REVIEW ARTICLE

Roles of microglial calcium channels in neurodegenerative diseases

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Abstract: Microglia are crucial for neurodevelopment, and the maintenance of central nervous system functions. Calcium signals in microglia regulate the neuronal plasticity critical for learning, memory, and neuron survival. CGrowing evidence highlights the pivotal function of calcium channels in microglia, along with their cognate proteins, in modulating oxidative stress, neuroinflammation, and multiple neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. In this review, we summarized the important role and regulatory mechanism of these critical calcium channels and their associated proteins, highlighting their potential as novel therapeutic targets for neurodegenerative diseases.

Keywords: Calcium channels; Microglia; Nervous system; Neurological disorders.

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INTRODUCTION

Microglial cells, serving as the intrinsic immune constituents of the central nervous system (CNS), originate from erythromyeloid progenitor cells in the embryonic yolk sac. They migrate to the CNS during embryogenesis, afterwards, they proliferate and extend throughout the brain parenchyma[1]. Within the cerebral framework, microglia represent the predominant immune cellular subtype, constituting more than 80% of the entire immune cell population[2]. Microglia play a crucial role in cerebral development, monitoring neuronal activity, and modulating learning and memory processes. Meanwhile, they also function as intrinsic phagocytes and sentinels of injury within the brain parenchyma[3,4]. Immune modulators produced by microglia extend to damaged areas and phagocytize cell debris, apoptotic neurons, and synapses. Specifically, microglial activation instigates the secretion of cytokines and chemokines. This process is concomitant with an elevation in intracellular calcium concentrations[5]. Microglia are activated in response to pathogenic insults, marked by alternated gene expression and cellular function. Advanced investigations employing single-cell RNA sequencing elucidate the continuous change of microglia correlating with disease progression. Microglia is highly heterogeneous. A recent study identifies a disease-associated microglial (DAM) signature, hallmarked with the increase of a spectrum of genes, such as Triggering Receptor Expressed on Myeloid Cells 2 (Trem2) and Apolipoprotein E (ApoE)[6,7].

Upon activation, microglia exhibit two distinct polarization patterns: pro-inflammatory and anti-inflammatory. Pro-inflammatory microglia release pro-inflammatory cytokines and chemokines,

whereas anti-inflammatory microglia enhance phagocytosis and secrete cytokines that facilitate tissue repair and neuroprotection[8]. Moreover, imbalanced microglial function has been suggested as a major contributor to various neurological diseases[9-11]. Activation of microglial cells facilitates calcium permeability of the cellular membrane, thereby enhancing the calcium influx into the cytoplasm[12,13]. This transient overload of intracellular calcium concentration is imperative for the activation of microglia[14].

Modifications in the ionic homeostasis of microglia about sodium (Na^+), calcium (Ca^{2+}), potassium (K^+), hydrogen (H^+), and chloride (Cl^-) ions are essential for the activation of microglia. This activation encompasses several physiological processes such as the release of cytokines, cellular migration, proliferation, and the synthesis of reactive oxygen species (ROS). Calcium signaling is particularly salient in the initiation of microglial activation and its related physiological responses[15]. Microgliosis and pathological remodeling of these cells are largely under the control of calcium signaling in microglia[16]. G protein-coupled receptors, ion channels, calcium-binding proteins, and ion exchangers are key regulators of calcium transportation through the membrane of cytoplasm, mitochondria, and the ER[13].

Activated microglia can be observed in chronic degenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). Neurodegenerative diseases are marked by a spectrum of cognitive and behavioral deficits that are attributable to insidious and progressive degeneration of neurons[17]. Aging significantly predisposes individuals to the development and exacerbation of these disorders, with data indicating that upwards of 90% of neurodegenerative cases are diagnosed in persons beyond the age of 60[18]. Additionally, aging causes microglia to respond to external stimuli more strongly[19]. The dysregulation of microglial transitional responses is thought to be the cause of persistent inflammation in the aging cerebral environment[20].

Intracellular calcium dysregulation is commonly observed during aging and neurodegeneration. Disruption in microglial calcium signaling has been implicated in the pathogenesis of several CNS disorders[21]. Cellular processes that contribute to the homeostasis of calcium are also disrupted in neurodegenerative diseases. Oxidative stress, disordered energy metabolism, and modifications in disease-related proteins all contribute to calcium-dependent synaptic dysfunction. Altered calcium homeostasis plays a critical role in the long-term neurodegenerative processes that contribute to both AD, PD, and other inflammation-mediated neural damage[22]. The role and regulatory role of microglial intracellular ionic homeostasis in neurodegenerative diseases are still unclear.

This review synthesizes recent developments in how calcium homeostasis contributing to the development neurodegenerative diseases while highlighting the potential emergent therapeutic strategies aiming at calcium homeostasis in the treatment of those diseases.

Ca^{2+} HOMEOSTASIS IN MICROGLIAL FUNCTION

Ca^{2+}, stored in the ER and mitochondria, serves as a vital secondary messenger, functioning both intracellularly and intercellularly[23]. Ca^{2+} functions as information-carrying messengers due to their reversible complexation with proteins[24]. Intracellular Ca^{2+} is implicated in various signaling activities such as enzyme activation, exocytosis, gene expression, programmed cell death, synaptic communication, and regulation of ROS[25]. Intracellular calcium signaling in neurons is pivotal for neural differentiation, the consolidation of memory, and the regulation of synaptic plasticity. Similarly, dysregulation of calcium homeostasis can induce neuronal damage and cell death[22]. Under resting state, the intracellular Ca^{2+} level is maintained at a low level (~10^{-7} M)[26]. Upon activation, Ca^{2+} influx is tightly controlled by complex molecular regulatory mechanisms.

Many microglial functions are mediated by calcium ions[27-29]. Specifically, the activation of microglia is associated with an elevation of intracellular calcium levels, a cascade that is essential for triggering the secretion of cytokines and chemokines[5]. Elevated intracellular calcium levels initiate signaling cascades, which are crucial for biological processes, including the activation of enzymatic pathways regulating gene transcription, cell proliferation, differentiation, and migration[30]. Normally, microglia are considered non-excitable cells[13]. Microglial intracellular calcium signaling is modulated by electrochemical calcium influx through channels and receptors, and efflux via various calcium pumps and exchangers against the concentration

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gradient[31]. The differential distribution of these channels and transporters allows distinct intracellular compartments to manage calcium uniquely. In microglia, calcium channels and transporters facilitate the entry and exit of Ca^{2+}, preserving intracellular Ca^{2+} balance[13].

Recent studies have revealed that dysregulated calcium signaling is associated with a spectrum of neurodegenerative diseases, such as AD, PD, Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD)[32,33]. This is connected with changes in calcium ion buffering capacity, activity of calcium channels and other calcium regulator proteins[34,35], and impaired mitochondrial and ER calcium processing[36], disrupted energy metabolism, and oxidative stress[22].

TYPES OF Ca^{2+} CHANNELS IN MICROGLIA

On the cytoplasmatic membrane of microglial cells, there are multiple types of calcium channels and calcium-related proteins, including store-operated Ca^{2+} entry (SOCE) channels, transient receptor potential (TRP) channels, voltage-gated Ca^{2+} channels (VGCCs), calcium homeostasis modulator family protein 2 (Calhm2), and Na+ /Ca^{2+} exchanger (NCX) (Figure 1).

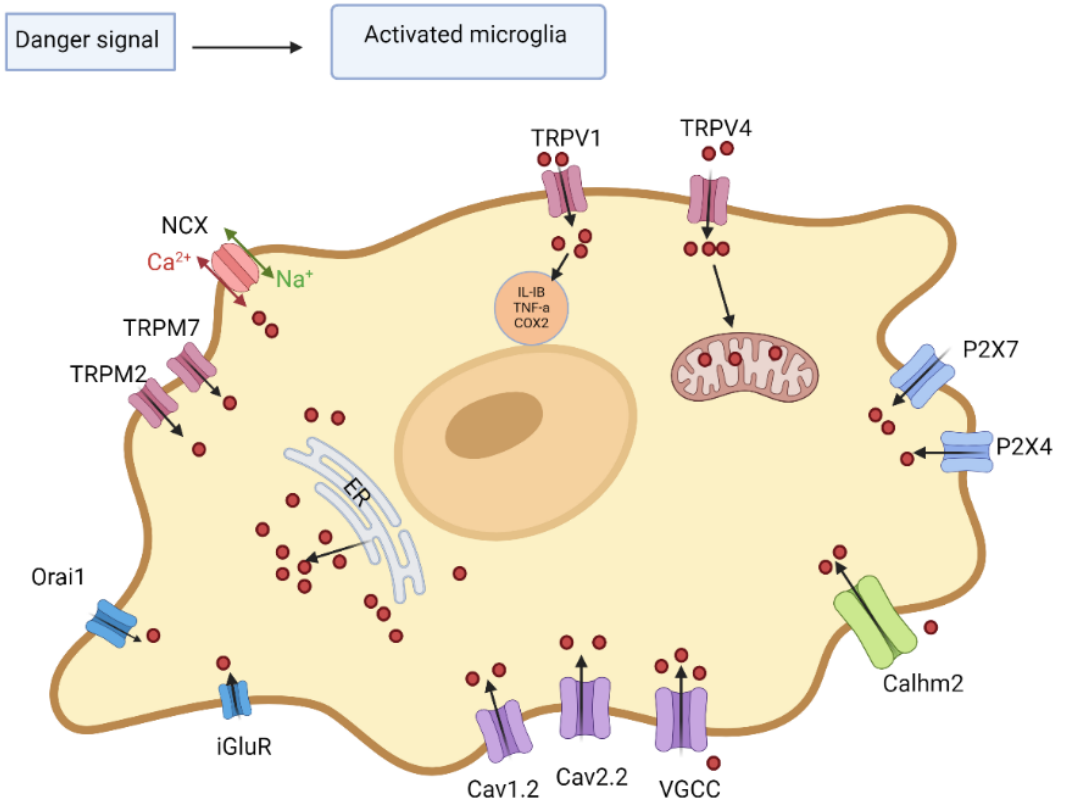

Figure 1. Activated microglial cell calcium channels and their related proteins regulating ion homeostasis mechanism in pathologic conditions. Schematic drawing of a microglial cell, illustrating receptors/channels known to increase calcium channels during pathologic conditions. Ca^{2+} entry pathway: Store-operated Ca^{2+} entry channels, Orai1; Transient receptor potential channel, TRPM2, TRPM7, TPPV1, TRPV4; Voltage-gated Ca^{2+} channels, Cav1.2, Cav2.2; The calcium homeostatic regulatory protein, calhm2. Receptor-operated Ca^{2+} channels, P2X4, P2X7; Bidirectional ion transporter: Sodium-calcium exchanger (NCX), facilitating the exchange of Ca^{2+} efflux for Na^{+} influx.

SOCE channels: Microglial cells exhibit high levels of SOCE, mediated by stromal interaction molecules (STIM1/2) and Orai plasma-membrane pore-forming subunits (Orai1/2/3)[37]. Purines are released from damaged brain cells, which stimulate microglia to migrate to injury sites and initiate phagocytosis. These processes are regulated by calcium-dependent purinergic signaling pathways,

involving either P2Y receptor-induced internal calcium release or P2X receptor-mediated plasmalemmal calcium influx[38]. Interestingly, it is reported that SOCE contributes to the purinergic activation in microglia[37,39].

TRP channel: TRP channels are typical non-selective cation channels, participating in calcium transportation across the plasma membrane and ER, thus maintaining microglial calcium homeostasis and dynamics[40,41]. TRP channels are ubiquitously present within the CNS, contributing to the regulation of intracellular calcium concentration ($[Ca^{2+}]i$) by facilitating calcium influx through the cytoplasmatic membrane and calcium release from intracellular stores[42]. Based on sequence homology, the 28 mammalian cation channels in the TRP family are categorized into six subfamilies: TRPC, TRPM, TRPV, TRPA, TRPP, and TRPML[43,44]. Specifically, TRPV, TRPM, and TRPC channels, located in microglia, participate in diverse functions such as osmotic regulation, cytokine production, cell proliferation, death, microgliosis, and oxidative stress response[43]. TRPV1 activity in microglia is primarily linked to neurotoxicity via pro-inflammatory cytokine production and induction of oxidative stress[44]. TRPV1, mainly present in intracellular organelles such as mitochondria, significantly contributes to triggering microglial migration[45]. TRPV1 activation elicits an elevation in mitochondrial calcium levels and induces membrane depolarization, subsequently leading to an upsurge in ROS generation[46].

VGCCs: VGCCs are commonly expressed on excitable cells. It contains several subunits, the α1, α2/δ, and β subunits[47,48]. Among these subunits, the α1 subunit is the principal component, containing the voltage-sensing domains and defining the unique properties characteristic of each VGCC subtype[47,49-52]. Voltage-gated calcium channels (VGCCs) are categorized into various families, such as Cav1, Cav2, and Cav3, each comprising multiple subtypes[53]. In diverse cellular contexts, the entry of Ca^{2+} into the cytosol through VGCCs regulates the enzymatic activity, gene expression, and a variety of biochemical mechanisms. The Cav1 calcium channel family is comprised of four distinct subfamilies, named Cav1.1 to Cav1.4, each of which exhibits a characterized sensitivity to calcium channel antagonists[54]. Among the Cav1 family, Cav1.3 has been reported to be associated with the pathophysiological mechanisms underlying PD. The Cav1.3 channel is reported to play a critical role in stabilizing pacemaker currents in substantia nigra pars compacta (SNc) dopaminergic neurons[55], and pharmacological blockade of this channel inhibits neuronal apoptosis in the SNc, and improves behavioral deficiencies in PD murine models[56]. Additionally, microglia have been reported to express Cav1.2 and Cav2.2 channel subtypes[53]. VGCCs remain closed at physiological or resting membrane potential and activate upon membrane depolarization[57]. The Cav family translates alterations in the cell surface membrane potential into localized increases in $[Ca^{2+}]i$[58].

Calhm2: The calcium homeostatic regulatory protein family (CALHMs) constitutes voltage-gated non-selective ion channels that play a crucial role in taste signaling and attenuating neuronal toxicity by facilitating major adenosine triphosphate (ATP) release[59]. The CALHMs contain 6 identified members (Calhm1 to Calhm6)[59]. The association between CALHMs and neurodegenerative disease research has recently drawn wide attention. Calhm1 encodes a 346-amino acid protein that regulates the permeability of calcium ions across the plasma membrane. The Calhm1 gene harbors a nonsynonymous polymorphism, P86L, which has been linked to AD development, potentially through the alteration of β-amyloid levels[60]. Moreover, Calhm1 is reported to express on type II taste bud cells and contributes to the release of ATP through a voltage-gated channel and affects taste perception[61]. Calhm1 regulates calcium homeostasis, influences the production of amyloid beta (Aβ), and modulates neuronal cell susceptibility to toxicity induced by Aβ[62]. Calhm1 expression is observed in murine cerebral tissues, yet it is absent in human cerebral samples. Moreover, calhm1 knockout mice do not exhibit any discernible cognitive abnormalities[63]. Calhm3 has been shown to form an isomeric channel with Calhm1, and taste-evoked ATP release was eliminated when Calhm3 was deleted[64]. Under cryo-EM conditions, Calhm2 is observed to be a quadruple transmembrane protein, and Calhm2 channels can form both gap junctions and undecameric channels[65]. It has been discovered that Calhm2 mediates the transfer of calcium and ATP, controlling calcium and ATP concentrations within and outside of cells[61,63-67]. It is important to note that the functional and biological significance of the remaining CALHM family members, specifically Calhm4 to Calhm6, remains to be elucidated.

Receptor-operated Ca^{2+} channels: Purinergic signaling is pivotal to the physiology of microglia

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in both physiological and pathological conditions[54]. There are seven subtypes of ligand-gated cation channel P2X: P2X1-7. Activation of these channels in reactive microglia predominantly exerts detrimental consequences, including neuronal hyperexcitability and inflammation[68]. The P2X4 subtype is particularly noted for its high calcium permeability and undergoes tight regulatory control in its translocation to the plasma membrane, with a predominant localization within lysosomal compartments. Expression of P2X4 receptors is notably increased in reactive microglial phenotypes discernible in an array of neuropathological contexts, including neuropathic pain, status epilepticus, and multiple sclerosis[69,70]. The P2X7 receptor is another prominent Ca^{2+} entry channel in microglial cells[71], which regulates IL-1β and IL-18 release, microglial activation, and neuroinflammation[72]. The P2X7 receptor in microglial cells acts as a pattern recognition receptor (PRR) that detects extracellular ATP, a danger-associated molecular pattern (DAMP) released from cells compromised by traumatic brain injury or neurodegeneration[73]. Despite the abundant expression of P2X7 in microglia, the channel remains inactive under normal physiological conditions, thereby limiting the intracellular ATP concentration lower than the high micromolar levels required for ion channel activation[74].

G protein-coupled receptors (GPCRs): Over 90% of non-sensory GPCRs are located in the brain. Diminished extracellular Ca^{2+} concentrations activate G protein-coupled calcium-sensing receptors, triggering the phospholipase C (PKC) signaling pathway. The presence of these receptors in microglial cells suggests their involvement in maintaining local ionic balance[75].

NCX: The NCX is a bidirectional ion transporter, facilitating the exchange of Ca^{2+} efflux and Na+ influx[38]. In physiological states, the NCX primarily facilitates the influx of Na^{+} along their concentration gradient into the cellular matrix while concurrently extruding calcium ions (Ca^{2+})[76]. Conversely, in pathological conditions, the NCX predominantly engages in reverse mode, which is marked by disrupted calcium homeostasis and influences a plethora of calcium-dependent processes occurring at both cellular and systemic levels[77].

MICROGLIAL ION CHANNELS IN AD

A close association between neuronal calcium dysfunction and the progression of AD (Figure 2), characterized by the accumulation of beta-amyloid (Aβ) plaques, neurofibrillary tangles, and neuroinflammation[78,79], raises a calcium-centered hypothesis for the disease[80,81], which states that AD begins with early dysregulation of calcium signaling, precipitating neurodegeneration through mitochondrial dysfunction, oxidative stress, and neuroinflammation[82]. Increased basal Ca^{2+} levels, rapid depletion of Ca^{2+} from ER stores, and a reduced response to ATP stimulation are reported in microglial cells of AD patients, as compared to healthy controls[83].

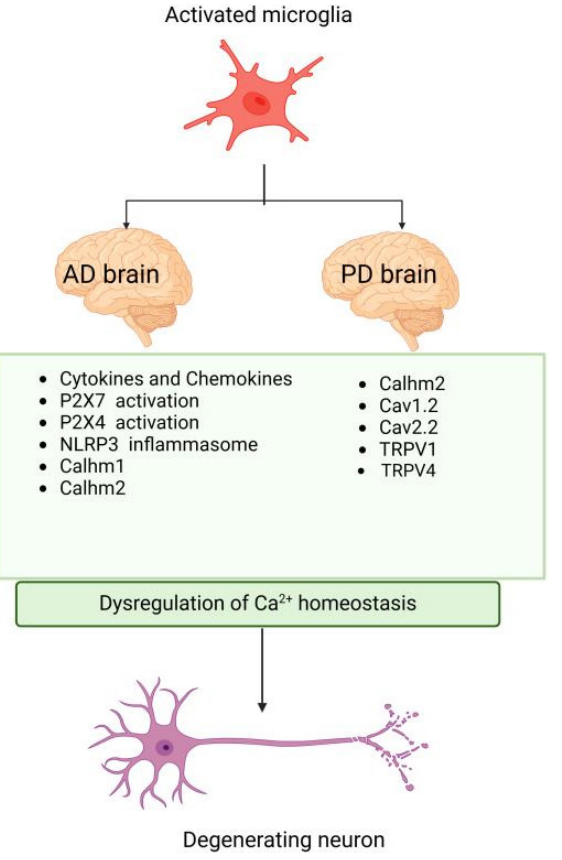

Figure 2. Schematic diagram of microglial Ca^{2+} homeostasis dysregulation in the brain of AD patients and PD patients. In AD brain: cytokines and chemokines; P2X4R, purinergic P2X4 receptor; P2X7R, purinergic P2X7 receptor; NLRP3, NOD-like receptor pyrin domain containing 3; Calhm1, 2, Calcium homeostasis modulator family member 1, 2; In PD brain: Calhm2, Calcium homeostasis Modulator family member 2; L-type VGGCs, L-type voltage-gated calcium channels, Cav1.2, Cav2.2; Transient receptor potential channel; TRPV1, TRPV4.

Numerous calcium channels and receptors (Figure 2), including Calhm2, P2X receptor, VGCCs[84], SOCE channels, and TRP channels, play a crucial role in mediating the influx of extracellular calcium[85,86]. Calhm1 P86L single nucleotide polymorphism has been identified as a potential risk factor for AD[59]. Concurrently, Calhm2 is expressed in the CNS. Our previous research shows that Calhm2 levels increase in brain samples from AD patients. Both conventional and microglial knockout of Calhm2 inhibit the inflammation, Aβ deposition/plaque formation, and cognitive impairments of 5×FAD mice. Mechanistically, Calhm2 knockout decreases the influx of extracellular calcium in microglia, reduces microglial proinflammatory activity, and enhances their ability to phagocytose Aβ, thereby rebalancing inflammation and phagocytosis[87].

NCX, particularly NCX3, is implicated in neuroprotection in AD, with its dysfunction linked to neuronal death via caspase-12 activation[88]. Moreover, upregulation of P2X7 is observed in the brains of AD patients, particularly in microglia around amyloid plaques[89,90]. P2X7 facilitates the release of Aβ-induced chemokines, while its deletion attenuates brain lesions and cognitive impairments in a transgenic amyloid mouse AD model[89]. P2X7 receptor expression is increased in both human microglial cells following exposure to Aβ42, and microglial cells isolated from AD patients[91]. Activation of the P2X7 receptor in microglia and peripheral immune cells are known to trigger the NLRP3 inflammasome, leading to caspase-1 activation and the subsequent conversion of pro-IL-1β into its active form, IL-1β[92]. Disruption of NLRP3 inflammasome activation, through pharmacological or genetic knockout, inhibits Aβ42-related microglial activation and neuroinflammation, enhances Aβ clearance through enhanced microglial phagocytosis, and substantially restores cognitive function in APP/PS1 mice[93]. Recent research has demonstrated that activation of P2X7R promotes microglial cells migration but decreases their phagocytic capacity[94]. Moreover, both pharmacological inhibition and genetic downregulation of P2X7R effectively prevent Aβ-induced activation of microglial cells and neuroinflammation *in vitro* and *in vivo* studies[92,95].

Under physiological conditions, P2X4 is expressed at a low level[96]. However, under pathological conditions, P2X4 is upregulated in reactive microglia, contributing to brain-derived neurotrophic factor (BDNF) release and the inflammatory response[68,97]. Reactive microglia show increased P2X4 receptor expression linked to neuroinflammation, with an elevated level of P2X4 receptors in plaque-associated microglia (PAM). Current findings suggest that microglial P2X4 facilitates lysosomal ApoE degradation, thereby indirectly impacting Aβ clearance in AD, which may contribute to synaptic dysfunction and cognitive decline, including memory impairment. Deletion of P2X4 reverses these cognitive deficits in APP/PS1 mice, suggesting its direct role in AD-associated topographic and spatial memory changes[98].

MICROGLIAL ION CHANNELS IN PD

PD ranks as the second most prevalent neurodegenerative disease associated with aging[99]. Typical symptoms of PD include bradykinesia, limb rigidity, and tremors. The key pathogenic characteristics are the gradual loss of dopaminergic (DA) neurons in the SNc and the intraneuronal inclusions, also known as Lewy bodies (LBs), which contain a significant amount of fibrillar alpha-synuclein (α-syn) aggregates[100,101]. Age, genetics, environment, immunological condition, and sex are all risk factors for developing PD[102-104]. A typical characteristic of PD is neuroinflammation, evidenced by astrocyte and microglia activation in the brain[105]. Moreover, disruption of calcium homeostasis is also frequently observed in models of both sporadic and familial PD[106].

In our recent investigation employing the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model, it was observed that both through conventional knockout and microglial-specific conditional knockout of Calhm2, markedly attenuated dopaminergic neuronal degeneration. This was accompanied by a reduction in the microglial population and a suppression of neuroinflammatory responses, culminating in a notable amelioration of motor impairments in murine models of PD[107].

Growing evidence demonstrates the involvement of Cav1.2 and Cav2.2 channels in the microglial cells associated with PD (Figure 2). The Cav1.2 channel, predominantly localized to the cell soma, is integral to the modulation of gene expression, whereas the Cav2.2 channel, resident at axonal terminals, is instrumental in orchestrating neurotransmitter release[108]. Notably, both Cav1.2 and Cav2.2 channels contribute to gene expression regulation

in microglia[109]. Furthermore, the use of specific antagonists targeting these VGCCs results in modified expression patterns of activation markers in microglial cells[53]. Cav1.2 channels in microglia possess neuroprotective properties and could be crucial in mitigating neurodegenerative disorders in PD[110]. The Cav1.2 channel has been reported to function as an inhibitory modulator of M1 activation and a facilitative regulator for M2 activation[111]. Blocking the Cav1.2 channel in microglia cells in an MPTP-induced PD mice model aggravates neurodegeneration, extends M1-type cytokine release, and exacerbates behavioral deficits, worsening PD symptoms[112]. However, inhibiting Cav2.2 channels in microglia ameliorates symptoms of age-related brain inflammation[109]. In the MPTP-induced PD mice model, the blockade of microglial Cav2.2 channels markedly diminished microglial accumulation at the SNc, and notably ameliorated functional deficits, thereby suggesting the neuroprotective role of microglia in PD[112], and that Cav2.2 channel and Cav1.2 channel have complimentary functions in microglia. These results indicate that Cav1.2 and Cav2.2 channels might act as regulation in the transition between the microglial M1 and M2, providing potential targeting for the treatment of chronic inflammatory disorders.

The TRPV1 channel, permeable to Ca^{2+}, is a temperature-sensitive cationic channels[113,114]. Recent studies have revealed that conjugated complexes comprised of TRPV1 antibody (anti-TRPV1) and ultra-small Cu2-xSe nanoparticles are capable of stimulating the TRPV1 channel on microglial cells. This activation induces a Ca^{2+} influx, subsequently triggering the ATG5 protein and the Ca^{2+}/CaMKK2/AMPK/mTOR signaling cascade. Such processes facilitate microglial autophagy to phagocytose, degradation of α-synuclein, and lead to the improvement of their athletic ability and memory function[115], suggesting the TRPV1 channel could act as a molecular target in the treatment of PD.

CALCIUM CHANNELS AS PROSPECTIVE PHARMACOLOGICAL TARGETS FOR NEURODEGENERATIVE DISEASES

Current clinical therapy for AD and PD only provides limited efficacy. Additionally, these treatments may precipitate psychiatric adverse effects. One of the treatment targets for AD and PD is neuroinflammation[116]. However, the activation of microglia can produce a variety of proinflammatory cytokines. The effect of targeting a single inflammatory factor in the treatment of AD and PD is still uncertain. Therefore, innovative treatments for neurodegenerative diseases are critically needed. Recent studies have shown that alterations in calcium signaling involve many aspects of key features associated with AD and PD, suggesting that calcium homeostasis is a therapeutic target[117]. Calcium antagonists, notably L-type Ca^{2+} channel inhibitors, are used clinically in the management of cardiovascular pathologies, including hypertension and cardiac arrhythmias, functioning through the inhibition of voltage-dependent calcium channels[118,119]. Moreover, calcium channel blockers might also reduce the risk and improve cognition in AD and PD.

L-type calcium channel blockers, such as Verapamil and Nimodipine, have been reported to elicit anti-inflammatory responses in microglial cells and provide neuroprotective effects[120]. Verapamil not only inhibits calcium influx into neurons but also targets brain microglia, attenuating inflammation and protecting dopaminergic neurons from damage. Verapamil exhibits neuroprotective properties, not only through blocking neuronal L-type calcium channels but also by inhibiting the excessive production of microglial activation. Moreover, Nicardipine has been documented to modulate calcium signaling within glial cells[121,122]. Studies have shown that the calcium channel blocker Nicardipine can reduce pro-inflammatory transcription factor activation and inhibit microglial activation, providing it a potential therapeutic agent for inflammation-associated neurodegenerative diseases[123].

Recent studies have shown that the downregulation of intracellular calcium concentrations, achieved through the targeted inhibition of calcium channel proteins, facilitates a decrease in the levels of neuroinflammation[124]. Our previous study demonstrates that the conditional knockout of Calhm2 in microglial markedly reduces Aβ deposition/plaque formation, concurrently enhancing cognitive capabilities in the AD murine model. Similarly, knockout of Calhm2 also inhibits neuroinflammation, and rescues the decrease of tyrosine hydroxylase (TH)-positive neurons in mouse PD models induced by the MPTP, thereby improving mechanical defects in Parkinson's disease model mice, which implies that Calhm2 is instrumental in the microglial modulation of neuroinflammation[107]. This finding suggests that targeting

microglial Calhm2 could represent a promising strategy for the new therapeutic interventions for neurodegenerative diseases[125].

CONCLUSION AND FUTURE PERSPECTIVE

In conclusion, the homeostasis of intracellular calcium (Ca^{2+}) is crucial in governing neuronal physiological processes such as proliferation, maturation, electrical activity characteristics, synaptic adaptability, and cognitive functions. Dysregulation of Ca^{2+} homeostasis in cells is associated with various neuropathological states, including necrotic and apoptotic cell death, impaired autophagic mechanisms, and neuronal degeneration. This review summarizes the significant role of calcium channels in the activation of microglia and the pathogenesis of diseases associated with neuroinflammation, especially in AD and PD, and highlights the relationship among calcium homeostasis, neuroinflammation, and neurological disorders, offering novel therapeutic strategies. Therefore, exploring effective Ca^{2+} ion channel inhibitors and elucidating their role in neurological diseases will be crucial in the future.

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Author Contributions

Shasha Wang reviewed the literature, wrote the manuscript, and prepared the figures; Jinyu Zhang, Jingdan Zhang, and Ao Li reviewed the manuscript; Jinbo Cheng and Zengqiang Yuan performed a comprehensive review of the literature.

Conflicts of Interest

The authors declare no conflicts of interest. ♦

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