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Review Article

Calcium signaling hypothesis: A non-negligible pathogenesis in Alzheimer's disease

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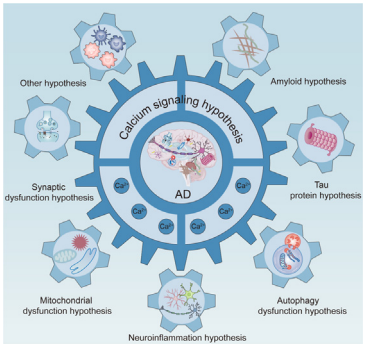
HIGHLIGHTS

- Disrupted calcium homeostasis drives Aβ aggregation and Tau phosphorylation, underpinning AD hypotheses.
- Disrupted calcium homeostasis serves as the pathological foundation underlying various hypotheses of AD.
- Mitochondrial calcium overload disrupts oxidative phosphorylation, causing metabolic dysfunction and oxidative stress.
- Calcium signaling in microglia, astrocytes, and neurons is central to neuroinflammation in AD.
- Dysregulated calcium signaling impairs autophagy by inhibiting autophagosome formation and lysosomal acidification.

GRAPHICAL ABSTRACT

The interplay between the Ca^{2+} signaling hypothesis and the pathogenesis of AD. The amyloid cascade hypothesis, Tau protein hypothesis, mitochondrial dysfunction hypothesis, neuroinflammation hypothesis, and autophagy dysfunction hypothesis, among others, collectively contribute to the onset and progression of AD through their impact on Ca^{2+} transport and Ca^{2+} signaling pathways.



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ABSTRACT

Background: Alzheimer's disease (AD) presents a significant challenge to global healthcare systems, with an exacerbation by an aging population. Although the plethora of hypotheses are proposed to elucidate the underlying mechanisms of AD, from amyloid-beta (Aβ) accumulation and Tau protein aggregation to neuroinflammation, a comprehensive understanding of its pathogenesis remains elusive. Recent research

Abbreviations: $[Ca^{2+}]_{ER}$, endoplasmic reticulum calcium concentration; $[Ca^{2+}]_{I}$, intracellular calcium concentration; $[Ca^{2+}]_{L}$, lysosomal calcium concentration; $[Ca^{2+}]_{M}$, mitochondrial calcium concentration; AD, Alzheimer's disease; AICD, APP intracellular domain; ALS, amyotrophic lateral sclerosis; APOEε4, apolipoprotein ε4; APP, amyloid precursor protein; ATP, adenosine triphosphate; Aβ, amyloid β peptide; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BBB, blood–brain barrier; Ca^{2+}, calcium; CALHM, calcium homeostasis modulator; CaMKII, calcium-calmodulin (CaM)-dependent protein kinase II; CaMKIV, calcium-calmodulin (CaM)-dependent protein kinase IV; CAX, cation/H^+ exchanger; CCB, calcium channel blocker; CDK-5, cyclin-dependent kinase 5; CP-AMPAR, Ca^{2+}-permeable AMPA receptor; CREB, cAMP-response element binding protein; Dyrk1A, dual-specificity tyrosine-regulated kinase 1A; ER, endoplasmic reticulum; ETC, electron transfer chain; GSK-3β, glycogen synthase kinase-3-beta; HD, Huntington's disease; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; LTD, long-term depression; LTP, long-term potentiation; MAM, mitochondria-associated membrane; MAPK, mitogen-activated protein kinase; MCU, mitochondrial Ca^{2+} uniporter; mPTP, mitochondrial permeability transition pore; mTOR, mammalian target of rapamycin; NCLX, mitochondrial Na^+/Ca^{2+} exchanger; NCX, Na^+/Ca^{2+} exchangers; NFT, neurofibrillary tangle; NMDAR, N-methyl-D-aspartic acid receptor; NNAT, neuronatin; NPC, nuclear pore complex; ORAI, calcium release-activated calcium modulator; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PKA, protein kinase A; PKC, protein kinase C; PMCA, plasma membrane Ca^{2+}-ATPase; PS1, presenilin-1; PS2, presenilin-2; PSEN, presenilin; ROS, reactive oxygen species; RyR, ryanodine receptor; sAPPα, soluble APP-alpha; SERCA, sarco-endoplasmic reticulum calcium-ATPase; SOCE, store-operated calcium entry; SP, senile plaque; STIM, stromal interaction molecule; Tau, microtubule-associated protein; TCA cycle, tricarboxylic acid cycle; TPC, two-pore channel; TRP, transient receptor potential; v-ATP, vacuolar type H^+-ATPase; VDAC, voltage-dependent anion channel; VGCC, voltage-gated calcium channel; $\Delta\Psi m$, mitochondrial membrane potential..

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has highlighted the critical role of calcium (Ca^{2+}) signaling pathway in the progression of AD, indicating a complex interplay between Ca^{2+} dysregulation and various pathological processes.

Aim of Review: This review aims to consolidate the current understanding of the role of Ca^{2+} signaling dysregulation in AD, thus emphasizing its central role amidst various pathological hypotheses. We aim to evaluate the potential of the Ca^{2+} signaling hypothesis to unify existing theories of AD pathogenesis and explore its implications for developing innovative therapeutic strategies through targeting Ca^{2+} dysregulation.

Key Scientific Concepts of Review: The review focuses on three principal concepts. First, the indispensable role of Ca^{2+} homeostasis in neuronal function and its disruption in AD. Second, the interaction between Ca^{2+} signaling dysfunction and established AD hypotheses posited that Ca^{2+} dysregulation is a unifying pathway. Third, the dual role of Ca^{2+} in neurodegeneration and neuroprotection, highlighting the nuanced effects of Ca^{2+} levels on AD pathology.

Contents

Introduction

Aging is a critical risk factor for many types of dementia, and statistics show that its prevalence is rising rapidly in people aged 65 years old and older. Moreover, according to clinical diagnostic standards, by the middle of the 20th century, the number of dementia patients worldwide had reached up to approximately 10 million. Starting in 2030, the global cost of dementia will increase at a rate of 2 trillion dollars per year, of which, up to 85% of the cost is related to the daily care of patients [1]. AD is a progressive neurodegenerative disease and the most common cause of dementia. Symptoms including progressive memory loss, abnormal behavior, and cognitive impairment caused by AD can significantly affect the quality of life of patients. In the face of an aging global population, AD may rapidly become one of the costliest, deadliest, and most socially impactful diseases in this century [2]. Therefore, uncovering the specific pathogenesis of AD is essential. Since the first AD patient was reported in 1907, this disease has been gained extensive concern by many scholars. Similarly, a variety of hypotheses are also proposed to explain the occurrence and progression of AD, including the amyloid-beta (Aβ) hypothesis, the neuroinflammation hypothesis, and the cell senescence hypothesis [2]. With the in-depth studies, the amyloid cascade hypothesis has become the mainstream thought in the pathogenesis of AD. This hypothesis holds that the pathogenesis of AD is caused by abnormal cleavage of the Aβ precursor protein (APP) by α-secretase, β-secretase, and γ-secretase, thereby resulting in the excessive deposition of Aβ outside neurons. Then, Aβ promotes the hyperphosphorylation of microtubule-associated protein Tau and the formation of neurofibrillary tangles (NFTs) in neurons, ultimately leading to neuronal dysfunction and death [3]. Although clinical trials of antibodies based on this hypothesis have made significant progress in recent years, concerns remain about the safety of these drugs [4,5]. Research status leads us to reconsider a fundamental question: how does AD occur and develop? Nowadays, numerous studies have investigated Ca^{2+} signaling [6]. Ca^{2+} homeostasis plays an essential regulatory role in many aspects of the nervous system, including the growth and differentiation of neurons, the generation of action potentials, and the development of learning and memory processes. Previous studies have

documented that disordered level of Ca^{2+} can activate molecular mechanisms such as dysfunctional autophagy and apoptosis [7]. As early as the 1980 s, a hypothesis has been proposed that an imbalance in Ca^{2+} homeostasis may disrupt neuronal function and lead to neurodegenerative diseases, including AD. Similarly, correcting disordered intracellular calcium concentration ($[Ca^{2+}]_I$) in neurons is beneficial to prevent and delay the progression of AD [8]. In addition, previous studies have reported that the occurrence of Ca^{2+} disturbance may be earlier and independent of the generation of senile plaques (SP) and NFTs, suggesting that the Ca^{2+} signaling hypothesis may become a novel entry point for the studies on AD [9].

Some researchers have summarized the relationship between Ca^{2+} and AD. However, only the changes of Ca^{2+} in AD have been discussed, without an in-depth discussion for the role of Ca^{2+} in the pathogenesis of AD. Moreover, an editorial statement on AD and dementia points out that scholars need to integrate known hypotheses of AD as much as possible to find a joint biological event to explain these hypotheses [10]. In response to this statement, the latest Ca^{2+} signaling hypothesis proposes that the disruption of Ca^{2+} homeostasis may be a common signal pathway leading to the pathogenesis of AD due to multiple factors [6]. However, this postulate has yet to be fully tested, and the relationship between Ca^{2+} disorders and other AD pathological processes has yet been systematically elucidated. Therefore, to elucidate the relationship between the Ca^{2+} signaling and AD, this article will draw upon existing studies for elucidating the underlying mechanisms, thereby shedding light on the crucial role of Ca^{2+} signaling in AD to identify potential intervention targets and providing the valuable insights for in-depth studies in the future.

New developments in AD studies

AD is a neurodegenerative disease characterized by the deposition of extracellular SPs and the formation of intracellular NFTs. Numerous experiments have shown that Aβ peptides and Tau protein are two key inducers of AD. In 1999, scholars have discovered that using a synthetic Aβ polymer (AN1792) can significantly reduce the burden of brain plaques in APP-transgenic mice [11,12]. This study initiated subsequent studies on Aβ-targeted immunotherapy for the prevention and treatment of AD. However, clinical trials were abandoned shortly after the initiation because synthetic Aβ antibodies can cause severe meningitis and abnormal immune responses [11]. With the research and development of AD diagnostic biomarkers, positron emission tomography, and other technologies, many human Aβ monoclonal antibodies have been developed and applied in clinical studies, including aducanumab, donanemab, and lecanemab [13]. Recently, the results of phase III clinical trial of the Aβ monoclonal antibody (donanemab) have demonstrated that it has the potential to alleviate AD in the long term (beyond just relieving symptoms) [4,14]. In the follow-up survey of the subjects who received the donanemab trial, it was found that the reduction of Tau protein was more evident after Aβ clearance in the brain regions of the patients [15], which undoubtedly supports the amyloid cascade hypothesis of AD. From the first anti-Aβ therapy in AD mice to the recent successful phase III clinical trials, more than two decades of clinical trials have suggested that the immunotherapy for AD should focus on identifying and alleviating the side effects of antibody administration, how to use early biological indicators of AD better, when the treatment efficacy is the best, and which monoclonal monomer has the best clinical effect. However, challenges persist, as other drugs do not seem to achieve the expected therapeutic effect [16], and these drugs may also cause various side effects, such as cerebral edema [4]. Consequently, numerous issues in current clinical trials of AD are worth pondering.

In clinical studies, this strategy seems correct in inhibiting Aβ production and enhancing its clearance to restore cognitive function. Nevertheless, the persistent question of why drugs like aducanumab can effectively reduce Aβ levels without a commensurate improvement in cognitive function remains a subject warranting further investigation and elucidation [17]. Recent studies have also found that particular types of Aβ [18,19] and Tau protein with unique phosphorylation sites [20] seem to have a protective effect on AD, suggesting that the toxic side effects associated with Aβ immunotherapy may be due to unclear targets of these monoclonal antibodies. For instance, in the AD brain, the neurotoxicity of dense-core plaques is significantly less than that of loose-core plaques [21]. Moreover, soluble Aβ exceeding physiological concentrations is more damage to neurons than Aβ oligomers, and the long-term increase in soluble Aβ content is also an important reminder of AD symptoms [19]. Similarly, for Tau protein, the downstream pathological protein of Aβ, the phosphorylation of Tau at Thr205 can weaken the postsynaptic excitotoxicity caused by Aβ [20], while phosphorylation at Ser305 can effectively reduce Tau aggregation [22]. These findings raise questions about the targets of Aβ immunotherapy, potentially explaining the less successful efficiency of targeting the amyloid of AD during clinical trials.

It is reported that after Aβ immunotherapy, secondary inflammatory reactions may occur in the brains of AD patients, and the combination of Aβ antibodies with non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin may serve as an effective auxiliary measure [23]. In addition, NSAIDs have also received the attention from many scholars in clinical trials of AD. Several epidemiological studies have shown that NSAIDs have preventive and therapeutic effects on AD, which is quite different from the conclusions of many clinical trials [24]. Due to liver and kidney toxicity of NSAIDs, these drugs are usually used at small doses in their clinical trials [25]. Animal studies have shown that enhancing the delivery of ibuprofen into the mouse brain by solvent expansion can effectively inhibit brain inflammation and memory deficits [26], suggesting that anti-inflammatory drugs at small doses may not be able to effectively pass through the blood–brain barrier (BBB) to achieve sufficient anti-inflammatory effects. While some NSAIDs seem to impair cognitive function [27], whether this will affect the criteria of curative effect in AD patients is still unknown. It is worth noting that some NSAIDs as the γ-secretase modulators may ameliorate or aggravate AD by inhibiting the aggregation of Aβ, rather than their anti-inflammatory effects [28]. Long-term administration of NSAIDs may reduce the risk of AD, but only if preventive application is started before the initiation of the disease [29,30]. However, long-term application of NSAIDs may cause a variety of adverse reactions, including gastrointestinal discomfort, cardiovascular events, and blood safety issues, and may even lead to serious adverse events. Meanwhile, naprosin treatment at low dose for two years did not reduce the risk of AD in individuals who are cognitively intact, but at high risk [25]. In clinical trials of NSAIDs for AD, the efficacy may be affected by combinatorial factors such as timing, dose, and adverse reactions, which may partly explain the unsatisfactory results.

In summary, the studies on current AD treatments mainly focus on immunotherapy targeting Aβ. However, imprecise target selection appears to limit therapeutic efficacy. Future studies should further investigate how to accurately distinguish the deleterious effects of Aβ and Tau, thereby enhancing targeted intervention strategies including pharmacological approaches targeting Ca^{2+} signaling pathways [31], combination therapies integrating Aβ and Tau interventions [32], gene therapy [33], and precision exercise interventions [34]. In addition, utilizing early biomarkers to optimize treatment timing and select the most effective monoclonal antibodies appears to be a good approach. At the same time,

clinical trial designs need to minimize confounding factors, recruit patients at different stages of the disease as experimental subjects and extend the trial duration to evaluate the long-term benefits of new treatments thoroughly.

Regulation of calcium levels in normal neurons

Ca^{2+} is a tightly regulated second messenger with diverse functions, including neurotransmitter release, action potential conduction, synaptic function, and neuronal growth and differentiation [35]. Ca^{2+} concentrations can generally reach up to 1–2 mM in the intercellular space, while $[Ca^{2+}]_I$ is usually around 100 nM. However, following stimulation by various signaling events, $[Ca^{2+}]_I$ may temporarily or locally increase. To fulfill physiological activity requirements, Ca^{2+} levels within specific cytoplasmic microdomains can reach up to 10 μM [36]. Ca^{2+} regulation in neurons is highly compartmentalized. Different parts including cell membrane, endoplasmic reticulum (ER), and mitochondria maintain Ca^{2+} balance through specific mechanisms. These mechanisms include Ca^{2+} release, storage-operated Ca^{2+} entry (SOCE), and mitochondrial Ca^{2+} transport, which ensure the precise regulation of Ca^{2+} inside and outside cells [6]. First, the cell membrane serves as the primary channel that controls the entry of Ca^{2+} from outside the cell to inside the cell. Upon the stimulation from action potentials or neurotransmitters, a small amount of extracellular Ca^{2+} enters the cytoplasm through transient receptor potential (TRP) channels, N-methyl-D-aspartic acid receptor (NMDAR), voltage-gated calcium channel (VGCC), calcium homeostasis modulator (CALHM), Na^+/Ca^{2+} exchangers (NCXs) and plasma membrane Ca^{2+}-ATPase (PMCA), thereby allowing for signal transduction and other functions. Subsequently, a small influx of Ca^{2+} into the cell can activate phospholipase C on the cell membrane to generate inositol 1,4,5-trisphosphate (IP3). Upon binding to either inositol 1,4,5-trisphosphate receptor (IP3R) or ryanodine receptor (RyR), IP3 elicits the release of Ca^{2+} from the ER into the cytoplasm, known as calcium-induced Ca^{2+} release [9]. Secondly, ER is the largest Ca^{2+} storage site so far, and the ER calcium concentration ($[Ca^{2+}]_{ER}$) is between 100 and 800 μM [37]. Depletion of $[Ca^{2+}]_{ER}$ activates SOCE to replenish it. SOCE involves stromal interaction molecules (STIMs) on the cell membrane, calcium release-activated calcium modulator (ORAI) channels, and sarco-endoplasmic reticulum calcium-ATPase (SERCA) on the ER membrane. Upon $[Ca^{2+}]_{ER}$ depletion, STIM proteins, sensing $[Ca^{2+}]_{ER}$, bind and open ORAI channels, thus causing a rapid influx of Ca^{2+}, after which SERCA pumps transport Ca^{2+} back into the ER, utilizing adenosine triphosphate (ATP) for storage [9,38]. Thirdly, mitochondria play a central role in intracellular Ca^{2+} signaling as Ca^{2+} sensors or buffers. The voltage-dependent anion channel (VDAC) located in the outer mitochondrial membrane and the mitochondrial Ca^{2+} uniporter (MCU) in the inner mitochondrial membrane can jointly regulate the mitochondrial membrane permeability to uptake and release Ca^{2+} through the exchange with sodium (Na^+) and hydrogen (H^+) ions [39]. An appropriate increase in mitochondrial matrix Ca^{2+} levels aids in stimulating ATP formation, thus supplying energy for energy-intensive cellular activities [40]. In addition, the exchange of Ca^{2+} between these organelles also plays an essential role in regulating neuronal Ca^{2+} homeostasis. There is a unique ER subdomain between the ER and the mitochondrial membrane, the so-called mitochondria-associated membrane (MAM), and the ER transfers Ca^{2+} into the mitochondria through MAM [41]. Calcium from the cytoplasm or ER can also enter the nucleus through the nuclear pore complex, thus activating calmodulin (CaM)-dependent protein kinase II (CaMKII) and IV (CaMKIV), and participating in the regulation of critical gene expression in neurons, such as cAMP-response element binding protein associated with memory capacity [42]. Interestingly, to prevent excessive changes in Ca^{2+} concentration from adversely affecting neurons, these organelles jointly achieve strict control of $[Ca^{2+}]_I$ by finely regulating Ca^{2+} flow and storage to ensure normal function and survival of neurons. For example, when $[Ca^{2+}]_I$ is too high, PMCA and NCX on the cell plasma membrane actively transport Ca^{2+} to the outside neuron to maintain the resting Ca^{2+} level [43]. Therefore, Ca^{2+} regulation is a delicate and complex process in neurons, covering transmembrane transport, interactions between organelles, and the regulation of molecular mechanisms, which maintain the function and stability of the nervous system (Fig. 1).

AD and calcium

AD, a complex neurodegenerative disease, can be classified as either early-onset (EOAD) or late-onset (LOAD) based on the onset time. EOAD is closely related to genetic factors such as presenilin-1 (PS1), presenilin-2 (PS2), and APP gene mutations. LOAD is predominantly influenced by non-genetic factors, including age, cardiovascular and cerebrovascular diseases, sedentary lifestyles, and environmental factors [1]. Aging is a significant risk factor for LOAD, and the core mechanism may be the imbalance of Ca^{2+} homeostasis [44]. With advancing age, the functionality of intracellular Ca^{2+} pumps and channels may decline, thus impairing the cells' capability to maintain Ca^{2+} concentrations effectively and resulting in Ca^{2+} overload [45]. This imbalance in Ca^{2+} homeostasis further exacerbates neuronal hyperexcitability, making it more vulnerable to damage from external risk factors and ultimately leading to synaptic dysfunction [46]. This imbalance in Ca^{2+} homeostasis further exacerbates the hyperexcitability of neurons, making them more vulnerable to damage from external risk factors, ultimately leading to synaptic dysfunction [47,48]. The Ca^{2+} signaling hypothesis suggests that these multiple risk factors may cause pathophysiological changes, including neuronal apoptosis, synaptic loss, Aβ aggregation, and abnormal Tau phosphorylation by deteriorating the Ca^{2+} handling system of neurons. The mouse experiments through the classic AD model have also documented that inhibiting Ca^{2+} regulation-related protein [49] seems to be helpful for preventing and rescuing neuronal hyperactivity. Therefore, the imbalance of Ca^{2+} homeostasis may be the pathogenesis of AD (Fig. 1).

Although Ca^{2+} levels in AD increase with the extension of age and are expected to become a new diagnostic biomarker, there are conflicting results regarding serum Ca^{2+} levels and AD prevalence. On the one hand, a genome-wide association analysis of serum Ca^{2+} among 61,079 European individuals has found that individuals with high serum Ca^{2+} levels are less likely to develop AD [50]. On the other hand, when using the total reflection X-ray fluorescence spectrum to detect the changes in plasma metal elements in AD patients, it is found plasma Ca^{2+} levels in AD patients are significantly higher when compared with ordinary elderly [51]. However, hippocampal Ca^{2+} imaging data from 5xFAD mice at different ages have demonstrated that $[Ca^{2+}]_I$ is decreased, rather than increased [52]. Such conflicting results suggest that the relationship between Ca^{2+} levels and AD may be more complex than expected.

However, the application of new technologies, such as gene-edited calcium sensors and multiphoton microscopy, provides new tools for the in-depth exploration of the complex mechanisms involved. For example, the application of new calcium sensors, Yellow Cameleon 3.6, has confirmed that Aβ-mediated disruption of Ca^{2+} homeostasis can cause AD-like changes in neurons and synapses, which undoubtedly supports the Ca^{2+} signaling hypothesis [53]. Abnormal microRNA signaling has been found to be the

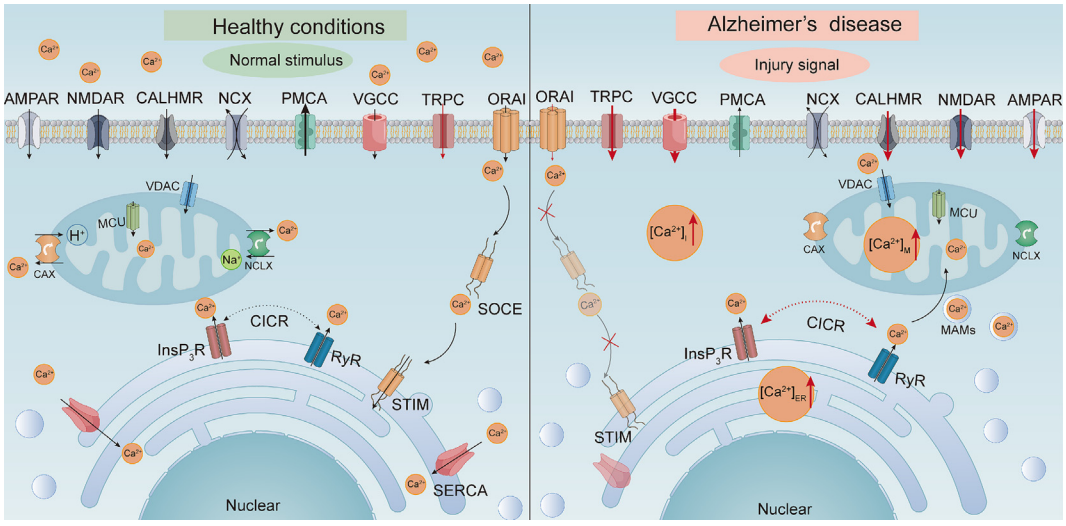

Fig. 1. Regulatory processes of Ca^{2+} concentration in neurons of AD. Under normal circumstances, Ca^{2+} enters the cytoplasm and mitochondria through Ca^{2+}-related transporters to participate in physiological activities. The incoming Ca^{2+} can induce the ER to release more calcium to maintain the cytosolic calcium concentration. When the stimulation ends, ER can utilize SERCA to recycle Ca^{2+} in the cytoplasm or excrete excessive Ca^{2+} out of neurons to restore $[Ca^{2+}]_I$ in the resting state. Moreover, when $[Ca^{2+}]_{ER}$ is depleted, neurons can replenish Ca^{2+} to ER through the SOCE signal pathway. In AD, due to the stimulation of injury factors, the calcium entering the cell can be increased and the excretion can be decreased, and the ER continuously releases Ca^{2+}, thereby leading to the increase of $[Ca^{2+}]_I$, $[Ca^{2+}]_M$, and $[Ca^{2+}]_{ER}$ in neurons.

cause of early neuronal Ca^{2+} homeostasis disorders, and whether exercise-induced circulation-specific microRNAs promote health as an innovative therapeutic strategy is also worthy of further study [54,55].

In summary, although the relationship between Ca^{2+} level changes and AD is complex and there are research conflicts, the development of new technologies can help to deeply understand the role of Ca^{2+} imbalance in the pathogenesis of AD. Moreover, imbalanced Ca^{2+} homeostasis is not only a critical link connecting multiple risk factors of AD, but also a potential target for future prevention and treatment strategies for AD (Table 1).

Calcium and amyloid cascade hypothesis

The metabolic pathways of APP include β-secretase-mediated Aβ pathway and α-secretase-mediated non-Aβ pathway. In normal neurons, most APP is cleaved into soluble APP-alpha (sAPPα), P3 fragment, and APP intracellular domain (AICD) by α-secretase and γ-secretase. In contrast, in AD, because the function of β-secretase is superior to that of α-secretase, many APPs release β-carboxyl terminal fragments (β-CTF) under the action of β-secretase. The β-CTF will be produced by γ-secretase through *endo*-proteolytic (ε) cleavage to produce small molecules of Aβ peptides, such as Aβ40 and Aβ37 [56]. On the one hand, these Aβ peptides can activate most of Ca^{2+} transporters such as Ca^{2+}-permeable AMPA receptors (CP-AMPAR), CALHM, and so on, thus resulting in massive Ca^{2+} influx. However, dysregulated Ca^{2+} homeostasis will lead to Aβ generation and Aβ plaque formation, which in turn aggravates Aβ toxicity, thereby resulting in the destruction of synaptic plasticity [57]. Moreover, physiological Aβ pore influx activates the CaMKII and CaMKIV signal pathways under neuronal injury conditions to meet the neurons' demand for a high threshold and promote neuronal survival. At the same time, Aβ aggregation blocks the Aβ pore, interrupting calcium signal transmission [58]. On the other hand, APP-mediated aberrant Ca^{2+} signaling impairs synaptic plasticity by regulating the SOCE signal pathway and APP metabolism [59]. Enhanced SOCE can delay the maturation of APP and promote its metabolism to non-Aβ pathways [60]. In contrast, the inhibition of SOCE can up-regulate Aβ42 in human glioma H4 cells [61]. In addition, elevated $[Ca^{2+}]_I$ activates the NFAT/beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) signal pathway to promote Aβ production [62], while correcting calcium homeostasis can significantly inhibit Aβ accumulation and alleviate neuronal damage [63]. Previous studies have shown that in the cellular normal $[Ca^{2+}]_I$ state, phosphorylated NFAT is retained in the cytoplasm for inhibiting Aβ production [64]. However, excessive $[Ca^{2+}]_I$ triggered by stimulation of AMPAR receptors can increase α-secretase activity to suppress Aβ production [65]. For example, the SOCE signal pathway in astrocytes is inhibited after the knockout of APP [66], and the supplementation of APPα could be helpful for the restoration of Ca^{2+} disturbance and impaired SOCE in APP knockout mice [59], suggesting that APP seems to play an essential role in regulating the SOCE signal pathway. It has been reported that the reduction of dendritic spines in AD neurons may be related to the cleavage of STIM by γ-secretase, which leads to the interruption of the SOCE/Ca^{2+}/CaMKII signal pathway [67]. Additionally, in PS1 mutant cells, the increased $[Ca^{2+}]_I$ and intracellular zinc release is helpful for creating an acidic environment to increase the activity of β-secretase (optimal pH: 4.5) and γ-secretase (optimal pH: 6.3) [68], thus leading to an imbalance in the production and clearance of Aβ [69]. Therefore, abnormal Ca^{2+} signaling and level can aggravate the Aβ burden in AD brain tissues by affecting metabolic pathway of Aβ (Fig. 2).

Calcium and Tau protein hypothesis

Numerous experiments have shown that the hyperphosphorylation of Tau protein is the result of Aβ aggregation. Consequently, researchers often integrate the Aβ and Tau protein hypotheses into the amyloid cascade hypothesis [70]. Tau protein is a microtubule-binding protein with multiple sites that various protein kinases can conduct the phosphorylation progress, including protein kinase A (PKA), protein kinase C (PKC), cyclin-dependent kinase 5 (CDK-5), CaMKII, glycogen synthase kinase-3-beta (GSK-3β) and mitogen-activated protein kinase (MAPK) [71]. During the pathological process of AD, the activation of these kinases will accelerate the phosphorylation of Tau protein, thereby resulting in the detachment of Tau from microtubules to form NFTs, eventually leading to neuronal dysfunction and correcting their functional expression

Table 1
Changes of calcium in AD.

Objects	Ca^{2+} detection technology	Tissue sources	Change in Ca^{2+} concentration	Change in AD-related indicators	Change in other indicators	References
J20 mice	Oregon-green Bapta-1 Ca^{2+} imaging	Hippocampus dentate gyrus and hypothalamus	$[Ca^{2+}]_I$ ↑	Aβ ↑	Calbindin-D28K ↑	[227]
$APP^{-/-}$/$APLP2^{-/-}$ mice	Fura2-AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_I$ ↑	APP ↓	SOCE ↓	[59]
HEK293 cells	Fluo3-AM Ca^{2+} imaging	—	$[Ca^{2+}]_I$ ↑	Tau and p-Tau ↑	CaMKIV ↑	[228]
Caenorhabditis elegans	—	—	$[Ca^{2+}]_I$ ↓, $[Ca^{2+}]_M$ ↑	Neurodegeneration	ROS ↑	[229]
HEK293 and HeLa cells	Fluorescent probe	—	$[Ca^{2+}]_I$ ↓, $[Ca^{2+}]_{ER}$ ↓	Aβ ↑	SOCE and ORAI ↓	[61]
AD brain tissue	Fluorescence probe	Temporal lobe, hippocampus and basal ganglia	Calcification ↑	Aβ, Tau and p-Tau ↑	Calcium phosphate mineral ↑	[230]
Caenorhabditis elegans	GCaMP6f Ca^{2+} imaging	—	$[Ca^{2+}]_M$ ↑	Neurodegeneration	MAM and ROS ↑; autophagy ↓	[231]
APP/PS1 mice	Fluo-4-AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_I$ ↑	Aβ oligomer and neuronal excitability ↑	BACE1 and VGCC ↑	[64]
$Aldh2^{-/-}$ mice	Oregon-green Bapta-1 Ca^{2+} imaging	Dorsal side of hippocampus	$[Ca^{2+}]_I$ ↓	p-Tau ↑; LTP and post synaptic excitability ↓	VGCC ↓	[232]
SH-SY5Y cells and brain tissue from AD	Fura-2-AM Ca^{2+} imaging	Medium frontal gyrus	$[Ca^{2+}]_I$ ↑, $[Ca^{2+}]_M$ ↓	Neurodegeneration	STIM and mitochondrial function ↓	[110]
TgCRND8 mice	Whole-cell patch-clamp recording	Cerebellum	—	APP ↑; LTP ↓	CaM, CaMKII and PKC ↑; ROS ↑	[233]
SH-SY5Y cells, and 5xFAD mice	Single-cell imaging	Cortex and hippocampus	$[Ca^{2+}]_L$ ↓	Aβ ↑; Synaptic plasticity and cognitive function ↓	TPC ↑; autophagy ↓ lysosomal alkalization,	[234]
Mouse neuroblastoma	Ca^{2+} probe	Hippocampus	$[Ca^{2+}]_M$ ↑	APOEε4 ↑	ERS and MAM ↑; mitochondrial function ↓	[185]
APP/PS1 mice	Fura4-AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_I$ ↑ (neurons and astrocytes)	Aβ and neuronal excitability ↑	TRPA1 and activated astrocytes ↑	[143]
AD brain tissue, and 3xTG mice	—	Temporal lobe	$[Ca^{2+}]_I$ ↑, $[Ca^{2+}]_{ER}$ ↓	Aβ and Tau ↑	Activated microglia and calreticulin ↑	[235]
J20 mice	Oregon green BAPTA-1 Ca^{2+} imaging	Cortex	$[Ca^{2+}]_I$ ↑ (astrocytes)	Aβ ↑	PMCA, connexin hemichannel and release of neurotransmitters ↑	[236]
3xTG mice	Fura-2-AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_{ER}$ ↑, $Ca^{2+}]_M$ ↓, (astrocytes)	Aβ ↑; Memory function ↓	ROS, MAM and ERS ↑ ATP ↓	[237]
APP/PS1 mice, human AD brain	Fluo-4AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_I$ ↑ (astrocytes)	Aβ ↑; Memory function ↓	SOCE, activated astrocyte, TNF-α and IL-1β ↑	[238]
Human AD brain, and BV2 cells	—	Cerebral, cortex	$[Ca^{2+}]_I$ ↑ (microglia)	Aβ ↑	SERCA ↑; activated microglia function ↓	[239]
Human AD brain tissue, and 5xFAD mice	Fluo-4-AM Ca^{2+} imaging	Hippocampus	$[Ca^{2+}]_I$ ↑ (microglia)	Aβ ↑; Memory function ↓	Calhm2 and CaMKII ↑, activated microglia ↑, NF-κB and NLRP3 ↑	[128]
APP/PS1 mice	OGB-1 AM Ca^{2+} imaging	Cortex	$[Ca^{2+}]_I$ ↑	PSEN mutation; Neuronal excitability ↑	NMDAR and release of neurotransmitters ↑; SOCE ↓	[46]
Murine neuroblastoma	Fura-2 AM Ca^{2+} imaging	—	$[Ca^{2+}]_L$ ↓, $[Ca^{2+}]_I$ ↑	PSEN1 mutation	TRP ↑; v-ATPase ↓; autophagy ↓	[168]

Note: Legend: ↑, level increase; ↓, level decrease; →, no significant change. Abbreviations: $[Ca^{2+}]_I$: intracellular calcium concentration; $[Ca^{2+}]_{ER}$: endoplasmic reticulum calcium concentration; $[Ca^{2+}]_M$: mitochondrial calcium concentration; Aβ: amyloid β peptide; Tau: microtubule-associated protein Tau; STIM: stromal interaction molecule; CaMKII: calcium-calmodulin (CaM)-dependent protein kinase II; NMDAR: N-methyl-D-aspartic acid receptor; SOCE: store-operated calcium entry; PSEN: presenilin; CDK-5: cyclin-dependent kinase 5; GSK-3β: glycogen synthase kinase-3-beta; ERS: endoplasmic reticulum stress; ROS: reactive oxygen species; NLRP3: NOD-like receptor thermal protein domain associated protein 3; v-ATP: vacuolar type H^+-ATPase; ATP: adenosine triphosphate; MAM: mitochondria-associated membrane; AMPK: AMP-activated protein kinase; PMCA: plasma membrane Ca^{2+}-ATPase; ORAI: calcium release-activated calcium modulator; IL-1: interleukin-1; TPC: two-pore channel; NF-κB: nuclear factor-κB.

to delay the procession of AD. Given that Ca^{2+} signaling mediates the activation of numerous protein kinases, such as GSK-β [72], disrupted intracellular Ca^{2+} homeostasis significantly influences Tau protein phosphorylation and NFT formation. On the one hand, calpains are a class of Ca^{2+}-activated intracellular cysteine proteases. The nervous system has two subtypes, including calpain1 and calpain2, with very similar structures, and their most significant difference is that their activation is correlated with Ca^{2+} concentration. The activation of calpain1 requires micromolar Ca^{2+} level, while calpain2 requires millimolar Ca^{2+} level [73]. Calpain1 can remove a part of the carbon-terminal region of Tau-associated protein kinases, such as GSK-3β and dual-specificity tyrosine-regulated kinase 1A (DYRK1A), to significantly enhance the capability to phosphorylate Tau protein [72,74]. Moreover, the truncated C-terminus will interact with protein phosphorylation 2A (PP2A), thus eliminating the inhibitory phosphorylation site on the protein kinase and further enhancing its activity [75]. Studies have shown that increased $[Ca^{2+}]_I$ at the early stage of AD accelerates the hyperphosphorylation of Tau protein and the loss of synaptic proteins through the CaM/calpain signaling pathway to regulate the activity of protein kinases associated with Tau protein, including CDK5 and GSK-3β [76,77].

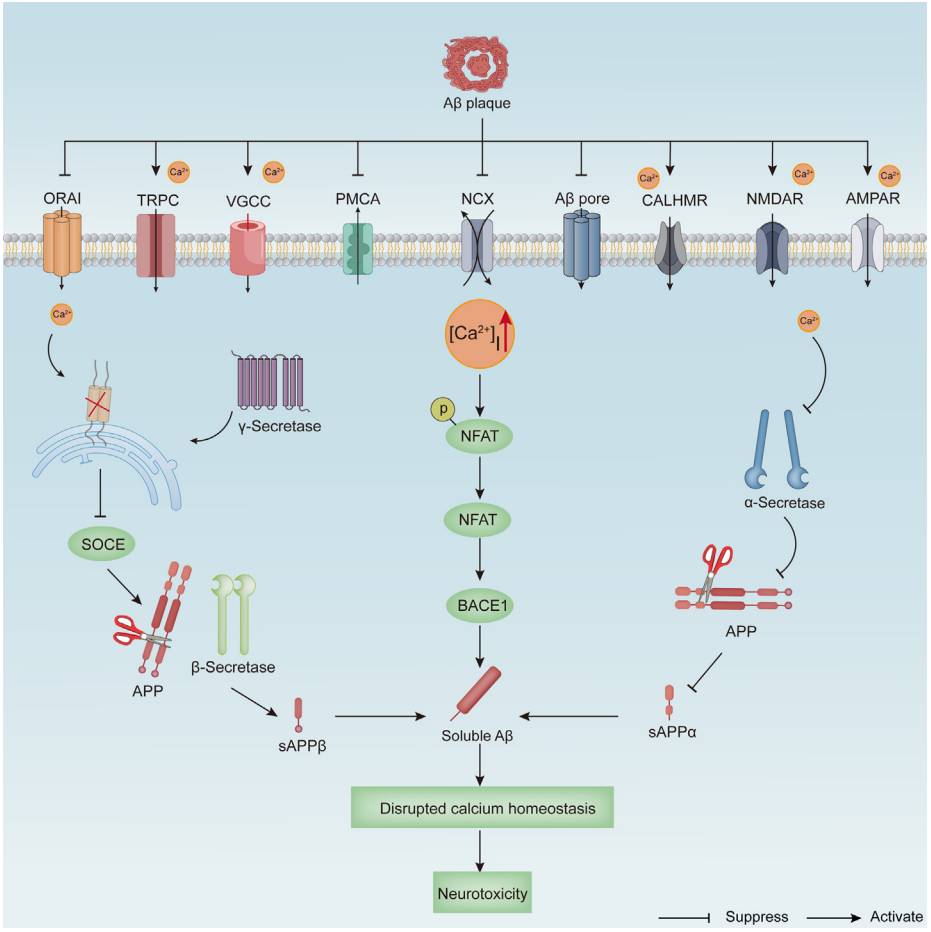

Fig. 2. Ca^{2+} and the amyloid cascade hypothesis. Aβ plaque-mediated entry of Ca^{2+} into cells can accelerate the production of Aβ by affecting the expression of α-, β- and γ-secretases and exacerbate the imbalance of Ca^{2+} homeostasis in neurons, thereby causing neurotoxicity and ultimately leading to the occurrence and development of AD.

Therefore, Ca^{2+} signaling can accelerate Tau phosphorylation by directly or indirectly regulating the activity of Tau protein-related kinases.

On the other hand, Ca^{2+} signaling appears to cleave Tau protein directly. For example, the over-activation of calpain can not only directly cut Tau into more easily entangled Tau protein fragments (17 k Da), but also hydrolyze Tau protein through activated cysteine proteases-3 to accelerate the formation of NFTs [78]. Interestingly, the hyperphosphorylated Tau protein will eliminate the hydrolysis by calpains and accelerate its accumulation in the brain. The mechanism may be that the metabolic rate of Ca^{2+}-induced hyperphosphorylated Tau protein in the brain is slower than that of un-phosphorylated Tau protein [79,80]. At the same time, increased expression of calpastatin, the sole inhibitor of calpain, can protect neurons by blocking the activation of protein kinases and inhibiting the aggregation of hyperphosphorylated Tau [81].

Additionally, a sustained increase in neuronal Ca^{2+} concentration enhances calcineurin activity, thereby inhibiting the action of phosphatase on phosphorylated Tau [82]. In addition, animal and human experimental data suggest that neurons with high cytosolic calcium concentrations are more susceptible to the formation of NFTs that facilitate the spread of phosphorylated Tau in the brain [83]. However, a Ca^{2+} imaging study *in vivo* using AD transgenic mice has shown an opposite result, suggesting that Aβ-mediated neuronal excitability is blocked in the presence of Tau protein in the brain. These results also show that Tau can reduce Aβ-induced Ca^{2+} influx and then inhibit neuronal hyperexcitability [84]. Moreover, studies have shown that calpain1 has neuroprotective effects in postnatal development and adulthood, while calpain2 may impair learning and memory capacity by inhibiting LTP and MAPK [85]. These results indicate that the role of Ca^{2+} signaling in Tau protein is far more complex than imagined, and the mechanism deserves further exploration. Therefore, Aβ-mediated dysregulation of Ca^{2+} homeostasis plays a vital role in the pathogenesis of AD by affecting the production and aggregation of Aβ peptides and the Ca^{2+}/calpain signaling regulates the phosphorylation of Tau protein (Fig. 3).

Calcium and mitochondrial dysfunction hypothesis

Calcium and energy metabolism hypothesis

The brain, a high-energy-demand organ, consumes approximately 25% of total energy in the body. The nervous system mainly depends on a constant supply of glucose and oxygen due to a lack of energy reserves. At rest, the brain needs to utilize 25% of total glucose and 20% of oxygen in the body, suggesting why neurons are vulnerable to reduced mitochondrial bioenergetic function. The disturbance of energy metabolism is one of the early and widespread features in AD. Consistent with impaired energy metabolism, gene-level studies have confirmed that the expression of 15 proteins related to glycolysis, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (OXPHOS) is significantly reduced in the AD brain [86]. Numerous studies have confirmed a significant decrease in glucose utilization in the hippocampus and cortex of brain tissues in MCI and AD patients, which can appear decades

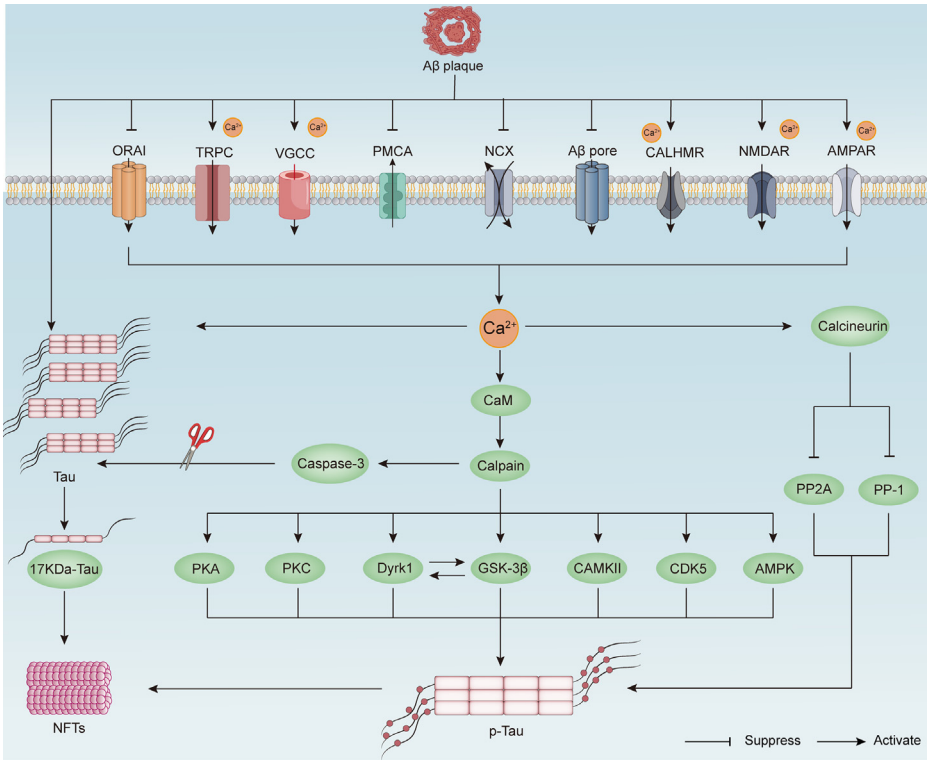

Fig. 3. Ca^{2+} and the Tau protein hypothesis. Aβ increases the activity of protein kinases (PAK, PKC, Dyrk1A, GSK-3β, CaMKII, CDK5, and AMPK) and inhibits the activity of phosphorylases (PP2A and PP-1) through the Ca^{2+}/CaM/calpain signaling pathway, and finally accelerates the hyperphosphorylation of Tau protein and the formation of NFTs. Also, the phosphorylase activity for phosphorylated Tau protein is decreased. In addition, calpain can directly hydrolyze Tau protein into more entangled Tau protein fragments.

before the onset of AD [87,88]. Enhanced Ca^{2+} signaling can down-regulate glucose transporter expression to inhibit glucose uptake of cells [89].

Activating the mitochondrial Na^+/Ca^{2+} exchanger (NCLX), a key sodium-Ca^{2+} exchange protein, promotes mitochondrial Ca^{2+} efflux, potentially enhancing mitochondrial function [90]. However, the timely energy supply depends on glucose intake and is closely related to the role of Ca^{2+} in regulating OXPHOS. Physiologically, appropriate mitochondrial Ca^{2+} level ($[Ca^{2+}]_M$) promotes pyruvate to enter mitochondria through malate-aspartate shuttle and activates OXPHOS to enter mitochondria and accelerate ATP production [91]. For senescent cells, enhancing the capability of mitochondria to absorb Ca^{2+} can be helpful for reducing $[Ca^{2+}]_I$ and delaying aging [92]. Likewise, in the early stage of AD, mitochondrial Ca^{2+} uptake is greater than excretion to appropriately increase $[Ca^{2+}]_M$ for enhancing energy supply and restoring the normal function of neurons. However, under the influence of risk factors such as age, Aβ, or reactive oxygen species (ROS), $[Ca^{2+}]_M$ continues to increase to form mitochondrial Ca^{2+} overload, thereby reducing mitochondrial membrane potential ($\Delta\Psi m$), ultimately damaging OXPHOS and impeding AD pathology [93]. Moreover, sustained mitochondrial Ca^{2+} overload will cause the irreversible opening of the mitochondrial permeability transition pore (mPTP), thus resulting in the release of a large amount of Ca^{2+} and the release of pro-apoptotic factors, eventually leading to neuronal apoptosis [39,94]. Thus, mitochondrial Ca^{2+} overload exacerbates the progression of AD by impairing mitochondrial respiration and inducing apoptosis [95]. However, in this process, $[Ca^{2+}]_I$ seems to play a more important role than $[Ca^{2+}]_M$ [96], which may be related to the regulation of cytosolic Ca^{2+} in regulating OXPHOS substrates from the cytoplasm into the mitochondrial matrix [91]. In addition, higher $[Ca^{2+}]_M$ forms a calcium phosphate precipitate as a physical barrier around complex I to inhibit NADPH-dependent electron transfer chain (ETC) [97]. Moreover, increased $[Ca^{2+}]_I$ limits the transfer of ATP from mitochondria to ER and accelerates the formation of mis-folded proteins [98]. Previous studies have shown that mis-folded proteins in AD will further aggravate the disruption of mitochondrial Ca^{2+} homeostasis by directly entering mitochondria and activating mPTP or indirectly interacting with VDAC [99]. Lowering $[Ca^{2+}]_M$ can rescue this phenotype [100]. Confusingly, many *in vivo* experiments could not reach a consistent conclusion: the phenomenon of mitochondrial Ca^{2+} overload precedes the formation of Aβ plaques [93,101]. Furthermore, exercise-mediated circulating metabolites have a unique role in enhancing brain energy metabolism and thus promoting brain health [102]. Therefore, although low $[Ca^{2+}]_M$ is essential for mitochondria to maintain the ATP production rate, mitochondrial Ca^{2+} overload will damage the structure and oxidative phosphorylation function of mitochondria and lead to the disorders of neuronal energy metabolism.

Calcium and oxidative stress

Although the central nervous system consumes significant amounts of oxygen, its limited antioxidant capacity renders it particularly vulnerable to oxidative stress. Increased oxidative stress in the AD brain is mainly related to the excessive accumulation of ROS caused by mitochondrial dysfunction [103]. Ca^{2+} transport within cells, via pumps or channels, generates short-lived but highly reactive ROS at specific cellular locations. The ROS, in turn, regulates the Ca^{2+} flux. Studies have shown that Ca^{2+} and ROS interact, influencing their respective signal pathways and playing a crucial role in developing and exacerbating age-related diseases [38]. Furthermore, complexes I and III in the ETC are the primary

sources of ROS. Yet, the precise nature of the relationship between ROS production and Ca^{2+} homeostasis in AD remains to be fully elucidated. Research indicates that under hypoxia, the activity of complex I could result in the increase of the H^+ content in the mitochondrial matrix, thereby dissolving calcium phosphate and increasing the half-life of the ubiquinone cycle on complex III, eventually causing the generation of ROS [104]. Furthermore, abnormal $[Ca^{2+}]_M$ levels can upset the balance between oxidative and antioxidative processes, leading to increased mitochondrial ROS production. The generated ROS will stimulate lipid peroxidation, activating phospholipase C and producing IP3, which increases $[Ca^{2+}]_M$ and ultimately leads to the continuous opening of mPTP and apoptosis [105]. Mitochondrial Ca^{2+} overload aggravates AD pathology by promoting superoxide formation and neuronal death [106], whereas Tau-induced mitochondrial Ca^{2+} overload appears to aggravate mitochondrial depolarization [107]. At the same time, Tau-induced ROS production upregulates AMPAR and NMDAR expression, elevating $[Ca^{2+}]_M$ and reducing mitochondrial membrane potential ($\Delta\Psi m$), which contributes to neuronal excitotoxicity [108]. The result illustrates the vital regulatory relationship between Tau-mediated Ca^{2+} overload and ROS.

Furthermore, NADPH oxidase inhibitors can suppress electron leakage from complex I, a primary source of oxygen radicals in the aging brain, thus alleviating ROS-mediated mitochondrial inner membrane depolarization [109]. Concurrently, in the case of low function of SOCE, $[Ca^{2+}]_M$ and complex I activity will be significantly reduced simultaneously. However, the decreased $[Ca^{2+}]_M$ can induce the depolarization of mitochondrial inner membrane by activating L-type voltage calcium channels to increase $[Ca^{2+}]_M$. The result suggests that SOCE plays an essential role in maintaining the regular operation of ETC and there are multiple regulatory mechanisms for mitochondrial Ca^{2+} homeostasis [110]. In addition, ROS induced by elevated Ca^{2+} concentrations in cardiomyocytes oxidizes RyR2 in the ER to stimulate Ca^{2+} release and promote mitochondrial ROS clearance [111]. The evidence suggests that the amelioration of oxidative stress corrects Ca^{2+} disturbance and mitochondrial dysfunction in Aβ-treated human neuronal stem cells [112]. However, it has also been found experimentally that high $[Ca^{2+}]_M$ can mainly affect mitochondrial function by reducing the rate of NADH-dependent ATP production and has little correlation with ROS-mediated oxidative stress [113]. Therefore, mitochondrial Ca^{2+} overload participates in oxidative stress by increasing electron leakage of the ETC and disrupting oxidative and antioxidant systems.

Calcium and the MAM hypothesis

Fluorescent probe-based experiments have demonstrated that mitochondria are sensitive to local Ca^{2+} concentrations, rather than to the broader Ca^{2+} levels across the cytoplasm [114]. Adjacent to mitochondria (Ca^{2+} receivers) and ER (Ca^{2+} generators), Ca^{2+} channels facilitate the formation of transient regions with high calcium concentrations (greater than 10 μM) around contact points, which can regulate various cellular functions [115]. This contact site between the mitochondrial outer membrane and the ER is called the MAM, as the membrane with a dynamic intracellular formation process, and the enrichment of cholesterol, sphingomyelin, and Ca^{2+}-related proteins including RyR and MCU. To prevent excessive mitochondrial Ca^{2+} uptake from the ER, the optimal MAM distance is maintained at 10–50 nM [116]. *In vivo* and *in vitro* studies of AD have revealed up-regulated expression of MAM-associated proteins and increased connectivity and communication between ER and mitochondria [117,118]. Multiple protein complexes in MAM are involved in the pathological process of AD. For example, the fission1 protein involved in mitochondrial fission interacts with the transmembrane protein of the ER to trigger the transfer of Ca^{2+} from the ER to the mitochondria, thereby leading to mitochondrial apoptosis [119]. In addition, essential proteins that regulate the protein folding of the ER, such as calnexin and calreticulin, are enriched on MAM and jointly regulate the Ca^{2+} signal communication between the ER and mitochondria [120]. Notably, mitochondria do not contain Aβ-related metabolic proteins. However, PS1, PS2, and the carbon-terminal fragment C99 of APP are enriched in MAM, indicating that MAM may be the production site of Aβ in mitochondria [121]. Previous studies have shown that Ca^{2+} in MAM can stimulate the formation of Aβ and NFTs in cells [122,123], thus shortening the distance between ER and mitochondria and increasing the number of MAM [121]. Although the studies on the MAM hypothesis and Ca^{2+} in AD are still in its infancy, it is worth for scholars to explore the underlying mechanisms in depth (Fig. 4).

Calcium and neuroinflammation hypothesis

In macrophages, when mitochondria lose their capacity to absorb and exchange Ca^{2+}, it disrupts Ca^{2+} signaling pathways, contributing to chronic inflammation associated with aging [92]. At a time when the studies on the underlying mechanisms of AD are progressing slowly, more and more scholars tend to explain AD from the perspective of neuroinflammation. The neuroinflammation hypothesis proposes that under the long-term stimulation of injury signals, such as danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), the continuously activated M1 pro-inflammatory phenotype microglia directly or indirectly damage neurons by releasing pro-inflammatory factors, eventually leading to the occurrence and development of AD. Ca^{2+} has long been recognized as an essential signal for PAMPs and DAMPs to trigger immunity [124]. The major feature of neuroinflammation is the chronic activation of microglia and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasomes. Neuronal Ca^{2+} imbalance may be a key factor or even one of the pathogeneses of neuroinflammation-mediated synaptic dysfunction in aging and neurodegenerative diseases [125].

On the one hand, Ca^{2+} signaling is closely related to the activation of glial cells. Activating Ca^{2+}-dependent PKC/MAPK/NF-κB signal pathway promotes the conversion of resting microglia into the M1 phenotype and the release of inflammatory factors [126], whereas inhibiting this Ca^{2+} signaling pathway can elevate the presence of the M2 anti-inflammatory phenotype in microglia [127]. The expression of CALHAM2 increases Ca^{2+} concentration in disease-associated microglia. CALHAM2 promotes the activation of microglia, manifested by increased cell body size, reduced dendrite length, and enhanced phagocytic capacity of microglia. In the AD environment, conditional deletion of CALHAM2 reduces the number of activated microglia surrounding Aβ plaques in the cortex and hippocampus to inhibit the expression of inflammatory cytokines and enhance cognitive performance [128]. Previous studies have also shown that the activation of NLRP3 inflammasomes is positively correlated with the level of $[Ca^{2+}]_I$ [129]. Likewise, the activation of glial cells and immune-along inflammatory responses are sufficiently evident in Tau alone, suggesting that neuroinflammation may be less correlated with Aβ [130,131]. In addition, the calcium channel blocker (CCB) nicardipine can significantly delay the activation of microglia induced by lipopolysaccharide [132]. The activation of astrocytes also depends on intracellular Ca^{2+} signaling. Elevated $[Ca^{2+}]_I$ seems to play an anti-inflammatory role for astrocytes [133], which may be due to different sensitivity of different branches of astrocytes to calcium signals, thus resulting in different roles in neuroinflammation [134]. In neurodegenerative diseases, Ca^{2+} homeostasis in astrocytes seems to be associated with neuronal synaptic function and

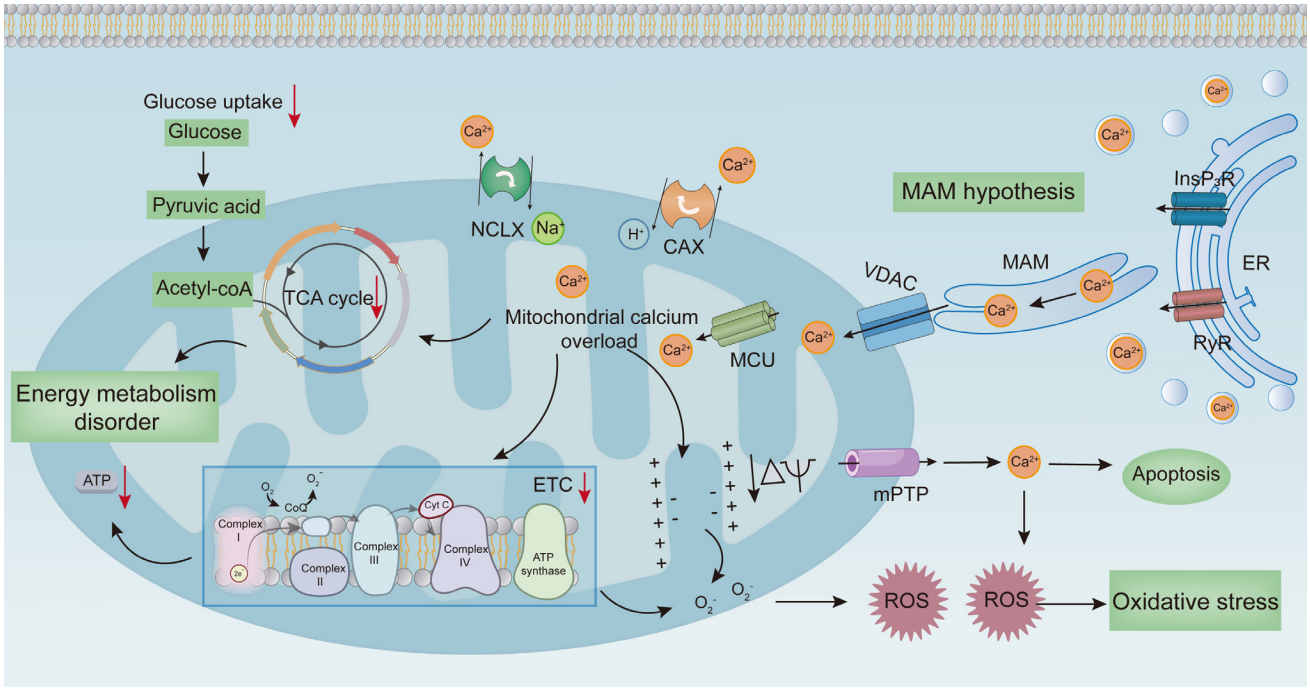

Fig. 4. Ca^{2+} and the mitochondrial dysfunction hypothesis. Mitochondria take up Ca^{2+} from the VDAC of the outer membrane and the MCU of the inner membrane, ER continuously transports Ca^{2+} to the mitochondria through MAM, and the mitochondria exclude Ca^{2+}. These three aspects lead to mitochondrial calcium overload. Abnormally elevated $[Ca^{2+}]_M$ reduces the mitochondrial membrane potential, suppresses the functions of the tricarboxylic acid cycle and the oxidative respiratory chain, and promotes the production of ROS, eventually triggering apoptosis, oxidative stress, and energy metabolism disorders.

neurotransmitter release [135]. Blocking Ca^{2+} influx in microglia and astrocytes can delay neuronal damage induced by neuroinflammation in AD [136].

On the other hand, Ca^{2+} signaling communication between microglia, astrocytes, and neurons also plays a vital role in neuroinflammation in AD. During neuroinflammation process, there is a large amount of calcium-dependent communication and exchange between glial and neuronal cells. Complement C3 released by activated astrocytes can promote the transformation of microglia into M1 pro-inflammatory microglia [137]. Complement C3 released by astrocytes binds to C3 receptors on neurons or microglia to activate inflammatory responses in brain tissues, eventually decreasing synapse density and shortening neuronal dendrites [137,138]. The fluctuation of Ca^{2+} among three kinds of cells plays an important role [139–141]. Moreover, the fluctuation of Ca^{2+} levels in astrocytes can regulate the axonal conduction velocity of neurons, thereby modulating the excitability of neurons [142]. Long-term maintenance of low Ca^{2+} levels in astrocytes is a potential therapeutic modality to prevent cognitive impairment in AD, but does not affect neuronal function in healthy mice [143]. Moreover, it is worth noting that enhanced Ca^{2+} signaling can disrupt the integrity of the BBB to break the immune privilege, ultimately aggravating AD [144]. Therefore, Ca^{2+} signaling in microglia and astrocytes and their communication with neurons play an important role in AD neuroinflammation (Fig. 5).

Calcium and autophagy dysfunction hypothesis

Autophagy is an evolutionarily conserved lysosome-dependent cellular event in eukaryotes that can facilitate the degradation and recycling of damaged organelles and mis-folded proteins. Autophagy includes the steps of autophagosome formation, recognition and transport of cargo, autophagosome-lysosome fusion, and autophagolysosomal digestion. Since the lysosomes of neurons mainly exist in the cell body, autophagosomes that can wrap damaged organelles and proteins must be transported to the cell body to fuse with lysosomes for degradation. This also leads to the maintenance of autophagy function associated with neurological diseases. The accumulation of many autophagic structures in AD models can cause the decline of autophagic flux and the accumulation of many denatured and dysfunctional proteins. Correcting dysfunctional autophagy is beneficial to delay or even reverse the pathogenesis of AD [145]. The Ca^{2+} signaling for regulating autophagy can come from different organelles in neurons or other cells [146]. Both large-scale increase in Ca^{2+} levels and localized Ca^{2+} levels in specific cells are strongly associated with autophagy [147].

Calcium and autophagosome formation

After autophagy is initiated, the autophagic membrane will gradually extend to form an independent compartment that can enclose cellular components that need to be decomposed through autophagosomes. The formation of autophagosomes is vital in the overall autophagy flux. Critical factors associated with autophagosome formation, such as Beclin1 and Vps34, are considered the role of Ca^{2+} signaling. Intracellular Ca^{2+} signals from different resources and pathways can initiate transcription factor EB (TFEB) and activate the formation of autophagosomes [148,149]. Moreover, the Ca^{2+}/CaMKII signal pathway can not only relieve the suppression of autophagy by the mammalian target of rapamycin (mTOR), but also induce autophagy by promoting the phosphorylation of Unc-51-like kinase complex by AMPK [148]. Short-term change in $[Ca^{2+}]_{ER}$ can promote the aggregation of puncta protein FIP200 to specify the site of autophagosome complex formation. In addition, the changes in frequency, amplitude, and duration of $[Ca^{2+}]_{ER}$ reveal the continuous increase, thereby causing the accumulation of small and incomplete autophagosomes [150]. These results can explain why autophagosome formation mainly occurs near the ER [151]. In APP/PS1 mice, Aβ can suppress autophagosome

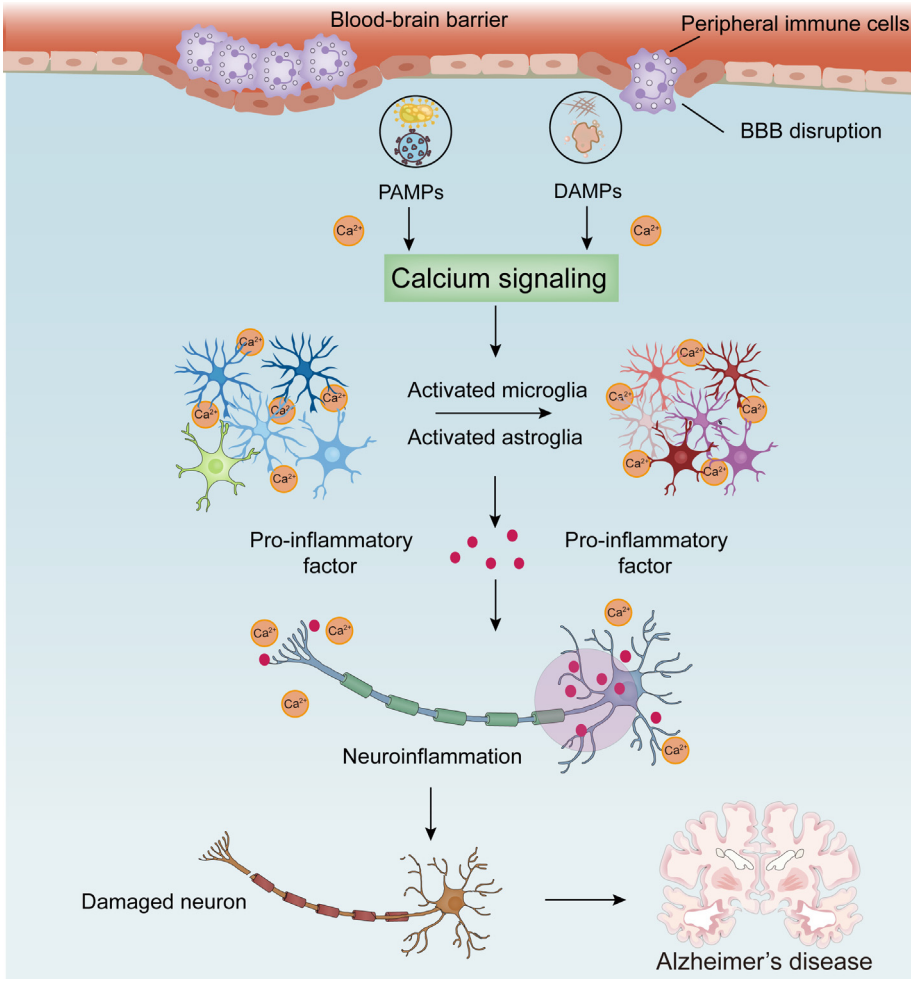

Fig. 5. Ca^{2+} and the neuroinflammation hypothesis. Aberrant Ca^{2+} signaling is helpful for activating microglia and astrocytes into a pro-inflammatory phenotype, thus resulting in the sustained release of inflammatory cytokines. Activated glial cells and inflammatory factors can damage neurons through calcium oscillations.

formation by activating Ca^{2+}/CaMKKβ/AMPK signaling to reduce the accumulation of pathological autophagic vacuoles and blocking this signal pathway for inducing autophagy [152]. However, increased Ca^{2+} signaling is a double-edged sword for autophagy. Calpain, the downstream of Ca^{2+} signaling, can cleave autophagy-related gene 5, thereby inhibiting autophagosome formation and interrupting Ca^{2+} signaling to restore the basal level of autophagy [153]. In the early stage of AD, the restoration of autophagy associated with Ca^{2+} signaling protects neurons from various stress responses. Damage signals persist during aging process, and excessive $[Ca^{2+}]_I$ exhibits the more suppression of autophagy than the activation of autophagosome formation, thereby resulting in impaired autophagy flux and aggregation of insoluble proteins [154,155], which may be due to too high Ca^{2+} level for stimulating the function of mTOR more than that of AMPK [156,157].

Calcium and dysfunctional lysosomal acidification

Lysosome is an essential part of the endolysosomal system, and its acidic environment is crucial for the degradation by autophagy and the regulation of Ca^{2+} concentration. Lysosomal calcium concentration ($[Ca^{2+}]_L$) can be accommodated (~0.5 mM), which is almost same as that of the ER, but abnormal lysosomal Ca^{2+} homeostasis is closely related to autophagolysosome defects [158]. In five AD models, the disrupted acidification of autophagolysosomes can cause the accumulation of Aβ and SP, and correcting abnormal pH of lysosomes can be beneficial to enhance the low-level autophagy and other AD-related pathologies [159]. Like the ER membrane, lysosomes also possess a series of Ca^{2+} processing proteins or channels to maintain lysosomal calcium homeostasis. Ca^{2+} released from lysosomes through VGCC, mucolipin family of transient receptor potential (TRPML) channels, two-pore channels (TPCs), and cation/H^+ exchanger (CAX) promotes the fusion of autophagosomes and lysosomes, and reduces the accumulation of immature autophagic structures [147]. It is generally believed that the vacuolar-type H^+-ATPase (v-ATP) in lysosomes is the prerequisite and primary regulator for maintaining the acidic environment in lysosomes and the fusion of autophagosomes and lysosomes. Down-regulated expression of v-ATP in the AD brain can result in lysosomal alkalization and suppressed autophagy [160,161]. However, the fusion of lysosomes and autophagosomes lacking v-ATPase is not disrupted, but prolonged. Fusion is only interrupted when Ca^{2+} signaling and v-ATP are simultaneously inhibited, and the fusion can be restored only by supplementing Ca^{2+} [162]. This result indicates that Ca^{2+} channels are more critical than v-ATPase in regulating lysosomal acidification. The acidification of normal lysosomes is to form a difference in H^+ concentration to activate CAX, thereby stimulating lysosomes for replenishing Ca^{2+} [163]. The ER and lysosomes excessively release Ca^{2+} to increase $[Ca^{2+}]_I$ and destroy the function of v-ATP, which is the final cause of lysosome alkalization in AD [9,158]. The alkaline environment in lysosomes inhibits the activity of various

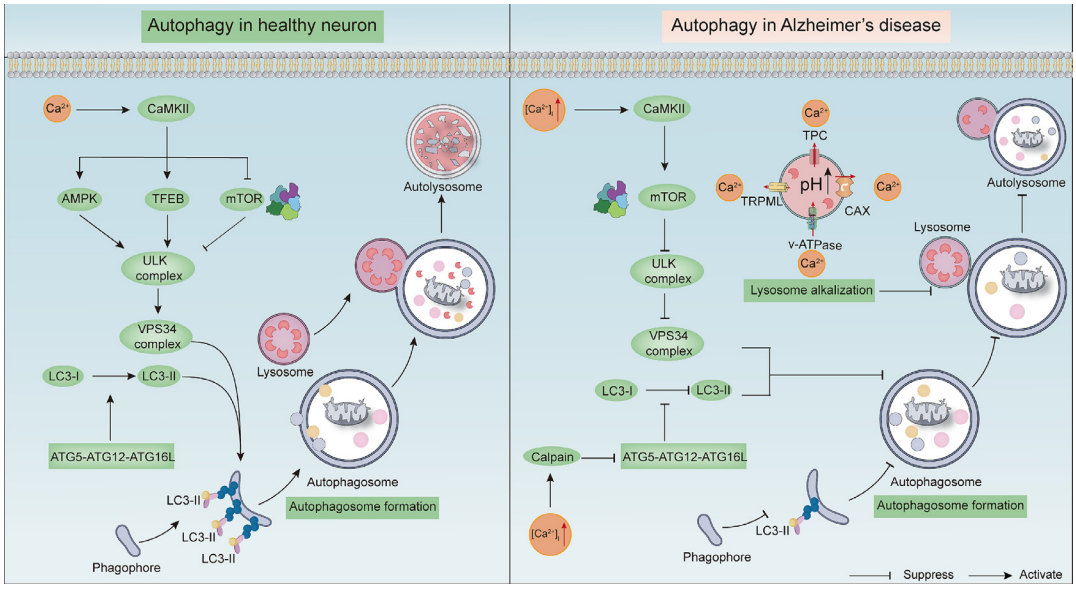

Fig. 6. Ca^{2+} and the autophagy dysfunction hypothesis. On the one hand, the enhanced Ca^{2+} signaling hinders the formation of autophagosomes by inhibiting the formation of the ATG5-ATG12-ATG16L complex and promoting the expression of mammalian target of rapamycin (mTOR). On the other hand, it can also cause the excessive release of Ca^{2+} from lysosomes, thereby causing the pH rise in the lysosomal cavity and delaying the fusion process of autophagosomes and lysosomes, which eventually leads to a decrease in the clearance rate of denatured or dysfunctional proteins and cell debris.

proteases, such as cathepsins and hydrolases, thereby resulting in deficient autophagy and the aggregation of many erroneous proteins [164]. Similarly, the restoration of lysosomal v-ATPase expression following pharmacological blockade of Ca^{2+} release from the ER leads to a drop in lysosomal pH, the restoration of autophagic flux, and the reduction of erroneous protein aggregation [164]. Normally, during retrograde transport to the soma, autophagosomes, and endosomes, the immature autolysosomes drop in a stepwise pH of 4.5 [165]. Abnormally enhanced calcium signaling blocks the reverse axoplasmic transport and prevents the acidification of autolysosomes [166]. This suggests that Ca^{2+} signaling of the ER may be a key event in the regulation of the autophagy-lysosomal process by v-ATPase. Notably, PS, a genetic risk factor associated with AD, can block the maturation process of autophagy by depleting Ca^{2+} stores in the ER and increase autophagy levels by causing the acidification of lysosomes and restoring Ca^{2+} homeostasis [167,168]. Such results suggest that there are other regulatory mechanisms for acid-base in lysosomes. However, it has also been reported that increased Ca^{2+} signaling can further increase lysosomal pH and maintain basal levels of autophagy [169]. The specific mechanism still needs to be further studied. Therefore, Ca^{2+} signaling prevents autophagy process by affecting the formation of autophagosomes and the acidification of lysosomes, thereby leading to AD-related pathology (Fig. 6).

Calcium and synaptic dysfunction hypothesis

AD is an age-dependent neurodegenerative disorder that leads to a progressive decline in short-term memory, long-term memory impairments, disorientation, and behavioral changes in the elderly. Research indicates early AD changes include synaptic structure and function impairments, offering a plausible explanation for the initial decline in short-term memory observed in the disease [170]. Indeed, synaptic loss is closely associated with cognitive decline in AD, as synaptic plasticity underpins a series of events critical for cognitive function in the brain. Consequently, many scholars consider AD as a disease characterized by synaptic dysfunction. Ca^{2+} homeostasis is fundamental to synaptic plasticity and cognitive functions [171]. Upon receiving a strong stimulus, neurons typically trigger a rapid and transient influx of Ca^{2+} through NMDARs, activating the CaM/CAMKII/AMPK signal pathway to produce LTP, thereby enhancing synaptic plasticity. However, during aging process, particularly in neurodegenerative diseases, the cellular regulation of Ca^{2+} functions declines, leading to synaptic dysfunction, impaired plasticity, and neuronal degeneration. In AD, neurons subjected to chronic Ca^{2+} overload respond to even minor stimuli with sustained intracellular Ca^{2+} influx, activating calcineurin and inducing LTD, which ultimately weakens synapses and diminishes cognitive functions [172]. Calcineurin [173] and calpain [174] inhibition has been shown to improve synaptic structure and cognitive functions in several AD mouse models, a mechanism linked to the overactivation of RyR in the neuronal ER [175]. Consistently, RyR-induced Ca^{2+} overload is the most pronounced in the synaptic terminals and dendritic spines of AD neurons [176]. Studies show that in AD, RyR promotes Ca^{2+} overload, thereby binding to proteins involved in synaptic vesicle fusion, reducing neurotransmitter vesicle release, and impairing synaptic plasticity [177].

Moreover, the application of RyR conformational modulators not only reduces intracellular Ca^{2+} concentration, but also restores synaptic plasticity, suggesting RyR as potential therapeutic targets for AD-associated synaptic dysfunction [178]. This hypothesis is further supported by studies on human neurons from AD patients [179]. Additionally, dysregulated Ca^{2+} signaling interacts with Aβ accumulation, Tau hyperphosphorylation, oxidative stress, and neuroinflammatory responses to further compromise Ca^{2+} regulatory mechanisms, ultimately leading to synaptic dysfunction and cognitive impairment or decline [180]. Therefore, synaptic dysfunction in AD is closely associated with imbalanced Ca^{2+} homeostasis, particularly the overactivation of RyR, making it a likely target for potential AD therapies.

Calcium and other corresponding hypotheses in AD

APOE can cause neuroinflammatory response, synaptic dysfunction, and neuronal degeneration by altering cellular homeostasis, eventually leading to AD, named the APOE cascade hypothesis [181]. In neurons with different APOE types, Ca^{2+} plays different

Table 2
Calcium signaling-related drugs in AD.

Categories	Drug type	Drugs	References
Drugs approved for clinical use in AD	NMDA receptor antagonist	Memantine	FDA-approved drug
	Cholinesterase inhibitor	Donepezil; Rivastigmine; Galantamine; Huperzine A	FDA-approved drugs
	Anti-amyloid monoclonal antibodies	Aducanumab; Lecanemab; Donanemab	FDA-approved drugs
Drugs in clinical trials with potential for Ca^{2+} signaling regulation	Cholinesterase inhibitor	Donepezil	[240]
	NMDA receptor antagonist	Memantine	[200]
	Antiepileptic drug	Levetiracetam	[241]
	Mood stabilizer	Lithium	[242]
	Ca^{2+}-activated potassium channel inhibitor	Senicapoc	[243]
	Immunosuppressant	Rapamycin	[244]
	NMDAR-positive allosteric modulator	Dalzanemdor	[245]
	Hormone	Insulin	[246]
	Chinese traditional medicine	Quercetin; Polygalae; Zexieyin formula	[247–249]
	Antioxidant reagent	Edaravone	[250]
	Endocannabinoid receptor agonist	Cannabidiol	[251]
Drugs in current research for Ca^{2+} signaling regulation	Ca^{2+} channel blocker	Lomerizine; Diltiazem; Bepridil; Verapamil; Felodipine; Nimodipine	[252–257]
	Muscle relaxant	Dantrolene	[258]
	Alkaloids	Tetrandrine; Dauricine	[259,260]
	Antiallergic drug	Tranilast	[261]
	Synthetic products	New small molecules	[262,263]
	Natural products	Urolithin A; Nobiletin; Hyperoside	[264–266]
	Septin-related compound	ReS19-T	[267]
	Fat-soluble vitamin	Vitamin D	[268]

roles. For example, APOEε4 regulates lipid metabolism, immune response, and molecular transport between cells by increasing $[Ca^{2+}]_I$ [182,183]. The APOEε4-mediated decline in lipid uptake function of microglia can disrupt the normal neuronal Ca^{2+} and potassium homeostasis and disrupt the communication between neurons and microglia [184]. APOEε4 impairs neuronal mitochondrial function by promoting mitochondrial Ca^{2+} overload, potentially providing a new therapeutic target for the intervention of AD [185].

The cholinergic hypothesis proposes that the onset of AD is due to the abnormal function of acetylcholinesterase and acetylcholine transferase in the brain. The acetylcholine receptors in the central nervous system are involved in regulating Ca^{2+} transport [186]. The receptors of α7 nicotinamide can lead to a large amount of Ca^{2+} influx and the activation of Ca^{2+} channels, as well as final neuronal apoptosis and cognitive impairment [187,188]. However, activating acetylcholine receptors, such as M1-type acetylcholine receptors, increases cytoplasmic Ca^{2+} concentration and appears to have positive effects in AD patients [189].

Increasing studies have found that insulin resistance is the real cause of brain lesions in AD patients. This point of view proposes that increased glucose concentration in brain tissue and decreased neuronal sensitivity to insulin may lead to abnormal glucose metabolism in the brain and trigger a series of neuropathological features associated with AD. Therefore, AD is also known as type-III diabetes [190]. Dysregulation of hippocampal Ca^{2+} homeostasis plays a critical role between diabetes and aging [191]. Under physiological conditions, insulin can correct the flux of Ca^{2+} by reducing the Aβ42/Aβ40 ratio. The insulin signaling can promote the more uptake of palmitic acid by neurons to increase $[Ca^{2+}]_I$ and ATP production [192]. Impaired insulin signaling can accelerate aging-associated Ca^{2+} homeostasis, whereas the correction of neuronal insulin resistance appears to counteract age-dependent dysregulation of Ca^{2+} homeostasis [191].

Ferroptosis may be an Aβ- and Tau-independent underlying mechanism of neuronal loss in AD, and excessive iron imbalance can deplete endogenous antioxidant glutathione and cause neuronal degeneration [193]. Dysregulated iron can aggravate Ca^{2+} homeostasis by activating Ca^{2+} channels, thus leading to iron-dependent neuronal death [194]. Observed by synchrotron X-ray spectromicroscopy, the centers of amyloid plaques from brain tissues of AD patients are mainly dominated by iron and Ca^{2+} [195]. The increased Ca^{2+} signaling induced by iron overload can damage the mitochondria of hippocampal neurons and cause neuronal degeneration [196]. The Ca^{2+} signaling pathway is a crucial mediator of ferroptosis, and blocking this signaling pathway can promote neuronal survival by correcting abnormal iron metabolism [197]. In summary, the dysregulation of Ca^{2+} homeostasis serves as a crucial link connecting these various theories to the neuropathological characteristics of AD.

Correcting calcium disturbance as a potential therapeutic strategy for AD

Numerous drugs targeting Ca^{2+} channels have been developed and achieved significant outcomes in mitigating symptoms of AD. To provide a comprehensive overview of calcium signaling-related drugs, both FDA-approved drugs and those still under clinical or pre-clinical investigations are summarized here (Table 2) [198]. Memantine, an NMDAR antagonist, is the first drug approved by the FDA for treating patients with moderate to severe AD. It can prevent excessive Ca^{2+} influx and neuronal excitotoxicity, which are due to the sustained release of glutamate from presynaptic neurons. However, due to the moderate affinity and non-competitive action of memantine on NMDARs, it preserves the primary function of glutamic acid binding to NMDARs [199]. Memantine is also reported to ameliorate cognitive deficits in APP/PS1 and 3xTG mice by inhibiting Aβ aggregation and preventing glutamate-mediated loss of neuronal dendritic spines and synapses [200]. In addition to inhibiting NMDA receptors, memantine can reduce $[Ca^{2+}]_I$ and enhance SOCE to correct Ca^{2+} disturbance [201].

An increasing number of clinical trials have validated that combining memantine with acetylcholine receptor antagonists more

effectively alleviates cognitive loss of AD patients. However, they only stop at the symptom relief level slightly [202]. While theoretically, memantine could reduce $[Ca^{2+}]_I$, thereby ameliorating symptoms, and its effect on the overall Ca^{2+} homeostasis within cells is minimal; hence, the cognitive improvement that it offers is significantly limited [203].

Antihypertensive drugs, such as CCBs, have been reported to prevent dementia during the treatment of hypertensive patients. This notion is further supported by the fact that cognitive function does not decrease over 20 months in MCI patients treated with nilvadipine [204]. Without affecting the normal physiological status of neurons, CCBs can improve the cognitive function of AD by reducing the level of Aβ42 [205]. Therefore, CCBs, especially those acting on L-type voltage-gated regulators, may be precise targets for the therapy of AD [206,207]. Recently, a *meta*-analysis including more than 50,000 participants reveals no association between CCBs and the prevalence of AD, and CCBs are more inclined to enhance the prevention of AD through the reduction effect of blood pressure [208]. Currently, it remains undetermined whether the positive effects of CCBs on AD treatment are directly related to or independent of antihypertensive effects. Moreover, large doses of Ca^{2+} blockers can completely block the Ca^{2+} signaling in neurons, thereby aggravating neuronal deformation and damage [209]. However, numerous clinical trials have confirmed that using L-type calcium channel blockers such as nilvadipine does not alleviate memory dysfunction in AD patients. Nilvadipine appears to be effective only in AD patients with mild or earlier symptoms [210]. Consistently, several observational studies spanning more than a decade have documented that the application of CCBs, including nilvadipine, is associated with decreased prevalence of AD in older patients [211]. In addition, nilvadipine seems to mitigate AD by affecting multiple aspects such as Aβ, Tau, APOE protein or inflammatory responses [212,213], which further supports the viewpoint of correcting calcium signaling hypothesis using CCBs for mitigating AD. These contradictory results further suggest a close relationship between CCBs and dementia, indicating that their neuroprotective effects warrant further investigation.

Calcium dysregulation in other neurodegenerative diseases

In addition to AD, the impaired Ca^{2+} homeostasis has also attracted much attention in neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [214], with common feature including misfolding and deposition of abnormal proteins, such as α-synuclein in PD, huntingtin in HD, and transactive response DNA binding protein 43 (TDP-43) in ALS [215]. These faulty proteins further exacerbate the pathological process by disrupting the Ca^{2+} signaling pathway [216]. At the same time, the impaired Ca^{2+} homeostasis also promotes the aggregation of these proteins and accelerates the degeneration of synapses [214,217]. Ca^{2+} imbalance has thus become a common pathological mechanism of other neurodegenerative diseases [180].

Regulation of Ca^{2+} homeostasis is a core component of multi-target combination therapy [218]. For example, previous studies have shown that calpain inhibition can reduce neuronal damage and alleviate synaptic degeneration in PD and ALS [219]. In addition, normalization of mitochondrial Ca^{2+} flux has a significant neuroprotective effect in restoring neuronal function [220], thereby providing a novel direction for treating various neurodegenerative diseases [221,222]. Ca^{2+}-binding proteins are important determinants for the susceptibility of neurons in the central nervous system to develop into neurodegenerative diseases and have potential prediction value as early biomarkers [223,224]. Ca^{2+}-based biomaterials that mimic the biomineralization process [225,226] also seem worthy of attention in diagnosing and preventing diseases.

Impaired Ca^{2+} homeostasis is a critical pathological link in a single disease and a core mechanism shared by different neurodegenerative diseases. Intervention measures based on the regulation of the Ca^{2+} signaling pathway will not only be beneficial to the treatment of AD, but also can provide novel solutions and inspiration for preventing and treating a series of neurodegenerative diseases.

Limitations and future directions

Nowadays, although in-depth discussions on clinical trials targeting Ca^{2+} and Aβ in AD are conducted, these studies on Ca^{2+} signaling are mainly based on cell and animal experiments. But a large amount of *in vivo* test data is highly necessary for further clarifying corresponding conclusions. Also, the data from *in vitro* systems, genetic animal models, and AD-derived human tissues are complex and inconsistent. Some animal experiments have used classic AD transgenic animals characterized by Aβ plaques and NFTs, as well as *in vivo* immunofluorescence techniques. Although many studies can support the viewpoint of calcium signaling hypothesis, it is difficult to predict the preference order of calcium signaling hypothesis, amyloid cascade hypothesis, Tau protein hypothesis, neuroinflammation hypothesis, autophagy dysfunction hypothesis, and other hypotheses during the aging process and which hypothesis plays a dominant role in AD.

After summarizing current experiments, some suggestions and questions for current studies on the Ca^{2+} signaling hypothesis of AD are proposed and highly necessary: for example, developing transgenic animals characterized by dysregulated Ca^{2+} homeostasis for mitigating AD is highly necessary. Is the suppressed SOCE signal pathway or the destruction of the involved proteins in AD due to the saturation of $[Ca^{2+}]_{ER}$ and $[Ca^{2+}]_I$? Which stage of AD is involved in the down-regulation of SOCE? What is the physiological function of ER to transfer calcium to mitochondria through MAM? Is neuronal hyperexcitability primarily calcium-dependent? What is the difference in degree between the increase in intracellular calcium ion concentration caused by aging and the calcium overload in AD? What is the critical role of action potential in maintaining Ca^{2+} in AD? Which calcium level can play a protective role in AD? What is the role of calcium signaling in astrocytes in neuroinflammation? Is the prevention effect of CCBs on cognitive decline with the concomitant effect during the hypotensive function? What is the preference order of amyloid cascade hypothesis, neuroinflammation hypothesis, mitochondrial dysfunction hypothesis, autophagy dysfunction hypothesis, calcium signaling hypothesis, or other hypotheses for rescuing the pathogenesis of AD? Are calcium-mediated neuroinflammation hypotheses, mitochondrial dysfunction, and autophagy dysfunction resulting from the accumulation of Aβ and NFTs? These unresolved questions could be resolved by developing transgenic animals characterized by Ca^{2+} disturbance since many current studies have used classical animal models of AD, such as APP/PS1 or 5xFAD mice. In addition, *in vivo* fluorescent calcium probes of different organelles and cryo-EM can help us to further explore which level of $[Ca^{2+}]_I$, $[Ca^{2+}]_M$ $[Ca^{2+}]_{ER}$, or $[Ca^{2+}]_L$ can induce the occurrence and development of AD. Figuring out why serum calcium levels are decreased in MCI patients and early-stage AD will be beneficial to the development of biomarkers for diagnosing AD at the early stage. Whether CaM or calpain is a potential target for the prevention and treatment of AD based on the Ca^{2+} signaling hypothesis.

Conclusion

To sum up, with the continuous increase in human life expectancy, the pathogenesis of AD remains a complex challenge for scientists. Therefore, exploring a solution to this complex issue is of urgent importance. Although AD involves a variety of complex pathogenesis and hypotheses, with the continuous focus on the Ca^{2+} signaling hypothesis, Ca^{2+} may be a core factor and an essential aspect in all mechanisms. Therefore, the Ca^{2+} signaling hypothesis is a common signal pathway through which multiple risk factors such as aging and cerebrovascular diseases and pathogenic factors induce AD pathology. Neurodegeneration in AD is the result of a variety of events. Additionally, this article also offers a comprehensive analysis and discussion on how the Ca^{2+} signaling hypothesis contributes to critical pathophysiological processes in AD, such as synaptic loss, plaque formation, neuroinflammation, thereby providing a complete framework of the Ca^{2+} signaling hypothesis, with the most significant innovation. The Ca^{2+} signaling hypothesis may be one of the bridges connecting different pathogenesis of AD, and it is also an essential factor involved in different stages of corresponding hypotheses and mechanisms. In most of hypotheses, too high Ca^{2+} level may reveal the negative effect, including promoting Aβ and ROS generation, stimulating the hyperphosphorylation of Tau protein, activating pro-inflammatory glial cells, enhancing mitochondrial Ca^{2+} overload, and suppressing autophagy initiation and autophagy-lysosome fusion. However, there is also an upside to Ca^{2+} signaling. Appropriately elevated Ca^{2+} can increase the supply of ATP, activate autophagic flux, inhibit inflammatory responses, and even promote the metabolic process of non-Aβ pathways. Therefore, the effect of altered Ca^{2+} homeostasis on neurons in AD is concentration-dependent and dual-faced. Furthermore, the present study could support the amyloid cascade hypothesis, rather than the separation of Aβ and Tau into two independent hypotheses. Although Ca^{2+} can be used as the basal hypothesis for significant pathogenesis in AD, and Ca^{2+} homeostasis is a dynamic process, the changes in Ca^{2+} concentration or the role of Ca^{2+} signals in the pathogenesis of AD as the specific dynamic process is still unclear. Novel research tools, such as *in vivo* Ca^{2+} imaging, are needed to explore this dynamic process. In addition, the reason for contradictory results is always inseparable from Aβ or Tau protein, which may be due to the reason that many studies still use model mice with the overexpression of Aβ-related and Tau proteins. Therefore, the most significant and urgent problem in AD studies is to develop animal models suitable for clarifying these corresponding hypotheses. Moreover, the joint role and critical connections of the Ca^{2+} signaling hypothesis in multiple mechanisms are systematically summarized and elucidated in this study. Furthermore, this study also provides essential information for gaining insight into the pathogenesis of AD. More importantly, understanding the central role of the Ca^{2+} signaling hypothesis in AD may provide new avenues for the prevention and treatment of AD to facilitate the discovery and development of novel drugs for AD.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

CRediT authorship contribution statement

Minghui Wang: Conceptualization, Writing – original draft. **Hu Zhang:** Writing – original draft. **Jiling Liang:** Writing – original draft. **Jielun Huang:** Writing – original draft. **Tong Wu:** Conceptualization, Writing – review & editing. **Ning Chen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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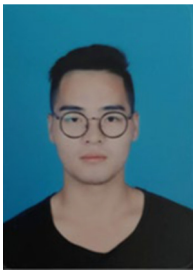

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