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Original Article

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Dysregulation of Calcium Signaling Homeostasis in the Onset and Progression of Alzheimer's Disease and Its Therapeutic Potential

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Abstract

Alzheimer's disease (AD), the most common neurodegenerative disorder, accounts for 60–70% of all dementia cases and is clinically characterized by progressive memory impairment, executive dysfunction, and neuropsychiatric symptoms. The traditional pathogenic framework has focused on β-amyloid (Aβ) deposition and Tau neurofibrillary tangles; however, recent trials of Aβ-targeting monoclonal antibodies (e.g., aducanumab, lecanemab) have shown that plaque reduction does not consistently translate into robust neuroneuroneurocognitive benefit, suggesting that AD pathogenesis extends far beyond protein aggregation alone. The "calcium hypothesis" posits that Aβ and Tau aggregation represent downstream events, whereas disruption of neuronal calcium homeostasis is an upstream driver that may precede overt pathology. Disturbances in calcium signaling act as a central hub linking proteinopathy, synaptic dysfunction, neuronal hyperexcitability, glial activation, vascular dysregulation, and metabolic failure. Dysregulated calcium homeostasis in AD encompasses coordinated abnormalities at the level of membrane channels (e.g., L-type voltage-gated calcium channels [L-VGCCs], TRPC family), endoplasmic reticulum (ER; ryanodine receptors [RyRs]), mitochondria, lysosomes, and glial cells, thereby coupling protein pathology to synaptic failure, energy deficits, neuroinflammation, and impaired cerebral perfusion. Notably, all currently approved symptomatic AD treatments—including the noncompetitive NMDA receptor antagonist memantine and acetylcholinesterase inhibitors—impinge on calcium signaling pathways. Emerging agents targeting RyRs (e.g., dantrolene, S107), TRPC3 antagonists (Pyr3, Pyr10), and lysosomal calcium channel inhibitors (e.g., Ned-19) have also demonstrated therapeutic potential in preclinical models. Here, we systematically review (i) the physiological roles of calcium signaling homeostasis in neuronal function, (ii) the manifestations and mechanisms of calcium dyshomeostasis in AD, (iii) the impact of abnormal calcium signaling on cognition and neuronal network function, and (iv) the therapeutic potential and drug development progress of calcium channel–related targets. We further discuss the challenges and prospects of cross-channel network analysis and genotype-informed combination strategies, with the goal of providing a theoretical foundation for calcium homeostasis–targeted therapies in AD.

Keywords

Alzheimer's disease; calcium signaling homeostasis; voltage-gated calcium channels; neuroinflammation

1. Introduction

Alzheimer's disease (AD) accounts for approximately 60-70% of all dementia cases, with its primary clinical features including progressive memory impairment, executive dysfunction, and neuropsychiatric symptoms. Historically, research has focused on β-amyloid (Aβ) deposition and Tau neurofibrillary tangles. However, recent studies on monoclonal antibodies targeting Aβ, such as aducanumab and lecanemab, although able to reduce plaque burden, have not shown a significant improvement in neuroneuroneurocognitive function, suggesting that the pathogenesis of AD may extend beyond the singular mechanism of "protein deposition"[1].

The calcium hypothesis posits that Aβ and Tau may merely be downstream products, while the true early driver of the

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disease is the disruption of neuronal calcium homeostasis. Abnormal calcium signaling may precede visible pathological deposition and plays a central role in synaptic dysfunction, neuronal hyperexcitability, glial cell activation, vascular constriction, and low perfusion. It serves as a hub that connects "proteinopathy, synaptic function, energy metabolism, and systemic disease." Dysregulation of calcium homeostasis plays an early driving role in AD pathogenesis and involves coordinated abnormalities across several levels, including membrane calcium channels (e.g., L-VGCCs, TRPC), the endoplasmic reticulum (e.g., RyRs), mitochondria, and lysosomes. These disruptions impact synaptic function, energy metabolism, neuroinflammation, and vascular perfusion, ultimately linking protein pathology with neuroneuroneurocognitive decline.

Currently, the FDA-approved symptomatic treatments for AD, such as the non-competitive NMDA receptor antagonist memantine and acetylcholinesterase inhibitors, all act on calcium signaling pathways. Emerging novel targets, such as RyR modulators (e.g., dantrolene, S107), TRPC3 antagonists (e.g., Pyr3, Pyr10), and lysosomal calcium channel inhibitors (e.g., Ned-19), also show potential therapeutic value[2].

This review aims to provide a comprehensive overview of the physiological roles of calcium signaling homeostasis in neuronal function, the manifestations and mechanisms of calcium dysregulation in AD pathology, the effects of calcium abnormalities on neuroneuroneurocognitive function and neuronal networks, and the therapeutic potential and drug development progress related to calcium channels and associated mechanisms. The goal is to provide a theoretical foundation for the development of AD treatment strategies targeting calcium homeostasis.

2. Physiological roles of calcium signaling homeostasis in neuronal function

Calcium signaling homeostasis is a crucial process by which neurons maintain dynamic intracellular calcium ion concentration balance. As an important second messenger, calcium ions are maintained at concentrations of 50-300 nmol/L in resting cytoplasm, and upon activation, their concentration rapidly rises to the micromolar range. This dynamic regulation involves a complex network of mechanisms that participate in the modulation of neuronal function[1]. This homeostasis is controlled by voltage-gated calcium channels (VGCCs) on the cell membrane, receptor-operated calcium channels (such as NMDA receptors [NMDARs] and α7 nicotinic acetylcholine receptors [α7nAChRs]), and intracellular calcium stores, such as the endoplasmic reticulum (ER), where ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (IP_3Rs) mediate calcium release. Additionally, calcium-buffering proteins (e.g., CALB1) and mitochondrial calcium uptake and release play pivotal roles in regulating this balance. The ER's RyRs and IP_3Rs mediate calcium release, while the sarco/endoplasmic reticulum calcium ATPase (SERCA) pumps calcium back into the ER. Mitochondria, in turn, take up ER-released calcium to support oxidative phosphorylation and ATP synthesis, thereby meeting the high metabolic demands of neurons[3]. L-type voltage-gated calcium channels (L-VGCCs), such as Ca_V1.2, play a central role in integrating synaptic signals and maintaining neuronal firing. Their activity follows a narrow inverted U-shaped relationship: both hypoactivity and hyperactivity of calcium channels reduce neuronal firing, whereas excessive activation of L-VGCCs can engage calcium-dependent SK potassium channels (e.g., SK3), reducing delayed firing and impairing working memory[4]. The RNA-binding protein DJ-1 regulates this process by suppressing the translation of Ca_V1.2 and its auxiliary subunit α2δ2, thereby lowering dendritic L-VGCC calcium activity and altering neuronal excitability[5]. Furthermore, RyRs amplify calcium signals through calcium-induced calcium release (CICR), leading to calcium-dependent inactivation of VGCCs and activation of SK potassium channels. This mechanism regulates afterhyperpolarization currents (e.g., I_AHP), thereby modulating neuronal firing patterns[6]. The BIN1 protein interacts with Ca_V1.2 in glutamatergic neurons, regulating calcium transients and electrical activity. Loss of BIN1 increases Ca_V1.2 expression and reduces activity-dependent endocytosis, disturbing neuronal excitability balance[7].

During synaptic transmission, the precise spatiotemporal regulation of calcium signaling is a core element in neurotransmitter release. The rapid calcium influx mediated by presynaptic membrane VGCCs converts membrane depolarization signals into neurotransmitter release signals. Local calcium concentration changes trigger synchronous release via low-affinity calcium sensors such as synaptotagmin-1, while overall increases in calcium levels accelerate vesicle recruitment and regulate short-term plasticity. The ER is widely present at axon terminals, and calcium release through RyRs and IP_3Rs plays a key role in regulating synaptic transmission. For instance, during high-frequency stimulation, RyR-mediated calcium release promotes asynchronous neurotransmitter release, thereby maintaining the excitability balance of neural networks[8,9]. Postsynaptically, NMDARs exhibit high calcium permeability and act as coincidence detectors, driving long-term potentiation (LTP). Additionally, α7 nicotinic acetylcholine receptors (α7nAChRs) modulate synaptic transmission and mediate calcium influx, contributing to information processing[10]. The maintenance of neuronal plasticity highly depends on calcium homeostasis. In hippocampal synaptic plasticity, NMDAR-mediated calcium influx activates

downstream signaling pathways that regulate LTP and dendritic spine remodeling. RyRs in the hippocampus modulate cytosolic and nuclear calcium signals through CICR, activating the phosphorylation of the transcription factor CREB and the expression of the Npas4 gene, thereby regulating structural synaptic plasticity. Blocking RyR function significantly inhibits LTP, long-term depression (LTD), and dendritic spine plasticity. For example, RyR3 predominantly amplifies calcium signals in dendritic spines, playing a role in synaptic plasticity, while RyR2 is localized in dendrites and somata to regulate gene expression[11]. Furthermore, Ca_V1.2 is closely localized to the dendritic spines of pyramidal cells in layer III of the dorsolateral prefrontal cortex (dlPFC), interacting with the calcium-storing ER. It participates in the regulation of delay-period neuronal firing associated with memory by promoting endogenous calcium release. The precise regulation of its expression and activity is critical for working memory.

3. Manifestations and mechanisms of calcium signaling imbalance in Alzheimer's disease

3.1 ER and mitochondrial calcium dysregulation

In AD, dysregulation of ER and mitochondrial Ca^{2+} is a core feature of calcium signaling disturbance, driven by altered channel function and organelle dysfunction. Pathological hyperactivation of RyRs is a key initiating event. In aged nonhuman primate dlPFC, enhanced PKA phosphorylation of RyR2 (pS2808-RyR2) increases pathological Ca^{2+} leak, which correlates with abnormal Tau phosphorylation[12]. Aβ oligomers can directly sensitize RyRs, markedly increasing channel open probability. The RyR3 isoform shows brain region–specific changes during AD progression, and Aβ peptides selectively upregulate RyR3 expression. In familial AD PS1 mutant mouse models, RyR expression and RyR-mediated Ca^{2+} responses are enhanced in hippocampal and cortical pyramidal neurons, whereas the negative RyR modulator dantrolene reverses this phenotype[10]. In neurons from AD models and patients, excessive RyR-mediated Ca^{2+} release promotes synaptic structural and functional deficits, impairs lysosomal proteolysis, enhances Tau hyperphosphorylation, and facilitates $A\beta_{42}$ aggregation, ultimately driving neuroneuroneurocognitive decline[3]. Mechanistically, $A\beta_{42}$ activates NMDAR-mediated Ca^{2+} influx, which further stimulates RyR-dependent CICR, creating a vicious cycle of ER Ca^{2+} leak and mitochondrial Ca^{2+} overload[11]. $A\beta_{42}$ oligomers also directly target hippocampal RyRs, increasing ER Ca^{2+} release, disrupting cytosolic Ca^{2+} homeostasis, and—under high-frequency stimulation—overactivating presynaptic BK channels, which suppress neurotransmitter release and impair LTP, while single-evoked transmission shows enhanced release probability, producing complex effects on synaptic plasticity[8].

Targeting RyRs shows significant therapeutic promise. A RyR2 E4872Q mutation, which shortens RyR2 open time and increases A-type K^+ currents in CA1 pyramidal neurons, limits hyperexcitability and ameliorates memory deficits, neuronal loss, and spine loss in 5xFAD mice in a manner independent of Aβ burden[13]. Rycal compounds such as S107 stabilize calstabin2 binding to the RyR2 macromolecular complex, reducing Ca^{2+} leak in AD models, attenuating amyloid precursor protein (APP) processing and Aβ generation, and rescuing hippocampal synaptic plasticity and cognition. The β-blocker R-carvedilol similarly shortens RyR2 open time, pharmacologically limiting hyperexcitability and memory impairment in AD models[6,14]. Dantrolene normalizes RyR-Ca^{2+} signaling, alleviating mitochondrial Ca^{2+} overload, reducing ROS, improving mitophagy, and rescuing LTP and post-tetanic potentiation (PTP). Genetically abolishing the PKA phosphorylation site on RyR2 (RyR2-S2808A) prevents hyperphosphorylation, calstabin2 dissociation, and Ca^{2+} leak, and improves neuroneuroneurocognitive function[14].

3.2 Abnormal expression and regulation of VGCCs and calcium-related proteins

Aberrant expression and regulation of VGCCs is another key contributor to calcium dyshomeostasis in AD. For L-type channels, Ca_V1.2 (encoded by CACNA1C) is critical for dendritic structure and synaptic plasticity. Conditional deletion of Ca_V1.2 in forebrain glutamatergic neurons reduces dendritic complexity and spine density in hippocampal CA1 pyramidal neurons and alters presynaptic short-term plasticity, underscoring its importance for structural and functional integrity. CACNA1C polymorphisms show sex-specific effects, with risk alleles conferring greater behavioral vulnerability in females, supporting a link to AD and psychiatric disease risk[15]. Among N/P/Q-type channels, Ca_V2.3 downregulation is closely tied to Tau pathology. High-molecular-weight soluble Tau oligomers derived from human AD brain reduce bursting in hippocampal CA1 excitatory neurons; normalizing Tau levels restores Ca_V2.3 expression and complex bursting, rescuing theta and ripple oscillations essential for memory[16]. Auxiliary VGCC subunits are also implicated. Autoantibodies against Ca_Vα2δ impair the coupling between presynaptic Ca^{2+} influx and vesicle exocytosis, strongly reducing glutamatergic and GABAergic transmission without altering Ca^{2+} currents themselves, potentially contributing to memory impairment and excitation–inhibition imbalance in AD[17]. Clinically, brain-penetrant calcium channel blockers (CCBs) appear to reduce dementia risk. Angiotensin II–stimulating dihydropyridine CCBs are associated with ~40% lower incidence of dementia compared with angiotensin II–inhibiting agents, possibly via enhanced AT_2/AT_4 receptor signaling, neuroprotection from ischemic injury, improved memory, and facilitation of Aβ clearance[18]. In patients

treated with CCBs, the link between high systolic blood pressure variability (BPV) and dementia is attenuated, suggesting CCBs may mitigate BPV-related neuroneurocognitive decline[19]. Among specific agents, amlodipine use is associated with lower mortality and ischemic stroke risk in dementia, whereas nifedipine may increase mortality, suggesting pharmacodynamic differences among CCBs influence neuroprotective outcomes[20].

Nimodipine reduces pericyte intracellular Ca^{2+}, dilating first–third-order capillaries and arterioles and increasing cerebral blood flow by about 40%–51%; it also attenuates Aβ-induced pericyte constriction in human AD cortical tissue[12]. Lomerizine, an L- and T-type VGCC blocker, suppresses LPS-induced proinflammatory cytokines and NLRP3 inflammasome activation, and reduces Tau hyperphosphorylation and activation of kinases such as GSK3α/β and DYRK1A, supporting its potential in AD therapy[21]. Overall, these findings support a central role of VGCC dysregulation in AD initiation and progression and highlight brain-penetrant CCBs (e.g., nimodipine, flunarizine) as candidates for risk reduction and disease modification[22].

3.3 Interactions between calcium signaling and neuroinflammation

The interplay between calcium dyshomeostasis and neuroinflammation is a critical driver of AD progression, particularly via microglia and astrocytes. In astrocytes, the neurotoxic Aβ fragment $Aβ_{25–35}$ modulates Ca^{2+} signaling through multiple mechanisms. Under acute exposure, $Aβ_{25–35}$ elevates intracellular Ca^{2+} via activation of P2Y purinergic receptors and opening of connexin hemichannels (CXs). Under chronic exposure, however, $Aβ_{25–35}$ reduces Ca^{2+} levels, associated with increased plasma membrane Ca^{2+}-ATPase (PMCA) activity, enhanced Ca^{2+} extrusion, and proton influx that suppresses CX activity. CX hemichannels shape Ca^{2+} signaling and mediate ATP release, triggering autocrine P2Y1 activation and forming a feed-forward Ca^{2+} amplification loop. Aβ also induces astrocytic glutamate release via Ca^{2+}-dependent (anion channels, lysosomal exocytosis) and Ca^{2+}-independent (CX hemichannels) mechanisms; aberrant ATP and glutamate release from astrocytes is a major contributor to neuroinflammation and excitotoxicity[23]. Activated astrocytes in AD show increased GFAP expression and hypertrophy, particularly around Aβ plaques. Their activation is driven not only by Aβ but also by microglial cytokines such as IL-1α, TNFα, and C1q, which convert astrocytes to a neurotoxic A1 phenotype. The caspase-1/IL-1β axis further modulates astrocyte-mediated inflammation; caspase-1 inhibition reduces IL-1β levels and restores AMPA receptor GluA1 membrane trafficking by rescuing Stargazin–GluA1 interactions, linking inflammatory signaling and calcium-dependent synaptic modulation[24].

Microglia exhibit heterogeneous activation states, often conceptualized as M1 (proinflammatory) and M2 (anti-inflammatory/repair) phenotypes that shift from M2-dominant in early disease to M1-dominant in later stages[25]. M1-type microglia release cytokines that recruit and activate glia, while pathological Tau drives microglial activation via TPC2-dependent lysosomal Ca^{2+} release; TPC2 inhibitors such as tetrandrine suppress Iba-1+ microglial activation and neuroinflammation. Aβ disrupts calcium transporters (e.g., Ca^{2+}-ATPases), increasing cytosolic Ca^{2+} and promoting Ca^{2+}-dependent activation of microglial inflammasome pathways[26]. Tau hyperphosphorylation increases somatic L-type Ca^{2+} channels (LTCCs), and chronic LTCC blockade with nimodipine improves mitochondrial function and gene expression, implicating LTCC-mediated Ca^{2+} signaling in microglial activation and energy failure[27]. Observations from Huntington's disease cortex, where microglia adopt diverse Iba-1^+/$TMEM119^+$ morphologies with proliferation[28], underscore the phenotypic diversity that may similarly arise from Ca^{2+} signaling heterogeneity in AD microglia.

3.4 Lysosomes and transient receptor potential (TRP) channels

Pathological Tau aggregation induces lysosomal alkalinization via TPCN2-dependent Ca^{2+} leak. As a major intracellular Ca^{2+} store, the lysosome relies on tight Ca^{2+} homeostasis to maintain V-ATPase function and acidic pH. TPCN2 overactivation disrupts this balance, leading to defective autophagic flux. Tetrandrine, a TPCN2 inhibitor, reduces lysosomal Ca^{2+} leak, restores acidification and autophagy, and attenuates Tau pathology and neurotoxicity. Among TRP channels, TRPM2 is expressed in microglia and promotes NLRP3 inflammasome activation and neuroinflammation; TRPM2 deficiency alleviates neuroneurocognitive deficits. TRPV2 activity is modulated by phosphorylation and palmitoylation, affecting microglial Aβ phagocytosis. Blocking TRPV2 palmitoylation enhances microglial clearance of Aβ and mitigates AD-related pathology[1].

Additional mechanisms linking calcium dyshomeostasis to AD pathology have emerged. SARS-CoV-2 infection activates TGF-β signaling, leading to RyR2 oxidation and phosphorylation, ER Ca^{2+} leak, and Tau hyperphosphorylation reminiscent of AD-like signaling changes[29]. MAPT N279K mutations increase 4R Tau isoforms, enhancing Ca^{2+} oscillations, mitochondrial dysfunction, and ROS production in cortical neurons[30]. Pathological Tau also destabilizes septin fibers, promoting store-operated Ca^{2+} channel (SOCC) overactivation; pharmacological restoration of septin function normalizes Ca^{2+} homeostasis and confers neuroprotection[31].

4. Impact of calcium signaling abnormalities on cognition and neuronal networks

Calcium dyshomeostasis impairs cognition by inducing neuronal hyperexcitability, synaptic dysfunction, network disor-

ganization, and cell death. Aβ oligomers drive Ca^{2+} overload through several mechanisms: they potentiate NMDAR and RyR-dependent CICR, amplifying postsynaptic Ca^{2+} signals and impairing LTP[10]; they selectively upregulate TRPC3 in excitatory neurons via a calcineurin–NFAT pathway, promoting Ca^{2+} overload and hyperexcitability, whereas TRPC3 antagonists (Pyr3, Pyr10) prevent Ca^{2+} overentry and preserve dendritic structure[32]. BIN1 loss disturbs Ca_V1.2 function in glutamatergic neurons, leading to abnormal Ca^{2+} transients and electrical activity and decreased expression of synaptic markers such as HOMER1 and synaptophysin (SYP), thereby contributing to synaptic dysfunction[7]. $A\beta_{42}$ oligomers enhance RyR-mediated Ca^{2+} release, overactivating presynaptic BK channels, hyperpolarizing membranes, reducing Ca^{2+} influx, and decreasing glutamate release; dantrolene partially reverses these effects[8]. RyR-driven Ca^{2+} release also loads mitochondria with excess Ca^{2+}, collapsing membrane potential, increasing ROS production and caspase-3 activation, and promoting apoptosis[3]. RyR2 leak reduces lysosomal ATP synthase subunits (V1B2, V0a1), leading to lysosomal de-acidification, impaired protease activity, Tau accumulation, and autophagy failure; dantrolene rescues ATPase expression, lysosomal pH, and proteolysis[33]. Additionally, p3 peptides ($A\beta_{17-40/42}$) form large-pore ion channels in the plasma membrane, permitting unregulated Ca^{2+} influx and triggering Tau phosphorylation and downstream toxicity[34].

Vascular and systemic factors further exacerbate AD-related neuroneurocognitive impairment via calcium pathways. Elevated systolic blood pressure and pulse pressure associate with higher brain Aβ burden and atrophy, with these relationships modulated by antihypertensive class; in treated patients, high SBP correlates negatively with Aβ burden (especially with diuretic use), whereas untreated patients show a positive correlation. Interactions between blood pressure, antihypertensives, CSF Tau, and entorhinal cortical atrophy suggest complex blood pressure–brain pathology coupling[35]. In heart failure, RyR2 post-translational modifications (phosphorylation, oxidation) cause calstabin2 dissociation and ER Ca^{2+} leak, leading to hippocampal mitochondrial Ca^{2+} overload, oxidative stress, and neuroneurocognitive impairment; S107 crosses the blood–brain barrier, repairs RyR2 leak, and ameliorates heart–brain pathophysiological coupling[6]. Genetic or pharmacologic restriction of RyR2 open time (RyR2 E4872Q or R-carvedilol) boosts A-type K^+ currents in CA1, suppresses hyperexcitability, and improves memory in AD models with or without AD-causing mutations[13,40]. Diabetes-related hyperglycemia and hyperinsulinemia upregulate S100 proteins (S100B, S100A8). At high concentrations, S100B interacts with RAGE to amplify inflammation and ROS, exacerbating Aβ and Tau pathology; S100A8 is highly expressed in activated microglia and promotes chronic neuroinflammation[36].Together, glial Ca^{2+} abnormalities (e.g., astrocytic TRPA1/mGluR5-mediated Ca^{2+} overload; microglial Kv1.3/KCa3.1/P2X-driven inflammasome activation and phagocytic imbalance) and systemic comorbidities (hypertension, heart failure, diabetes) converge on calcium homeostasis, driving neuronal hyperexcitability, synaptic failure, mitochondrial injury, and network dysfunction. Agents targeting these pathways (e.g., TRPA1 blockers, RyR stabilizers, Kv1.3 inhibitors) therefore represent promising strategies for AD intervention.

5. Therapeutic potential of calcium channels and related mechanisms

5.1 Calcium channel blockers and modulators

CCBs exhibit multiple mechanisms of benefit in AD and related neurocognitive disorders. Felodipine, delivered via liposomal nanoparticles (felodipine@LND) in combination with low-intensity pulsed ultrasound (LIPUS), modulates ER unfolded protein response (UPR) signaling, suppresses NLRP3 inflammasome activation, reduces Aβ aggregation, and promotes mitophagy, thereby improving anxiety-like behavior and spatial and object recognition memory in 5xFAD mice[37]. Mendelian randomization analyses further suggest that genetically predicted CCB target inhibition reduces AD risk independently of blood pressure lowering (OR=0.959, 95% CI 0.941–0.977)[38]. Cav2.1 (P/Q-type) channels are enriched in parvalbumin-positive GABAergic interneurons (PV-INs); their dysfunction impairs GABA release and inhibitory transmission, leading to deficits in neurocognitive flexibility and selective attention[39]. Thus Cav2.1 modulators that restore PV-IN function may be of therapeutic value in AD. Cav1.2 is essential for persistent firing in prefrontal pyramidal neurons; optimal activity is required for working memory, whereas either overactivation (e.g., stress-induced β_1-adrenergic signaling) or suppression impairs cognition. β_1-AR antagonists (e.g., betaxolol) and L-type blockers (e.g., nimodipine) alleviate stress-induced working memory deficits[4]. Aβ and Tau aggregates enhance L-type Ca^{2+} influx, whereas nimodipine and nifedipine block this effect, preventing Ca^{2+} overload and ROS generation[1].

RyR stabilizers intervene at the level of ER Ca^{2+} release. Increased RyR2 open probability directly induces CA1 pyramidal hyperactivity, spine loss, and memory impairment and aggravates pathology in 5xFAD mice[40]. Restricting RyR2 open time (RyR2 E4872Q or R-carvedilol) boosts A-type K^+ currents, suppresses hyperactivity, and rescues learning and memory, independent of Aβ accumulation[13]. RyR-mediated Ca^{2+} release also exacerbates mitochondrial dysfunction in AD neurons; the RyR modulator Ryanodex reduces resting mitochondrial Ca^{2+}, lowers oxidative stress, and restores mitochondrial function[3]. Dantrolene attenuates RyR-related Ca^{2+} leak, normalizes lysosomal ATP synthase levels and

acidification, and improves autophagic clearance of Tau[33].

5.2 Key molecular targets in calcium signaling and emerging small molecules

The mTORC1–DJ-1 pathway regulates L-VGCC function in AD-relevant circuits: DJ-1 selectively binds and represses translation of Cacna1c and Cacna2d2 mRNAs, reducing dendritic L-VGCC activity, suggesting both DJ-1 and Ca_V1.2 as potential therapeutic targets[5]. Lysosomal Ca^{2+} signaling has emerged as another key axis. TRPML1 is a lysosomal Ca^{2+} release channel that, when activated, can promote TFEB/TFE3-mediated autophagy and lysosome biogenesis. Corynoxine enhances TRPML1-dependent Ca^{2+} release, activates TFEB/TFE3, boosts autophagy and lysosomal function, reduces Aβ pathology, and improves cognition in 5xFAD mice[41].

TPCN2 overactivity in AD increases lysosomal Ca^{2+} release and pH, impairing autophagy–lysosome function. Tetrandrine and Ned-19 inhibit TPCN2, restoring lysosomal acidity and proteolytic activity and reducing Aβ plaque burden, offering a strategy to correct autophagy–lysosomal defects[2]. Mechanosensitive channel Piezo1 represents a novel modulator of calcium homeostasis. In microglia, Piezo1 activation by Yoda1 enhances Ca^{2+} influx, promotes microglial clustering around plaques, and increases Aβ phagocytosis, reducing hippocampal and cortical Aβ load in 5xFAD mice[42]. In erythrocytes from AD patients, Piezo1 activity is increased and modulated by Aβ; combining Piezo1-mediated Ca^{2+} responses with machine learning may improve AD diagnosis, although small-molecule Piezo1 modulators remain underdeveloped[43].

5.3 Multi-target drug design and combination strategies

The multi-target agent sodium oligomannate (GV-971) exemplifies calcium-centric gut–brain modulation. GV-971 co-activates sweet taste receptors and TRPA1 channels in enteroendocrine cells (EECs), inducing Ca^{2+} oscillations, promoting cholecystokinin (CCK) and 5-HT release, and enhancing vagal afferent signaling. Chronic oral GV-971 increases intestinal and serum neurotransmitter levels and improves cognition in APP/PS1 mice; combined blockade of sweet taste receptors (lactisole) and TRPA1 (HC-030031) suppresses Ca^{2+} oscillations and vagal activation, confirming coordinated EEC Ca^{2+} signaling as a key mechanism[44]. Early-life adversity–induced overexpression of miR-499-5p targets CACNB2 (encoding the regulatory β subunit of Ca_V1.2), reducing its mRNA, decreasing Ca_V1.2 surface expression and current density, and impairing dendritogenesis and plasticity in hippocampal neurons. miR-499-5p thus represents a potential target for strategy combinations that restore Ca^{2+} channel function[45]. Proteomics of semantic dementia temporal cortex reveals enrichment of VGCC-related proteins (e.g., CACNB4) and mRNA-processing ribonucleoprotein complexes, suggesting that joint modulation of calcium signaling and RNA metabolism may be effective for correcting calcium dyshomeostasis[46].

AI-assisted ion channel analysis frameworks integrating 1D CNNs, BiLSTM, and attention mechanisms can learn multi-channel kinetics (K^+, Na^+, Ca^{2+}) from automated patch-clamp data. In AD drug discovery, such tools have characterized voltage-dependent inhibition of endogenous channels by memantine and its antagonistic interactions with Ca^{2+} channels, enabling rational multi-target design[47]. In chronic kidney disease–associated neurocognitive impairment, combined targeting of microglial KCa3.1 (TRAM34) and neuronal IL-1R1 (anakinra) restores K^+ homeostasis, reduces neuroinflammation, and alleviates Ca^{2+}-dependent neuronal dysfunction, providing a conceptual framework for multi-factor interventions centered on calcium imbalance[48].

6. Challenges and future directions in targeting calcium homeostasis

Research on calcium homeostasis in AD faces several challenges but also clear opportunities. At the systems level, AD-related Ca^{2+} dyshomeostasis involves complex molecular networks and multi-organ interactions, underscoring the need to construct a comprehensive "calcium signaling map" for AD. Abnormal Ca^{2+} dynamics arise early in hippocampal neurons and astrocytes and depend on coordinated regulation of synaptic channels (RyRs, VGCCs, α7nAChRs, NMDARs), organellar release channels (ER RyRs/IP_3Rs, lysosomal TRPML/TPC, mitochondrial PTP), and inter-organelle coupling[1,10]. The context-dependent roles of RyRs and IP_3 signaling across models highlight the need for integrative systems analysis rather than single-channel focus. Genotype-informed precision therapy is another priority. PSEN1/PSEN2 mutations alter RyR and SERCA function and are linked to abnormal ER Ca^{2+} release and mitochondrial dysfunction[3,10]. CACNA1C variants modulate cognitive circuits, making Cav1.2 an attractive genotype-stratified target[1,4,12]. BIN1 and MAPT genotypes further shape calcium signaling pathways[1,7,49], providing additional axes for individualized intervention.

Combination therapies that integrate calcium-pathway modulators with anti-Aβ/Tau and anti-inflammatory drugs may yield synergistic benefits. For instance, blocking TRPA1 interferes with Aβ-induced astrocytic glutamate release; modulating Cav2.1 in PV-INs alongside anti-amyloid/Tau therapies and microglial-targeting agents could normalize network function more effectively than monotherapy. Given the limited clinical efficacy of single-pathway approaches targeting Aβ or Tau alone, incorporating calcium homeostasis modulation is likely essential for robust disease modification[40].

7. Conclusions

Calcium signaling homeostasis plays a pivotal role in the initiation and progression of AD through multi-system, multi-level mechanisms involving membrane calcium channels, ER, mitochondria, lysosomes, and glial cells. Calcium dyshomeostasis is not merely a downstream marker but an early and central event that governs neuronal excitability, synaptic plasticity, energy metabolism, neuroimmune responses, and vascular function, thereby linking proteinopathy to cognitive decline. Despite substantial progress, major gaps remain in our systems-level understanding of calcium signaling networks, cell-type–specific differences, and inter-pathway crosstalk in AD. Future work should aim to establish a comprehensive AD calcium signaling atlas and to map dynamic Ca^{2+} changes across organelles and cell types, leveraging single-cell omics, high-resolution calcium imaging, and AI-based analytical frameworks. Such efforts will be crucial for achieving early detection of calcium dyshomeostasis, developing precise and individualized interventions, and designing rational combination therapies that can effectively target calcium homeostasis in AD.

Conflict of interest

All authors declare no conflicts of interest.

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