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Calcium channel blockers and Alzheimer's disease★

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Abstract

Alzheimer's disease is characterized by two pathological hallmarks: amyloid plaques and neurofibrillary tangles. In addition, calcium homeostasis is disrupted in the course of human aging. Recent research shows that dense plaques can cause functional alteration of calcium signals in mice with Alzheimer's disease. Calcium channel blockers are effective therapeutics for treating Alzheimer's disease. This review provides an overview of the current research of calcium channel blockers involved in Alzheimer's disease therapy.

Key Words: Alzheimer's disease; calcium channel; calcium homeostasis; Alzheimer's disease pathogenesis; β-amyloid; calcium channel blocker

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INTRODUCTION

Calcium plays an important role in many aspects of normal neuronal physiology, including synaptic plasticity and learning[1]. Though disturbances in calcium homeostasis have been observed in cells from Alzheimer's disease (AD) patients for many years[2-3], little attention was paid to calcium channel blockers as therapeutic targets. There are multiple types of calcium channels in the membrane, beta-amyloid (Aβ)-formed calcium channels and calcium-related proteins[4-5]. This review provides an overview of the current research of calcium channel blockers involved in AD therapy.

OVERVIEW OF CALCIUM CHANNELS IN AD

Calcium homeostasis can be disrupted in human aging[6]. Calcium channels can be basically divided into voltage-gated calcium channels and glutamate receptors calcium channel, such as N-methyl-D-aspartate (NMDA) receptor channels and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Voltage gated calcium channels are subdivided into type L, type Q, type P, and type N, to name a few[7].

Calcium channel adjusts the concentration of calcium and contributes to physiological functions through gates in the phospholipid bilayer. Type N and Q voltage-gated calcium channels support neuronal synaptic transmission between the hippocampal CA1 and CA3 regions[8]. L-type calcium channels mainly exist in the cell body of central neurons and proximal dendrites, while P-type calcium channels exist in a specific area of Purkinje cells, and at the end of axons[9].

NMDA receptor channels include glutamate receptor channels and voltage-gated channels, and have high permeability for calcium. NMDA receptor channels are most dense in the cerebral cortex and the hippocampus[10].

POSTULATED MECHANISMS ASSOCIATED WITH CALCIUM DYSREGULATION AND AD PATHOGENESIS

Aβ, a secreted form of APP (sAPPα) and the amyloid precursor protein intracellular domain (AICD) are generated by sequential cleavages of the amyloid precursor protein by β and γ-secretases[11]. These processes likely happen in the endoplasmic reticulum (ER) and plasma membrane. The formation of calcium permeable channels enhances calcium influx into the cell.

Phosphatidylserine in the plasma membrane surface facilitates the association of Aβ oligomers with the plasma membrane. While calcium-related mitochondrial impairment can happen, phosphatidylserine can be triggered flipping from the inner position to the surface of the cell membrane[12]. At the same time, Aβ interacts with Fe^{2+} and Cu^{2+} to generate reactive oxygen species. The formation of

reactive oxygen species leads to lipid peroxidation which generates the neurotoxic aldehyde 4-hydroxynonenal. 4-hydroxynonenal can impair membrane transporters, guanosine triphosphate-binding proteins, and calcium channels through covalent modifications[13]. In addition, Aβ causes oxidative stress and dysregulation of calcium, which impairs the electron transport chain, decreases production of adenosine triphosphate (ATP) and increases production of superoxide anion radicals[14]. Then membrane depolarization is caused by the loss of membrane integrity and the reduction in ATP levels. These results lead to calcium influx through NMDA channels and voltage-gated calcium channels[15]. Aβ oligomers also directly affect the activity of NMDA receptors and voltage-gated calcium channels. AICD translocates to the nucleus and interacts with transcription regulators in ways that perturb calcium homeostasis[16]. Recent studies show that presenilins function as ER calcium leak channels. Furthermore, flavin adenine dinucleotide-associated mutations impair this Ca^{2+} leak-channel function which results in excessive accumulation of Ca^{2+} in the ER. Finally, calcium is released through ryanodine receptors and inositol 1, 4, 5-trisphosphate receptor channels[17] (Figure 1).

A previous study also showed that presenilins can interact directly or indirectly with inositol 1, 4, 5-trisphosphate receptors, ryanodine receptors, and smooth ER Ca^{2+}-ATPases to alter ER calcium release and uptake[18]. Calcium homeostasis modulator 1, which is likely associated with a passive Ca^{2+} leak channel, is located mainly in the ER. The protein reelin enhances Ca^{2+} influx through NMDA receptor channels by binding to the apolipoprotein E receptor 2 which could block the actions of reelin[19]. In addition, amyloidogenic APP processing might prevent α-secretase cleavage of APP and generate a secreted form of APPα[20]. The sAPPα activates a cyclic guanosine monophosphate signaling pathway that activates K^+ channels, which hyperpolarizes the membrane and reduces Ca^{2+} influx[21]. Calcium influx through calcium homeostasis modulator 1 reduces Aβ generation and promotes the α-secretase pathway. The store-operated calcium channels localized in the plasma membrane allow Ca^{2+} refilling *via* capacitive calcium entry[22]. Calcium levels become raised in the cytosol, which activates calcium-related proteins and facilitates long-term depression, inhibits long-term potentiation, modifies neuronal cytoskeleton, causes synaptic loss, oxidative damage, excitotoxicity, cellular apoptosis and necrosis, and increases Aβ production and tau hyperphosphorylation[23]. Mitochondria absorb excessive calcium in the cytosol through mitochondrial Ca^{2+} uniporters.

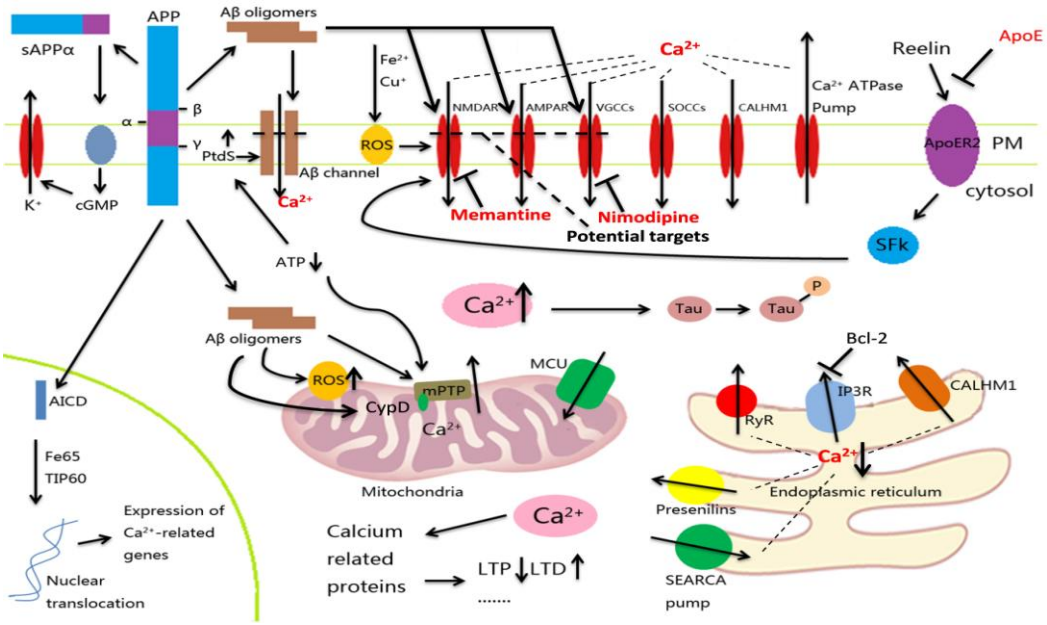

Figure 1 Postulated mechanisms associated with calcium dysregulation and calcium channel blockers in Alzheimer's disease. Beta-anyloid oligomers, which can insert in the plasma membrane, can form pores or interact with calcium channels to influence calcium influx or release from the endoplasmic reticulum (ER) or mitochondrial stores. Amyloid precursor protein intracellular domain (AICD) which can move to the nucleus interacts with Fe65 and Tip60 to modify gene transcription. Presenilins can function as ER calcium leak channels which can be repaired by flavin adenine dinucleotide (FAD)-associated mutants. FAD-associated mutant presenilins can also interact with inositol (1, 4, 5)-trisphosphate receptors (IP3R), ryanodine receptors (RyR), and smooth ER Ca^{2+}-ATPases (SERCA) to influence calcium levels. The mechanisms describe potential targets for treating calcium dysregulation. Some drugs that target calcium channels, such as memantine and nimodipine, are efficacious for treating Alzheimer's disease. The star represents potential targets for the future.

PtdS: Phosphatidylserine; cGMP: cyclic guanosine monophosphate; NMDAR: N-methyl-D-aspartate receptor; AMPAR: amino-3-hydroxy-5-methyl-4-isoxazol propionate receptor; VGCCs: voltage-gated Ca^{2+} channels; SOCCs: store-operated calcium channels; CALHM1: calcium homeostasis modulator 1; PM: plasma membrane; ApoE: apolipoprotein E; ApoER2: ApoE receptor 2; SFk: src-family tyrosine kinase; ROS: reactive oxygen species; CypD: cyclophilin D; mPTP: mitochondrial permeability transition pore; MCU: mitochondrial Ca^{2+} uniporter; LTP: long-term potentiation; LTD: long-term depression.

This leads to calcium overloading in the mitochondria which results in the opening of mitochondrial permeability-transition pores.
This process damages the mitochondrial ultrastructure, inhibits mitochondrial ATP production and other energy-dependent functions, and releases calcium stored in the mitochondria. Thus, the neuronal calcium signaling is further deregulated [24]. The accumulation of Aβ in the mitochondria and the direct interaction of A with cyclophilin D also facilitates calcium-induced mitochondrial permeability transition pore opening[25].

CALCIUM CHANNEL BLOCKERS AND RECENT RESEARCH IN AD THERAPY

Because of their chemical structures, voltage-gated calcium channel blockers can be mainly divided into three parts: (1) dihydropyridines, such as nifedipine, nimoldipine, nicardipine; (2) benzothiazepines, such as diltiazem; (3) phenylalkylamines, such as verapamil[26]. Dihydropyridines are widely used to vasodilate arterial resistance vessels and to increase the reflex in the sympathetic response[27]. The overall hemodynamic effect is a drop in blood pressure and an increase in cardiac output, heart rate, and contractility[28].
Targeting the glutamatergic system, specifically NMDA receptors, offers a novel treatment approach because of the limited efficacy of existing drugs targeting AD. Memantine has been used in AD therapy as a noncompetitive NMDA receptor antagonist with low affinity[29]. Memantine increases the expression of the NMDA receptor subunit 2B and the postsynaptic density-95. Memantine also binds to NMDA receptors on brain cells to help reduce abnormal activity in the brain, and to block the activity of excessive glutamate. Memantine binds to NMDA receptors with a higher affinity than Mg^{2+} ions to inhibit the prolonged influx of Ca^{2+} ions, which leads to neuronal toxicity. Ketamine is a non-competitive NMDA receptor antagonist and likely impairs the memory function of the brain in AD[30].
AD cells produce Aβ which leads to cell death. Calcium channel blockers protect AD cells from Aβ oligomer production[31]. Recent research also indicates that isradipine has a better therapeutic effect compared with verapamil, diltiazem, isradipine and nimodipine. All of these drugs are L-voltage-gated calcium channel blockers[32].

OTHER CANDIDATES THAT BLOCK OR TARGET CALCIUM CHANNELS IN THE TREATMENT OF AD

Juliflorine, a piperidinium alkaloid, is isolated from the leaves of *Prosopis juliflora*. Juliflorine is a non-competitive inhibitor of the enzymes, acetylcholinesterase and butyrylcholinesterase[33]. Its potential calcium channel blocking activity and safety profile in the human neutrophil viability assay make juliflorine a leading candidate for the treatment of AD. Juliflorine can also be used as a scaffold to synthesize new derivatives[34].
The senescence-accelerated mouse (SAM) prone/8 (SAMP8) is a model for investigating the fundamental mechanisms of AD at the gene and protein levels, and the SAM resistant/1 (SAMR1) mouse is its normal control[35]. Calcium/calmodulin-dependent protein kinase II-α is one of the most abundant subunits of calcium/calmodulin dependent protein kinase II in the cerebral cortex and hippocampus[36]. A previous study has shown that the expression of mRNA and protein of calmodulin-dependent protein kinase II was significantly increased in the cerebral cortex and hippocampus of SAMP8 after 10 months of age, but was down-regulated when treated with some anti-AD drugs (for example, natural product huperzine A and some traditional Chinese medicinal prescriptions), suggesting that calmodulin-dependent protein kinase II may play an important role in age-related cognitive deterioration in AD, and may be a potential target for anti-AD drugs[37].
The ryanodine receptor plays a vital role in the regulation of calcium release from the ER in the brain, so the impairment of ryanodine receptors contributes to the pathogenesis of AD[38]. Recent studies have revealed that alterations in ryanodine receptor binding and function are very early events in the pathogenesis of AD, and may be fundamental to the progression of both neurofibrillary and β-amyloid pathologies[39]. Ryanodine receptors increase early in the disease, prior to the loss of ryanodine receptors that is correlated with the progression of neurofibrillary pathology and amyloid deposition. This means that ryanodine receptor-induced calcium release in the ER may be crucially involved in the formation of the pathological hallmarks of AD[40].

CONCLUSION

Ample evidence shows that calcium dysregulation plays an important role in AD. Although the precise pathogenesis of AD remains unclear, many calcium channel blockers have proved efficacious in numerous cell culture and animal models of AD. Furthermore, most of these treatments target receptor-operated calcium channels and voltage-gated calcium channels. There are still new potential targets on the horizon for the development of drugs directed towards calcium channels.

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