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Mini review

Modulation of L-type calcium channels in Alzheimer's disease: A potential therapeutic target

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ABSTRACT

Calcium plays a fundamental role in various signaling pathways and cellular processes in the human organism. In the nervous system, voltage-gated calcium channels such as L-type calcium channels (LTCCs) are critical elements in mediating neurotransmitter release, synaptic integration and plasticity. Dysfunction of LTCCs has been implicated in both aging and Alzheimer's Disease (AD), constituting a key component of calcium hypothesis of AD. As such, LTCCs are a promising drug target in AD. However, due to their structural and functional complexity, the mechanisms by which LTCCs contribute to AD are still unclear. In this review, we briefly summarize the structure, function, and modulation of LTCCs that are the backbone for understanding pathological processes involving LTCCs. We suggest targeting molecular pathways up-regulating LTCCs in AD may be a more promising approach, given the diverse physiological functions of LTCCs and the ineffectiveness of LTCC blockers in clinical studies.

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Abbreviations: Aβ, β-amyloid; AC, adenylyl cyclase; AD, Alzheimer's Disease; AHP, afterhyperpolarization; AR, adrenoceptor; BIN1, bridging integrator 1; BTZs, benzothiazepines; CaMKII, calmodulin-dependent protein kinase II; CDF, calcium-dependent facilitation; CDI, calcium-dependent inactivation; DHP, dihydropyridine; LTCC, L-type calcium channels; LTD, long-term depression; LTP, long-term potentiation; NFT, neurofibrillary tangles; NMDAR, *N*-methyl-D-aspartate receptor; PAA, phenylalkylamines; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; SFK, Src family kinase; VSD, voltage sensing domain.

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1. Introduction

A long-standing hypothesis for the etiology of Alzheimer's disease (AD) is the calcium hypothesis: a disruption in calcium homeostasis and high intracellular calcium concentration are associated with β-amyloid (Aβ) and neurofibrillary tangles (NFT), which alter synaptic plasticity and cognitive function, leading to neural degeneration and eventual cell death [43,83]. Aging and AD are associated with chronic elevations in Ca^{2+} influx *via* L-type calcium channels (LTCC). LTCC blockers have been successful in ameliorating AD pathology in animal models [34,121]. Nimodipine, which readily passes the blood–brain barrier, reversed some of the cognitive impairment in dementia patients in earlier studies [8,57,164]. However, inconsistent effects of LTCC blockers have been reported in recent years [4]. Although LTCC hyperfunction and associated calcium imbalance have been extensively studied in aging [82,84,90], how alteration of LTCC function occurs in AD and contributes to AD pathology are much less understood. Thus, evidence calls for further investigation of the role of LTCCs in AD and the potential therapeutic benefits of LTCC blockers. In this review, we first summarize the structure and function of LTCCs and drug targeting by LTCC blockers. We then discuss changes of LTCCs in aging and AD, and interactions of LTCCs with key pathogenic molecules Aβ and tau, with the hope of shedding light on intervention strategies in AD.

2. LTCC overview

2.1. Structure and function

LTCCs are the largest group of voltage-gated calcium channels. LTCCs are grouped based on their pharmacological responses to dihydropyridine (DHP) antagonists and agonists and their electrophysiological profiles [99,180]. LTCCs consist of four different pore-forming α_1 subunits named Cav1.1 (α_{1S}), Cav1.2 (α_{1C}), Cav1.3 (α_{1D}), and Cav1.4 (α_{1F}), associated with auxiliary subunits α_2-δ, β, and γ [9,151,180]. The Cav1.1 isoform, encoded by the CACNA1S gene, is found in skeletal muscle. It is involved in excitation–contraction coupling [9,132,152]. Mutations of Cav1.1 have been implicated in malignant hyperthermia and hypokalemic periodic paralysis [59,149]. The Cav1.4 isoform, encoded by the CACNA1F gene, can be found in the retina and is involved in photoreceptor transmitter release [110,111]. Mutations of the Cav1.4 isoform are linked to night blindness [11,87]. The Cav1.2 and Cav1.3 isoforms are primarily expressed in the heart and brain and they have been implicated in neurological disorders such as autism, bipolar disorder and Timothy's Syndrome (see reviews [120,149,180]). As such, they are the primary focus of this review.

The Cav1.3 isoform, encoded by the CACNA1D gene, can be found in the neuroendocrine system, neurons, cochlea and cardiac pacemaker cells and plays a role in cardiac pacemaking, synaptic regulation, excitation-transcription coupling, hearing and hormone release (see reviews [120,149,180]). Finally, the Cav1.2 isoform is encoded by the CACNA1C gene on chromosome 12p13 [138], and can be found in the heart, endocrine system, as well as neurons [180]. In the nervous system, Cav1.2 plays an important role in various processes including activation of calcium-dependent ions, enzymes and potassium channels [74,130]. Furthermore, they are thought to be important for the initiation of calcium-dependent gene transcription events such as excitation-transcription coupling, synaptic integration and plasticity, and dendritic development [47,174,180]. In addition, approximately 80 % of LTCCs in the hippocampus, a primary memory center of the brain, are comprised of the Cav1.2 isoform and contribute to up to half of the total calcium current in the region [16,58,68]. Cav1.2 subunits are expressed on both the somatic and dendritic regions of hippocampal neurons including synapses [68,107].

LTCCs are heteromultimers composed of a pore forming α_1 subunit which mediates the pharmacological and gating properties of the channel [69,151,180] (Fig. 1). The α_1 subunit is made up of six transmembrane α-helices (S1-S6) [145,153,178]. The S1-S4 helices make up the voltage sensing domain (VSD) of the transmembrane domain, whereas S5 and S6 and their connecting P loops (*P*1 and *P*2) make up the calcium conducting pore domain and selectivity

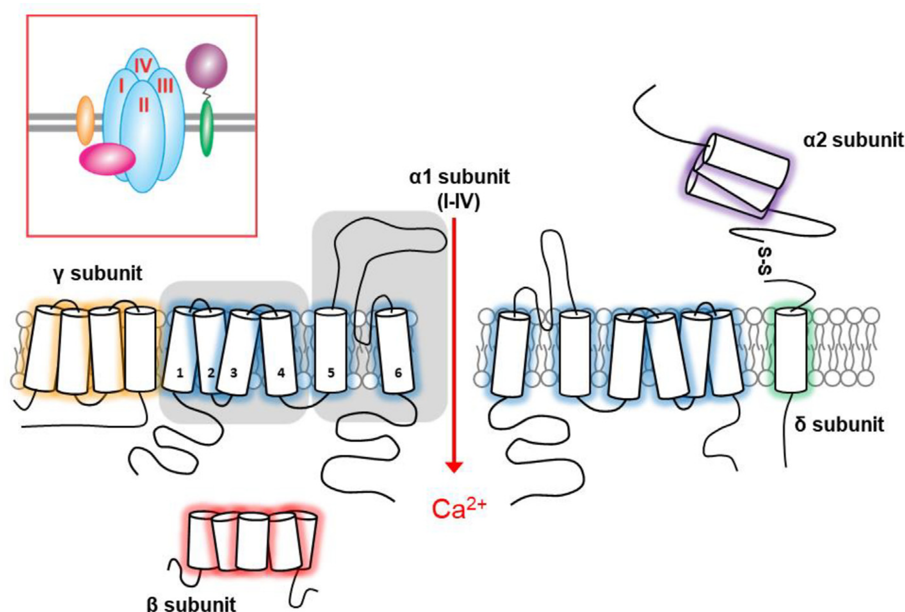

Fig. 1. Cross-section of the LTCC. A 3D schematic is shown in the upper left insert. The LTCC consists of four transmembrane α_1 subunits (I-IV) and four auxiliary subunits, α_2, δ, β and γ. Each α_1 subunit is comprised of 6 transmembrane helices: S1-S6, with S1-S4 involved in voltage sensing and S5-S6 making up the calcium pore domain [178]. The auxiliary γ subunit, consisting of 4 transmembrane domains binds to the α_1 subunit [31] while the β subunit binds to the α_1 subunit I-II interaction domain [5]. The extracellular α_2 subunit is linked to the δ subunit via disulfide bridges, and is involved in both trafficking and channel function [49].

filter (Fig. 1). Upon membrane depolarization, S4 is rearranged to have a positive arginine or lysine at every third residue and the VSD senses this change [30]. That information is then transmitted to S5 *via* the connecting cytosolic linker. Finally, the activation gate formed by the S6 helix opens the channel [30,178]. This conformational change to the activated state allows for selective flow of calcium into the neuron and as calcium ions flow into the cell, the channel slowly returns to a resting closed state. The N- and C- terminals of α_1 contribute to LTCC activation and inactivation *via* calmodulin interaction domains and LTCC modulating protein binding sites [48,124,171]. α_1 subunits are modulated by G-protein coupled protein kinases *via* phosphorylation. For example, protein kinase A (PKA) is known to mediate the opening and closing of the channel. When the α_1 subunit is phosphorylated by PKA in the hippocampus at serine 1928 proximal to the C terminus, the number of functionally upregulated LTCCs increases [64,66].

In addition to the α_1 subunit, LTCCs have up to four auxiliary subunits (α_2, β, δ and γ) which are involved in vesicle anchoring, trafficking, regulatory functions and promote expression of LTCCs along the membrane [5,29,178,180] (Fig. 1). The α_2, δ and β subunits are known to play a role in α_1 subunit trafficking and to influence biophysical properties of the channels [146,178]. The α_2 and δ subunits originate from the same gene. However, during post-translational modification, they are cleaved into separate proteins that are connected by a disulfide bond creating the α_2-δ subunit. The α_2 component is extracellular and the δ subunit spans the membrane (Fig. 1). The primary function of the α_2-δ subunit is to stabilize and promote the cell surface expression of LTCCs [40]. The site and mechanism by which α_2-δ promotes expression is unclear. However, knockout of this subunit results in reduced calcium channel currents in Purkinje neurons, impairing their function [10,50]. While the function of the α_2-δ is not entirely clear, it is known that they are essential for the relief of neuropathic pain as drugs such as gabapentin and pregabalin bind to α_2-δ [154]. The β subunit, on the other hand, is localized intracellularly and binds to the α_1 subunit interaction domain at the I-II linker [131,178] (Fig. 1). It has been suggested that this subunit, by binding to the α_1 subunit, promotes the postranslational events that ensure the insertion of only mature calcium channels into the lipid bilayer of the plasma membrane [15]. In addition to its involvement in trafficking, the β subunit has also been implicated in the modulation of LTCCs *via* phosphorylation of PKA and calmodulin-dependent protein kinase II (CaMKII). Finally, the γ subunit was initially not found in either Cav1.2 or Cav1.3 isoforms thus it was thought to not present in neurons [3]. However, a γ_2 subunit associated with neuronal Ca^{2+} channels was discovered later [5,80,94]. In contrast to β and α_2-δ subunits, γ_2 subunit suppresses α_1 subunit activation [80]. The mutation of γ_2 subunit is associated with absence epilepsy [94]. A knock out mouse model suggested γ subunit may function to limit the amount of Ca^{2+} entry during stimulation of skeletal muscle [62].

2.2. LTCC drug targeting and modulation

LTCCs can be targeted by three groups of drugs including phenylalkylamines (PAAs), benzothiazepines (BTZs), and DHPs [120,180]. Computational LTCC models created using the crystal structure of the KvAP channel [162] have been instrumental in drug targeting studies. These models have since been used to better understand the binding of BTZs [162], DHPs [163] and PAAs [32] to LTCCs. Using KvAP-based models, Zhorov's group was able to determine that all three ligands bind near the S5–S6 helices of domains III and IV. However, the DHPs and BTZs bind to LTCCs extracellularly whereas PAAs bind intracellularly through the open activation gate [32,162–163].

DHP derivatives including amlodipine, nifedipine, clevidipine, felodipine, and isradipine, are most commonly used to treat cardiovascular diseases such as angina, vasodilation or hypertension [150]. However, nimodipine, another DHP, readily passes the blood–brain barrier, making it a therapeutic measure for neuronal calcium dysregulation. The DHPs act on S6 by binding to Tyr1152, Ile1153, Ile1156 and Met1161 of the third transmembrane domain of the α_1 subunit and to Asn1472 of the fourth transmembrane domain [150]. These DHPs act as LTCC antagonists, and they bind to the pore-forming α_1 subunit in the inactivated state to prevent calcium influx by shifting the LTCC towards the closed state [139].

The activity of LTCCs can not only be regulated by membrane depolarization [69,89], but also by protein kinase phosphorylation [29,52,56,66,73,93,122,179]. For example, LTCC activity is, in part, modulated by interactions with calmodulin or calcium/CaMKII [52,73,93,179]. Calcium-dependent inactivation (CDI) occurs when the influx of calcium results in the binding of calcium to calmodulin on the C-terminus and this leads to a change in channel configuration [123,184]. This CDI phenomenon is a negative feedback mechanism that acts as a safety mechanism to prevent prolonged dangerous influx of calcium and it is crucial for post-action potential (AP) repolarization [13,112]. However, CDI can be impaired with age which results in AP prolongation. More specifically, there is a prolonged post-burst slow afterhyperpolarization (AHP) which is primarily a calcium-dependent potassium current. Thus it takes longer for the cell to repolarize to baseline [43,114,126,161]. This prolonged AHP is linked to deficits in hippocampal-dependent learning and memory tasks [106,113,161]. Furthermore, the prolonged slow AHP in aged animals can be rescued through the use of LTCC blockers such as nimodipine [114]. This suggests that LTCCs are involved in age-related prolongation of repolarization and limits further firing of neurons. Alternatively, calcium-dependent facilitation (CDF), also arises from the interaction of calcium ions, calmodulin and the α_1 subunit, yet has the opposite effect of enhancing the calcium flux. CDF is mediated by the CaMKII-dependent phosphorylation of Cav1.2 at Thr498 of the β_{2a} subunit and the tethering of the CaMKII to α_{1C} subunit [2,52,73,93]. It plays an important role in synaptic plasticity and excitation–contraction coupling [21,41,47]. CaMKII is a kinase that is essential for learning and memory [100] and the inhibition of CaMKII prevents phosphorylation, which, in turn, prevents CDF [179,185,186]. Its tethering to the α_1 subunit allows for control of the feedforward CDF mechanism [73].

As indicated above, phosphorylation is an important process that mediates LTCC function. Several other protein kinases besides CaMKII are critical as well. It is well established that PKA and protein kinase C (PKC) mediated phosphorylation can affect pore structure, thus affecting calcium influx [108,122,127,128]. Both PKA and PKC can phosphorylate Cav1.2 at Ser1928 on the α_{1C} subunit. Phosphorylation of Cav1.2 on Ser1928 by PKA augments Cav1.2 activity and synaptic plasticity [122,128]. Cav1.3 current is also elevated by cAMP/PKA signaling in cardiac [183], endocrine cells [103,167], and neurons [86]. The dominate phosphorylation sites in Cav1.3 for PKA are Ser1964 and Ser1743 and PKA phosphorylation of Cav1.3 requires β subunit [167]. In the neonatal hippocampus, PKC activation mediates $GABA_B$ enhancement of LTCC currents, alongside PKA [22]. Additionally, in retinal epithelial cells, PKC blockade reduces LTCC currents [148]. In contrast, Cav1.2 and Cav1.3 are down-regulated by nitric oxide/cGMP/protein kinase G (PKG) pathway in cardiac and endocrine cells [103,167]. The opposite modulations by PKA and PKG signaling in these cells enable fine-tuning of cellular functions.

Moreover, protein tyrosine kinases, such as Src family kinases (SFKs), also have the ability to regulate neurotransmitter release *via* SFK-mediated phosphorylation of the a_{1C} subunit [51]. Evans

and Pocock (2009), using cultured rat cerebellar cells, demonstrated that LTCC-mediated exocytosis requires tyrosine phosphorylation by a SFK and that inhibiting SFK through the use of PP1 prevents exocytosis [56]. While LTCC-mediated exocytosis is an important process in response to oxidative stress in the hippocampus, tyrosine phosphorylation of α_{1C} over-enhances this process which can lead to neuronal death. Hou et al. [71] demonstrated that LTCCs are functionally upregulated in post-ischemic brains, and this further enhances phosphorylation by SFKs and creates a positive feedback loop leading to a dangerous intracellular calcium overload [71]. However, how SFKs are activated and how they modulate LTCCs are still not clear. One possibility is that SFKs, such as Src, is activated by PKC *via* Pyk2 [42,95,135]. Stimulation of PKC triggers dimerization and subsequent *trans*-autophosphorylation of Pyk2, promoting binding and activation of Src [42].

Src increases LTCC currents in smooth muscle cells [65,72], retinal pigment epithelial cells [148], and neurons [12,54]. Phosphorylation of Cav1.2 at tyrosine residue Y2122 is involved in the upregulation of Cav1.2 activity by Src in rat neurons [12]. However, the target sites for Src in Cav1.2 in other species including human and rabbits are unknown, despite that Src activation enhances LTCC currents in both species [72,148].

3. LTCC in synaptic plasticity and learning: Effects of aging and implications in AD

3.1. LTCC-mediated plasticity changes in aging

With aging, the expression of LTCCs in the hippocampus increases [107,116,159] which, subsequently, increases the calcium current [28,46,159]. However, it is not simply the overall protein level of the Cav1 subunit that is overexpressed in aged animals. In fact, Nunez-Santana et al. [116] demonstrated that protein levels in whole tissue lysates of Cav1.2 and Cav 1.3 subunits are reduced in the aged CA1, CA3 and DG of the hippocampus in comparison to adult animals. In addition, there are no changes in Cav1.2 and Cav1.3 mRNA levels with age. The calcium dysregulation occurs as a result of an increased surface ratio of Cav1.2 in the CA1 and CA3 regions, and of Cav1.3 only in the CA3 region. In addition, the immunoreactivity of Cav1.2 is heightened in the somatic portion of these regions [116], which has been confirmed by a recent study [107]. Furthermore, LTCC activity is increased approximately 5-fold when they are phosphorylated [81,141,142]. Cav1.2 phosphorylation at Ser1928 is increased with age which enhances influx of calcium into the neuron [38]. However, the activation of LTCCs is phosphorylation site specific and phosphorylation at other sites such as Ser533 inhibits LTCC activity [77]. Another report showed increased expression of Cav1.3 in CA1 region was associated with working memory impairment in aged rats [168].

There are two ways that LTCCs can affect plasticity. On the one hand, LTCC activation can directly mediate long-term potentiation (LTP) or long-term depression (LTD). *N*-methyl-d-aspartate receptors (NMDARs) and LTCCs are the two major calcium mediators for synaptic plasticity, which initiate diverse calcium-dependent signaling cascades critical for memory formation. Changes in these receptors/channels with age directly influence synaptic plasticity and learning capacity across different developmental stages. In hippocampal CA1 neurons, both the decreased tendency for LTP and the increased tendency for LTD during aging are attributed to LTCC hyperfunction and concomitant reduced functionality of NMDARs [88,115]. Furthermore, the age-related increase in LTCCs is associated with a shift in the forms of synaptic plasticity in aged rats, which exhibit a reduced NMDAR-dependent and increased LTCC-dependent LTP and LTD at CA3-CA1 synapses [19,92,144]. This age-related modification of the expression and function of LTCCs in hippocampal neurons could contribute to dysregulated calcium homeostasis, resulting in synaptic dysfunction and cognitive decline [115], although a protective role of increased LTCC plasticity in aging has also been proposed [19,92]. Recently, we demonstrated that similarly to the hippocampus [19,92,134], there is an age-dependent increase in the contribution of LTCCs to LTD in the piriform cortex (PC), concurrent with a decreased role for NMDARs [129]. Moreover, inhibition of LTCCs in the aged PC blocks LTD [129] and could consequently enhance learning [107]. LTCC dysregulation is suggested in models for age-related cognitive decline [157] and is likely involved in AD.

On the other hand, LTCCs may directly influence learning and memory formation by altering neuronal excitability. In hippocampal CA1 neurons, calcium influx through LTCCs activates calcium-activated potassium channels, increasing AHPs and reducing neuronal excitability [44,46,107]. Consequently, the threshold for NMDAR-dependent LTP may be elevated [60,61]. Aging augments LTCC current, phosphorylation and AHP as aforementioned [38,44,107,158,159]. Several studies have indicated that the LTCC blockers can act by reducing the slow AHPs in the hippocampus [98,114,126]. This reduction in CA1 AHP has been shown to improve hippocampal-dependent learning [45,119].

3.2. LTCC modulation in Alzheimer's disease

Disruption in calcium homeostasis has been extensively implicated in aging and AD [4,43,83], where there is heightened calcium influx into neurons *via* LTCCs [53,102,158,159,166,176]. Hyperfunction of LTCCs and resultant increased intracellular calcium can impair neuronal function, adversely affecting synaptic function and plasticity. Several lines of evidence support the notion that LTCC hyperfunction contributes to AD pathogenesis. Coon et al. [33] demonstrated that hippocampal neurons in AD brains show significantly increased binding of isradipine, a DHP ligand, and increased cell loss in AD brains compared to controls. This suggests that the hippocampus, a primary memory center of the brain, is more vulnerable to calcium dysregulation in AD [33]. LTCC blockers have shown beneficial effects in reversing neuronal dysfunction and cognitive impairment in both humans and animal models [34,43,97].

Despite that numerous studies have implicated chronic upregulation of LTCCs in the etiology of AD, a critical gap in knowledge remains regarding how LTCCs are up-regulated during AD and how LTCC hyperfunction relates to neuropathology. We discuss below emerging evidence of relationship between LTCCs, amyloid and tau. The potential interaction pathways are summarized in Fig. 2. It is noteworthy to point out that besides direct effects on neurons, the LTCC dysregulation of brain vasculature is likely involved in AD pathogenesis. Cerebral hypoperfusion is an important contributor to the cognitive decline in AD [75]. Aging, as the biggest risk factor for AD, is also associated with vascular calcium dysregulation [67]. Heightened function of vascular LTCCs *via* Ser1928 phosphorylation [104,117] and associated vascular constriction may exacerbate AD pathology [156].

3.2.1. LTCC and β-amyloid

There is conflicting evidence linking Aβ deposits to LTCC hyperfunction. In cell cultures, Aβ peptide has been shown to increase LTCC expression [39,85,166,173]. Aβ was reported to directly associate with α_{1C} subunit and promote trafficking and insertion of LTCC at the plasma membrane [140], or act on β_3 subunit to facilitate Cav1.2 and Cav1.3 surface trafficking [85]. In rat cortical neurons, the expression of human amyloid precursor protein is sufficient to increase LTCC currents, however, the augment of LTCCs is independent of Aβ [137]. Interestingly, amyloid precursor

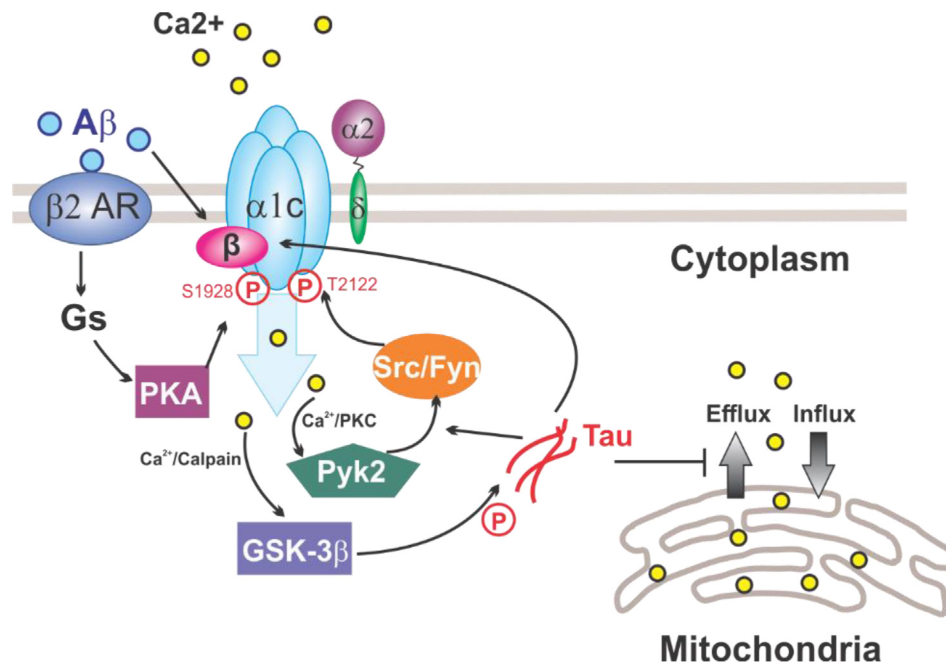

Fig. 2. LTCC modulations by Aβ and tau. Aβ and tau can interact with β subunits to facilitate Cav1.2 surface trafficking [85,169]. Additionally, Aβ stimulates β_2-adrenoceptor (β_2-ARs)-LTCC complex and enhances PKA phosphorylation of Cav1.2 at S1928 [170]. Tau could exert its effect through Pyk2 and Src/Fyn [14,91,96]. Elevated cytosolic Ca2 + and calpain result in tau hyperphosphorylation *via* GSK-3β [78]. Calcium influx through LTCCs augments calcium influx into mitochondria, whereas abnormal tau impairs calcium extrusion from mitochondria [23].

protein expression in the cortical neurons enhances AHP and inhibits spontaneous calcium oscillations, similar to the abnormal AHP and disruption of neuronal excitability observed in hippocampal neurons in aging [44,107,158]. However, direct measurement of LTCC current in a transgenic APP/PS1 mouse model failed to show elevation [160].

Besides direct association and interaction with LTCC subunits [85,140], Aβ can exert its effects on LTCCs through β_2-adrenoceptors (β_2-ARs). Soluble Aβ binds to N terminus of β_2-adrenoceptors to induce Gs/adenylyl cyclase (AC)/cAMP/PKA signaling [170]. Cav1.2 forms a unique signaling complex with the β_2-ARs and its effector proteins Gs, AC and PKA [7,37], thus β_2-ARs signaling can potently up-regulate LTCC channel activity. Phosphorylation at Ser1928 on Cav1.2 uncouples the β_2-ARs from Cav1.2 [122]. The existence of this complex suggests that Cav1.2 is a major target for β_2-ARs, whereby Aβ engages its effects. Notably, β_2-ARs are increased in the brains of AD patients, especially within the hippocampus [79]. Epidemiological studies showed reduced incidence of AD correlated with non-selective β-AR antagonist administration [133]. In animal studies, chronic treatment with β_2-AR blockers reduces Aβ production [182] and tau pathology [177].

Furthermore, Aβ stimulates glutamate release and glutamate spillover contributing to perisynaptic activation of glutamatergic receptors [155], which facilitates NMDAR-dependent LTCC dendritic Ca^{2+} spikes [175]. Aβ-enhanced Cav1.2 activity likely mediates synaptotagmin-3-mediated endocytosis of AMPARs at perisynaptic endocytic zones and facilitates LTD [6]. Indeed, Aβ42 oligomers application potently enhances LTD and impairs LTP in rodent models [136,143]. Altered plasticity, such as enhanced LTD, is correlated with forgetting [6].

Besides neurons, increased LTCC expression is associated with Aβ plaques in reactive astrocytes in a mouse model [36]. Particularly, up-regulation of Cav1.2 α_1 subunit is dependent on the presence of Aβ plaques [36]. Blocking LTCCs increases angiogenesis in organotypic brains slices of an Aβ mouse model [35].

3.2.2. LTCC and tau

While the link between Aβ and LTCCs requires further investigation, the relationship between tau and LTCC expression is becoming an exciting research avenue. Abnormal persistently phosphorylated soluble tau, termed pre-tangle tau, can begin as early as in childhood and first appears in the brain stem structure locus coeruleus [20]. Pre-tangle tau spreads to the transentorhinal/hippocampus memory pathway over decades before the onset of clinical symptoms. Recent data suggest that soluble pre-tangle tau is the more toxic forms among tau species [24,105]. Cell death and synaptic dysfunction occur in pre-tangle tau mice preceding NFT formation [125,181].

However, how pre-tangle tau drives neurotoxicity is not well understood. There is some evidence that interaction between tau and LTCCs may, at least partially, mediate synaptic dysfunction. In hippocampal neuronal culture, tau mediates bridging integrator 1 (BIN1) association with LTCCs and the shuffling of LTCCs to the plasma membrane [169]. Tau proline-rich domain interacts with both BIN1 and LTCC-β_1 SH3 domains. Recent evidence suggests that LTCC hyperfunction occurs due to tau hyperphosphorylation. In the 3xTG mouse model, there is selective hyperphosphorylation of tau in CA1 and widespread Aβ [118]. Wang & Mattson [172] found that LTCC amplitude and density were higher in the hippocampal CA1 of aged 3xTG mice compared to wild-type mice [172]. However, in the CA3 and DG regions of the hippocampus, where there is no increase in hyperphosphorylated tau, LTCC amplitude and density does not differ in 3xTG and wild-type mice. This study reinforces that the CA1 is particularly vulnerable to tau pathology, which leads to increased LTCC expression, and highlights the relationship between pre-tangle hyperphosphorylated tau and LTCC hyperfunction in the AD model. Increased LTCC activity is also associated with a mutant tau which is linked to frontotemporal dementia and parkinsonism in SH-SY5Y cell lines [63]. Mice expressing the mutant tau exhibits a larger AHP in dorsal entorhinal neurons [17] and altered intrinsic and synaptic properties in the hippocampus [18], likely due to LTCC hyperfunction associated with the tau mutation.

Interestingly, a recent study by Stan and colleagues [147] suggested that specific human tau isoforms, such as 0N4R, enhance LTCC currents in cultured hippocampal neurons. The resultant increase in Ca^{2+} entry is associated with increased medium and slow AHPs. The Cav1.2 and Cav1.3 β3 subunit that regulates trafficking and biophysical properties of the channel directly associates with 0N4R isoform and is required for tau-induced LTCC augmentation [147]. Similarly, expression of human 0N4R isoform of tau in Drosophila mushroom body increases LTCC expression in the neuronal membrane and results in odor memory deficiency [70]. Correcting LTCC expression to the wild-type level with RNAi knock-down restores memory in the human tau-expressing Drosophila [70].

Tau could influence both cytosolic and mitochondrial calcium signaling. A link between tau and LTCCs may be through the SFKs. Src and Fyn phosphorylation of Cav1.2 LTCC has been established [12,54,71,101]. Tau interacts with Src kinases and their activator Pyk2 [14,91,96] and could potentially enhance LTCC activation. Mutant or hyperphosphorylated tau has been associated with increased LTCC currents [63,172] and decreased mitochondrial biogenesis [165]. LTCC activation in turn mediates tau hyperphosphorylation *via* GSK-3β, which can be prevented by an LTCC blocker *in vitro* [109]. Additionally, mitochondrial dysfunction and associated alteration in Ca^{2+} homeostasis have emerged as important factors in AD and tauopathy [1,55]. Elevation of cytosolic Ca^{2+} leads to mitochondrial Ca^{2+} uptake *via* mitochondrial calcium uniporters [1]. MAPT mutant tau inhibits mitochondrial calcium efflux *via* inhibiting the Na^{+}/Ca^{2+} exchanger and makes neurons more vulnerable to calcium-induced cell death [23], which critically contributes to AD progression in humans and animal models [25–26,27,76].

4. Summary and overview

The present review highlights the challenges of understanding the biological function of LTCCs given their complexity. While their structures are still being illuminated, it is apparent that functionally, they are very complex and only a fraction of their biological functions have been revealed thus far. Despite their complexity, drugs targeting LTCCs have been used clinically to regulate calcium dysregulation in the heart and to manage pain. LTCC mediated calcium dysregulation has been implicated in both aging and AD, with overexpression and increased activity of these channels. However, a critical gap in knowledge remains regarding how LTCCs are upregulated in AD and how hyperfunction of LTCCs relates to neurotoxicity. LTCC blockers such as nimodipine can ameliorate the cognitive decline in animal models. However, LTCC blockers have limited and variable effects in clinical studies. The clinical ineffectiveness of LTCC blockers may be due to unfavorable side effects. Alternately, the reversal of LTCC-mediated AD pathology could be stage-dependent. Targeting early preclinical stages may prove to be more beneficial.

While the complete mechanistic understanding of the effects of Aβ on LTCCs is still lacking, the role of pathological tau, especially pre-tangle tau has drawn more attention given its early appearance in human brains. One hypothesis is that SFKs, specifically Src and Pyk2 kinase, are involved in pre-tangle tau mediation of LTCC hyperfunction. As indicated earlier, LTCCs are functionally up-regulated in diseased brains, and this further enhances phosphorylation by SFKs creating a positive feedback loop that leads to a dangerous intracellular calcium overload. Besides LTCC overexpression and hyperfunction-induced pathological changes, LTCCs have numerous physiological functions. Thus, finding alternative therapeutic strategies that can specifically target pathological up-regulation of Cav1.2 in the brain may be a more promising approach than targeting the channel itself.

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CRediT authorship contribution statement

Chelsea A. Crossley: Conceptualization, Writing – original draft, Writing – review & editing. **Vishaal Rajani:** Conceptualization, Visualization, Writing – review & editing, Funding acquisition. **Qi Yuan:** Conceptualization, Supervision, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition.

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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