REVIEW

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ROLE OF CALCIUM SIGNALING IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASES

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Abstract. *Calcium (Ca^{2+}) is a central intracellular second messenger regulating cellular homeostasis through tightly controlled signaling. Intracellular Ca^{2+} dynamics depend on coordinated interactions between the endoplasmic reticulum (ER), mitochondria, and plasma membrane channels, including SERCA (Sarcoplasmic/Endoplasmic Reticulum Ca^{2+}-ATPase, which is a calcium pump located in the sarcoplasmic and endoplasmic reticulum (SR and ER) pumps, inositol 1,4,5-trisphosphate receptors (IP_3Rs), ryanodine receptors (RyRs), transient receptor potential (TRP) channels, and store-operated calcium entry (SOCE). ER–mitochondria contact sites integrate calcium signaling with mitochondrial energetics, oxidative stress responses, autophagy, and apoptosis. Changes in calcium signaling play a key role as a risk factor in the pathogenesis of neurodegenerative diseases, with calcium influx pathways, including store-operated calcium entry (SOCE), critically implicated in their pathophysiology. Despite ongoing research, these diseases remain incurable, and current therapies provide only symptomatic relief. Restoration of calcium signaling homeostasis is proposed as a potential therapeutic target for the treatment of neurodegenerative disorders. Proper functioning of calcium signaling pathways is critical for neuronal function. It has been clearly demonstrated that dysregulation of calcium signaling is a common feature of neurodegenerative diseases. Abnormal Ca^{2+} signaling leads to mitochondrial dysfunction and synaptic instability, and restoration of normal calcium homeostasis is a potential strategy for treating these diseases. SOCE impairment is observed in Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD). This review summarizes mechanistic insights into calcium signaling alterations involved in neurodegeneration, focusing on ER calcium storage, SERCA function, SOCE regulation, and calcium-dependent signaling pathways. Emerging neuroprotective strategies targeting calcium homeostasis, including pharmacological agents and natural bioactive compounds, are discussed. Restoration of intracellular Ca^{2+} balance represents a promising therapeutic approach to reduce calcium-mediated cytotoxicity and slow neurodegenerative progression.*

Key words: *neurodegenerative diseases, calcium signaling, cellular homeostasis, endoplasmic reticulum, cell signaling, apoptosis, oxidative stress, mitochondrial dysfunction, Parkinson's disease*

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INTRODUCTION

Role of calcium in cellular homeostasis

Cells in the human body have the ability to rapidly self-destruct in response to genetic or external factors, a process known as apoptosis. This mechanism is essential for the development of the body, the maintenance of tissue balance, and defence against pathogens. Organized life requires programmed cell death, which depends on the internal mechanisms of the cells themselves. Mitochondria, which are organelles that produce energy through cellular respiration, play a central role in integrating cell death signals. They are involved in this process by interacting with proteins from the Bcl-2 (B-cell lymphoma 2) and Bax (Bcl-2-associated X protein) families. These proteins trigger the destruction of the cell, releasing key molecules, such as cytochrome c, which activates caspase enzymes, the main executors of apoptosis. Furthermore, calcium ions (Ca^{2+}), which are essential cellular mediators that regulate almost all aspects of cell and tissue physiology, can also trigger the process of cell death. Mitochondria play a crucial role in interpreting these signals, determining whether calcium ions will be perceived as a sign of life or cell death [1]. It is not yet fully understood whether Ca^{2+} functions as a conditional factor under stress conditions that "tips the balance" or serves as an inevitable signal to trigger cell death. The study by Scorrano et al. demonstrated that the transfer of Ca^{2+} from the endoplasmic reticulum to mitochondria is necessary for triggering programmed cell death in some, but not all, apoptotic signals [2]. By genetically inactivating key proteins and targeting their recovery to specific organelles, the authors show that the concentration of Ca^{2+} in the ER plays a crucial role in the cell's ability to self-destruct. This identifies the endoplasmic reticulum as a novel regulatory link in the apoptosis process. Thus, using Ca^{2+} as an intracellular mediator, cells balance between survival and death.

Calcium (Ca^{2+}) plays a key role in neuronal signalling and is essential for the normal functioning of various cellular processes. Impaired calcium signaling is observed in aging neurons and those affected by neurodegenerative diseases. In Alzheimer's disease, increased Ca^{2+} levels in the ER and reduced calcium entry into neuronal stores (SOCE) are associated with synaptic loss. In HD, decreased ER Ca^{2+} levels and increased SOCE, which are associated with synaptic loss, are observed. In PD, decreased levels of SOCE and ER Ca^{2+} are observed, which are associated with neuronal cell death.

Calcium is a universal biological mediator that controls cellular life from fertilization to programmed cell death. It acts as a conventional second messenger, released inside cells through interactions between first messengers and plasma membrane receptors, but it can also enter cells directly to deliver information. The unique feature of Ca^{2+} signaling is its dual role: although essential for proper cell function, Ca^{2+} can also mediate cell distress or toxic cell death if its concentration and movement within cells are not strictly regulated. Ca^{2+} concentration is controlled by reversible binding to specific proteins that either buffer Ca^{2+} or decode its signals to target proteins. Throughout the cell's life cycle, from fertilization to death, Ca^{2+} signaling regulates important activities, including gene expression, muscle contractions, mobility processes, and metabolic pathways involved in generating cellular energy [3]. Although Ca^{2+} is essential for many cellular functions, its dysregulation can lead to toxicity and cell death. Selective control of specific targets depends on the spatiotemporal modeling of Ca^{2+} signaling and decoding by various Ca^{2+}-sensitive elements. Recent advances in fluorescent technology and genetics have revealed Ca^{2+}-sensitive mechanisms in organelles. These developments have also identified human mutations and disorders associated with Ca^{2+}-sensitive proteins, providing new insights into intracellular calcium homeostasis and signaling [4].

Calcium homeostasis and regulation

Due to the toxicity of Ca^{2+}, its concentration in the cytoplasm must be kept low, with most Ca^{2+} stored in the endoplasmic reticulum. Ca^{2+} is transported into the ER by SERCA. It belongs to the P-type ATPase family and plays a key role in regulating intracellular calcium concentration and is released in a controlled manner during signaling by the opening of inositol 1,4,5-triphosphate (IP_3) or ryanodine receptor (RyR) channels for Ca^{2+} release [5]. A significant portion of the released Ca^{2+} is captured by mitochondria, which are strategically located near the Ca^{2+} release channels [6]. This proximity allows mitochondria to modulate, propagate, and synchronize Ca^{2+} signals [7], as well as prevent Ca^{2+} depletion in the ER through recycling [8].

The connection between ER and mitochondria allows Ca^{2+} signals to regulate not only cellular metabolism [9], but also the ability of mitochondria to participate in apoptosis [10]. The transition from a life signal to a death signal requires a coincidence between Ca^{2+} accumulation and proapoptotic stimuli, which depends on the intensity of the mitochondrial Ca^{2+} signal. This signal is largely determined by the Ca^{2+} content in the ER, which is maintained by the balance between

active pumping via SERCA and passive leakage through Ca^{2+} release channels. Studies show that the Ca^{2+} content in the ER affects the cell's sensitivity to apoptotic stress. Procedures that reduce Ca^{2+} concentration in the ER, such as genetic deletion of calreticulin (a Ca^{2+}-buffering protein in the ER) or overexpression of plasma membrane Ca^{2+} ATPases, protect cells from apoptosis [11, 12]. Conversely, increasing Ca^{2+} in the ER through overexpression of SERCA or calreticulin makes cells more sensitive to apoptotic stress [12, 13].

Role of calcium in oxidative stress and apoptosis processes

Calcium (Ca^{2+}) plays a central role in both apoptotic and necrotic cell death. Changes in intracellular calcium levels or the depletion of intracellular calcium stores can regulate cell death in almost all cell types. These calcium flows are controlled by membrane channels, whose activation is usually strictly regulated. The channels can be activated by ligands or voltage-dependent and are often subject to regulation by effector molecules, such as calmodulin. It is becoming clear that the activity of many calcium channels is modulated by reactive oxygen species (ROS) and reactive nitrogen species (RNS). This may be part of normal cell signaling or the result of externally induced toxins that generate ROS/RNS. It is becoming increasingly clear that many calcium channels are influenced by ROS or RNS, which may be part of normal cell signaling or the result of exogenous ROS/RNS, often generated by toxins [14].

In mice fed a fructose-rich diet (FRD), spontaneous Ca^{2+} release from the sarcoplasmic reticulum (SR) is increased, without significant changes in SR Ca^{2+} load. Hyperglycemia in HEK293 cells increases [^{3}H]ryanodine binding and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) phosphorylation of RyR2, which can be prevented by CaMKII inhibition [15]. Increased oxidative stress during FRD exacerbates calcium signaling and induces apoptosis. It is suggested that impaired calcium signaling, including mitochondrial interactions, plays a critical role in cell death in prediabetic states and diseases associated with oxidative stress. The HT22 hippocampal cell model subjected to glutamate-induced oxidative stress (leading to GSH depletion) shows reduced calcium influx through SOCE channels, particularly mediated by ORAI1. This protective effect can be reproduced by pharmacologically inhibiting SOCE or downregulating ORAI1 expression [16].

Calcium signaling and neurodegenerative diseases

Calcium (Ca^{2+}) serves as a crucial second messenger involved in the regulation of key physiological processes, such as cell growth and development, cell survival, neuron development, and maintenance of cell functions. The coordination between different proteins, pumps, and Ca^{2+} channels, as well as the storage of Ca^{2+} in different organelles, is essential for maintaining cytosolic Ca^{2+} levels, which provide the necessary spatial resolution for cellular homeostasis. A critical regulatory mechanism for Ca^{2+} homeostasis is calcium entry, controlled by SOCE – a mechanism for the entry of extracellular Ca^{2+} into the cell in response to the depletion of intracellular calcium stores, a process that controls the influx of Ca^{2+} into cells in response to the depletion of calcium reserves in the endoplasmic reticulum. When calcium levels in the ER drop, a signaling pathway is activated that opens specific calcium channels in the cell membrane, allowing extracellular calcium to enter the cell. This process is vital for various cellular functions, including signaling, gene expression, cell growth, and immune responses. SOCE is triggered by the depletion of internal Ca^{2+} reserves in the ER and is of interest to researchers because of its impact on the functions of both excitable and non-excitable cells [17].

It is known that Ca^{2+} regulates opposing processes, such as autophagy, which supports cell survival, but also participates in programmed cell death processes, such as apoptosis. The functional role of the transient receptor potential channels (TRP) involved in regulating intracellular calcium levels and Orai channels (associated with SOCE) is well-studied, but data on how they modulate opposing functions and influence excitatory and non-excitatory cell functions remain limited. It is important to note that disturbances in SOCE are associated with various pathological neurodegenerative diseases. The key role of autophagy in the pathogenesis of neurodegenerative diseases, such as Alzheimer's and Parkinson's, may offer new therapeutic opportunities for the treatment of these diseases [17]. AD is a neurodegenerative disease characterized by progressive memory loss, cognitive impairment, and behavioral changes. PD is a chronic, progressive neurodegenerative disease that affects motor function, causing tremors, rigidity, slow movements (bradykinesia), and postural instability.

Calcium (Ca^{2+}) plays a key role in neuronal signaling and is essential for the normal functioning of various cellular processes. Disruption of calcium signaling is observed in aging neurons and those affected by neurodegenerative diseases. Abnormal Ca^{2+} signal-

ing leads to mitochondrial dysfunction and synaptic instability, and restoration of normal calcium homeostasis is a potential strategy for treating these diseases. Interestingly, SOCE impairment is observed in AD, HD, and PD [18].

- In Alzheimer's disease, elevated levels of Ca^{2+} in the endoplasmic reticulum and reduced calcium influx into neuronal stores (SOCE) are observed, which are associated with synaptic loss.
- In Huntington's disease, decreased ER Ca^{2+}+ levels and increased SOCE are observed, which are associated with synaptic loss.
- In Parkinson's disease, decreased SOCE and Ca^{2+} levels in the ER are observed, which are associated with neuronal cell death.

The etiology of PD is associated with aging, environmental toxins, and genetic mutations, while its molecular pathogenesis involves various factors, such as impaired protein homeostasis, oxidative stress, mitochondrial dysfunction, synaptic transmission impairment, calcium homeostasis imbalance, prion-like α-synuclein transmission, and neuroinflammation. Autophagy, a process of mass degradation to maintain cellular homeostasis, is disrupted in the pathogenesis of PD. Several PD-related genes, such as SNCA, LRRK2, GBA, ATP13A2, VPS35, and FBXO7, are involved in or affected by the autophagy process. Various pathological events in PD directly or indirectly impair the autophagy pathway, leading to its dysregulation in neurotoxic models. Autophagy is considered a potential therapeutic target for PD. Modulation of the expression of autophagy-related genes (such as BECN1 and TFEB) provides neuroprotection in PD models, and autophagy inducers – small molecules such as rapamycin, trehalose, and lysosomal modulators have shown neuroprotective effects [19]. Calcium is an ambivalent signaling agent that carries information about vital cellular processes, such as excitation-contraction, secretion, gene transcription, and enzyme activity through protein phosphorylation and dephosphorylation. However, it also transmits signals that promote programmed cell death and, if uncontrolled, can accelerate toxic cell death [20].

Communication between mitochondria and the endoplasmic reticulum is critical for processes such as lipid metabolism, calcium signaling, autophagy, and mitochondrial dynamics. Disruptions in this communication are associated with neurodegeneration. The proteins involved in these interactions are important in diseases, such as Parkinson's and Alzheimer's [21]. Mutations in PINK1, which regulates mitochondrial function, are associated with PD. PINK1 and Parkin are involved in mitochondrial calcium homeostasis and contacts between mitochondria and the ER. Disruptions in calcium regulation contribute to the progression of PD [22]. Both diseases are associated with oxidative stress, mitochondrial dysfunction, and disturbances in calcium homeostasis. Studies suggest that restoring calcium balance may offer neuroprotective benefits. The compound astragaloside IV (AS-IV) has been studied for potential therapeutic effects in PD by activating the intracellular signaling pathway PI3K/AKT (Phosphoinositide 3-Kinase/Protein Kinase B) pathway, improving cell viability, and protecting neurons from apoptosis [23].

Mitochondria play a key role in cellular energy production, buffering intracellular calcium, and regulating apoptosis, and are major targets of oxidative stress, which leads to degeneration in astrocytes (glial cells in the CNS) [24]. Kaempferol, a widely distributed flavonoid, exhibits neuroprotective effects in neurological diseases, such as PD and AD, by modulating key signaling pathways involved in neurodegeneration and inflammation. Kaempferol exhibits potential therapeutic benefits by preserving neuron survival, reducing oxidative stress, increasing the activity of mitochondrial calcium channels, reducing neuroinflammation, promoting neurogenesis, and improving cognitive function [25].

Studies on rotenone-induced neurotoxicity highlight how calcium and GSK3β (glycogen synthase kinase 3 beta) signaling contribute to the aggregation of α-synuclein (a small, soluble protein expressed mainly in neurons of the central nervous system (CNS)). It plays an important role in synaptic plasticity, neurotransmitter release, mitochondrial function, and damage to neurons. Rotenone increases intracellular calcium levels and induces the aggregation and phosphorylation of α-synuclein in a calcium-dependent manner. Aggregated α-synuclein is normally degraded by autophagy, and rotenone disrupts this process. The weakening of autophagy and α-synuclein changes is altered by calcium clearance. Calcium regulates the activity of glycogen synthase kinase 3 beta (GSK3β). Yuan's team demonstrated that rotenone weakens the phosphorylation of AKT and GSK3β, and calcium clearance reverses these phenomena. Changes that regulate these pathways could potentially prevent damage in PD [26]. Statins have been found to protect against neurotoxicity in PD models, possibly through modulating autophagy, which is associated with improved cell survival and reduced α-synuclein aggregation [27].

The flavonoid fustin protects neurons from 6-OHDA-induced cell death by reducing oxidative stress, calcium overload, and signaling molecules associated with apoptosis [28]. Imbalances in calcium and iron homeostasis contribute to the progression of PD. The pathological hallmarks of PD, such as dopaminergic

neuronal death and intracellular α-synuclein deposition, are central to disturbances in homeostasis and the accumulation of iron and calcium. Understanding these mechanisms is crucial for developing treatments that target the underlying pathophysiology [29].

A study has found that the plant Sideritis scardica exhibits neuroprotective effects in a model of Alzheimer's disease. Its antioxidant and neuroprotective properties can be used as an adjuvant therapy in the treatment of this disease [30]. Neuroplastin, a glycoprotein, is associated with cognitive functions: intellectual abilities and creativity. It plays a protective role by preserving synapses, stimulating calcium signaling, and pathways affected in neuropsychiatric and neurodegenerative diseases [31]. Another study looked at the effects of epigallocatechin gallate (EGCG) in slowing the progression of multiple sclerosis (MS), a rare neurodegenerative disease characterized by α-synuclein aggregation and demyelination of large motor nerves. A randomized, double-blind, placebo-controlled study was conducted involving 92 patients with MS. Participants received either EGCG or a placebo, and after 48 weeks, no significant difference in disease progression was observed between the two groups, as measured by UMSARS motor scores. Although EGCG is generally well-tolerated, it causes hepatotoxicity in some patients, and higher doses (above 1,200 mg) should be avoided. Thus, EGCG does not effectively slow the progression of MS [32].

Another study investigated the neuroprotective potential of Salvia fruticosa (SF) extracts in a cellular model of Alzheimer's disease. SF extracts demonstrated strong antioxidant activity and significant neuroprotective effects against beta-amyloid (Aβ)-induced neurotoxicity, making them promising for possible adjuvant therapy of some neurodegenerative diseases [33]. The combination of two plant phenols, EGCG and ferulic acid (FA), has been tested in transgenic mice modeling cerebral amyloidosis. Combined treatment with EGCG and FA improves brain tissue function, reduces amyloid deposits, and shifts the processing of amyloid precursor protein to non-amyloidogenic pathways. This combination also alleviates neuroinflammation, oxidative stress, and synaptic toxicity, suggesting that EGCG and FA therapy is a promising therapeutic strategy for AD [34].

Calcium (Ca^{2+}) is a major ionic secondary messenger in the central nervous system, regulated by various mechanisms, including organelle stores, membrane channels, pumps, and intracellular Ca^{2+}-binding proteins. Disturbances in Ca^{2+} homeostasis are associated with neurodegenerative diseases, such as AD and PD. However, these disturbances are also implicated in neuropsychiatric disorders with a strong neurological component, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia. Although many studies have focused on plasma membrane Ca^{2+} channels and synaptic Ca^{2+}-binding proteins, increasing evidence suggests that intracellular Ca^{2+} stores, particularly the endoplasmic reticulum, play a crucial role in abnormal neurodevelopment. The review by Klocke et al. includes intracellular Ca^{2+}-processing regulators, such as sarco-ER Ca^{2+} ATPase 2 (SERCA2), ryanodine receptors (RyRs), inositol triphosphate receptors (IP3Rs), and parvalbumin (PVALB), in the onset of the above-mentioned diseases [35].

Ca^{2+} acts as a key second messenger, modulating intracellular cascades in nerve cells. Neurons have developed complex Ca^{2+} signaling pathways to link Ca^{2+} signals to their biochemical targets. Intracellular Ca^{2+} homeostasis relies heavily on the rapid redistribution of Ca^{2+} ions to various subcellular organelles, including the endoplasmic reticulum, which acts as a Ca^{2+} store. It is known that Ca^{2+} released into the neuronal cytoplasm is pumped back into the ER by sarco-/ER Ca^{2+} ATPase 2 (SERCA2), a P-type ion pump ATPase located on the ER membrane. Although SERCA2 is constitutively expressed in nerve cells, its precise role in brain physiology and pathophysiology is not well-characterized. Interestingly, SERCA2-dependent Ca^{2+} dysregulation has been implicated in several disorders affecting cognitive function, including Darier's disease, schizophrenia, Alzheimer's disease, and cerebral ischemia. The study by Britzolaki et al. assesses the key role of SERCA2 in the brain and its role in maintaining neuronal Ca^{2+} homeostasis, which may lead to the development of safer and more effective pharmacotherapies for debilitating neuropsychiatric disorders [36].

Calcium (Ca^{2+}) is a key regulator of cell survival, and intracellular Ca^{2+}homeostasis is essential for proper neuron function. Given the complexity of neurons, various mechanisms finely tune intracellular Ca^{2+} signaling. This review focuses on the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump, an integral ER protein. The well-established role of SERCA is to maintain low cytosolic Ca^{2+} levels by pumping free Ca^{2+} ions into the ER lumen through ATP hydrolysis. It should be noted that SERCA-mediated Ca^{2+} dysregulation is associated with neuropathological conditions, such as bipolar disorder, schizophrenia, PD, and AD. A number of literature data suggest the key role of SERCA in the neurobiology of neuropsychiatric and neurodegenerative disorders, emphasizing the importance of this pump in brain physiology and pathophysiology [37].

Furthermore, SERCA plays a critical role in maintaining Ca^{2+} homeostasis by transporting Ca^{2+} ions from the cytosol into the ER lumen. Impaired SERCA function is associated with impaired Ca^{2+} homeostasis

and ER stress, leading to chronic pathological conditions. Strategies to modulate the activity or expression of SERCA or related signaling pathways may provide a useful approach to combat conditions associated with ER stress. Natural dietary polyphenols, such as resveratrol, gingerol, ellagic acid, luteolin, or green tea polyphenols, have been described for their ability to enhance SERCA activity or influence Ca^{2+} signaling pathways. Viskupicova et al. summarize the potential Ca^{2+}-mediated effects of these polyphenols on SERCA pumps or related signaling pathways, highlighting their mechanisms for regulating Ca^{2+} homeostasis in ER stress conditions [38].

Cuprizone-induced demyelination in the corpus callosum significantly increases CD44 (hyaluronan receptor expressed by glial and progenitor cells) expression and promotes an activated astrocyte-like morphology. During remyelination, CD44 levels remain elevated but show partial normalization with reduced cellular activation. These findings suggest a dynamic role of CD44 in white matter injury and recovery and support its involvement in remyelination processes [39].

The endoplasmic reticulum, mitochondria, and lysosomes are interconnected both physically and functionally, creating sites of close contact between these organelles. As a result, the release of calcium (Ca^{2+}) from the ER, the primary intracellular calcium storage organelle, has an immediate effect on the physiological function of mitochondria and lysosomes. Lysosomes can act as a source of Ca^{2+}, influencing ER-based calcium signaling. Given the important role of mitochondria and lysosomes in cell survival, death, and adaptation, it is becoming increasingly clear that Ca^{2+} signaling from or to these organelles influences these processes. La Rovere and colleagues present recent research on the critical role of Ca^{2+} signaling in regulating cell survival through the control of basal mitochondrial bioenergetics and apoptosis, mitochondrial process and autophagy, lysosomal process, in response to cellular damage and stress [40].

Role of calcium in the mechanism of neuroprotection

In their study, Enders et al [41] focus on calcium channels in neurons and glial cells, with a special target: multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system. While the initial relapsing-remitting stage of MS can be effectively treated with immunomodulatory and immunosuppressive drugs, the subsequent progressive stage remains largely untreatable [41].

Ca^{2+} plays a crucial role in regulating brain functions, including neuronal plasticity, learning, memory, and neuronal survival. Ca^{2+} homeostasis is tightly controlled in both neurons and glial cells. These control points include G protein-coupled receptors, ion channels, Ca^{2+}-binding proteins, and transcriptional networks located in the plasma membrane, mitochondria, and endoplasmic reticulum. The interactions between Ca^{2+} signaling and ROS production can be either beneficial or harmful. In neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, and multiple sclerosis, Ca^{2+}-regulatory systems are compromised, leading to synaptic dysfunction, impaired plasticity, and neuronal death. Disruption of Ca^{2+} homeostasis is critical for cell death and degeneration following ischemic stroke and chronic neurodegeneration in diseases such as Alzheimer's and Parkinson's [42].

Studies reveal that mitochondrial dysfunction is an early marker in the pathogenesis of PD. Mitochondrial abnormalities include damage to the electron transport chain, changes in mitochondrial morphology, mitochondrial DNA mutations, and impaired calcium homeostasis. Mitochondrial dysfunction leads to reduced energy production, increased ROS generation, and stress-induced apoptosis [43].

Ca^{2+} plays a role in activating anti-apoptotic signals in neurons when its levels are moderately elevated, but it also initiates apoptotic processes, mainly caused by its accumulation in the mitochondria. This Ca^{2+} can come from external sources or intracellular stores via various transporters. To assess the role of Ca^{2+} in these processes, it is crucial to investigate all transport mechanisms, as pharmacological modulation of these transport mechanisms can lead to protective or toxic outcomes due to changes in intracellular ion concentrations [44].

Research by Garcia-Martinez et al. reveals that minocycline (a tetracycline antibiotic) at concentrations higher than those typically used to block inflammation and neuron death reversibly inhibits NMDA-induced increases in cytosolic and mitochondrial Ca^{2+} concentrations. Minocycline also reduces intracellular Ca^{2+} levels when added during NMDA stimulation, but not during high-K^{+} depolarization. In addition, it partially depolarizes mitochondria by 5-30 mV, preventing Ca^{2+} uptake and inhibiting NMDA-induced reactive oxygen species formation. The results indicate that mitochondria play a critical role in the neuroprotective effects of minocycline [45]. Minocycline suppresses the accumulation of α-synuclein and prevents the loss of dopaminergic neurons, reduces the inflammatory response in the substantia nigra, and slows neurodegeneration and motor deficits. Taurine (a sulfur-containing amino acid) limits bilirubin-induced damage to neurons by inhibiting Ca^{2+} overload and reducing the activation of pro-apoptotic proteases, such as caspase-3. This study may contribute to the development of taurine as a broad-spectrum agent for the prevention and/or treatment of neuronal

damage in neonatal jaundice [46]. The study by Sun et al. [47] examines the mechanisms of the neuroprotective functions of saponins based on recently reported data from preclinical and clinical studies. These mechanisms include antioxidant effects, modulation of neurotransmitters, anti-apoptosis, anti-inflammatory action, reduction of Ca^{2+} influx, modulation of neurotrophic factors, inhibition of Tau phosphorylation, and regeneration of neural networks [47].

It is known that rasagiline and selegiline (MAOB inhibitors) protect neurons from cell death, which has been demonstrated in various cell and animal models. Razagiline inhibits neurotoxin- and oxidative stress-induced impaired membrane permeability in isolated mitochondria, although the exact mechanism is not fully understood. Studies have investigated the possible mechanism of regulation of mitochondrial pore opening during apoptosis by rasagiline and selegiline. Pore opening was quantitatively measured using a system for simultaneous monitoring of calcium (Ca^{2+}) and superoxide (O^{2}+) ions. The relationship between pore opening, Ca^{2+} efflux, and increased ROS was demonstrated by inhibiting Bcl-2 overexpression upon incubation with cyclosporin A. Razagiline and selegiline inhibit mitochondrial Ca^{2+}efflux through the transitional pores of mitochondrial permeability in a dose-dependent manner. Ca^{2+} efflux has been confirmed as an initial signal in the mitochondrial apoptotic cascade, and the suppression of this efflux may explain the neuroprotective function of rasagiline and selegiline. Quantitative measurement of Ca^{2+} efflux can be used to evaluate the anti-apoptotic activity of both substances. Mitochondrial Ca^{2+} release is thought to be key to neuron death and is a possible target for neuroprotection by MAOB inhibitors – selegiline and rasagiline [48].

CONCLUSION

Studies on the neuroprotective role of calbindin-D28k (CB-D28k) have yielded conflicting results. However, more recent studies show that CB-D28k has a neuroprotective effect on dopaminergic neurons in various models of Parkinson's disease. For example, in a Calb1-transfected dopaminergic cell line (MN9D), treatment with the neurotoxin 6-hydroxydopamine significantly reduces the level of apoptosis by increasing AKT phosphorylation (p-AKT). This suggests that the PI3K/AKT signaling pathway activated by CB-D28k protects dopamine neurons [49].

In the review article by Sánchez et al. [50], it can be summarized that significant progress has been made in uncovering the possible mechanisms related to the effects of Ca^{2+} on the central nervous system and its regulatory and transport mechanisms. It is important to emphasize that this has led to the development of substances with a protective effect on nerve cells, whose mechanism is related to the influence of calcium homeostasis. Although most of them are still in the research phase or exhibit side effects, this remains a new, unexplored area that contributes to the development of new effective therapeutic strategies for neuroprotection in neurodegenerative diseases [50].

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