecting cells from oxidative stress [108].

The role of TRPV1 channels in pain and heat sensation has been known for some time, with studies on diabetic neuropathic pain [19, 109, 110], inflammatory pain [111, 112], hyperalgesia [113], and cancer-induced neuropathy [114]. However, research on the role of antioxidants in the inhibition or activation of TRPV1 channels in pain induction remains limited. In a cancer cell line (MCF-7), both melatonin and selenium inhibit cell proliferation caused by the anticancer drugs doxorubicin and cisplatin by modulating to TRPV1 channels [115, 116]. Balaban *et al*. [117] suggested that selenium modulates TRPV1-mediated calcium signaling, inhibits ROS production by enhancing GPx activity, and reduces mitochondrial depolarization in the neurons of dementia-induced rat [117].

We have previously reported that NAC and selenium in traumatic brain injury have protective effects on apoptosis, oxidative stress, and Ca^{2+} influx *via* inhibition of TRPV1 channel activation in hippocampal neurons. The effects of NAC are greater than those of selenium [118]. Studies by Yüksel *et al*. [37] investigated the effects of selenium on apoptosis, oxidative stress, and Ca^{2+} influx mediated by TRPM2 and TRPV1 cation channels in DRG and sciatic nerve neurons in a rat model of fibromyalgia. They reported that the pain associated with fibromyalgia is related to the activation of TRPM2 and TRPV1 channels induced by mitochondrial ROS production and apoptosis in the DRG and sciatic neurons. They also observed that the pain, oxidative damage, and apoptotic effects of fibromyalgia are minimized by the blockage of TRPM2 and TRPV1 in the neurons by selenium [37].

5.4. TRPV2

TRPV2 cation channels are members of the vanilloid subfamily. Although the molecular structure of these channels has the features of the vanilloid type, they are insensitive to vanilloids, such as capsaicin. TRPV2 channels are also different from TRPV1 channels in their ankyrin repeats and responses to temperature. Mammalian TRPV2 channels can be activated by temperatures higher than 52°C and by chemicals, such as aminoethoxydiphenyl borate (2-APB) and carvacrol [119]. Inhibition of TRPV2 channels can be achieved by antagonists, such as ruthenium red, transilat, amiloride, lanthanide ions (La^{3+}), and SKF96365 [62]. The expression pattern of TRPV2 channels is mainly in the brain, vascular smooth muscle cells, intestines, macrophages, neurons, neuroendocrine cells, key cells of innate immunity, and several types of cancers [119, 120]. Axelsson *et al*. [121] investigated the expression of TRPV2 channels in primary afferent nociceptors and keratinocytes, and they reported the colocalization of TRPV2 channels, CGRP, and substance P sensory neuropeptides in C-fiber primary afferents [121]. Mihara *et al*. [122] demonstrated that TRPV2 causes NO production through Ca^{2+} influx in myenteric neurons, and

they suggested that inhibition of the TRPV2 channel could be a therapeutic target in NO-related pathologies [122]. Another study [123] found that probenecid, a uricosuric drug, activates TRPV2 channels in sensory neurons, suggesting that this drug could be a useful agent for TRPV2-mediated pain. Experiments by Park *et al*. [124] investigated TRPV2 and TRPV3 polymorphisms in Korean patients with fibromyalgia and indicated that functionally expressed TRPV2 channels are not directly related to fibromyalgia but rather to the polymorphisms of TRPV2 channels [124]. More studies on the effects of antioxidants and oxidative stress on TRPV2 channels are needed.

5.5. TRPV3

TRPV3 cation channels are expressed in neuronal and non-neuronal tissues, including the keratinocytes, brain, testis [125], and skin and dermatological tissues [126]. TRPV3 channels are activated by 2-APB, carvacarol (from oregano), camphor, thyme, and eugenol. The activation threshold of these channels is between 30°C and 39°C, suggesting the role of TRPV3 channels at physiological temperatures [127]. Park *et al*. [124] reported that although TRPV3 channels are not directly related to fibromyalgia, the polymorphisms of these channels are associated with the severity of fibromyalgia. In a related study, Huang *et al*. [128] proposed that TRPV3 channels in keratinocytes mediate heat-induced prostaglandin release and trigger acute nociception and hyperalgesia in keratinocyte sensory function. However, a recent finding from this laboratory proposed that C57BL6 mice lacking TRPV3 channels have a similar heat sensitivity as the control mice [129]. Carreño *et al*. [130] investigated the single nucleotide polymorphisms of the TRPV1 and TRPV3 channels in the migraine susceptibility of a Spanish population and found that the TRPV1 and TRPV3 channels are important in genetic susceptibility to migraine [130]. Brederson *et al*. [131] reviewed the specific antagonists of TRPV3 channels used to reduce pain sensation, thermal hyperalgesia, and burn or inflammation in animal studies [131].

5.6. TRPV4

TRPV4 non-selective cation channels are also members of the vanilloid subfamily; they have at least three subunits of ankyrin repeats in the N-terminal region of the channel structure. TRPV4 channels are widely expressed in the brain, TG and DRG neurons, salivary glands, and in non-excitable tissues, including those in the liver, lungs, and trachea and in the basolateral membranes of the kidney epithelium [132]. TRPV4 channels are gated by temperature (25°C to 34°C), extracellular osmotic changes and alterations of pH (<6), and mechanical/chemical stimuli [132-134]. In addition, the activation of TRPV4 in the hippocampus, astrocytes, and DRG by extracellular H_2O_2 has been reported, although the channel is inhibited in the neurons by antioxidant treatments (Trolox, MitoE, and reduced glutathione, GSH). The prolonged activation of TRPV4 channels in neurons, such as those in the hippocampus and astrocytes, leads to Ca^{2+} overload, causing oxidative stress and cell injury [109]. Increased Ca^{2+} causes oxidative stress through multiple mechanisms, and it has been shown to be linked to cell injury induced by different insults [135]. There are a limited number of antagonists for TRPV4 cationic currents, but similar to other members of the vanilloid subfamily, ruthenium red is used to inactivate these channels. Trivalent cations, such as Gd^{3+} and La^{3+}, also inhibit TRPV4 channels [136]. The functional importance of TRPV4 channels is directly related to protease activated receptor 2 (PAR2), which mediates inflammatory and neurogenic pain. Inhibition of TRPV4 activation reduces PAR2-induced neurogenic inflammation in rat primary nociceptive neurons [136-138]. Alessandri-Haber *et al*. [139] assessed the role of TRPV4 in chemotherapeutic-induced neuropathic pain in the peripheral endings of the saphenous nerve and showed that taxol induces peripheral neuropathy and mechanical hyperalgesia, and that nociception is decreased by antisense treatment to TRPV4 channels. Materazzi *et al*. [140] reported that TRPV4 activation causes ROS-related neuropeptide release in sensory nerve endings in paclitaxel-induced neuropathy. Liu *et al*. [141] investigated the inhibition of TRPV4 channel expression by RNAi in DRG neurons and observed that substance P is co-expressed with TRPV4 channels in rat DRG neurons, as is the case also for TRPV1. Recent findings show that TRPV4-mediated Ca^{2+} influx can also be triggered by ROS and that TEMPOL or a mitochondrial-specific antioxidant (MitoQ) reverses excessive ROS production and Ca^{2+} influx [142]. Bai and Lipski investigated the potential role of TRPM2 and TRPV4 channels in oxidative stress-induced neuronal death in hippocampal tissue cultures and confirmed that amyloid β-induced neuronal damage is associated with oxidative stress and partly involved in the stress-sensitive TRPM2 and TRPV4 channels, as treatment with an antioxidant (Trolox) increased cell survival [143].

Inhibition of TRPV4 channels by RNAi or channel blockers eliminated acrolein-induced oxidative and cell injury in mouse cultured urothelial cells, whereas treatment with the antioxidant NAC had similar effects as TRPV4 antagonists in reducing Ca^{2+} influx [144]. Some reports also have contrasting findings, as in the studies by Ma *et al*., who found that the plant flavone and antioxidant apigenin trigger TRPV4-mediated Ca^{2+} signaling in transfected HEK-293 cells [145].

6. SELENIUM, CALCIUM SIGNALING, AND TRP CHANNELS

The dynamic and narrow concentration range of Ca^{2+} intracellular signaling requires well-coordinated regulatory mechanisms (Fig. **1**). Mitochondrial function is essential for neuronal survival because neurons critically depend on ATP synthesis generated by mitochondrial oxidative phosphorylation [13, 50, 146, 147]. Zeng *et al*. [148] reported that extracellular selenium application can inhibit TRPM2 cation channel currents induced by intracellular ADPR. This shows the dual role of selenium in TRP channels—Se acts as a potential inhibitor in TRPM2 channels *via* the extracellular site of the channel, and it also demonstrates its antioxidant ability *via* GPx; it helps reduce oxidative stress from the cytosol and decreases ROS-sensitive TRP channel gating induced by an intracellular oxidative status.

Mitochondrial depolarization activity depends on Ca^{2+} and is fueled by Ca^{2+} entry from the extracellular space *via* TRP channels when triggered by neuronal activity [13].

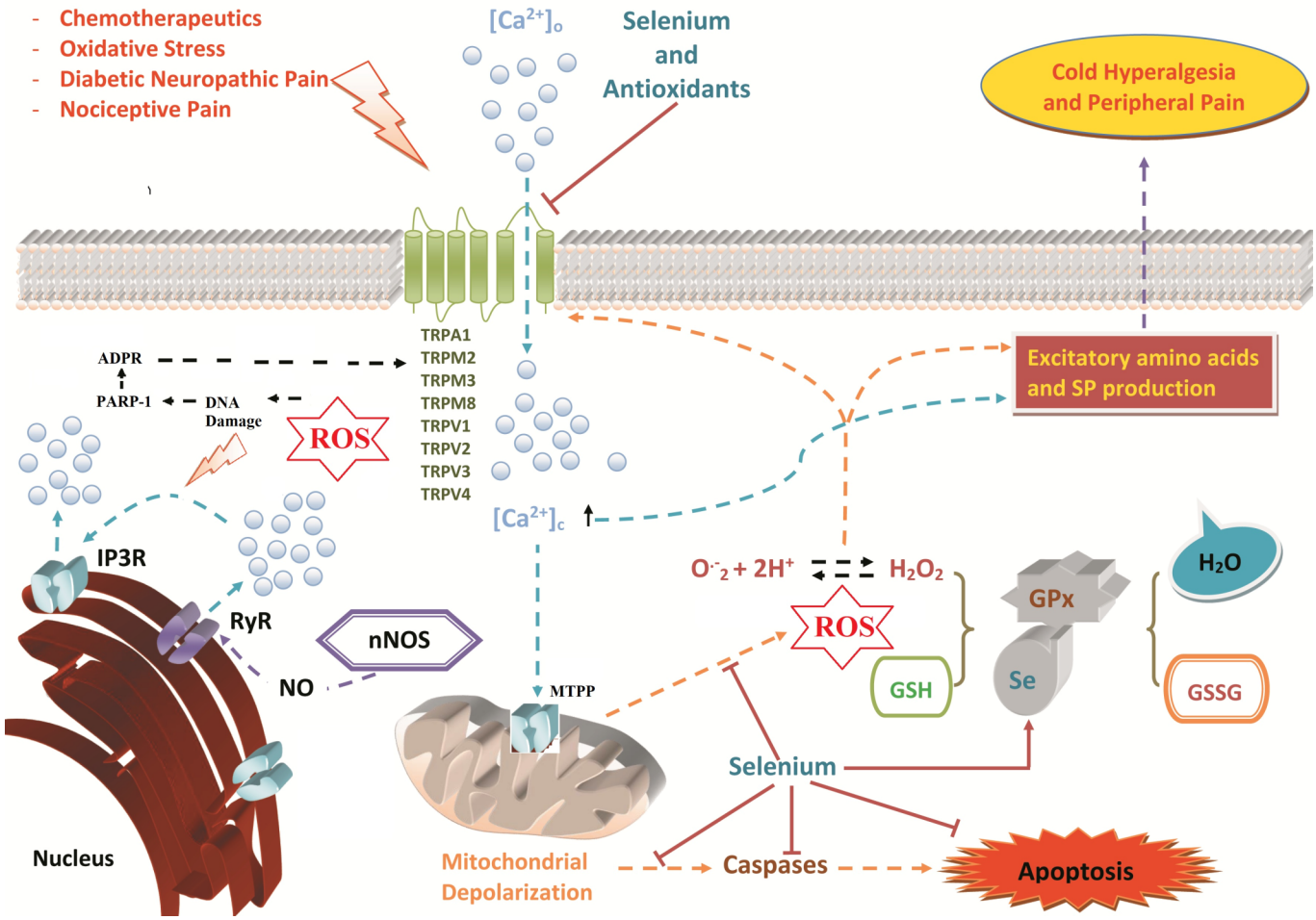

Fig. (1). Role of selenium supplementation in TRP channel-mediated pathological mechanisms in neurons. Neural tissues are very vulnerable to oxidative stress-dependent cell death because of their lipid-rich structures. Many TRP channels (TRPA1, TRPC5, TRPM2, and TRPV1) are expressed in neuronal tissues and have unique functional and structural properties [3, 199]. Other neural TRP channels (TRPM3, TRPM8, TRPV2, TRPV3, and TRPV4) act as thermal sensors to hot or cold temperature. Chemotherapeutic agents, oxidative stress, diabetic neuropathic pain, and inflammatory and nociceptive pain may stimulate TRP channels to rapidly increase cytosolic Ca^{2+} concentrations and trigger calcium-activated calcium channel (CACC) entry. Overloading of cytosolic Ca^{2+} concentrations results in depolarization of the mitochondria *via* the opening of mitochondria transition permeability pores (MTPP). As a result of mitochondrial dysfunction, either caspase activity may result in apoptosis, or ROS overproduction activates oxidative stress-sensitive TRP channels. Excessive Ca^{2+} entry and ROS stimulate the release of pain mediators, such as substance P and other excitatory amino acids, causing PKC activation, NO synthesis, RyR activation and IP3 receptor activation (IP3R) [13]. TRPM2 channel is activated in the peripheral neurons by ROS-induced DNA damage and ADP-ribose (ADPR) production through PARP-1 enzyme activation. Several reports have concluded that selenium (Se) inhibits the activation of TRP channels and Ca^{2+} signaling, as well as decreases mitochondrial depolarization and ROS overproduction. Supplementation with selenium prevents apoptotic cell death by reducing caspase 3 and 9 activities. Selenium is also a cofactor for the antioxidant GPx in reducing excessive ROS production in cytosolic compartments. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Overloaded Ca^{2+} in the cytosol induces apoptosis if the accumulation will not be buffered by the mitochondria [13, 44, 51]. Growing evidence indicates that the production of excessive ROS and the stimulation of apoptotic pathways, including caspase activities, such as caspase 3 and 9, are increased in the hippocampus and DRG by increased mitochondrial membrane depolarization [63, 88] because the neurons have high oxygen consumption and polyunsaturated fatty acid content. Caspase 3 is well known to be an important indicator of the extrinsic and intrinsic pathways of apoptosis. Yousuf *et al*. [149] examined the neuroprotective actions of selenium in cerebral ischemia-induced damage in rat hippocampus and reported that a low dose of intraperitoneal sodium selenite (0.1 mg/kg each day for a week) reduces intracellular Ca^{2+} concentrations, caspase 3 activity, and mitochondrial dysfunction. Uğuz and Nazıroğlu [150] reported that selenium reduces oxidative stress-induced activation of DRG neurons by decreasing oxidative stress-induced apoptotic pathways and cytosolic calcium levels. Similarly, Kahya *et al*. [150] reported the protective effects of selenium on caspase 3 and caspase 9 activity in diabetes-induced rats.

Reeves *et al*. [151] investigated the overexpression of selenium-containing protein M (Selenoprotein M) in murine HT22 hippocampal neurons, primary cultured neuronal cells,

and cerebellar C8-D1A astrocytes. The increased expression of selenoprotein M reduces ROS and apoptotic parameters, although shRNA-silenced selenoprotein M increases H_2O_2-induced apoptosis and ROS production. Selenoprotein M overexpression also attenuates the Ca^{2+} influx evoked by H_2O_2. Disturbances in Ca^{2+} mobilization have an important role in the etiology of pain. Ca^{2+} overload induces pain through substance P (and CGRP) production in neurons through direct channel activation or excessive ROS production and induction of apoptosis through depolarization of the mitochondria [65].

7. SELENIUM AND PAIN

Immune cell activation occurs in neurodegenerative diseases in the CNS. Inflammation in the CNS causes microglial and macrophage SN. Dominiak *et al*. [152] investigated the protective effect of Selol against inflammation in rat brain and found that Selol prevents LPS-mediated (100 μg/kg) inflammation in the CNS by regulating antioxidant levels. The authors suggested that Selol could be used to decrease inflammation in neurodegenerative diseases. Uğuz *et al*. [150] investigated H_2O_2-induced oxidative stress in the DRG sensory neurons of rats by monitoring lipid peroxidation, cytosolic Ca^{2+} release, GPx, glutathione (GSH), apoptosis, and cell viability (MTT assay). They proposed that selenium acts as a ROS scavenger in DRG neurons in oxidative stress-induced neurological diseases [150]. El-Ghazaly *et al*. [153] examined the limitations of selenium because of bioavailability and toxicity in a study in which rats were exposed to radiation and administered nano-Se orally (2.55 mg/kg). They demonstrated the positive effects of nano-Se on inflammation induced in irradiated rats. Anversa *et al*. [154] suggested the anti-nociceptive and anti-inflammatory effects of selenium-containing compound [1,2-bis-(4-methoxyphenylselanyl), an organic Se] styrene, through regulation of the serotoninergic system in mice. Similarly, Birmann *et al*. [155] suggested a selenium containing compound (3-(4-chlorophenylselanyl)-1-methyl-1H-indole) in the treatment of pain and inflammation. p,p'-methoxyldiphenyl diselenide ($OMePhSe_2$) contains a selenium molecule, and its anti-nociceptive action in the model of neuropathic pain was reported by Marcondes *et al*. [156]. Similarly, Sari *et al*. [157] observed its modulator role on antinociception in Swiss mice [157]. Oliveira *et al*. [158] reported the protective effects of a $MeOPhSe_2$-supplemented diet on depression and pain comorbidity in rats [158]. Mansel *et al*. [159] examined the protective effects of selenium on pain in women with fibrocystic changes in the breast. Yüksel *et al*. [37] evaluated the protective effects of selenium on ROS and of Ca^{2+} influx on fibromyalgia in the DRG and sciatic nerve induced rat fibromyalgia model, as well as examined selenium mediation by inhibition of TRP channels (TRPM2 and TRPV1). Barros-Neto *et al*. [160] investigated the relationship between chronic musculoskeletal pain and malnutrition and reported that myofascial pain is associated with changes in intracellular zinc and selenium stores caused by inadequate food intake.

Chronic pain and depression are common in many patients, leading to increased use of antidepressants and pain relievers. A study conducted by Brüning *et al*. [161] examined the effects of organoselenium (m-CF_3-$PhSe)_2$ on the immune system and the relationship between chronic pain and depression. They reported that m-CF_3-$PhSe_2$ decreases the levels of pro-inflammatory mediators and the damage caused by partial nerve ligation [161]. Patients with chronic pancreatitis have abdominal pain that is usually resistant to analgesic strategies, with some studies suggesting that the pain of chronic pancreatitis could be attributed to ROS-induced pancreatic damage, opening the possibility for the use of selenium as an antioxidant trace element to improve the quality of life and reduce pain in patients with chronic pancreatitis [162].

8. SELENIUM AND TRP CHANNELS IN DIABETES-INDUCED NEUROPATHIC PAIN

Diabetes is a metabolic disease affecting about 100 million people worldwide. Peripheral diabetic neuropathy occurs in about 60% of these patients, and diabetic neuropathy emerges as a complication of the disease. Oxidative stress and inflammation have a main role in diabetic neuropathic pain generation [13, 163-165]. Inhibition of ROS generation may contribute to the reduction of diabetic neuropathy [166]. Antioxidant applications can also be useful for the attenuation of diabetes and hyperglycemia-induced neuropathy. Different studies have evaluated the effects of alpha lipoic acid administration on diabetic neuropathy, and researchers have found significant results; a correlation exists between alpha lipoic acid administration and the reduction of diabetic neuropathy in patients with diabetes [167, 168]. There are several reports about the use of antioxidant treatments, such as those involving vitamin E [169], coenzyme Q10 [170], and the selenoprotein Selol [171], in limiting diabetic neuropathy both in patients and in experimental studies.

Selenium deficiency and excessive Ca^{2+} entry through activation of TRP channels have important roles in the etiology of diabetic neuropathic pain. There are several studies of TRP channel function in diabetic neuropathic pain, with a focus on the TRPC, TRPM, and TRPV channels. In a postmortem study, researchers found that TRP channel expression levels may change in diabetic neuropathic patients compared with normal human tissues [172]. The regulation of TRP channels is gaining prominence as a therapeutic target for neuropathic pain in diabetic patients [165]. TRPV1 channel activation without changes in expression levels occurs in native rat sensory neurons and HEK293 cells expressing TRPV1 (but not in TRPA1-deficient mice) stimulated by glucose and hypoxic conditions. Alkaline pH causes pain and TRPA1 activation [173]. Wei *et al*. [174] investigated the endogenous compounds affecting TRPA1 ion channel activation by mechanical hypersensitivity, a symptom of diabetes mellitus. They noted that the progress of hypersensitivity is prevented in streptozotocin-induced diabetic rats treated with a TRPA1-antagonist [174].

A limited number of studies have investigated neuropathic pain and TRP channel regulation by selenium and other antioxidant applications. Sözbir and Naziroglu [75] found that N-acetyl cysteine treatment has the regulatory effects of oxidative stress-induced TRPM2 channel activation and increased antioxidant parameters in rat brain. They

also suggested that modulation of TRPM2 *via* the ROS-dependent pathway can be a therapeutic target for the inhibition of diabetic neuropathy. In another study, Kahya *et al*. [19] proposed that the TRPM2 and TRPV1 channels are involved in the ROS-dependent mechanisms of diabetic neuropathic pain induction and that melatonin and selenium treatments can be a therapeutic approach to decrease peripheral pain.

9. SELENIUM AND CHEMOTHERAPEUTIC AGENT-INDUCED NEUROPATHIC PAIN

Anti-cancer drugs induce the activation of the cell membrane-embedded cation channels of DRG and dorsal horn neurons, including the Ca^{2+}, Na^{+}, and K^{+} channels, and NMDA receptors, and they change cytosolic ion concentration, especially $[Ca^{2+}]c$, which initiates other alterations to induce neuropathic pain [175]. It is well known that a poor antioxidant defense system and elevated oxidative stress arise after drug treatment, contributing to painful neuropathy [176]. Neuropathic pain occurs when pressure is applied to the nerve cells of cancer patients, who describe the symptoms as "a burning or heavy sensation, or numbness along the path of the affected nerve" [177]. The molecular basis of this pain shows the contributory role of TRP channels, especially of the TRPA1, TRPM8, and TRPV1 subtypes [178, 179]. Chiba *et al*. [180] investigated the role of TRPV1 in peripheral neuropathy after anticancer drug therapy and suggested the role of TRPV1 expression in vincristine-induced pain in peripheral neuropathy. Similarly, Chukyo *et al*. [181] reported that increases in TRPA1, TRPM8, and TRPV1 expression in DRG neurons may contribute to the development of oxaliplatin-induced neuropathic pain in the somatosensory system. Cisplatin and selenium synergistically interact in the TRPV1 channel function in a breast cancer cell line (MCF-7), suggesting that a combination of these drugs could have a greater anticancer effect by modulation of TRPV1 [115]. Li *et al*. [182] showed that the TRPA1 and oxidative stress signaling pathway has an important role in oxaliplatin-induced pain, and they also suggested that blocking miRNA-155 increases NADPH oxidase, resulting in oxidative stress and TRPA1 expression in rat dorsal horn neurons. Melatonin has powerful antioxidant properties, and several reports also found that it changes TRP channel gating. Torsney *et al*. [183] developed a rat model of paclitaxel-induced peripheral neuropathy and showed that melatonin can contribute to restricting mitochondrial dysfunction; because of antioxidant capacity, the development of neuropathy is limited. Zhang *et al*. [184] demonstrated that using an electroacupuncture antioxidant system could be activated and that paclitaxel-induced neuropathic pain decreases in the DRG neurons of rats. Collectively, in terms of the regulatory effect on TRP channels, selenium treatment may be useful in enhancing the antioxidative system and reducing neuropathic pain induced by chemotherapeutic agents. Further studies are needed to understand the effects of selenium supplementation on chemotherapeutic-induced neuropathic pain models.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Neuropathic pain is different from general pain and is described as a shooting or burning pain. The molecular pathways of DRG neurons have a major role in the induction of neuropathic pain. The neurons in the DRG and CNS are affected by complications of alcoholism, chemotherapy treatment, and diabetes. The treatment of neuropathic pain includes the use of anticonvulsant and antidepressant drugs, but their success rate in pain treatment is poor. However, accumulating evidence indicates the important roles of oxidative stress and overload Ca^{2+} in neurons in human and rodents with neuropathic pain.

ROS production occurs during physiological functions, such as phagocytosis and mitochondrial functions. The ROS in neurons and the brain are controlled by enzymatic and non-enzymatic antioxidants. A co-factor of GPx, selenium is believed to play a critical role in protecting neurons from hazardous mitochondrial and inflammation-induced ROS production. Increasing evidence implicates the protective role of selenium or selenium-containing molecules, such as $OMePhSe_2$ and 1,2-bis-(4-methoxyphenylselanyl), in the inhibition of excessive ROS production and overload Ca^{2+} entry in the etiology of several neuronal diseases, including inflammatory pain, hypersensitivity, allodynia, diabetic neuropathic pain, and nociceptive pain.

The expression level of TRP channels varies in tissues according to their functions in these tissues. For example, TRPM2 channels are mainly responsible for the phagocytic activity and are highly expressed in phagocytic cells. The high expression levels of seven TRP channels (TRPA1, TRPM3, TRPM8, TRPV1, TRPV2, TRPV3, and TRPV4) in the DRG and TG are mainly responsible for mediating neuropathic pain. Some TRP channels, such as TRPA1 and TRPV1, are activated by oxidative stress. Low selenium levels can be found in the plasma of patients with neuropathic pain and neurological diseases. A limited number of studies indicate the protective roles of selenium and its derivatives *via* regulation of TRP channels in humans and rodents with neurological diseases and pain. However, there are no reports of selenium activity in oxidative stress-dependent activated TRP channels, such as TRPM2 and TRPM7, suggesting the need to further investigate the effects of selenium on other TRP channels involved in peripheral pain models.

High levels of ROS and low levels of antioxidants are known to play a pivotal role in the pathobiology of peripheral pain [185]. As already mentioned, the TRPA1, TRPV1, and TRPV4 channels are activated by several stimuli, including oxidative stress [13, 186]. The involvement of cysteine residues and the antioxidant dithiothreitol in the N domain of TRPA1 has been established in a mass spectrometry study [187]. TRPA1 activation through oxidative modifications of the cysteine residues in the DRG of wild and TRPA1 knockout mice has also been reported [80, 188]. The activation of TRPV1 channels in different cells and neurons by oxidative alterations of multiple extracellular [189] and intracellular sources [190]. Cysteine groups as a source of the thiol redox system act as the main source of different antioxidants, such as GSH and Se–GPx [16, 191]. Therefore, TRPV1 is activated in the DRG [72] of rats by depletion of intracellular GSH, although the channel is inhibited in cells following treatment with thiol redox cycle members, such as GSH, selenium, and NAC [19, 72, 118]. Our recent results indicate the protective role of selenium through inhibition of TRPA1

and TRPV1 in different pain models [19, 37]. Therefore, this corroborates the growing evidence on the potential role of selenium as a modulator of TRP channel activation-induced neuropathic pain in the clinic. The relative contributions of the activation of TRP channels or the inhibition of oxidative stress by selenium and selenoproteins remain unclear, though. This topic should be clarified in future studies.

LIST OF ABBREVIATIONS

$[Ca^{2+}]c$	=	Cytosolic free calcium ion
CACC	=	Calcium activated calcium channel
CNS	=	Central nervous system
DRG	=	Dorsal root ganglion neuron
GPx	=	Glutathione peroxidase
GSH	=	Reduced glutathione
MTP	=	Mitochondria transition permeability
NAC	=	N-acetyl-cysteine
ROS	=	Reactive oxygen species
SCI	=	Spinal cord injury
Se	=	Selenium
TBI	=	Traumatic brain injury
TRP	=	Transient receptor potential
TRPA1	=	Transient receptor potential ankyrin 1
TRPM3	=	Transient receptor potential melastatin 3
TRPM8	=	Transient receptor potential melastatin 8
TRPV1	=	Transient receptor potential vanilloid 1
TRPV2	=	Transient receptor potential vanilloid 2
TRPV3	=	Transient receptor potential vanilloid 3
TRPV4	=	Transient receptor potential vanilloid 4
VGCC	=	Voltage-gated calcium channels

AUTHORS' CONTRIBUTIONS

Mustafa Nazıroğlu formulated the present hypothesis. Ahmi Öz and Kenan Yıldızhan were responsible for writing the report. Mustafa Nazıroğlu made critical revisions of the manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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