



## Review Elevating the Levels of Calcium Ions Exacerbate Alzheimer's Disease via Inducing the Production and Aggregation of β-Amyloid Protein and Phosphorylated Tau

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**Abstract:** Alzheimer's disease (AD) is a neurodegenerative disease with a high incidence rate. The main pathological features of AD are  $\beta$ -amyloid plaques (APs), which are formed by  $\beta$ -amyloid protein (A $\beta$ ) deposition, and neurofibrillary tangles (NFTs), which are formed by the excessive phosphorylation of the tau protein. Although a series of studies have shown that the accumulation of metal ions, including calcium ions (Ca<sup>2+</sup>), can promote the formation of APs and NFTs, there is no systematic review of the mechanisms by which Ca<sup>2+</sup> affects the development and progression of AD. In view of this, the current review summarizes the mechanisms by which Ca<sup>2+</sup> is transported into and out of cells and organelles, such as the cell, endoplasmic reticulum, mitochondrial and lysosomal membranes to affect the balance of intracellular Ca<sup>2+</sup> levels. In addition, dyshomeostasis of Ca<sup>2+</sup> plays an important role in modulating the pathogenesis of AD by influencing the production and aggregation of A $\beta$  peptides and tau protein phosphorylation and the ways that disrupting the metabolic balance of Ca<sup>2+</sup> can affect the learning ability and memory of people with AD. In addition, the effects of these mechanisms on the synaptic plasticity are also discussed. Finally, the molecular network through which Ca<sup>2+</sup> regulates the pathogenesis of AD is introduced, providing a theoretical basis for improving the clinical treatment of AD.

Keywords: calcium ions; transporters; mechanisms; Alzheimer's disease; review

#### 1. Introduction

Alzheimer's disease (AD), commonly known as dementia, is a neurodegenerative disease with a high incidence rate. AD may share common biological pathways and is often associated with diabetes and other comorbidities [1] Clinically, cognitive dysfunction is the main feature [2]. Although the pathogenesis of AD has not been definitely determined, it is generally believed that the pathogenesis of AD is related to the excessive production and deposition of  $\beta$ -amyloid protein (A $\beta$ ) and hyperphosphorylated tau protein [3]. On the one hand, A $\beta$  is produced mainly through the amyloid metabolic pathway when the amyloid precursor protein (APP) is cleaved by  $\beta$ -secretase and  $\gamma$ -secretase to produce A $\beta$  monomers [4]. On the other hand, the tau protein is hyperphosphorylated through the action of cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase (GSK) 3 $\beta$  [5]. Both the A $\beta$  and phosphorylated tau proteins have the ability to self-aggregate. Through this self-aggregation, they gradually form oligomers and fibers, which are deposited as  $\beta$ -amyloid plaques (APs) and neurofibrillary tangles (NFTs), respectively [6]. The formation of oligomers and fibers can mediate the pathological progress of AD by affecting the function of glial cells and neurons [7].

A series of studies have shown that the onset of AD is related to aging; an unhealthy lifestyle, including smoking and drinking; health status, such as degree of heart disease, hypertension, obesity and diabetes; and genetic factors, such as APOE4 expression [8–11].



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**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). For the production of A $\beta$ , mutations in APP and presenilin (PS), including PS1 and PS2, are the decisive factors [12–14]. However, the phosphorylation of tau protein greatly affects the stability of microtubes in neurons, resulting in neuronal tangles [15]. In addition to the production and deposition of A $\beta$  and phosphorylated tau protein, many metal ions contribute to metabolic disorders [16]. In PS-mutant AD brain tissue, a Ca<sup>2+</sup> metabolic disorder was evident before the formation of APs or NFTs [17], This observation was further corroborated by a series of evidence in different AD animal models [18–20], which indicated that the metabolic disorder caused by Ca<sup>2+</sup> located in the cytoplasm might be the cause of AD. Based on this hypothesis, previous studies have shown that Ca<sup>2+</sup> influx can increase the production and aggregation of A $\beta$  and phosphorylated tau protein and thus affect the learning and memory of patients with AD [17,21,22].

Moreover, the imbalance of  $Ca^{2+}$  leads to dysregulated metabolism that affects many neurophysiological functions related to AD, including the regulation of neuroinflammation, response to neuronal injury, neuronal regeneration, neurotoxicity, autophagy and synaptic plasticity [23–27]. The multifunctional AD-related neuropathological function of  $Ca^{2+}$  may be directly or indirectly mediated by A $\beta$  and/or phosphorylated tau proteins. As the main pathological features of AD, monomeric or aggregate A $\beta$  and phosphorylated tau proteins show regulatory effects on neuroinflammation, neuronal injury, neuronal regeneration, neurotoxicity, neuroprotection, autophagy and neural plasticity [16]. Either directly or indirectly,  $Ca^{2+}$  is involved in the regulation of these neuropathological functions through its specific transporters. Therefore, this review mainly explores the molecular mechanisms by which a  $Ca^{2+}$  imbalance in AD affects the regulation of A $\beta$ , tau, and neural plasticity, specifically from the perspective of  $Ca^{2+}$  transporters in cell, mitochondrial, endoplasmic reticulum (ER) and lysosomal membranes.

# 2. APP Metabolic Products Including $A\beta$ Facilitated the Influx of $Ca^{2+}$ into the Neurons of AD Animals and Patients

The concentration of Ca<sup>2+</sup> is strictly regulated under physiological conditions, whereas Ca<sup>2+</sup> concentration is obviously elevated in the brains of AD patients and APP/PS1 Tg mice [19]. Kuchibhotla et al. found that Ca<sup>2+</sup> is significantly increased in the dendrites and dendritic spines of neurons of APP/PS1 Tg mice [28]. In view of their observation, the natural question that arises is: What is the reason for Ca<sup>2+</sup> elevation during the course of AD development and progression? It has been reported that A $\beta_{1-40}$  has the ability to upregulate the influx of Ca<sup>2+</sup> in rat cortical synaptosomes and cultured cortical neurons [29,30]. Moreover, the A $\beta_{25-35}$  peptide has an effect similar to that of A $\beta_{1-40}$ , which can promote Ca<sup>2+</sup> influx by activating L- and T-type Ca<sup>2+</sup> channels in rat hippocampal slices [31]. Similar to the results in vivo, A $\beta$  increased the Ca<sup>2+</sup> influx in PC12 and SH-SY5Y cells in vitro [32,33]. In addition to activating ion channels, A $\beta$  has the ability to activate PKA, which increases Ca<sup>2+</sup> influx through L-VGCCs by activating calcium-binding proteins [34].

Because of the self-aggregating characteristics of A $\beta$ , the concentration of Ca2+ in the spines and dendrites of cortical pyramidal neurons around APs is higher than the normal value in adjacent resting neurons [22]. In addition to the effect of APs on Ca<sup>2+</sup> in neurons, Bacskai and his colleagues quantitatively measured the resting-state Ca<sup>2+</sup> concentration in astrocytes of APP/PS1 mice and observed the overall response of astrocytes to AP deposition. The results showed that the concentration of Ca<sup>2+</sup> in the astrocytes of 6-month-old mutant mice was elevated compared to that of the WT controls [35]. It was confirmed that the resting level of Ca<sup>2+</sup> reached 247 nmol/L in the cortical neurons of 3×Tg mice, which is twice that of the cortical neurons of non-Tg controls (110 nmol/L) [22]. Taking advantage of live cell imaging, the level of Ca<sup>2+</sup> was found to be elevated in neurites, which were 20 µm from the central AP region, indicating the critical roles of APs in the homeostasis of Ca<sup>2+</sup> in the spines and dendrites of neurons [36]. In astrocytes of 6-month-old APP/PS1 mice, Ca<sup>2+</sup> was elevated in response to the deposition of APs [35]. In transient occlusion of the middle cerebral artery (MCAO) of hAPP695 transgenic (Tg) rats, Ca<sup>2+</sup> colocalized with APs and was deposited in the thalamus [37]. Arispe et al. found that the aggregates of A $\beta_{1-40}$ 

and  $A\beta_{1-42}$  can form a cation channel on the surface of an artificial lipid membrane that allows the passage of  $Ca^{2+}$  [38]. However, the channel showed low selectivity, and thus it also permitted the passage of Li<sup>+</sup>, K<sup>+</sup> and Na<sup>+</sup> [39]. In SH-SY5Y cells, oligomeric A $\beta$  cannot selectively increase the  $Ca^{2+}$  permeability of cellular membranes, thereby increasing both  $Ca^{2+}$  influx from the extracellular space and  $Ca^{2+}$  leakage from intracellular  $Ca^{2+}$  stores [35]. The pore formation of A $\beta$  was confirmed and corroborated by atomic force microscopy [40], electron microscopy [41,42] and a theoretical model [43,44]. For example, high-resolution transmission electron microscopy revealed the presence of  $A\beta$  pores distributed in situ in the cell membranes of post-mortem AD patients [36]. In addition, the formation of A $\beta$  pores is also considered a mechanism of neurotoxicity induction, which destroys cell homeostasis by inducing the leakage of  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  through this highly conductive channel [45]. This observation reinforces the extreme toxicity of A $\beta$  oligomers, which potentially disrupts the homeostasis of  $Ca^{2+}$  in neurons [46–48]. The formation of A $\beta$  pores is enhanced by the presence of phosphatidylserine, a cell surface marker of early apoptosis [49]. However, this kind of pore can be blocked by  $Zn^{2+}$ , because  $Zn^{2+}$  can form a complex with A $\beta$  to prevent the aggregation of A $\beta$ , which inhibits the insertion of A $\beta$  oligomers into the membrane, leading to the formation of pores [50-53]. In addition, the extent of the pore-forming activity of A $\beta$  in the lipid bilayer is inversely proportional to the cholesterol level in the lipid mixture. Treatment with cyclodextrin significantly enhanced the toxicity of A $\beta$  in PC12 cells by decreasing or inhibiting the increase in the cholesterol level of these cells [54]. In contrast, Kawahara and Kuroda found that increasing the cholesterol content on the surface of the cell membrane significantly reduced A $\beta$ -induced Ca<sup>2+</sup> influx [55]. In addition to A $\beta$ , sAPP is involved in regulating the homeostasis of Ca<sup>2+</sup>. For instance, sAPP mediates the effects of glutamate on the regulation of the homeostasis of Ca<sup>2+</sup> by increasing the production of cyclic (c) GMP to activate K<sup>+</sup> channels, which results in reduced Ca<sup>2+</sup> levels in hippocampal neurons [56]. In addition, it has been reported that a PS1 mutation is a key factor for sAPP stabilization of the homeostasis of  $Ca^{2+}$  in hippocampal neurons [57]. A possible explanation for this effect may involve the reversed regulation of APP695 and InsP3R genes at the mRNA and protein levels during differentiation [58]. The APP intracellular domain (AICD), which is released after InsP3R cleavage of APP may act as a transcription factor to activate the Ca<sup>2+</sup> signaling system [59,60]. As the cleavage fragments of APP are produced by different secretases, PSEN2 mutation has shown its effects on impairing the fusion between autophagosomes and lysosomes in PSEN2<sup>T122R</sup> mutated SH-SY5Y cells [61]. However, these effects are not caused by the activity of g-secretase but by decreasing the  $Ca^{2+}$  released from ER in an ER-dependent mechanism [61].

# 3. $Ca^{2+}$ Transporters on the Surface of the Nerve Cell Membrane Are Responsible for Promoting the Influx of $Ca^{2+}$ during the Course of AD Development and Progression

In addition, there are many natural  $Ca^{2+}$  transporters on the surface of the nerve cell membrane (Figure 1). As an antagonist of N-methyl-D-aspartic acid receptor (NMDAR), memantine significantly inhibits  $Ca^{2+}$  influx and was the first Food and Drug Administration (FDA)-approved drug for the treatment of moderate to severe AD in patients [62]. This drug was designed because A $\beta$  can interact with endogenous  $Ca^{2+}$  channels in the cell membrane to increase NMDAR-dependent  $Ca^{2+}$  influx [63]. On the basis of this drug, memantine nitrate-06 (MN-06) was developed to protect the neurotoxicity against glutamate via inhibiting the influx of  $Ca^{2+}$  and decreasing the activity of PI3-K/Akt/GSK-3 $\beta$  pathways in primary cultured rat cerebellar granule and hippocampal neurons [64]. Although A $\beta$  oligomers can promote  $Ca^{2+}$  influx through NMDAR channels in a short period of time [65], sustained exposure to A $\beta$  oligomers decreases the expression of NMDAR, the extent of  $Ca^{2+}$  influx and the glutamate current in neurons [66–68]. In addition to targeting NMDARs, the antagonists of amino-3-hydroxy-methylisoxazole-4-propionate receptor (AMPAR), such as LY451395, LY450108 and S18986, reverse  $Ca^{2+}$  influx in AD animal models [69–72].



**Figure 1.** A $\beta$  is involved in regulating Ca<sup>2+</sup> influx via modulating Ca<sup>2+</sup> transporters on the neuronal membranes, which result in depressing LTP and inducing cognitive decline of AD animals. A $\beta$  can activate Ca<sup>2+</sup> transporters, including NMDAR, AMPAR, LTCC, Na<sup>+</sup>/K<sup>+</sup>-ATPase, CALHM1, TRPV1 and Cav1.2 etc., which result in promoting Ca<sup>2+</sup> entry into the cytoplasm, leading to elevate the concentration of Ca<sup>2+</sup> in the neuronal cells. In addition, oligomeric A $\beta$  can not selectively increase Ca<sup>2+</sup> permeability of cell membrane, leading to the influx of Ca<sup>2+</sup> from the extracellular space. More importantly, these transporters of Ca<sup>2+</sup> have the ability to mediate the effects of Ca<sup>2+</sup> on the synaptic plasticity via different mechanisms.

In addition to glutamate receptors, there are a series of voltage gated Ca<sup>2+</sup> channels (VGCCs) on the surface of the cell membrane that mediate the transportation of  $Ca^{2+}$ . For example, A $\beta$  blocked presynaptic P/Q-VGCC, which resulted in reduced Ca<sup>2+</sup> influx into hippocampal neurons [73]. In contrast,  $A\beta_{1-40}$  concurrently enhanced the high threshold and low conductance of N- and T-VGCC and the high conductance of L-VGCC, which resulted in an increasing postsynaptic Ca<sup>2+</sup> response in cortical neurons [29,74,75]. In addition, A<sub>β</sub> impaired ion motive ATPases, which resulted in membrane depolarization and the opening of NMDAR pores and VGCCs, leading to an influx of Ca<sup>2+</sup> and impaired Ca<sup>2+</sup>-ATPase, which resulted in inhibited Ca<sup>2+</sup> efflux in primary cultured neurons and synaptosomes of an adult post-mortem hippocampus [76]. Although the mechanism by which CALHM1 serves as a cation channel in the brain is not completely clear, it has been reported as a pore-forming subunit whose activation can regulate Ca<sup>2+</sup> influx, and it is regulated by the voltage and extracellular Ca<sup>2+</sup> concentration of mouse cortical neurons [77]. As a potential  $Ca^{2+}$  transporter, it is further confirmed in CALHM1 knocking out mice [78]. As an important biomarker of AD, APOE does not directly regulate Ca<sup>2+</sup> influx as a canonical cation channel, but it can promote the influx of  $Ca^{2+}$  by activating P/Q-VGCC in neurons [79,80]. In primary cultured astrocytes of APOE4<sup>-/-</sup> mice, APOE4 was found to be responsible for impairing neurons after brain injury [81].

#### 4. ER Is an Important Reservoir to Elevate the Levels of Ca<sup>2+</sup> in the Neurons of AD

As an important reservoir of  $Ca^{2+}$  in neurons, endoplasmic  $Ca^{2+}$  can pass through InsP3Rs and ryanodine receptors (RyRs) to enter the cytosol (Figure 2). In the resting state, the intracellular level of  $Ca^{2+}$  remains at a relatively low level, between 50–300 nM. After activation,  $Ca^{2+}$  is mainly stored in the endoplasmic reticulum (ER), where the concentration of  $Ca^{2+}$  is approximately 100–500 nM and can be released into the cytoplasm through InsP3R and RyR [82,83]. Previous studies have shown that  $A\beta_{25-35}$  induces the transportation of  $Ca^{2+}$  in association with the activation of phospholipase C (PLC) and the production of inositol triphosphate (InsP3) [84]. In neurons, the addition of experimental A $\beta$  significantly increased the Ca<sup>2+</sup> response induced by InsP3R [85]. More specifically, exposing RyRs to A $\beta_{1-42}$  increases the probability of channel opening, which results in an increased Ca<sup>2+</sup> flux [86]. Similarly, A $\beta$  aggregates have the ability to increase Ca<sup>2+</sup> flux from the ER via InsP3R and RyR in human brain tissues and cells and in hippocampal CA1 pyramidal neurons [82,83,87,88].



**Figure 2.**  $Ca^{2+}$  channels in the ER involved in regulating phosphorylation of tau, production of A $\beta$ , which deposited in APs and NFTs, leading to impair learning ability via influencing synaptic plasticity. The accumulation of A $\beta$  in the neuronal cells induces the Ca<sup>2+</sup> influx from the intracellular Ca<sup>2+</sup> store, ER. In addition, Ca<sup>2+</sup> depletion from ER triggers a sustained extracellular Ca<sup>2+</sup> influx to the cytosol via a SOCE pathway, including TRPC1 and Orai1 by activating the STIM. During these processes, InsP3R and RyR2 played important roles in inducing Ca<sup>2+</sup> influx from ER to cytosol, which results in regulating synaptic plasticity, phosphorylation of tau, deposition of A $\beta$ , leading to cognitive impairment.

In addition to A $\beta$ , PS1 exhibits the ability to interact with three key components of the Ca<sup>2+</sup> signaling cascade, namely, InsP3R [89,90], RyR [91–93] and sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) [94]. Recently, Cheung et al., found that PS can physically interact with InsP3R to stimulate its gating activity, which results in an increase in Ca<sup>2+</sup> even though there is no increase in Ca<sup>2+</sup> in the lumens of the ER [90]. In SH-SY5Y cells, a PS1 mutation enhances the activity of PLC, leading to an increase in the level of IP<sub>3</sub>, which results in the release of Ca<sup>2+</sup> from the ER [95]. Similarly, a PS mutation can stimulate Ca<sup>2+</sup> release from the ER via InsP3R and RyR [93,96,97]. In the ER membrane, there is a sarcoplasmic/endoplasmic reticulum ATPase (SERCA) pump in addition to InsP3R and RyR. In CHO cells, PS mutants bound to the SERCA pump, which disturbed the balance of Ca<sup>2+</sup> [94]. In 3 × Tg mice, InsP3R and RyR mediated the release of Ca<sup>2+</sup> from the ER, from which it entered the cytosol [90,91]. Interestingly, APOE4 may trigger the release of ER-Ca<sup>2+</sup> via RyR, which promotes the formation of APs and NFTs [98–101]

However, the depletion of ER Ca<sup>2+</sup> induces a continuous influx of extracellular Ca<sup>2+</sup> into the cytoplasm by activating a classical store operated Ca<sup>2+</sup> entry (SOCE) pathway. This process initially requires the sensor molecule of canonical systemic Ca<sup>2+</sup> interactions in the ER (stromal interaction molecule, Stim) to sense ER Ca<sup>2+</sup> depletion, which leads to activated Ca<sup>2+</sup> channels on the surface of the cell membrane, such as Ca<sup>2+</sup> release-activated Ca<sup>2+</sup> (CRAC) channels, also known as calcium channel protein 1 (CRACM1,

Orai1) channels [102,103]. Although Stim-related proteins, including Orai and TRPC, are located on the surface of the cell membrane, we prefer to discuss their roles in Ca<sup>2+</sup> transportation because of their close relationship with the ER. As expected, SOCE disruption by the Stim1<sup>D76A</sup> mutation attenuated Ca<sup>2+</sup> entry in primary neurons from AD mice with human mutant-PS1-knock-in skin fibroblasts from familial AD patients [104,105]. Other studies have shown that the expression level of Stim2 was downregulated by this PS1 mutant, which resulted in insufficient signals transmitted to the plasma membrane to activate SOCE, leading to reduced influx of Ca<sup>2+</sup> when Ca<sup>2+</sup> was depleted from the ER [106]. Moreover, PS1<sup>ΔE9</sup> mutation induces the influx of Ca<sup>2+</sup> via activating Stim1 in a SOCE-dependent mechanism in mouse hippocampal neurons [107]. Although there was no direct evidence showing their association with the activation of SOCE, TRPC3 and TRPC6 played roles in regulating the homeostasis of intracellular Ca<sup>2+</sup> [108–110].

## 5. Mitochondria and Lysosomes Also Act as Important Organelles for Regulating the Dyshomeostasis of Ca<sup>2+</sup> during the Development and Progression of AD

In addition to the ER, mitochondria and lysosomes play important roles in the regulation of  $Ca^{2+}$  homeostasis, which has been reviewed in detail in a previous study [22] (Figures 3 and 4). In brief, there is evidence showing that the PS1<sup>L286V</sup> mutant can promote disorders in Ca<sup>2+</sup> homeostasis in neurons by damaging mitochondria [111,112]. In PS1<sup>M146L</sup> mutant lymphoblasts, activation of InsP3R results in opening mPTP transporters in mitochondria [113]. In a series of AD-related mice and cell models, VDAC and MCU mediated the mitochondrial uptake of  $Ca^{2+}$  [114–116]; the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger is critical for  $Ca^{2+}$  export across the inner mitochondrial membrane (IMM) [117–119]; and the mitochondrial permeability transition pore (mPTP) is critical for the efflux of  $Ca^{2+}$  from neuronal mitochondria [120]. Although there is no direct evidence showing the involvement of A $\beta$  in mitochondrial Ca<sup>2+</sup> transportation, A $\beta$  has the ability to open the mPTP, leading to the release of cytochrome C and caspases from mitochondria [100,121]. This evidence also indicates that the excessive accumulation of  $A\beta$  may be involved in the regulation of mitochondrial Ca<sup>2+</sup> homeostasis. In contrast to that internalized by mitochondria, the Ca<sup>2+</sup> uptake into lysosomes is mainly realized by the cooperation of a vacuolar type H<sup>+</sup>-ATPase (v-ATPase) and a putative  $Ca^{2+}/H^+$  exchanger (CAX) [122,123]. The excretion of Ca<sup>2+</sup> from lysosomes is mainly realized by TRPML and TPC [124]. When  $Ca^{2+}$  flows out of lysosomes through these VGCCs, defective autophagic lysosomes form, leading to autophagy [125]. Furthermore, the mutation or deletion of PS1 in AD leads to the disequilibrium of lysosomal  $Ca^{2+}$  by reducing the activity of the v-ATPase proton pumps on the lysosome, leading to AD pathogenesis [126]. In PS1 and 2 double knockout neurons, the number of lysosomal Ca<sup>2+</sup> stores were significantly decreased, which resulted in a damaged autophagy process [127]. The imbalance of these processes (Table 1) affects the clearance of disease-related proteins in the pathogenesis of AD.



**Figure 3.** The mechanisms of Ca<sup>2+</sup> transportation between mitochondria and ER. Ca<sup>2+</sup> is taken up to the mitochondria via MCU. Under physiological or pathological conditions, Ca<sup>2+</sup> is continuously shuffled between ER and mitochondria via VDAC. Moreover, Ca<sup>2+</sup> in mitochondria induces the formation of mPTP, which traversed Ca<sup>2+</sup> and small molecules, such as ROS and cytochrome C from mitochondria to cytosol, leading to the potential apoptosis of neurons. The loss of neurons will cause the cognitive dysfunction. Deficient or mutation: Defective PS1 due to exon 9 deletion ( $\Delta$ E9), as well as PS1<sup>M146V</sup> or PS1<sup>L286V</sup> mutations, lead to Ca<sup>2+</sup> flow to mitochondria via mitochondria associated endoplasmic reticulum membrane, (MAM), which further promotes apoptosis.



**Figure 4.**  $Ca^{2+}$  potentially contribute to regulate the degradation of A $\beta$  and the deposition of hyperphosphorylated tau via its transporters, including v-ATPase and TRPML1 etc., in the membrane of lysosome. TRPML1 and v-ATPase are responsible for inducing the efflux of  $Ca^{2+}$  from lysosome. The accumulation of  $Ca^{2+}$  in the cytosol can stimulate the phosphorylation of tau in the neurons, leading to the deposition of hyperphosphorylated tau in NFTs. In addition, the loss of PS1 induces the release of  $Ca^{2+}$  into the cytosol via TRPML1, which results in blocking the fusion between autophagosome and lysosome, leading to prevent the degradation of A $\beta$ .

Cat.	Stimulator or Mediator	Mechanism	Experimental Model	Reference
Αβ	Αβ <sub>1-40</sub>	$A\beta_{1-40} \rightarrow IL-1\beta \rightarrow Ca^{2+}$ influx	Rat cortical synaptosomes and cultured cortical neurons	[29]
	$A\beta_{25-35}$	$A\beta_{25-35} \rightarrow L-/T-VGCC \rightarrow Ca^{2+}$ influx	Rat CA1 pyramidal neurons	[31]
	Αβ	$A\beta \rightarrow Ca^{2+}$ influx $A\beta \rightarrow PKA \cup L-VGCC \rightarrow Ca^{2+}$ influx	APP/PS1 Tg mice Neurons	[30] [34]
	APs	$Ca^{2+}$ in the spines and dendrites of cortical pyramidal neurons of $APs \rightarrow Ca^{2+}$ in the adjacent resting neurons.	The spines and dendrites of cortical pyramidal neurons in 3 × Tg AD animals	[22]
		$APs \rightarrow Ca^{2+}$ influx	The astrocytes of 6-month-old APP/PS1 mice	[35]
		$A\beta \rightarrow$ Formation of cation channels $\rightarrow$ Ca <sup>2+</sup> passage	Artificial lipid membranes	[39]
		leakage from intracellular $Ca^{2+}$ stores	SH-SY5Y cells	[35]
		$\begin{array}{l} A\beta {\rightarrow} \mbox{Formation of pores in the cell} \\ membrane of post-mortem {\rightarrow} \\ Ca^{2+} \mbox{ influx} \end{array}$	Post-mortem of AD brains	[36]
	sAPP	$sAPP \rightarrow cGMP \rightarrow K^+ channel \rightarrow Ca^{2+}$	Hippocampal neurons	[56]
	$\gamma$ -secretase	$\gamma\text{-}secretase{\rightarrow}ER\text{-}Ca^{2+}$	SH-SY5Y cells (control and PSEN2 <sup>T122R</sup> -expressing)	[61]
СМ	NMDAR	memantine nitrate-06 (MN-06) $\neg$ NMDAR $\rightarrow$ Ca <sup>2+</sup> influx	Primary rat cerebellar granule hippocampal neurons	[64]
		$A\beta \cup endogenous Ca^{-1} channels \rightarrow NMDAR \rightarrow Ca^{2+} influx$	Mature hippocampal neurons	[63]
	AMPAR	LY451395, LY450108 and S18986 <sup>⊣</sup> AMPAR→Ca <sup>2+</sup> influx	AD animal models	[69–72]
	P/Q-VGCC	$A\beta \dashv P/Q$ -VGCC $\rightarrow$ Ca <sup>2+</sup> influx	Hippocampal neurons	[73]
	N/T/L-VGCC	$A\beta_{1\rightarrow 0}\rightarrow N/1/L$ - VGCC $\rightarrow$ postsynaptic Ca <sup>2+</sup> response	Cortical neurons	[29,74,128]
	Na <sup>+</sup> /K <sup>+</sup> -ATPase	Aβ∃ion-motive ATPases⊣NMDAR and VGCCs→Ca <sup>2+</sup> influx Aβ⊣Ca <sup>2+</sup> -ATPase⊣Ca <sup>2+</sup> efflux	Primary neurons and synaptosomes of adult post-mortem hippocampus	[76]
	CALHM1	Voltage∪extracellular Ca <sup>2+</sup> →CALHM1	hippocampal slices from wild-type Calhm1 <sup>+/+</sup> , Calhm1 <sup>+/-</sup> , and Calhm1 <sup>-/-</sup> mice	[78]
	APOE	APOE→G-protein-linked PLC→Ca <sup>2+</sup> influx and mobilization	Neurons	[79]
		APOE4>E3>E2 $\rightarrow$ P/Q type Ca <sup>2+</sup> -channels $\rightarrow$ intracellular free Ca <sup>2+</sup>	Rat hippocampal astrocytes and neurons	[80]
		$APOE\epsilon 4 {\rightarrow} intracellular\ Ca^{2+}$	Primary cultured astrocytes of $APOE^{-/-}$ mice	[81]
ER	Aβ/InsP3R	$A\beta \rightarrow InsP3R \rightarrow Ca^{2+}$ response	Cultured neurons	[87]
	$A\beta_{1-42}/RyR$	$A\beta_{1\!-\!4\!2} {\rightarrow} RyRs {\rightarrow} Ca^{2+} \ flux$	primary cultured hippocampal neurons	[88]
	Aβ aggregates/InsP3R/RyR	Aβ aggregates→InsP3R and RyR→Ca <sup>2+</sup> flux from ER	Human brain tissues and cells, hippocampal CA1 pyramidal neurons	[82,129]
	PS1/InsP3R/RyR/SERCA	PS1∪InsP3R, RyR and SERCA→Ca <sup>2+</sup> signaling cascade	Primary rat cortical neurons	[89-91,93,94]
	PS/InsP3R	$PS \cup InsP3R \rightarrow Ca^{2+} flux$	Primary cortical neurons	[90]

**Table 1.** The levels of  $Ca^{2+}$  are elevated in the AD patients and animal models.

Cat.	Stimulator or Mediator	Mechanism	<b>Experimental Model</b>	Reference
	PS1 <sup>mut</sup> /InsP3	$PS1^{mut} \rightarrow PLC \rightarrow InsP_3 \rightarrow Ca^{2+} flux$ from ER	SH-SY5Y cell	[95]
	PS <sup>mut</sup> /RyR	PS <sup>mut</sup> →InsP3R and RyR→Ca <sup>2+</sup> release from ER	PC12 cells, mouse neurons and lipid bilayers	[93,96,130,131]
	PS <sup>mut</sup> /SERCA	$PS^{mut} \cup SERCA {\rightarrow} Ca^{2+} \ influx$	SH-SY5Y cells and patient-derived fibroblasts	[132]
	APOE4/RyR	APOE4 $\rightarrow$ RyR $\rightarrow$ Ca <sup>2+</sup> release from ER $\rightarrow$ APs and NFTs	Rat primary hippocampal neurons	[98–100]
	Stim1 <sup>D76A</sup>	Stim1 <sup>D76A</sup> mutation <sup>−</sup> SOCE→Ca <sup>2+</sup> influx PS1 <sup>M146V</sup>	Primary neurons from the PS1 <sup>mut</sup> mice	[104,105]
	Stim2	mutation $\exists$ STIM2 $\rightarrow$ SOCE $\rightarrow$ Ca <sup>2+</sup> influx PS1 $\land$ F9	PS1 <sup>M146V</sup> mice	[106]
	Stim1	mutation $\rightarrow$ Stim1 $\rightarrow$ SOCE $\rightarrow$ Ca <sup>2+</sup> influx	mouse hippocampal neurons	[107]
	TRPC3	BDNF $\rightarrow$ TRPC3 $\rightarrow$ Ca <sup>2+</sup> influx.	Pontine neurons and SH-SY5Y cells	[108,110]
	TRPC6	PS2 $\rightarrow$ TRPC6 $\dashv$ Ca <sup>2+</sup> influx	HEK293 cells	[109]
MT	PS1 <sup>L286V</sup> and PS1 <sup>M146L</sup>	$\begin{array}{c} \mathrm{PS1}^{\mathrm{L286V}}\\ \mathrm{mutation}^{-1}\mathrm{Mitochondria} \rightarrow\\ \mathrm{Ca}^{2+} \mathrm{flux} \end{array}$	PS1 <sup>L286V</sup> mutated PC12 cells and PS1 <sup>M146L</sup> lymphoblasts	[111–113]
	VDAC	hAPPSwe→VDAC1→Ca <sup>2+</sup> flux to the mitochondria	Tg2576 mice	[114]
	MCU	MCU→Ca <sup>2+</sup> flux to the mitochondrial matrix	COS-7 cell	[115,116]
	Na <sup>+</sup> /Ca <sup>2+</sup> exchanger	Na <sup>+</sup> /Ca <sup>2+</sup> exchanger→Ca <sup>2+</sup> across IMM	HEK293T cells	[117–119]
	mPTP	mPTP→Efflux of Ca <sup>2+</sup> from mitochondria	SH-SY5Y cells	[120]
LM	v-ATPase/CAX	V-ATPase and CAX $\rightarrow$ Ca <sup>2+</sup> influx to lysosomes	Rat kidney fibroblasts	[122,123,133]
	TRPML/TPC	TRPML and TPC→Ca <sup>2+</sup> efflux from lysosomes	HEK293 cells	[124]
	VGCC	$VGCC \rightarrow Ca^{2+}$ release autophagic fusion and/or autophagy flux.	Cacna1a <sup>-/-</sup> and Cacna2d2 <sup>-/-</sup> mice	[125]
	PS1 <sup>mut/-</sup>	PS1 $\neg$ v-ATPase $\rightarrow$ Ca <sup>2+</sup> uptake by lysosomes	APP/PS1 mice	[126]
	PS1/2 <sup>-/-</sup>	PS1 and 2 knockout <sup>−</sup> Ca <sup>2+</sup> uptake by lysosomes→autophagy process	PS1/2 <sup>-/-</sup> neurons	[127]

Table 1. Conts.

# 6. The Roles of $Ca^{2+}$ in the Production and Deposition of $A\beta$ during the Course of AD Development and Progression

An increase in Ca<sup>2+</sup> levels is functionally related to most pathological features and pathogenic factors of AD, such as presenilin and APP mutations, APOE4 expression, CALHM1 mutation, Aβ plaque formation, tau hyperphosphorylation, apoptosis and synaptic dysfunction [100]. In the following discussion, we discuss these features individually. This section focuses on the regulation of  $Ca^{2+}$  metabolism during the production and deposition of A $\beta$  and phosphorylation of tau protein (Table 2). In HEK293 cells overexpressing human APP, the Ca<sup>2+</sup> ion carrier A23187 can increase A $\beta$  production by increasing intracellular free Ca<sup>2+</sup> [134,135]. In primary cultured neurons from 3  $\times$  Tg mice, Ca<sup>2+</sup> chelator, BAPTA/AM and TRPV1 antagonist, capsazepine lowered the levels of Aß and phosphorylated tau [136]. In SH-SY5Y neurons cultured in vitro, increased Ca<sup>2+</sup> levels also led to an increase in the production of A $\beta$  [36]. Other studies have shown that Ca<sup>2+</sup> can promote the formation of the A $\beta_{1-40}$ oligomer, which is also the main cause of AD neurotoxicity [137]. In addition, the increase in intracellular Ca<sup>2+</sup> levels can also trigger the aggregation of A $\beta$ , which forms fibrils, indicating that Ca<sup>2+</sup> instability is a possible cause of sporadic AD [138]. The results of circular dichroism (CD) spectra demonstrated that 1–2 mM Ca<sup>2+</sup> have the ability to alter the unfolded A $\beta_{1-42}$  to  $\beta$ -sheet structure, which results in shortening the time of forming A $\beta_{1-42}$  fibrils by thioflavin

T staining [139]. During the formation of A $\beta$  fibrils, Ca<sup>2+</sup> seemed to accelerate the seeding effects of A $\beta_{1-42}$  in AD [139].

**Table 2.** The roles of  $Ca^{2+}$  in the production and depositon of A $\beta$  as well as the phosphorylation of tau.

Cat.	Stimulator or Mediator	Mechanism	Experimental Model	Reference
Ca <sup>2+</sup>	Αβ	$Ca^{2+}$ ionophore, A23187 $\rightarrow$ free $Ca^{2+}\rightarrow A\beta$ production	hAPP overexpressed HEK293 cells, Primary cultured neurons from $3 \times Tg$	[134–136]
		$Ca^{2+} \rightarrow A\beta$	SH-SY5Y cells	[36]
		$Ca^{2+} \rightarrow A\beta_{1-40}$ oligomers	Neurons	[137]
		$Ca^{2+} \rightarrow A\beta$ fibrils	AD mice and in vitro Aβ peptides	[138,139]
СМ	NMDAR	Memantine $\neg$ MDAR $\rightarrow$ A $\beta$	SH-SY5Y cells	[138]
	AMPAR	AMPAR $\rightarrow$ Ca <sup>2+</sup> $\rightarrow$ tau phosphorylation	PS1 <sup>mut</sup> mice	[140,141]
		Memantine $-NMDAR \rightarrow A\beta_{1_{-40}}$	APP23 mice	[142]
		NMDAR→ADAM10	Primary mouse cortical neurons	[143]
	AMPAR	$AMPAR \rightarrow \alpha$ -secretase $\rightarrow$ s $APP\alpha \dashv A\beta$	Cortical neurons	[144]
	CALMH1	$CALHM1^{P86L} \rightarrow sAPP\beta \rightarrow A\beta$	APP Tg mice	[138,145]
	L-VGCC	L-VGCC $\rightarrow$ Ca <sup>2+</sup> $\rightarrow$ A $\beta$	Rat cortical neurons	[134,138]
	Cav1.2	Isradipine $dav1.2 \rightarrow A\beta$	$3 \times Tg$ mice	[34]
	APOE4	APOE4 $\rightarrow$ A $\beta$ 42 in CSF	AD patients	[34]
	APOE	АРОЕ1-3⊣Аβ	hAPOE isoforms (PDAPP/TRE) expressing Aβ-amyloidosis mice	[146]
ER	InsP3R	InsP3R <sup>-/-</sup> receptor $\exists A\beta$	InsP3R <sup>-/-</sup> Sf9 and DT40 cells	[90]
	RyR	RyR→NFTs	AD patients, Primary cultured rat neurons	[101,147]
		$RyR \rightarrow Ca^{2+} \rightarrow A\beta$	βAPP expressed HEK293 cells	[134,135]
		Dantrolene→RyR→β-/γ- secretase→phosphorylation of APP and formation of APs	Dantrolene treated AD mice	[148,149]
	RyR2	APP mutation→RyR2 <sup>PTM</sup> →Ca <sup>2+</sup> leakv dβ	SH-SY5Y cells	[150]
		FKBP12.6URvR2 $\rightarrow$ Ca <sup>2+</sup> leakv $\dashv$ APs	$3 \times Tg$ mice	[150]
	RvR3	$R_V R^{3-/1} A P_s$	APP/PS1 mice	[151]
	SERCA	Thansigargin or siRNA SERCA	$PS1^{-/-}$ and $PS2^{-/-}$ fibroblasts	[94]
		There is a range of SERCA $\lambda C a^{2+} \lambda A^{2}$	APP overexpressed HEK293 cells	[135]
		$10 \text{ nM thapsigargin} \rightarrow A\beta$	APP overexpressed CHO cells	[150]
	Stim1/Orail	20 nM thapsigargin $\exists A\beta$ Stim1/Orai1 $\rightarrow$ SOCE $\rightarrow$ Ca <sup>2+</sup> $\rightarrow$ A $\beta$ /APs	APP expressed HEK293 cells	[105]
	COCE	SOCE→mushroom spines	PS1 <sup>M146V</sup> knockin	[150 154]
	SOCE	HABHmemory functions	hippocampal neurons	[153,154]
		$SOCE \rightarrow Ca^{2+}$ influx $\dashv A\beta \rightarrow AD$	Human neuroblastoma cells, Primary cultured hippocampal neurons	[155,156]
		SOCE inhibition $\rightarrow A\beta_{1-42}$	SH-SY5Y cells, Human neuroglioma H4 cells	[157,158]
MT	VDAC1	Reduced expression of VDAC1⊣βAPP, Tau, PS1, PS2, and BACE1	VDAC1 <sup>+/-</sup> vs VDAC1 <sup>+/+</sup> mice	[159]
	mPTP	$APP^{KM670/671NL}/PS1^{L166P} \cup dutasteride$ $\dashv_m PTP \rightarrow APs$	Primary neurons and APP/PS1 Tg mice	[160]
Ca <sup>2+</sup>	p-tau	$Ca^{2+} \rightarrow p$ -tau	SH-SY5Y cells	[100]
	1	$Ca^{2+} \rightarrow GSK3\beta \rightarrow p-tau$	SH-SY5Y cells	[161]
		Ca <sup>2+</sup> →p-tau	Primary hippocampal neurons and the immortalized GnRH neurons (GT1-7 cells).	[162]
		Ca <sup>2+</sup> →mPGES- 1/PGE <sub>2</sub> /EPs/CDK5/p35/p25→p-tau	N2a and APP/PS1 Tg mice	[19]
	NFTs	$Ca^{2+} \rightarrow Ca^{2+}$ -activated kinases $\rightarrow$ p-tau $\rightarrow$ NFTs	SH-SY5Y, N2a and AD mice models	[100,163]

## 7. Ca<sup>2+</sup> Transporters on the Cell Membrane Are Potentially Contributed to the Role of A $\beta$ in the Pathogenesis of AD

Since Ca<sup>2+</sup> has been shown to play a role in the production and aggregation of A $\beta$ , transporters on the surface of the cell membrane must have the potential to regulate the role of A $\beta$  in the pathogenesis of AD. In SH-SY5Y cells and APP23 Tg mice, memantine, an antagonist of NMDAR, showed an inhibitory effect on the production of A $\beta$  [138,142]. This result confirmed the theory that the activation of NMDAR can induce the production of A $\beta$  [143]. In addition, a recent study with an AD Tg mouse model showed that Ca<sup>2+</sup>-permeable (CP) AMPAR was abnormally expressed in the brains of APP/PS1 Tg mice [164,165]. In line with this finding, recent studies have found that the direct injection of A $\beta$  oligomers into hippocampal neurons in the CA1 region leads to the rapid insertion of CP AMPAR into synapses [164,165]. The activation of A $\beta$  [144]. In addition to these glutamate receptors, the CALMH1<sup>P86L</sup> polymorphic protein also increased the production of A $\beta$  [138,145]. In rat cortical neurons, L-VGCC promoted A $\beta$  production by increasing the Ca<sup>2+</sup> influx [138,166] In this scenario, APOE, as a transmembrane protein, also participates in the regulation of A $\beta$  production [34,146].

## 8. Ca<sup>2+</sup> Leakage from ER Modulates the Production and Deposition of A $\beta$ via Activating Ca<sup>2+</sup> Transporters on ER

In addition to extracellular Ca<sup>2+</sup> influx, the ER, as an intracellular reservoir, plays a regulatory role in the production of A $\beta$ . For example, knocking out the expression of InsP3R in Sf9 and DT40 cells significantly reduced A $\beta$  production [90]. In addition, previous studies have shown that RyR protein and mRNA expression levels were significantly increased in SH-SY5Y neuroblastoma cells and Tg2576 mice overexpressing wild-type  $\beta$ APP or  $\beta$ APPswe [149]. RyR, another important Ca<sup>2+</sup> transporter on the surface of the ER membrane, also regulates A $\beta$  production [96]. By inhibiting RyR activity, dantrolene decreased the activity levels of  $\beta$ - and  $\gamma$ -secretases and the formation of APs [148,149]. In AD patients with mild cognitive impairment, RyR2 expression is increased [167,168]. In mutant-APP-overexpressing SH-SY5Y neurons, the post-translational modification of RyR2 can affect Ca<sup>2+</sup> leakage from the ER, leading to reduced production of A $\beta$  from APP [150]. In addition, it has been reported that enhancing the binding of FKBP12.6 with RyR2 can stabilize the leakage of  $Ca^{2+}$  from the RyR2 channel, leading to the formation of fewer APs [150]. In addition to RyR2, the RyR3 level showed an upward trend in the hippocampus of several AD mouse models [96,148,149]. In contrast to RyR2, some studies have shown that knocking out RyR3 reduces the formation of APs in the brains of AD mouse models [151]. By knocking out the expression of RyR3, RyR3 was found to exert a neuroprotective effect in the early stage of AD but promoted the development of AD in the late stage in a  $3 \times Tg$  mouse model [151,169]. Thapsigargin inhibition or siRNA knockout of SERCA, a Ca<sup>2+</sup> channel in the ER, resulted in a decrease in A $\beta$  production, while SERCA overexpression increased A $\beta$  production [94]. Thapsigargin, a compound that inhibits Ca<sup>2+</sup> uptake into the ER through SERCA, can increase the effects of caffeine on stimulating the release of A $\beta$  by increasing the level of Ca<sup>2+</sup> in the cytoplasm [135]. These conflicting reports are reconciled by previous reports showing that lower concentrations (10 nM) of thapsigargin stimulated the formation of A $\beta$ , whereas higher concentrations (20 nM) of thapsigargin inhibited the production of A $\beta$  in APP-overexpressing CHO cells [152].

On the basis of SOCE, the overexpression of Stim1 and Orai1 can accelerate the production and deposition of A $\beta$  [105]. In PS1<sup>M146V</sup>-overexpressing hippocampal neurons, SOCE is required for maintaining the morphology of mushroom spines, which results in modulating the production of A $\beta$  and promoting memory functions [153,154]. In human neuroblastoma cells, the influx of Ca<sup>2+</sup> mediated by SOCE can reduce the secretion of A $\beta$ , suggesting that the loss of SOCE in the pathogenesis of AD leads to the production of A $\beta$  and accelerates the onset of AD [155–157]. Consistent with this hypothesis, inhibition of SOCE by overexpressing Orai2 results in the increased production of A $\beta_{1-42}$  in SH-SY5Y

and human neuroglioma H4 cells, suggesting a potential way to rescue the defects of AD and prevent the formation of APs by downregulating the expression of Orai2 [157,158].

# 9. $Ca^{2+}$ Transporters on the Membranes of Mitochondria Are Also Involved in Regulating the Production and Deposition of $A\beta$ during the Course of AD Development and Progression

In mitochondria, the abnormal interaction of voltage-dependent anion channel 1 (VDAC1) with A $\beta$  and phosphorylated tau has the ability to induce the dysfunction of mitochondria during the course of AD development and progression [170]. In addition, A $\beta$  can induce the opening of mPTP, which results in enhanced permeability of the brain mitochondria [171,172]. These observations indicated that A $\beta$  might induce the efflux of Ca<sup>2+</sup> from mitochondria, which enhances the pathogenesis of AD. In support of this hypothesis, a report suggested that reduced VDAC1 expression in VDAC1<sup>+/-</sup> mice decreased the mRNA expression levels of AD-related genes, including  $\beta$ APP, Tau, PS1, PS2 and BACE1, compared with their expression levels in VDAC1<sup>+/+</sup> mice [159]. Furthermore, in primary cultured neurons and APP/PS1 Tg mice carrying human APP<sup>KM670/671NL</sup> and PS1<sup>L166P</sup> mutants, treatment with dutasteride decreased the formation of APs by disrupting the function of the mPTP [160].

#### 10. The Roles of Ca<sup>2+</sup> in Regulating the Phosphorylation of Tau

Apart from the production and deposition of  $A\beta$ ,  $Ca^{2+}$  also induced the phosphorylation of tau via the GSK3 $\beta$ -activating pathway in SH-SY5Y cells [100,161]. In addition, a similar phenomenon was observed in primary cultured hippocampal neurons and immortalized GnRH neurons (GT1–7 cells) [162]. Similarly, we found that mPGES-1/PGE<sub>2</sub>/EPs/CDK5/p35/p25 signaling cascades mediated the effects of Ca<sup>2+</sup> in stimulating the phosphorylation of tau in n2a and APP/PS1 Tg mice [19]. Furthermore, Ca<sup>2+</sup> triggered Ca<sup>2+</sup>-activated kinases, which mediated the phosphorylation of tau, leading to the formation of NFTs in AD mouse models [100,163]. Although there are few reports showing the involvement of transporters in mediating the effects of Ca<sup>2+</sup> on the phosphorylation of tau in PS1<sup>mut</sup>-knock-in mice [140,141]. Furthermore, alterations to the RyR Ca<sup>2+</sup> release channel correlate with the formation of NFTs in AD patients [147]. On the basis of these observations, multiple transporters may mediate the effects of Ca<sup>2+</sup> on the production and deposition of A $\beta$  and hyperphosphorylated tau during the course of AD development and progression.

#### 11. Ca<sup>2+</sup> Accelerates the Cognitive Decline Associated with AD

As Ca<sup>2+</sup> has been observed to be critical for the production and deposition of A $\beta$ and hyperphosphorylated tau via its transporters, we also address its roles in the learning ability and memory of AD patients and experimental models (Table 3). In aging people, elevated levels of serum Ca<sup>2+</sup> is thought to be associated with cognitive decline [173,174]. In AD patients, disorders of Ca<sup>2+</sup> metabolism are also reported to be associated with dementia [175]. For this reason, A $\beta$  oligomers were identified as critical for the influx of Ca<sup>2+</sup> that results in impaired learning and memory through the inhibition of LTP, a form of synaptic plasticity [176–178]. Because of the presence of A $\beta$ , Ca<sup>2+</sup>-dependent enzymes located in the spine, such as calpain, are associated with synaptic dysfunction. Treatment with calpain inhibitors improved learning ability and memory by inducing LTP in A $\beta$ -treated APP/PS1 Tg mice [179].

Cat.	Stimulator or Mediator	Mechanism	Experimental Model	Reference
Ca <sup>2+</sup>		Serum $Ca^{2+} \rightarrow cognitive decline Ca^{2+} \rightarrow dementia ca^{2+} \rightarrow dementia ca^{2+} ca^{2+}$	Aging people AD patients	[174] [175]
	Aβ oligomes	AB oligomers→Ca- influx <sup>-I</sup> LTP→synaptic plasticity→learning and memory	AD models, Hippocampal slices and APP/PS1 Tg mice	[176–178]
	Calpain	Inhibitor calpain $\rightarrow A\beta$ learning and memory	APP/PS1 mice	[179]
	Calcineurin	Inhibitor <sup>- </sup> calcineurin <sup>- </sup> learning and memory	Tg2576 mice	[180]
СМ	NMDAR	Calcineurin→removing NMDAR/AMPAR by	APP/PS1 mice	[181]
		Antagonist MMDAR synaptic	Rats	[182,183]
		Blocking NMDAR $\neg$ Ca <sup>2+</sup> $\neg$ cognition	AD patients and AD mouse models	[184,185]
		network dysfunction/excitotoxicity→ cognitive decline	APP/PS1 mice	[186]
	L-VGCC	L-VGCC $\rightarrow$ Ca <sup>2+</sup> currents $\rightarrow$ cognitive decline	CA1 synapses of 3 $\times$ Tg AD mice	[187]
		Nifedipine $\exists Ca^{2+}$ channel $\rightarrow$ cognitive impairment	KK-A(y) mice	[188]
		Nimodipine⊣L-VGCC⊣ learning ability	Mild-to-moderate AD patients	[189]
	T-VGCC	ST101⊣T-VGCC⊣LTP/p-CaMKII →cognitive decline	Rat cortical slices	[190]
	NMDAR	MK-801 $\dashv$ NMDAR $\rightarrow$ Ca <sup>2+</sup> $\rightarrow$	Traumatic brain injury (TBI) mice	[191]
	Cav 2.1	Cav $2.1^{-/-1}$ Ca <sup>2+-1</sup> learninig ability	Cav 2.1 knocking out mice	[192]
	TRPV1	SB366791 TRPV1 cognitive performance	Dopamine D3 receptor (D3R) <sup>-/-</sup> mice	[193]
	APOE4	APOE4 $\rightarrow$ serum Ca <sup>2+</sup> $\dashv$	Aging people	[194]
	CALHM1	CALHM1 <sup>P86L</sup> polymorphism→AD	Chinese populations	[195]
ER	InsP3	PS1 <sup>M146V</sup> →InsP3→InsP3R1→Ca <sup>2+</sup> →memory loss	PS1 <sup>M146V</sup> mice	[196]
	InsP3R	SOCE∪InsP3R→Ca <sup>2+</sup> − cognitive impairment	Sporadic or mild AD patients	[197]
	RyR	Dantrolene⊣RyR⊣synaptic plasticity→cognitive ability	AD mouse model	[198]
	RyR2/RyR3	RyR3 <sup>-/-</sup> /RyR2 <sup>+/+-</sup> social behavior and memory	RyR3 <sup>-/-</sup> /RyR2 <sup>+/+</sup> mice	[199,200]
		$RyR^{r_{1M}} \rightarrow ER \rightarrow Ca^{2+} leaky \rightarrow cognitive deficits$	$3 \times Tg$ mice	[150]
	Stim2/SOCE	STIM2 <sup>−</sup> ∪SOCE <sup>−</sup> ¬mushroom spines→LTP→memory	PS <sup>mut</sup> mice	[106,201]
		$SOCE^{-} \rightarrow cognitive decline \rightarrow AD$	Hippocampal slice cultures	[202]
MT	VDAC1	$\gamma$ -secretase $\rightarrow$ neurotoxicity $\rightarrow$ cell death $\rightarrow$ dementia $\rightarrow$ AD	APP, APP/PS1 and 3 $\times$ Tg mice	[203]
	mPTP	DS16570511, DS44170716 <sup>-I</sup> MCU→Ca <sup>2+</sup> influx to mitochondria→ mPTP→apoptotic cell death Tetrandrine	HEK293 cells	[204,205]
LM	TPC	NED-19 <sup>-</sup> TPCE2 <sup>-</sup> re-acidify	MEFs cells	[206]
		Beclin1 <sup>-/-</sup> $\rightarrow$ A $\beta$	hAPP mice	[207]

### **Table 3.** $Ca^{2+}$ accelerates the cognitive decline of AD.

## 12. Transporters on the Cell Membrane Mediated the Effects of Ca<sup>2+</sup> on Inducing the Cognitive Decline of AD

Since the levels of  $Ca^{2+}$  are increased by activating calcineurin (CaN), the effects of A $\beta$  in inducing deficits in learning and memory were blocked by inhibitors of CaN in APP/PS1 Tg mice [180]. Activation of the Ca<sup>2+</sup>-dependent protein phosphatase calcineurin (CaN) potentially impaired the cognition of AD by eliminating both NMDA and AMPA receptors through endocytosis [181]. In addition to CaN, NMDAR-specific antagonists showed beneficial effects on learning ability and memory in rats [182,183]. Consistent with this observation, blocking NMDAR attenuated cognitive decline by restoring the metabolic balance of Ca<sup>2+</sup> in AD patients and AD mouse models [184,185]. The sustained expression of another glutamate receptor serving as a Ca<sup>2+</sup> transporter, CP-AMPAR, in the early stage of AD accelerated the onset of neuronal network dysfunction and neuronal excitotoxicity, leading to successive cognitive decline by dysregulating the flux of Ca<sup>2+</sup> [186]. These observations indicate that glutamate receptors, including NMDAR and AMPAR, are critical for mediating the effects of Ca<sup>2+</sup> dysregulation on the learning ability of AD patients.

In addition, the increase in L-type Ca<sup>2+</sup> currents in CA1 synapses leads to a decrease in cognitive function in  $3 \times Tg$  AD mice [187]. Furthermore, treatment with nifedipine, a calcium channel blocker, attenuated cognitive impairment in KK-A(y) mice, a type 2 diabetic mouse model [188]. These observations confirmed that nimodipine can enhance the learning ability of mild-to-moderate AD patients [189,208]. Similarly, ST101, an inhibitor of T-VGCC, can attenuate cognitive decline by enhancing LTP and the autophosphorylation of CaMKII in rats [190]. As an inhibitor of NMDAR, MK-801 attenuates cognitive decline by decreasing the concentration of  $Ca^{2+}$  in mice with traumatic brain injury (TBI) [191]. In Cav 2.1-knockout mice, ablation of Cav2.1 voltage-gated Ca<sup>2+</sup> channels enhanced learning ability by reducing intracellular Ca<sup>2+</sup> levels [192]. SB366791, a specific TRPV1 antagonist, ameliorated the poor cognitive performance of dopamine D3 receptor (D3R)-knockout mice [193]. Although it is not regarded as a canonical Ca<sup>2+</sup> transporter, APOE4 shows the ability to worsen cognitive function by increasing serum Ca<sup>2+</sup> levels in older people [194]. Moreover, the CALHM1P86L polymorphic protein has been found to be associated with AD in the ethnic Chinese Han population, even though no direct evidence has shown a relationship between Ca<sup>2+</sup> and learning ability [195].

#### 13. Ca<sup>2+</sup> Transporters on ER Are also Involved in Impairing the Memory of AD

For intracellular stores, the generation of InsP3 can enhance memory loss by activating the release of intracellular Ca<sup>2+</sup> through a metabotropic glutamate receptor-activating mechanism [196]. As the natural ligand of InsP3R, InsP3 usually exerts its effects via its receptor to impair memory by triggering the release of  $Ca^{2+}$  from the ER in AD patients [197]. In addition to InsP3R, RyR was also shown to be critical for the cognitive decline of AD patients and mouse models [209]. For example, the expression of RyR2 was upregulated in patients with mild cognitive impairment and AD [167]. In addition, an inhibitor of RyRs, dantrolene, enhanced the learning ability of an AD mouse model via the rescue of lost synaptic plasticity [198]. To clarify the effect, the expression of RyR3 was knocked down, which resulted in impaired social behavior and memory in rats [199]. This result seemed to conflict with the outcomes induced by treatment of RyRs inhibitors. However, these conflicting results are reconciled by the fact that RyR3 knockdown induces the mRNA expression of RyR2 in the hippocampus of rats completing water maze tests compared with the swimming rat controls [200]. These observations demonstrate the key roles of RyR2 in affecting the learning ability of organisms affected by AD. In addition to its expression, the post-translational modification of RyR can induce cognitive deficits by stabilizing the leakage of  $Ca^{2+}$  from the ER [150].  $Ca^{2+}$  depletion by InsP3R and RyR stimulates SOCE. Accordingly, the reduced expression of synaptic STIM2 and impaired SOCE destabilized mushroom spines, which resulted in reduced LTP-mediated memory formation in PS<sup>mut</sup> mice [106,107,201]. Consistent with this observation, attenuation of SOCE in AD neurons

might account for the cognitive decline associated with AD, suggesting possible roles for SOCE in regulating memory functions [202].

## 14. Ca<sup>2+</sup> Transporters on Mitochondria and Lysosomes Potentially Contribute to the Memory Loss of AD

Although there is no direct evidence to show the relationship between Ca<sup>2+</sup> from mitochondria and lysosomes and the learning ability of AD patients, to the best of our knowledge, VDAC1 is a hub protein that interacts with more than 150 other proteins, including phosphorylated tau,  $A\beta$ , and  $\gamma$ -secretase, and it contributes to their toxic effects, triggering cell death and potentially leading to the dementia characteristic of AD [203]. In addition, DS16570511 and DS44170716 inhibit Ca<sup>2+</sup> uptake in mitochondria by MCU, which resulted in the inhibition of Ca<sup>2+</sup>-induced mPTP opening and rescued cells from apoptotic death [204]. For lysosomes, tetrandrine and NED-19 inhibited TPCE2 to re-acidify the lysosome environment and reverse dysregulated autophagy [206], which is important for the degradation of aggregated proteins during the course of AD development and progression [207,210]. On the basis of these observations, Ca<sup>2+</sup> has the ability to modulate the learning ability of AD patients via the functions of its transporters.

#### 15. The Roles of Ca<sup>2+</sup> in Synaptic Plasticity

In neuroscience, synaptic plasticity refers to the connection between nerve cells, whose strength can be adjusted by cell-adhesion molecules, cytoskeletal proteins, ion channels and various receptor proteins [211,212]. Indeed, emerging evidence has revealed the central roles of Ca<sup>2+</sup> in mediating the synaptic dysfunction in AD [213]. Given the roles of Ca<sup>2+</sup> in producing A $\beta$ , mutations of APP and PS1 have shown led to disruptions of synaptic processes by controlling the homeostasis of Ca<sup>2+</sup> during the course of AD development and progression [214]. In addition, the C-terminus of APP has the ability to impair LTP in mice [215]. In fact, A $\beta$  induces Ca<sup>2+</sup> influx, which results in activating LTD, leading to erased memories in the early cognitive decline of AD patients [28]. Similarly, A $\beta$  oligomers mediate the inhibitory effects of Ca<sup>2+</sup> on LTP in hippocampal slices [176]. By knocking out the expression of PS1 in mice, LTP is reduced because of the disrupted function of the ER, Ca<sup>2+</sup> leakage and reduction in the ER Ca<sup>2+</sup> pool in AD [216]. In contrast, BAPTA-AM, as a chelator of Ca<sup>2+</sup>, induced LTP in aged rat hippocampal slices [217]. All this evidence demonstrated the effects of Ca<sup>2+</sup> on synaptic plasticity.

## 16. Ca<sup>2+</sup> Transporters on the Cell Membrane Are Involved in Regulating the Synaptic Plasticity

CaN is a member of the serine/threonine protein phosphatase family. It is a unique serine/threonine protein phosphatase that is regulated by Ca<sup>2+</sup> and calmodulin. Currently, it is a multifunctional signaling enzyme, especially in regulating synaptic plasticity. For example, overexpressing CaN in young animals induces aging-like deficits of LTP, and deactivating CaN increases the synaptic strength in aged animals, which facilitates LTP [218]. Similarly, Ca<sup>2+</sup>-dependent CaN activation results in LTD by removing NMDAR and AMPAR via endocytosis in aged or APP Tg mice [180,219]. By inhibiting the activity of CaN, LTP is induced by inhibitors or A $\beta$  in APP and Tg2576 mice [28,180].

With respect to  $Ca^{2+}$  transporters in the cell membrane, A $\beta$  oligomers induce the dysfunction of  $Ca^{2+}$  and inhibit LTP in an NMDAR-dependent mechanism [220]. In addition, NMDAR mediated the entry of  $Ca^{2+}$  into spines and dendrites, which resulted in insufficient activation of LTP in the rat hippocampus [221]. Interestingly, NMDAR-dependent LTD requires transient incorporation of  $Ca^{2+}$ -permeable (CP)-AMPAR into the synapse, which is mediated by AKAP150-anchored PKA and calcineurin [222]. Consistent with this observation, infusion of A $\beta$  oligomers into the CA1 region of the hippocampus resulted in a rapid insertion of CP-AMPAR into synapses [165]. More directly, AMPAR mediated the effects of  $Ca^{2+}$ , increasing not only LTP but also LTD. The mutation of GluR2, a subunit of AMPAR, obviously induced LTP in hippocampal slices [223]. CP-AMPAR

insertion into synapses was required for the induction of LTP, which was induced by specific stimuli, leading to the assembly of heteromeric AMPARs containing both GluA1 and GluA2 subunits in CA1 hippocampal neurons [224]. In addition, CP-AMPAR mediated the effects of glycine on the induction of LTP-dependent spine enlargement via CaMKI-activating mechanisms in mature hippocampal neurons [225]. In cultured rat hippocampal neurons,  $Ca^{2+}/calmodulin binding$  to PSD-95 induced the loss of synaptic PSD-95 and surface AMPARs, which resulted in activated LTD [226].

In addition to NMDAR and AMPAR, the activation of VGCC induced LTP via CaMKII in hippocampal slides [227]. In addition, Cav1.2 expression is essential for LTP, synaptic plasticity, and memory in the hippocampus [228]. As Ca<sup>2+</sup> transporters in the cell membrane, TRPs are involved in regulating synaptic plasticity. For example, TRPV1 activation by capsaicin and resiniferatoxin induces a switch from LTD to LTP by enhancing Ca<sup>2+</sup> influx [229]. Treatment with the agonist of TRPV1 and 4-endocannabinoid anandamide (AEA) induced LTP in CB1<sup>-/-</sup> or TRPV1<sup>-/-</sup> mice [230,231]. In addition, the inhibition of TRPM2 enhanced LTP in traumatically injured brains of mice [232]. In contrast, TRPM4 reduction eliminated NMDAR-dependent LTP in CA1 hippocampal neurons [233].

## 17. ER Transporters Are Responsible for Releasing Ca<sup>2+</sup> from Internal Stores, Leading to Regulate the Synaptic Plasticity

With respect to intracellular Ca<sup>2+</sup>, LTD is induced via InsP3-mediated Ca<sup>2+</sup> influx mechanisms [234]. Similarly, the activation of metabotropic glutamatergic receptors induced the production of InsP3 to release Ca<sup>2+</sup> from internal stores, which resulted in promoting LTD in hippocampal slices [235]. Blocking InsP3R led to a switch of LTD to LTP and the elimination of heterosynaptic LTD, whereas blocking RyR eliminated both LTP and homosynaptic LTD at synapses that were activated, normally at low frequencies, in rat hippocampal slides and  $3 \times Tg$  mice [196,236]. In addition, knocking out the expression of RyR3 concurrently increases LTP and reduced LTD [237,238]. As critical genes for AD, presynaptic inactivation of PSs impairs LTP by controlling RyR-mediated Ca<sup>2+</sup> release from the ER [239]. As Ca<sup>2+</sup> depletion from the ER induces SOCE, it is reasonable to speculate that SOCE is involved in regulating synaptic plasticity. In FVB/NJ mice, reduction of SOCEmediated Ca<sup>2+</sup> entry reduced CaMKII activity, leading to destabilization of the mushroom spine and reducing LTP-mediated memory formation [240]. In the same experimental model, the overexpression of STIM1 in mouse brain neurons enhanced contextual learning and attenuated long-term depression [240]. With respect to mitochondrial Ca<sup>2+</sup> stores, knocking out the expression of VDAC1 disrupts synaptic plasticity [159]. Similar to the effects of inhibiting mPTP by cyclosporine A, porin-deficient mice showed deficits in longand short-term synaptic plasticity [241]. Based on these observations, these transporters mediated the regulatory effects of  $Ca^{2+}$  on synaptic plasticity (Table 4).

**Table 4.** The roles of Ca<sup>2+</sup> in synaptic plasticity.

Cat.	Stimulator or Mediator	Mechanism	Experimental Model	Reference
Ca <sup>2+</sup>		$A\beta \rightarrow Ca^{2+}$ influx $\rightarrow LTD$ memory $\neg AD$	Tg2576 mice	[28]
		A $\beta$ oligomers $\rightarrow$ Ca <sup>2+</sup> /LTP	Hippocampal slices	[176]
		PS1 <sup>-/-</sup> -LTP	$PS1^{-/-}$ mice	[216]
		BAPTA-AM-Ca <sup>2+</sup> -LTP.	Aged rat hippocampal slices	[217]
СМ	CaN	$CaN^+ \dashv LTP$ $CaN^- \rightarrow synpatic strength \rightarrow LTP$	CaN <sup>+</sup> mice	[218]
		$Ca^{2+} \rightarrow CaN \rightarrow LTD$	Aged or APP mice	[180,219]
		Inhibitors-CaN-LTP	APP mice	[180]
		Aβ − CaN− synaptic plasticity	Tg2576 mice	[28]
	NMDAR	A $\beta$ oligomers $\rightarrow$ NMDAR $\rightarrow$ Ca <sup>2+</sup> ILTP	Hippocampal CA1 and DG regions	[220]
		NMDAR $\rightarrow$ Ca <sup>2+</sup> ITP	Rat hippocampus	[221]

Cat.	Stimulator or Mediator	Mechanism	Experimental Model	Reference
	AMPAR	$AMPAR \rightarrow Ca^{2+} \rightarrow LTP \cup LTD$	CA1 pyramidal cells	[242]
		$GluR2^{-/-} \rightarrow LTP$	$GluR2^{-/-}$ mice	[223]
		CP-AMPAR→LTP	CA1 hippocampal neurons	[224]
		$Glycine \rightarrow CP-AMPAR \rightarrow CaMKI \rightarrow LTP$	Mature hippocampal neurons	[225]
		Ca <sup>2+</sup> /Calmodulin∪PSD-95⊣PSD- 95∪AMPAR⊣LTD	Rat hippocampal neurons	[226]
	VGCC	VGCC→CaMKII→LTP	Hippocampus slides	[227]
	Cav1.2	Cav1.2 <sup>+</sup> $\rightarrow$ LTP, synaptic plasticity, and the memory	Ca(V)1.2 (cKO) mice	[228]
	TRPV1	Capsaicin and resiniferatoxin→TRPV1→LTP	Hippocampus slides	[229]
		Capsaicin→TRPV1→Ca <sup>2+</sup> influx→LTP	Hippocampus slides	[229]
	TRPV1/4	Endocannabinoid anandamide (AEA) $\rightarrow$ TRPV1/4 $\rightarrow$ LTP	CB1 <sup>-/-</sup> mice TRPV1 <sup>-/-</sup> mice	[230,231]
	TRPM2	Inhibitor TRPM2 LTP	Traumatic injured brain of mice	[232]
	TRPM4	TRPM4 <sup>−</sup> <sup>-</sup> NMDAR→LTP	CA1 hippocampal neurons	[233]
ER	IP3	IP3 $\rightarrow$ Ca <sup>2+</sup> efflux from ER $\rightarrow$ LTD	Myosin-Va mutation mice or rats	[234]
		Metabotropic glutamatergic receptors→InsP3→Ca <sup>2+</sup> efflux from ER→LTD	Hippocampal slices	[235]
	InsP3R/RyR	InsP3R <sup>−</sup> →LTP∪ <sup>- </sup> LTD RyR <sup>−</sup>  LTP∪LTD	Rat hippocampus slides, $3 \times Tg$ AD mice	[196,243]
	RyR	$RvR3^{-/-} \rightarrow LTP \cup \dashv LTD$	RyR3 <sup>-/-</sup> mice, $3 \times$ Tg mice	[237,238]
	-	$PS^- \rightarrow RyR \rightarrow Ca^{2+}$ release from ER +LTP	PS conditioned neurons from CA1 and CA3	[239]
	SOCE	$SOCE^{}Ca^{2+}$ influx $\rightarrow$ CaMKII $\rightarrow$ LTP $\rightarrow$ memory	FVB/NJ mice	[240]
		STIM1 <sup>+</sup> LTD <sup>-</sup> contextual learning	FVB/NJ mice	[240]
MT	VDAC	VDAC1 <sup>-/-</sup> -synaptic plasticity	$VDAC1^{-/-}$ mice	[159]
	mPTP	Cyclosporine A → mPTP → long and short term synaptic plasticity	Porin-deficient or cyclosporin A-treated mice	[241]

CM, cell membrane; MT, mitochondria; LM, lysosome; PTM, post-translational modification;  $\rightarrow$ , stimulate, activate, induce, result in, lead to;  $\dashv$ , inhibit, block, suppress, deactivate, degrade; +, overexpress, activate, upregulate, induce; -, knockdown, deplete, ablate, siRNA, deactivate, downregulate, deficiency; -/-, knock out;  $\cup$ , interact, facilitate, associate, potentiate, recruit, and.

#### **18. Conclusions**

During the development and progression of AD,  $Ca^{2+}$  is elevated in the cytosol of neuronal cells via its transportation from the extracellular space and intracellular stores through transporter-dependent mechanisms.  $Ca^{2+}$  accumulated in neuronal cells has the ability to induce the production and deposition of A $\beta$  and hyperphosphorylated tau in APs and NFTs, leading to impaired learning ability in AD patients. Moreover, transporters in the cell membrane, endoplasmic reticulum, mitochondria and lysosomal membranes are critical for mediating the effects of  $Ca^{2+}$  on synaptic plasticity, which contribute to the cognitive decline associated with AD.

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#### References

- Surguchov, A. Caveolin: A New Link Between Diabetes and AD. *Cell. Mol. Neurobiol.* 2020, *40*, 1059–1066. [CrossRef] [PubMed]
  Elgh, E.; Åstot, A.L.; Fagerlund, M.; Eriksson, S.; Olsson, T.; Näsman, B. Cognitive Dysfunction, Hippocampal Atrophy and Glucocorticoid Feedback in Alzheimer's Disease. *Biol. Psychiatry* 2006, *59*, 155–161. [CrossRef] [PubMed]
- Tarasoff-Conway, J.M.; Carare, R.O.; Osorio, R.S.; Glodzik, L.; Butler, T.; Fieremans, E.; Axel, L.; Rusinek, H.; Nicholson, C.; Zlokovic, B.V.; et al. Clearance systems in the brain—implications for Alzheimer disease. *Nat. Rev. Neurol.* 2015, *11*, 457–470. [CrossRef] [PubMed]
- 4. Kamal, A.; Almenar-Queralt, A.; Leblanc, J.F.; Roberts, E.A.; Goldstein, L.S.B. Kinesin-mediated axonal transport of a membrane compartment containing β-secretase and presenilin-1 requires APP. *Nat. Cell Biol.* **2001**, *414*, 643–648. [CrossRef]
- 5. Mazanetz, M.P.; Fischer, P.M. Untangling tau hyperphosphorylation in drug design for neurodegenerative diseases. *Nat. Rev. Drug Discov.* **2007**, *6*, 464–479. [CrossRef] [PubMed]
- Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* 2002, 297, 353–356. [CrossRef]
- Tomiyama, T.; Matsuyama, S.; Iso, H.; Umeda, T.; Takuma, H.; Ohnishi, K.; Ishibashi, K.; Teraoka, R.; Sakama, N.; Yamashita, T.; et al. A Mouse Model of Amyloid Oligomers: Their Contribution to Synaptic Alteration, Abnormal Tau Phosphorylation, Glial Activation, and Neuronal Loss In Vivo. J. Neurosci. 2010, 30, 4845–4856. [CrossRef]
- Heyman, A.; Wilkinson, W.E.; Stafford, J.A.; Helms, M.J.; Sigmon, A.H.; Weinberg, T. Alzheimer's disease: A study of epidemiological aspects. Ann. Neurol. 1984, 15, 335–341. [CrossRef]
- 9. Patterson, C.; Feightner, J.W.; Garcia, A.; Hsiung, G.-Y.R.; Macknight, C.; Sadovnick, A.D. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. *Can. Med. Assoc. J.* **2008**, *178*, 548–556. [CrossRef]
- Corder, E.H.; Saunders, A.M.; Strittmatter, W.J.; Schmechel, D.E.; Gaskell, P.C.; Small, G.W.; Roses, A.D.; Haines, J.L.; Pericak-Vance, M.A. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993, 261, 921–923. [CrossRef]
- 11. O'Donoghue, M.C.; Murphy, S.E.; Zamboni, G.; Nobre, A.C.; Mackay, C.E. APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review. *Cortex* **2018**, *104*, 103–123. [CrossRef]
- 12. Haass, C.; Lemere, C.A.; Capell, A.; Citron, M.; Seubert, P.; Schenk, D.; Lannfelt, L.; Selkoe, D.J. The Swedish mutation causes early-onset Alzheimer's disease by β-secretase cleavage within the secretory pathway. *Nat. Med.* **1995**, *1*, 1291–1296. [CrossRef]
- 13. Sinha, S.; Lieberburg, I. Cellular mechanisms of beta -amyloid production and secretion. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 11049–11053. [CrossRef]
- Citron, M.; Westaway, D.; Xia, W.; Carlson, G.; Diehl, T.; Levesque, G.; Johnson-Wood, K.; Lee, M.; Seubert, P.; Davis, A.; et al. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid β-protein in both transfected cells and transgenic mice. *Nat. Med.* 1997, *3*, 67–72. [CrossRef]
- 15. Alonso, A.D.C.; Grundke-Iqbal, I.; Iqbal, K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. *Nat. Med.* **1996**, *2*, 783–787. [CrossRef]
- Wang, P.; Wang, Z.-Y. Metal ions influx is a double edged sword for the pathogenesis of Alzheimer's disease. *Ageing Res. Rev.* 2017, 35, 265–290. [CrossRef]
- 17. Etcheberrigaray, R.; Hirashima, N.; Neec, L.; Prince, J.; Govonid, S.; Racchie, M.; Tanzi, R.E.; Alkon, D.L. Calcium Responses in Fibroblasts from Asymptomatic Members of Alzheimer's Disease Families. *Neurobiol. Dis.* **1998**, *5*, 37–45. [CrossRef]
- Yu, J.-T.; Chang, R.C.-C.; Tan, L. Calcium dysregulation in Alzheimer's disease: From mechanisms to therapeutic opportunities. Prog. Neurobiol. 2009, 89, 240–255. [CrossRef]
- 19. Cao, L.-L.; Guan, P.-P.; Liang, Y.-Y.; Huang, X.-S.; Wang, P. Calcium Ions Stimulate the Hyperphosphorylation of Tau by Activating Microsomal Prostaglandin E Synthase 1. *Front. Aging Neurosci.* **2019**, *11*, 108. [CrossRef]
- 20. Cao, L.-L.; Guan, P.-P.; Liang, Y.-Y.; Huang, X.-S.; Wang, P. Cyclooxygenase-2 is Essential for Mediating the Effects of Calcium Ions on Stimulating Phosphorylation of Tau at the Sites of Ser 396 and Ser 404. *J. Alzheimer's Dis.* **2019**, *68*, 1095–1111. [CrossRef]
- Zempel, H.; Thies, E.; Mandelkow, E.-M. A Oligomers Cause Localized Ca2+ Elevation, Missorting of Endogenous Tau into Dendrites, Tau Phosphorylation, and Destruction of Microtubules and Spines. J. Neurosci. 2010, 30, 11938–11950. [CrossRef] [PubMed]
- 22. Tong, B.C.-K.; Wu, A.J.; Li, M.; Cheung, K.-H. Calcium signaling in Alzheimer's disease & therapies. *Biochim. Biophys. Acta BBA Bioenerg.* 2018, 1865, 1745–1760. [CrossRef]
- 23. Sama, D.M.; Norris, C.M. Calcium dysregulation and neuroinflammation: Discrete and integrated mechanisms for age-related synaptic dysfunction. *Ageing Res. Rev.* 2013, 12, 982–995. [CrossRef] [PubMed]
- 24. Song, Y.; Li, D.; Farrelly, O.; Miles, L.; Li, F.; Kim, S.E.; Lo, T.Y.; Wang, F.; Li, T.; Thompson-Peer, K.L.; et al. The Mechanosensitive Ion Channel Piezo Inhibits Axon Regeneration. *Neuron* **2019**, *102*, 373–389.e6. [CrossRef] [PubMed]
- Wahlestedt, C.; Golanov, E.; Yamamoto, S.; Yee, F.; Ericson, H.; Yoo, H.; Inturrisi, C.E.; Reis, D.J. Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions. *Nat. Cell Biol.* 1993, 363, 260–263. [CrossRef] [PubMed]
- 26. Decuypere, J.-P.; Bultynck, G.; Parys, J.B. A dual role for Ca2+ in autophagy regulation. Cell Calcium 2011, 50, 242–250. [CrossRef]
- 27. Liu, S.J.; Zukin, R.S. Ca2+-permeable AMPA receptors in synaptic plasticity and neuronal death. *Trends Neurosci.* 2007, 30, 126–134. [CrossRef]

- Kuchibhotla, K.V.; Goldman, S.T.; Lattarulo, C.R.; Wu, H.-Y.; Hyman, B.T.; Bacskai, B.J. Aβ Plaques Lead to Aberrant Regulation of Calcium Homeostasis In Vivo Resulting in Structural and Functional Disruption of Neuronal Networks. *Neuron* 2008, *59*, 214–225. [CrossRef]
- MacManus, A.; Ramsden, M.; Murray, M.; Henderson, Z.; Pearson, H.A.; Campbell, V.A. Enhancement of 45Ca2+ Influx and Voltage-dependent Ca2+ Channel Activity by β-Amyloid-(1–40) in Rat Cortical Synaptosomes and Cultured Cortical Neurons. *J. Biol. Chem.* 2000, 275, 4713–4718. [CrossRef]
- 30. Calvo-Rodriguez, M.; Hou, S.S.; Snyder, A.C.; Kharitonova, E.K.; Russ, A.N.; Das, S.; Fan, Z.; Muzikansky, A.; Garcia-Alloza, M.; Serrano-Pozo, A.; et al. Increased mitochondrial calcium levels associated with neuronal death in a mouse model of Alzheimer's disease. *Nat. Commun.* **2020**, *11*, 1–17. [CrossRef]
- Li, L.; Tsai, H.-J.; Li, L.; Wang, X.-M. Icariin Inhibits the Increased Inward Calcium Currents Induced by Amyloid-β25-35 Peptide in CA1 Pyramidal Neurons of Neonatal Rat Hippocampal Slice. *Am. J. Chin. Med.* 2010, *38*, 113–125. [CrossRef]
- Yallampalli, S.; Micci, M.-A.; Taglialatela, G. Ascorbic acid prevents β-amyloid-induced intracellular calcium increase and cell death in PC12 cells. *Neurosci. Lett.* 1998, 251, 105–108. [CrossRef]
- Ekinci, F.J.; Linsley, M.-D.; Shea, T.B. β-Amyloid-induced calcium influx induces apoptosis in culture by oxidative stress rather than tau phosphorylation. *Mol. Brain Res.* 2000, 76, 389–395. [CrossRef]
- 34. Anekonda, T.S.; Quinn, J.F. Calcium channel blocking as a therapeutic strategy for Alzheimer's disease: The case for isradipine. *Biochim. Biophys. Acta BBA Mol. Basis Dis.* **2011**, *1812*, 1584–1590. [CrossRef]
- 35. Hermes, M.; Eichhoff, G.; Garaschuk, O. Intracellular calcium signalling in Alzheimer's disease. J. Cell. Mol. Med. 2009, 14, 30–41. [CrossRef]
- 36. Demuro, A.; Parker, I.; Stutzmann, G.E. Calcium Signaling and Amyloid Toxicity in Alzheimer Disease. *J. Biol. Chem.* **2010**, *285*, 12463–12468. [CrossRef]
- Mäkinen, S.; Van Groen, T.; Clarke, J.; Thornell, A.; Corbett, D.; Hiltunen, M.; Soininen, H.; Jolkkonen, J. Coaccumulation of Calcium and β-Amyloid in the Thalamus after Transient Middle Cerebral Artery Occlusion in Rats. *Br. J. Pharmacol.* 2007, 28, 263–268. [CrossRef]
- Arispe, N.; Diaz, J.; Durell, S.R.; Shafrir, Y.; Guy, H.R. Polyhistidine Peptide Inhibitor of the Aβ Calcium Channel Potently Blocks the Aβ-Induced Calcium Response in Cells. Theoretical Modeling Suggests a Cooperative Binding Process. *Biochemistry* 2010, 49, 7847–7853. [CrossRef]
- 39. Arispe, N.; Rojas, E.; Pollard, H.B. Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: Blockade by tromethamine and aluminum. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 567–571. [CrossRef]
- Lin, H.; Bhatia, R.; Lal, R. Amyloid β protein forms ion channels: Implications for Alzheimer's disease pathophysiology. *FASEB J.* 2001, *15*, 2433–2444. [CrossRef]
- Lashuel, H.A.; Hartley, D.; Petre, B.M.; Walz, T.; Lansbury, P.T., Jr. Amyloid pores from pathogenic mutations. *Nat. Cell Biol.* 2002, 418, 291. [CrossRef] [PubMed]
- 42. Lashuel, H.A.; Hartley, D.M.; Petre, B.M.; Wall, J.S.; Simon, M.N.; Walz, T.; Lansbury, P.T. Mixtures of Wild-type and a Pathogenic (E22G) Form of Aβ40 in Vitro Accumulate Protofibrils, Including Amyloid Pores. *J. Mol. Biol.* **2003**, *332*, 795–808. [CrossRef]
- 43. Durell, S.; Guy, H.; Arispe, N.; Rojas, E.; Pollard, H. Theoretical models of the ion channel structure of amyloid beta-protein. *Biophys. J.* **1994**, 67, 2137–2145. [CrossRef]
- Jang, H.; Ma, B.; Lal, R.; Nussinov, R. Models of Toxic β-Sheet Channels of Protegrin-1 Suggest a Common Subunit Organization Motif Shared with Toxic Alzheimer β-Amyloid Ion Channels. *Biophys. J.* 2008, 95, 4631–4642. [CrossRef]
- 45. Pollard, H.B.; Rojas, E.; Arispe, N. A New Hypothesis for the Mechanism of Amyloid Toxicity, Based on the Calcium Channel Activity of Amyloid β Protein (AβP) in Phospholipid Bilayer Membranes. *Ann. N. Y. Acad. Sci.* **1993**, *695*, 165–168. [CrossRef]
- 46. Kayed, R.; Head, E.; Thompson, J.L.; McIntire, T.M.; Milton, S.C.; Cotman, C.W.; Glabe, C.G. Common Structure of Soluble Amyloid Oligomers Implies Common Mechanism of Pathogenesis. *Science* **2003**, *300*, 486–489. [CrossRef]
- 47. Demuro, A.; Mina, E.; Kayed, R.; Milton, S.C.; Parker, I.; Glabe, C.G. Calcium Dysregulation and Membrane Disruption as a Ubiquitous Neurotoxic Mechanism of Soluble Amyloid Oligomers. *J. Biol. Chem.* **2005**, *280*, 17294–17300. [CrossRef]
- 48. Deshpande, A.; Mina, E.; Glabe, C.; Busciglio, J. Different Conformations of Amyloid beta Induce Neurotoxicity by Distinct Mechanisms in Human Cortical Neurons. *J. Neurosci.* 2006, *26*, 6011–6018. [CrossRef]
- Lee, G.; Pollard, H.B.; Arispe, N. Annexin 5 and apolipoprotein E2 protect against Alzheimer's amyloid-β-peptide cytotoxicity by competitive inhibition at a common phosphatidylserine interaction site. *Peptides* 2002, 23, 1249–1263. [CrossRef]
- 50. Abramov, A.Y.; Canevari, L.; Duchen, M.R. Changes in Intracellular Calcium and Glutathione in Astrocytes as the Primary Mechanism of Amyloid Neurotoxicity. *J. Neurosci.* 2003, *23*, 5088–5095. [CrossRef]
- 51. Arispe, N.; Pollard, H.B.; Rojas, E. Zn2+ interaction with Alzheimer amyloid beta protein calcium channels. *Proc. Natl. Acad. Sci.* USA **1996**, *93*, 1710–1715. [CrossRef]
- 52. Bush, A.I. The metallobiology of Alzheimer's disease. Trends Neurosci. 2003, 26, 207–214. [CrossRef]
- 53. Rhee, S.K.; Quist, A.P.; Lal, R. Amyloid β Protein-(1–42) Forms Calcium-permeable, Zn2+-sensitive Channel. *J. Biol. Chem.* **1998**, 273, 13379–13382. [CrossRef]
- 54. Arispe, N.; Doh, M. Plasma membrane cholesterol controls the cytotoxicity of Alzheimer's disease AβP (1–40) and (1–42) peptides. *FASEB J.* **2002**, *16*, 1526–1536. [CrossRef]

- 55. Kawahara, M.; Kuroda, Y. Intracellular Calcium Changes in Neuronal Cells Induced by Alzheimer's β-Amyloid Protein Are Blocked by Estradiol and Cholesterol. *Cell. Mol. Neurobiol.* **2001**, *21*, 1–13. [CrossRef]
- 56. Barger, S.W.; Fiscus, R.R.; Ruth, P.; Hofmann, F.; Mattson, M.P. Role of Cyclic GMP in the Regulation of Neuronal Calcium and Survival by Secreted Forms of β-Amyloid Precursor. *J. Neurochem.* **2002**, *64*, 2087–2096. [CrossRef]
- 57. Guo, Q.; Robinson, N.; Mattson, M.P. Secreted β-Amyloid Precursor Protein Counteracts the Proapoptotic Action of Mutant Presenilin-1 by Activation of NF-κB and Stabilization of Calcium Homeostasis. *J. Biol. Chem.* **1998**, 273, 12341–12351. [CrossRef]
- Murray, J.N.; Igwe, O.J. Regulation of ?-amyloid precursor protein and inositol 1,4,5-trisphosphate receptor gene expression during differentiation of a human neuronal cell line. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 2003, 27, 351–363. [CrossRef]
- 59. Cao, X.; Südhof, T.C. A Transcriptively Active Complex of APP with Fe65 and Histone Acetyltransferase Tip60. *Science* **2001**, *293*, 115–120. [CrossRef]
- Leissring, M.A.; Murphy, M.P.; Mead, T.R.; Akbari, Y.; Sugarman, M.C.; Jannatipour, M.; Anliker, B.; Müller, U.; Saftig, P.; De Strooper, B.; et al. A physiologic signaling role for the -secretase-derived intracellular fragment of APP. *Proc. Natl. Acad. Sci. USA* 2002, 99, 4697–4702. [CrossRef]
- 61. Fedeli, C.; Filadi, R.; Rossi, A.; Mammucari, C.; Pizzo, P. PSEN2 (presenilin 2) mutants linked to familial Alzheimer disease impair autophagy by altering Ca2+ homeostasis. *Autophagy* **2019**, *15*, 2044–2062. [CrossRef] [PubMed]
- 62. Bullock, R. Efficacy and Safety of Memantine in Moderate-to-Severe Alzheimer Disease: The Evidence to Date. *Alzheimer Dis. Assoc. Disord.* 2006, 20, 23–29. [CrossRef] [PubMed]
- 63. De Felice, F.G.; Velasco, P.T.; Lambert, M.P.; Viola, K.; Fernandez, S.J.; Ferreira, S.T.; Klein, W.L. Aβ Oligomers Induce Neuronal Oxidative Stress through an N-Methyl-D-aspartate Receptor-dependent Mechanism That Is Blocked by the Alzheimer Drug Memantine. J. Biol. Chem. 2007, 282, 11590–11601. [CrossRef] [PubMed]
- 64. Liu, Z.; Qiu, X.; Mak, S.; Guo, B.; Hu, S.; Wang, J.; Luo, F.; Xu, D.; Sun, Y.; Zhang, G.; et al. Multifunctional memantine nitrate significantly protects against glutamate-induced excitotoxicity via inhibiting calcium influx and attenuating PI3K/Akt/GSK3beta pathway. *Chem. Interact.* 2020, 325, 109020. [CrossRef]
- 65. Kelly, B.L.; Ferreira, A. β-Amyloid-induced Dynamin 1 Degradation Is Mediated by N-Methyl-D-Aspartate Receptors in Hippocampal Neurons. *J. Biol. Chem.* **2006**, *281*, 28079–28089. [CrossRef]
- 66. Shankar, G.M.; Li, S.; Mehta, T.H.; Garcia-Munoz, A.; E Shepardson, N.; Smith, I.; Brett, F.M.; A Farrell, M.; Rowan, M.J.; A Lemere, C.; et al. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* 2008, 14, 837–842. [CrossRef]
- 67. Snyder, E.M.; Nong, Y.; Almeida, C.G.; Paul, S.; Moran, T.; Choi, E.Y.; Nairn, A.C.; Salter, M.W.; Lombroso, P.J.; Gouras, G.K.; et al. Regulation of NMDA receptor trafficking by amyloid-β. *Nat. Neurosci.* **2005**, *8*, 1051–1058. [CrossRef]
- Dewachter, I.; Filipkowski, R.; Priller, C.; Ris, L.; Neyton, J.; Croes, S.; Terwel, D.; Gysemans, M.; Devijver, H.; Borghgraef, P.; et al. Deregulation of NMDA-receptor function and down-stream signaling in APP[V717I] transgenic mice. *Neurobiol. Aging* 2009, 30, 241–256. [CrossRef]
- 69. Chappell, A.S.; Gonzales, C.; Williams, J.; Witte, M.M.; Mohs, R.C.; Sperling, R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. *Neurology* 2007, *68*, 1008–1012. [CrossRef]
- Trzepacz, P.T.; Cummings, J.; Konechnik, T.; Forrester, T.D.; Chang, C.; Dennehy, E.B.; Willis, B.A.; Shuler, C.; Tabas, L.B.; Lyketsos, C. Mibampator (LY451395) randomized clinical trial for agitation/aggression in Alzheimer's disease. *Int. Psychogeriatrics* 2013, 25, 707–719. [CrossRef]
- 71. Bloss, E.B.; Hunter, R.G.; Waters, E.M.; Muñoz, C.; Bernard, K.; McEwen, B.S. Behavioral and biological effects of chronic S18986, a positive AMPA receptor modulator, during aging. *Exp. Neurol.* **2008**, *210*, 109–117. [CrossRef]
- 72. Jhee, S.S.; Chappell, A.S.; Zarotsky, V.; Moran, S.V.; Rosenthal, M.; Kim, E.; Chalon, S.; Toublanc, N.; Brandt, J.; Coutant, D.E.; et al. Multiple-Dose Plasma Pharmacokinetic and Safety Study of LY450108 and LY451395 (AMPA Receptor Potentiators) and Their Concentration in Cerebrospinal Fluid in Healthy Human Subjects. J. Clin. Pharmacol. 2006, 46, 424–432. [CrossRef]
- Nimmrich, V.; Grimm, C.; Draguhn, A.; Barghorn, S.; Lehmann, A.; Schoemaker, H.; Hillen, H.; Gross, G.; Ebert, U.; Bruehl, C. Amyloid Oligomers (A 1-42 Globulomer) Suppress Spontaneous Synaptic Activity by Inhibition of P/Q-Type Calcium Currents. J. Neurosci. 2008, 28, 788–797. [CrossRef]
- 74. Rovira, C.; Arbez, N.; Mariani, J. Aβ(25–35) and Aβ(1–40) act on different calcium channels in CA1 hippocampal neurons. *Biochem. Biophys. Res. Commun.* **2002**, *296*, 1317–1321. [CrossRef]
- 75. Hermann, D.; Mezler, M.; Müller, M.K.; Wicke, K.; Gross, G.; Draguhn, A.; Bruehl, C.; Nimmrich, V. Synthetic Aβ oligomers (Aβ1–42 globulomer) modulate presynaptic calcium currents: Prevention of Aβ-induced synaptic deficits by calcium channel blockers. *Eur. J. Pharmacol.* **2013**, 702, 44–55. [CrossRef]
- 76. Mark, R.J.; Hensley, K.; A Butterfield, D.; Mattson, M.P. Amyloid beta-peptide impairs ion-motive ATPase activities: Evidence for a role in loss of neuronal Ca2+ homeostasis and cell death. *J. Neurosci.* **1995**, *15*, 6239–6249. [CrossRef]
- 77. Malenka, R.C. Synaptic plasticity in the hippocampus: LTP and LTD. Cell 1994, 78, 535–538. [CrossRef]
- 78. Tanis, J.E.; Ma, Z.; Krajacic, P.; He, L.; Foskett, J.K.; Lamitina, T. CLHM-1 is a Functionally Conserved and Conditionally Toxic Ca2+-Permeable Ion Channel in Caenorhabditis elegans. *J. Neurosci.* **2013**, *33*, 12275–12286. [CrossRef]
- 79. Wang, X.S.; Gruenstein, E. Rapid elevation of neuronal cytoplasmic calcium by apolipoprotein E peptide. *J. Cell Physiol.* **1997**, 173, 73–83. [CrossRef]

- 80. Müller, W.; Meske, V.; Berlin, K.; Scharnagl, H.; Marz, W.; Ohm, T. Apolipoprotein E Isoforms Increase Intracellular Ca2+Differentially Through a ω-Agatoxin IVa-Sensitive Ca2+-Channel. *Brain Pathol.* **1998**, *8*, 641–653. [CrossRef]
- 81. Wu, H.; Zhou, S.; Zhao, H.; Wang, Y.; Chen, X.; Sun, X. Effects of apolipoprotein E gene polymorphism on the intracellular Ca2+ concentration of astrocytes in the early stages post injury. *Exp. Ther. Med.* **2017**, *15*, 1417–1423. [CrossRef] [PubMed]
- Ferreiro, E.; Oliveira, C.R. Involvement of endoplasmic reticulum Ca2+ release through ryanodine and inositol 1,4,5-triphosphate receptors in the neurotoxic effects induced by the amyloid-? peptide. *J. Neurosci. Res.* 2004, 76, 872–880. [CrossRef] [PubMed]
- Supnet, C.; Grant, J.; Kong, H.; Westaway, D.; Mayne, M. Amyloid-β-(1-42) Increases Ryanodine Receptor-3 Expression and Function in Neurons of TgCRND8 Mice. J. Biol. Chem. 2006, 281, 38440–38447. [CrossRef] [PubMed]
- 84. Ishikawa, H.; Ozawa, H.; Saito, T.; Takahata, N.; Takemura, H. Calcium mobilization evoked by amyloid β-protein involves inositol 1,4,5-trisphosphate production in human platelets. *Life Sci.* **1998**, *62*, 705–713. [CrossRef]
- 85. Schapansky, J.; Olson, K.; Van Der Ploeg, R.; Glazner, G. NF-κB activated by ER calcium release inhibits Aβ-mediated expression of CHOP protein: Enhancement by AD-linked mutant presenilin 1. *Exp. Neurol.* **2007**, *208*, 169–176. [CrossRef] [PubMed]
- 86. Shtifman, A.; Ward, C.W.; Laver, D.R.; Bannister, M.L.; Lopez, J.R.; Kitazawa, M.; LaFerla, F.M.; Ikemoto, N.; Querfurth, H.W. Amyloid-β protein impairs Ca2+ release and contractility in skeletal muscle. *Neurobiol. Aging* **2010**, *31*, 2080–2090. [CrossRef]
- Müller, M.; Cárdenas, C.; Mei, L.; Cheung, K.-H.; Foskett, J.K. Constitutive cAMP response element binding protein (CREB) activation by Alzheimer's disease presenilin-driven inositol trisphosphate receptor (InsP3R) Ca2+signaling. *Proc. Natl. Acad. Sci. USA* 2011, 108, 13293–13298. [CrossRef] [PubMed]
- Marcantoni, A.; Cerullo, M.S.; Buxeda, P.; Tomagra, G.; Giustetto, M.; Chiantia, G.; Carabelli, V.; Carbone, E. Amyloid Beta42 oligomers up-regulate the excitatory synapses by potentiating presynaptic release while impairing postsynaptic NMDA receptors. *J. Physiol.* 2020, 598, 2183–2197. [CrossRef]
- 89. Stutzmann, G.E. Calcium Dysregulation, IP3 Signaling, and Alzheimer's Disease. Neuroscience 2005, 11, 110–115. [CrossRef]
- Cheung, K.-H.; Shineman, D.; Müller, M.; Cárdenas, C.; Mei, L.; Yang, J.; Tomita, T.; Iwatsubo, T.; Lee, V.M.-Y.; Foskett, J.K. Mechanism of Ca2+ Disruption in Alzheimer's Disease by Presenilin Regulation of InsP3 Receptor Channel Gating. *Neuron* 2008, 58, 871–883. [CrossRef]
- 91. Stutzmann, G.E.; Smith, I.; Caccamo, A.; Oddo, S.; LaFerla, F.M.; Parker, I. Enhanced Ryanodine Receptor Recruitment Contributes to Ca2+ Disruptions in Young, Adult, and Aged Alzheimer's Disease Mice. J. Neurosci. 2006, 26, 5180–5189. [CrossRef] [PubMed]
- 92. Rybalchenko, V.; Hwang, S.-Y.; Rybalchenko, N.; Koulen, P. The cytosolic N-terminus of presenilin-1 potentiates mouse ryanodine receptor single channel activity. *Int. J. Biochem. Cell Biol.* **2008**, *40*, 84–97. [CrossRef] [PubMed]
- 93. Hayrapetyan, V.; Rybalchenko, V.; Rybalchenko, N.; Koulen, P. The N-terminus of presenilin-2 increases single channel activity of brain ryanodine receptors through direct protein–protein interaction. *Cell Calcium* **2008**, *44*, 507–518. [CrossRef]
- Green, K.N.; DeMuro, A.; Akbari, Y.; Hitt, B.D.; Smith, I.F.; Parker, I.; LaFerla, F.M. SERCA pump activity is physiologically regulated by presenilin and regulates amyloid β production. J. Cell Biol. 2008, 181, 1107–1116. [CrossRef]
- Cedazo-Mínguez, A.; Popescu, B.O.; Ankarcrona, M.; Nishimura, T.; Cowburn, R.F. The Presenilin 1 ΔE9 Mutation Gives Enhanced Basal Phospholipase C Activity and a Resultant Increase in Intracellular Calcium Concentrations. J. Biol. Chem. 2002, 277, 36646–36655. [CrossRef]
- 96. Mattson, M.P.; LaFerla, F.M.; Chan, S.L.; A Leissring, M.; Shepel, P.; Geiger, J.D. Calcium signaling in the ER: Its role in neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.* 2000, 23, 222–229. [CrossRef]
- 97. Cheung, K.-H.; Mei, L.; Mak, D.-O.D.; Hayashi, I.; Iwatsubo, T.; Kang, D.E.; Foskett, J.K. Gain-of-Function Enhancement of IP3 Receptor Modal Gating by Familial Alzheimer's Disease-Linked Presenilin Mutants in Human Cells and Mouse Neurons. *Sci. Signal.* **2010**, *3*, ra22. [CrossRef]
- Ohkubo, N.; Mitsuda, N.; Tamatani, M.; Yamaguchi, A.; Lee, Y.-D.; Ogihara, T.; Vitek, M.P.; Tohyama, M. Apolipoprotein E4 Stimulates cAMP Response Element-binding Protein Transcriptional Activity through the Extracellular Signal-regulated Kinase Pathway. J. Biol. Chem. 2001, 276, 3046–3053. [CrossRef]
- 99. Namba, Y.; Tomonaga, M.; Kawasaki, H.; Otomo, E.; Ikeda, K. Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. *Brain Res.* **1991**, 541, 163–166. [CrossRef]
- 100. Stutzmann, G.E. The Pathogenesis of Alzheimers Disease—Is It a Lifelong "Calciumopathy"? *Neuroscientist* **2007**, *13*, 546–559. [CrossRef]
- 101. Resende, R.; Ferreiro, E.; Pereira, C.; Oliveira, C.R. ER stress is involved in Aβ-induced GSK-3β activation and tau phosphorylation. J. Neurosci. Res. 2008, 86, 2091–2099. [CrossRef] [PubMed]
- 102. Putney, J.W. Capacitative calcium entry in the nervous system. Cell Calcium 2003, 34, 339–344. [CrossRef]
- 103. Park, C.Y.; Hoover, P.J.; Mullins, F.M.; Bachhawat, P.; Covington, E.D.; Raunser, S.; Walz, T.; Garcia, K.C.; Dolmetsch, R.E.; Lewis, R.S. STIM1 Clusters and Activates CRAC Channels via Direct Binding of a Cytosolic Domain to Orai 1. *Cell* 2009, *136*, 876–890. [CrossRef] [PubMed]
- 104. Bojarski, L.; Herms, J.; Kuznicki, J. Calcium dysregulation in Alzheimer's disease. Neurochem. Int. 2008, 52, 621-633. [CrossRef]
- 105. Zeiger, W.; Vetrivel, K.S.; Buggia-Prévot, V.; Nguyen, P.D.; Wagner, S.L.; Villereal, M.L.; Thinakaran, G. Ca2+ Influx through Store-operated Ca2+ Channels Reduces Alzheimer Disease β-Amyloid Peptide Secretion. J. Biol. Chem. 2013, 288, 26955–26966. [CrossRef]

- Sun, S.; Zhang, H.; Liu, J.; Popugaeva, E.; Xu, N.-J.; Feske, S.; White, C.L.; Bezprozvanny, I. Reduced Synaptic STIM2 Expression and Impaired Store-Operated Calcium Entry Cause Destabilization of Mature Spines in Mutant Presenilin Mice. *Neuron* 2014, *82*, 79–93. [CrossRef]
- Ryazantseva, M.; Goncharova, A.; Skobeleva, K.; Erokhin, M.; Methner, A.; Georgiev, P.; Kaznacheyeva, E. Presenilin-1 Delta E9 Mutant Induces STIM1-Driven Store-Operated Calcium Channel Hyperactivation in Hippocampal Neurons. *Mol. Neurobiol.* 2018, 55, 4667–4680. [CrossRef]
- Li, H.-S.; Xu, X.-Z.S.; Montell, C. Activation of a TRPC3-Dependent Cation Current through the Neurotrophin BDNF. *Neuron* 1999, 24, 261–273. [CrossRef]
- Lessard, C.B.; Lussier, M.P.; Cayouette, S.; Bourque, G.; Boulay, G. The overexpression of presenilin2 and Alzheimer's-diseaselinked presenilin2 variants influences TRPC6-enhanced Ca2+ entry into HEK293 cells. *Cell. Signal.* 2005, 17, 437–445. [CrossRef]
- 110. Chen, Y.; Yan, Q.; Zhou, P.; Li, S.; Zhu, F. HERV-W env regulates calcium influx via activating TRPC3 channel together with depressing DISC1 in human neuroblastoma cells. *J. Neuro Virol.* **2019**, 25, 101–113. [CrossRef]
- 111. Keller, J.N.; Guo, Q.; Holtsberg, F.W.; Bruce-Keller, A.J.; Mattson, M.P. Increased Sensitivity to Mitochondrial Toxin-Induced Apoptosis in Neural Cells Expressing Mutant Presenilin-1 Is Linked to Perturbed Calcium Homeostasis and Enhanced Oxyradical Production. J. Neurosci. 1998, 18, 4439–4450. [CrossRef]
- 112. Kruman, I.; Guo, Q.; Mattson, M.P. Calcium and reactive oxygen species mediate staurosporine-induced mitochondrial dysfunction and apoptosis in PC12 cells. *J. Neurosci. Res.* **1998**, *51*, 293–308. [CrossRef]
- 113. Toglia, P.; Ullah, G. The gain-of-function enhancement of IP3-receptor channel gating by familial Alzheimer's disease-linked presenilin mutants increases the open probability of mitochondrial permeability transition pore. *Cell Calcium* **2016**, *60*, 13–24. [CrossRef]
- 114. Cuadrado-Tejedor, M.; Vilariño, M.; Cabodevilla, F.; Del Río, J.; Frechilla, D.; Pérez-Mediavilla, A. Enhanced Expression of the Voltage-Dependent Anion Channel 1 (VDAC1) in Alzheimer's Disease Transgenic Mice: An Insight into the Pathogenic Effects of Amyloid-β. J. Alzheimer's Dis. 2011, 23, 195–206. [CrossRef]
- 115. Williams, G.S.B.; Boyman, L.; Chikando, A.C.; Khairallah, R.J.; Lederer, W.J. Mitochondrial calcium uptake. *Proc. Natl. Acad. Sci.* USA 2013, 110, 10479–10486. [CrossRef]
- 116. Kirichok, Y.; Krapivinsky, G.; Clapham, D.E. The mitochondrial calcium uniporter is a highly selective ion channel. *Nat. Cell Biol.* **2004**, 427, 360–364. [CrossRef]
- 117. Gunter, T.; Buntinas, L.; Sparagna, G.; Eliseev, R.; Gunter, K. Mitochondrial calcium transport: Mechanisms and functions. *Cell Calcium* 2000, *28*, 285–296. [CrossRef]
- 118. Palty, R.; Ohana, E.; Hershfinkel, M.; Volokita, M.; Elgazar, V.; Beharier, O.; Silverman, W.F.; Argaman, M.; Sekler, I. Lithium-Calcium Exchange Is Mediated by a Distinct Potassium-independent Sodium-Calcium Exchanger. J. Biol. Chem. 2004, 279, 25234–25240. [CrossRef]
- 119. Lytton, J. Na+/Ca2+ exchangers: Three mammalian gene families control Ca2+ transport. Biochem. J. 2007, 406, 365–382. [CrossRef]
- Baumgartner, H.K.; Gerasimenko, J.V.; Thorne, C.; Ferdek, P.; Pozzan, T.; Tepikin, A.V.; Petersen, O.H.; Sutton, R.; Watson, A.J.; Gerasimenko, O.V. Calcium elevation in mitochondria is the main Ca2+ requirement for mitochondrial permeability transition pore (mPTP) opening. *J. Biol. Chem.* 2009, 284, 20796–20803. [CrossRef]
- 121. Du, H.; Yan, S.S. Mitochondrial permeability transition pore in Alzheimer's disease: Cyclophilin D and amyloid beta. *Biochim. Biophys. Acta BBA Mol. Basis Dis.* 2010, 1802, 198–204. [CrossRef] [PubMed]
- 122. Ohsumi, Y.; Anraku, Y. Calcium transport driven by a proton motive force in vacuolar membrane vesicles of Saccharomyces cerevisiae. *J. Biol. Chem.* **1983**, 258, 5614–5617. [CrossRef]
- Patel, S.; Docampo, R. Acidic calcium stores open for business: Expanding the potential for intracellular Ca2+ signaling. *Trends Cell Biol.* 2010, 20, 277–286. [CrossRef] [PubMed]
- 124. Garrity, A.G.; Wang, W.; Collier, C.M.; Levey, S.A.; Gao, Q.; Xu, H. The endoplasmic reticulum, not the pH gradient, drives calcium refilling of lysosomes. *eLife* **2016**, *5*, e15887. [CrossRef]
- 125. Tian, X.; Gala, U.; Zhang, Y.; Shang, W.; Jaiswal, S.N.; Di Ronza, A.; Jaiswal, M.; Yamamoto, S.; Sandoval, H.; DuRaine, L.; et al. A voltage-gated calcium channel regulates lysosomal fusion with endosomes and autophagosomes and is required for neuronal homeostasis. *PLoS Biol.* 2015, 13, e1002103. [CrossRef]
- McBrayer, M.; Nixon, R.A. Lysosome and calcium dysregulation in Alzheimer's disease: Partners in crime. *Biochem. Soc. Trans.* 2013, 41, 1495–1502. [CrossRef]
- 127. Coen, K.; Flannagan, R.S.; Baron, S.; Carraro-Lacroix, L.R.; Wang, D.; Vermeire, W.; Michiels, C.; Munck, S.; Baert, V.; Sugita, S.; et al. Lysosomal calcium homeostasis defects, not proton pump defects, cause endo-lysosomal dysfunction in PSEN-deficient cells. J. Cell Biol. 2012, 198, 23–35. [CrossRef]
- Fox, A.P.; Nowycky, M.C.; Tsien, R.W. Single-channel recordings of three types of calcium channels in chick sensory neurones. J. Physiol. 1987, 394, 173–200. [CrossRef]
- Sun, L.; Wei, H. Ryanodine Receptors: A Potential Treatment Target in Various Neurodegenerative Disease. *Cell. Mol. Neurobiol.* 2020, 1–12. [CrossRef]
- 130. Chan, S.L.; Mayne, M.; Holden, C.P.; Geiger, J.D.; Mattson, M.P. Presenilin-1 Mutations Increase Levels of Ryanodine Receptors and Calcium Release in PC12 Cells and Cortical Neurons. *J. Biol. Chem.* **2000**, 275, 18195–18200. [CrossRef]

- Yang, M.; Wang, Y.; Liang, G.; Xu, Z.; Chu, C.T.; Wei, H. Alzheimer's Disease Presenilin-1 Mutation Sensitizes Neurons to Impaired Autophagy Flux and Propofol Neurotoxicity: Role of Calcium Dysregulation. J. Alzheimer's Dis. 2019, 67, 137–147. [CrossRef]
- 132. Greotti, E.; Capitanio, P.; Wong, A.; Pozzan, T.; Pizzo, P.; Pendin, D. Familial Alzheimer's disease-linked presenilin mutants and intracellular Ca2+ handling: A single-organelle, FRET-based analysis. *Cell Calcium* **2019**, *79*, 44–56. [CrossRef]
- 133. Churchill, G.C.; Okada, Y.; Thomas, J.M.; Genazzani, A.A.; Patel, S.; Galione, A. NAADP Mobilizes Ca2+ from Reserve Granules, Lysosome-Related Organelles, in Sea Urchin Eggs. *Cell* **2002**, *111*, 703–708. [CrossRef]
- Querfurth, H.W.; Selkoe, D.J. Calcium Ionophore Increases Amyloid.beta. Peptide Production by Cultured Cells. *Biochemistry* 1994, 33, 4550–4561. [CrossRef]
- Querfurth, H.W.; Jiang, J.; Geiger, J.D.; Selkoe, D.J. Caffeine Stimulates Amyloid β-Peptide Release from β-Amyloid Precursor Protein-Transfected HEK293 Cells. J. Neurochem. 1997, 69, 1580–1591. [CrossRef]
- 136. Kim, J.; Lee, S.; Kim, J.; Ham, S.; Park, J.H.Y.; Han, S.; Jung, Y.-K.; Shim, I.; Han, J.-S.; Lee, K.W.; et al. Ca2+-permeable TRPV1 pain receptor knockout rescues memory deficits and reduces amyloid-β and tau in a mouse model of Alzheimer's disease. *Hum. Mol. Genet.* 2019, 29, 228–237. [CrossRef]
- 137. Itkin, A.; Dupres, V.; Dufrêne, Y.F.; Bechinger, B.; Ruysschaert, J.-M.; Raussens, V. Calcium Ions Promote Formation of Amyloid β-Peptide (1–40) Oligomers Causally Implicated in Neuronal Toxicity of Alzheimer's Disease. PLoS ONE 2011, 6, e18250. [CrossRef]
- 138. Green, K.N.; LaFerla, F.M. Linking Calcium to Aβ and Alzheimer's Disease. Neuron 2008, 59, 190–194. [CrossRef]
- 139. Ahmad, A.; Muzaffar, M.; Ingram, V.M. Ca2+, within the physiological concentrations, selectively accelerates Aβ42 fibril formation and not Aβ40 in vitro. *Biochim. Biophys. Acta BBA Proteins Proteom.* **2009**, 1794, 1537–1548. [CrossRef]
- 140. Guo, Q.; Fu, W.; Sopher, B.L.; Miller, M.W.; Ware, C.B.; Martin, G.M.; Mattson, M.P. Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. *Nat. Med.* **1999**, *5*, 101–106. [CrossRef]
- Leissring, M.A.; Akbari, Y.; Fanger, C.M.; Cahalan, M.D.; Mattson, M.P.; LaFerla, F.M. Capacitative Calcium Entry Deficits and Elevated Luminal Calcium Content in Mutant Presenilin-1 Knockin Mice. J. Cell Biol. 2000, 149, 793–798. [CrossRef] [PubMed]
- Inoue, Y.; Ueda, M.; Masuda, T.; Misumi, Y.; Yamashita, T.; Ando, Y. Memantine, a Noncompetitive N-Methyl-d-Aspartate Receptor Antagonist, Attenuates Cerebral Amyloid Angiopathy by Increasing Insulin-Degrading Enzyme Expression. *Mol. Neurobiol.* 2019, *56*, 8573–8588. [CrossRef] [PubMed]
- Wan, X.-Z.; Li, B.; Li, Y.-C.; Yang, X.-L.; Zhang, W.; Zhong, L.; Tang, S.-J. Activation of NMDA Receptors Upregulates A Disintegrin and Metalloproteinase 10 via a Wnt/MAPK Signaling Pathway. J. Neurosci. 2012, 32, 3910–3916. [CrossRef] [PubMed]
- 144. Hoey, S.E.; Buonocore, F.; Cox, C.J.; Hammond, V.J.; Perkinton, M.S.; Williams, R.J. AMPA Receptor Activation Promotes Non-Amyloidogenic Amyloid Precursor Protein Processing and Suppresses Neuronal Amyloid-β Production. *PLoS ONE* 2013, 8, e78155. [CrossRef] [PubMed]
- 145. Dreses-Werringloer, U.; Lambert, J.-C.; Vingtdeux, V.; Zhao, H.; Vais, H.; Siebert, A.; Jain, A.; Koppel, J.; Rovelet-Lecrux, A.; Hannequin, D.; et al. A Polymorphism in CALHM1 Influences Ca2+ Homeostasis, Aβ Levels, and Alzheimer's Disease Risk. *Cell* 2008, 133, 1149–1161. [CrossRef]
- 146. Castellano, J.M.; Kim, J.; Stewart, F.R.; Jiang, H.; DeMattos, R.B.; Patterson, B.W.; Fagan, A.M.; Morris, J.C.; Mawuenyega, K.G.; Cruchaga, C.; et al. Human apoE Isoforms Differentially Regulate Brain Amyloid- Peptide Clearance. *Sci. Transl. Med.* 2011, 3, 89ra57. [CrossRef]
- 147. Kelliher, M.; Fastbom, J.; Cowburn, R.; Bonkale, W.; Ohm, T.; Ravid, R.; Sorrentino, V.; O'Neill, C. Alterations in the ryanodine receptor calcium release channel correlate with Alzheimer's disease neurofibrillary and β-amyloid pathologies. *Neuroscience* 1999, 92, 499–513. [CrossRef]
- 148. Chakroborty, S.; Briggs, C.; Miller, M.B.; Goussakov, I.; Schneider, C.; Kim, J.; Wicks, J.; Richardson, J.C.; Conklin, V.; Cameransi, B.G.; et al. Stabilizing ER Ca2+ Channel Function as an Early Preventative Strategy for Alzheimer's Disease. *PLoS ONE* 2012, 7, e52056. [CrossRef]
- 149. Oulès, B.; Del Prete, D.; Greco, B.; Zhang, X.; Lauritzen, I.; Sevalle, J.; Moreno, S.; Paterlini-Bréchot, P.; Trebak, M.; Checler, F.; et al. Ryanodine Receptor Blockade Reduces Amyloid- Load and Memory Impairments in Tg2576 Mouse Model of Alzheimer Disease. J. Neurosci. 2012, 32, 11820–11834. [CrossRef]
- Lacampagne, A.; Liu, X.; Reiken, S.; Bussiere, R.; Meli, A.; Lauritzen, I.; Teich, A.F.; Zalk, R.; Saint, N.; Arancio, O.; et al. Post-translational remodeling of ryanodine receptor induces calcium leak leading to Alzheimer's disease-like pathologies and cognitive deficits. *Acta Neuropathol.* 2017, 134, 749–767. [CrossRef] [PubMed]
- 151. Liu, J.; Supnet, C.; Sun, S.; Zhang, H.; Good, L.; Popugaeva, E.; Bezprozvanny, I. The role of ryanodine receptor type 3 in a mouse model of Alzheimer disease. *Channels* 2014, *8*, 230–242. [CrossRef]
- 152. Buxbaum, J.D.; Ruefli, A.A.; Parker, C.A.; Cypess, A.M.; Greengard, P. Calcium regulates processing of the Alzheimer amyloid protein precursor in a protein kinase C-independent manner. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4489–4493. [CrossRef]
- Zhang, H.; Wu, L.; Pchitskaya, E.; Zakharova, O.D.; Saito, T.; Saido, T.C.; Bezprozvanny, I. Neuronal Store-Operated Calcium Entry and Mushroom Spine Loss in Amyloid Precursor Protein Knock-In Mouse Model of Alzheimer's Disease. J. Neurosci. 2015, 35, 13275–13286. [CrossRef]
- 154. Kyung, T.; Lee, S.; Kim, J.E.; Cho, T.; Park, H.; Jeong, Y.-M.; Kim, D.; Shin, A.; Kim, S.; Baek, J.; et al. Optogenetic control of endogenous Ca2+ channels in vivo. *Nat. Biotechnol.* **2015**, *33*, 1092–1096. [CrossRef]

- 155. Yoo, A.S.; Cheng, I.; Chung, S.; Grenfell, T.Z.; Lee, H.; Pack-Chung, E.; Handler, M.; Shen, J.; Xia, W.; Tesco, G.; et al. Presenilin-Mediated Modulation of Capacitative Calcium Entry. *Neuron* **2000**, *27*, 561–572. [CrossRef]
- 156. Calvo-Rodriguez, M.; Hernando-Perez, E.; Nuñez, L.; Villalobos, C. Amyloid β Oligomers Increase ER-Mitochondria Ca2+ Cross Talk in Young Hippocampal Neurons and Exacerbate Aging-Induced Intracellular Ca2+ Remodeling. *Front. Cell. Neurosci.* 2019, 13. [CrossRef]
- 157. Mattson, M.P.; Cheng, B.; Culwell, A.R.; Esch, F.S.; Lieberburg, I.; Rydel, R.E. Evidence for excitoprotective and intraneuronal calcium-regulating roles for secreted forms of the β-amyloid precursor protein. *Neuron* **1993**, *10*, 243–254. [CrossRef]
- 158. Scremin, E.; Agostini, M.; Leparulo, A.; Pozzan, T.; Greotti, E.; Fasolato, C. ORAI2 Down-Regulation Potentiates SOCE and Decreases Aβ42 Accumulation in Human Neuroglioma Cells. *Int. J. Mol. Sci.* **2020**, *21*, 5288. [CrossRef]
- 159. Manczak, M.; Sheiko, T.; Craigen, W.J.; Reddy, P.H. Reduced VDAC1 Protects Against Alzheimer's Disease, Mitochondria, and Synaptic Deficiencies. J. Alzheimer's Dis. 2013, 37, 679–690. [CrossRef]
- 160. Šoškić, V.; Klemm, M.; Proikas-Cezanne, T.; Schwall, G.P.; Poznanović, S.; Stegmann, W.; Groebe, K.; Zengerling, H.; Schoepf, R.; Burnet, M.; et al. A Connection between the Mitochondrial Permeability Transition Pore, Autophagy, and Cerebral Amyloidogenesis. J. Proteome Res. 2008, 7, 2262–2269. [CrossRef]
- Hartigan, J.A.; Johnson, G.V. Transient Increases in Intracellular Calcium Result in Prolonged Site-selective Increases in Tau Phosphorylation through a Glycogen Synthase Kinase 3β-dependent Pathway. J. Biol. Chem. 1999, 274, 21395–21401. [CrossRef]
- 162. Yamamoto, H.; Hiragami, Y.; Murayama, M.; Ishizuka, K.; Kawahara, M.; Takashima, A. Phosphorylation of tau at serine 416 by Ca2+/calmodulin-dependent protein kinase II in neuronal soma in brain. *J. Neurochem.* **2005**, *94*, 1438–1447. [CrossRef]
- 163. Avila, J.; Pérez, M.; Lim, F.; Gómez-Ramos, A.; Hernández, F.; Lucas, J.J. Tau in neurodegenerative diseases: Tau phosphorylation and assembly. *Neurotox. Res.* 2004, *6*, 477–482. [CrossRef]
- 164. La Ferla, F.M.; Green, K.N.; Oddo, S. Intracellular amyloid-β in Alzheimer's disease. Nat. Rev. Neurosci. 2007, 8, 499–509. [CrossRef]
- 165. Whitcomb, D.J.; Hogg, E.L.; Regan, P.; Piers, T.; Narayan, P.; Whitehead, G.; Winters, B.L.; Kim, D.-H.; Kim, E.; George-Hyslop, P.S.; et al. Intracellular oligomeric amyloid-beta rapidly regulates GluA1 subunit of AMPA receptor in the hippocampus. *Sci. Rep.* 2015, *5*, 10934. [CrossRef]
- 166. Pierrot, N.; Ghisdal, P.; Caumont, A.-S.; Octave, J.-N. Intraneuronal amyloid-β1-42 production triggered by sustained increase of cytosolic calcium concentration induces neuronal death. J. Neurochem. 2004, 88, 1140–1150. [CrossRef]
- 167. Bruno, A.M.; Huang, J.Y.; Bennett, D.A.; Marr, R.A.; Hastings, M.L.; Stutzmann, G.E. Altered ryanodine receptor expression in mild cognitive impairment and Alzheimer's disease. *Neurobiol. Aging* **2012**, *33*, 1001.e1–1001.e6. [CrossRef]
- 168. Antonell, A.; Lladó, A.; Altirriba, J.; Botta-Orfila, T.; Balasa, M.; Fernández, M.; Ferrer, I.; Sánchez-Valle, R.; Molinuevo, J.L. A preliminary study of the whole-genome expression profile of sporadic and monogenic early-onset Alzheimer's disease. *Neurobiol. Aging* 2013, 34, 1772–1778. [CrossRef]
- 169. Chami, M.; Checler, F. Ryanodine receptors. Channels 2014, 8, 168. [CrossRef] [PubMed]
- 170. Manczak, M.; Reddy, P.H. Abnormal interaction of VDAC1 with amyloid beta and phosphorylated tau causes mitochondrial dysfunction in Alzheimer's disease. *Hum. Mol. Genet.* **2012**, *21*, 5131–5146. [CrossRef] [PubMed]
- 171. Ren, R.; Zhang, Y.; Li, B.; Wu, Y.; Li, B. Effect of β-amyloid (25-35) on mitochondrial function and expression of mitochondrial permeability transition pore proteins in rat hippocampal neurons. *J. Cell. Biochem.* **2011**, *112*, 1450–1457. [CrossRef] [PubMed]
- 172. Moreira, P.I.; Santos, M.S.; Moreno, A.; Oliveira, C. Amyloid β-Peptide Promotes Permeability Transition Pore in Brain Mitochondria. *Biosci. Rep.* **2001**, *21*, 789–800. [CrossRef] [PubMed]
- 173. Toescu, E.C.; Verkhratsky, A. The importance of being subtle: Small changes in calcium homeostasis control cognitive decline in normal aging. *Aging Cell* **2007**, *6*, 267–273. [CrossRef] [PubMed]
- 174. Reijo, T.; Mikko, B.; Antti, S.; Timo, S.; Mikko, B. Serum Calcium And Prediction Of Cognitive Decline In Old Age. J. Am. Geriatr. Soc. 2008, 56, 1573–1574. [CrossRef]
- 175. Heck, A.; Fastenrath, M.; Coynel, D.; Auschra, B.; Bickel, H.; Freytag, V.; Gschwind, L.; Hartmann, F.; Jessen, F.; Kaduszkiewicz, H.; et al. Genetic Analysis of Association Between Calcium Signaling and Hippocampal Activation, Memory Performance in the Young and Old, and Risk for Sporadic Alzheimer Disease. *JAMA Psychiatry* 2015, 72, 1029–1036. [CrossRef]
- 176. Walsh, D.M.; Townsend, M.; Podlisny, M.B.; Shankar, G.M.; Fadeeva, J.V.; El Agnaf, O.; Hartley, D.M.; Selkoe, D.J. Certain Inhibitors of Synthetic Amyloid -Peptide (A) Fibrillogenesis Block Oligomerization of Natural A and Thereby Rescue Long-Term Potentiation. J. Neurosci. 2005, 25, 2455–2462. [CrossRef]
- 177. Bliss, T.V.P.; Collingridge, G.L. A synaptic model of memory: Long-term potentiation in the hippocampus. *Nat. Cell Biol.* **1993**, 361, 31–39. [CrossRef]
- 178. Hu, W.-Y.; He, Z.-Y.; Yang, L.-J.; Zhang, M.; Xing, D.; Xiao, Z.-C. The Ca2+channel inhibitor 2-APB reverses β-amyloid-induced LTP deficit in hippocampus by blocking BAX and caspase-3 hyperactivation. *Br. J. Pharmacol.* **2015**, *172*, 2273–2285. [CrossRef]
- 179. Trinchese, F.; Fa', M.; Liu, S.; Zhang, H.; Hidalgo, A.; Schmidt, S.D.; Yamaguchi, H.; Yoshii, N.; Mathews, P.M.; Nixon, R.A.; et al. Inhibition of calpains improves memory and synaptic transmission in a mouse model of Alzheimer disease. *J. Clin. Investig.* 2008, 118, 2796–2807. [CrossRef]
- 180. Dineley, K.T.; Hogan, D.; Zhang, W.-R.; Taglialatela, G. Acute inhibition of calcineurin restores associative learning and memory in Tg2576 APP transgenic mice. *Neurobiol. Learn. Mem.* **2007**, *88*, 217–224. [CrossRef]
- 181. Berridge, M.J. Calcium hypothesis of Alzheimer's disease. Pflügers Arch. Eur. J. Physiol. 2010, 459, 441–449. [CrossRef]

- 182. Dudek, S.M.; Bear, M.F. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 4363–4367. [CrossRef]
- 183. Morris, R.G.M.; Anderson, E.; Lynch, G.S.; Baudry, M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nat. Cell Biol.* **1986**, *319*, 774–776. [CrossRef]
- Hsiung, G.-Y.R.; Feldman, H.H. Pharmacological treatment in moderate-to-severe Alzheimer's disease. *Expert Opin. Pharmacother.* 2008, 9, 2575–2582. [CrossRef]
- 185. Minkeviciene, R.; Banerjee, P.; Tanila, H. Memantine Improves Spatial Learning in a Transgenic Mouse Model of Alzheimer's Disease. J. Pharmacol. Exp. Ther. 2004, 311, 677–682. [CrossRef]
- 186. Palop, J.J. Epilepsy and Cognitive Impairments in Alzheimer Disease. Arch. Neurol. 2009, 66, 435–440. [CrossRef]
- 187. Wang, Y.; Mattson, M.P. L-type Ca2+ currents at CA1 synapses, but not CA3 or dentate granule neuron synapses, are increased in 3xTgAD mice in an age-dependent manner. *Neurobiol. Aging* **2014**, *35*, 88–95. [CrossRef]
- 188. Tsukuda, K.; Mogi, M.; Li, J.-M.; Iwanami, J.; Min, L.-J.; Sakata, A.; Fujita, T.; Iwai, M.; Horiuchi, M. Diabetes-Associated Cognitive Impairment Is Improved by a Calcium Channel Blocker, Nifedipine. *Hypertension* **2008**, *51*, 528–533. [CrossRef]
- 189. Doody, R.S.; I Gavrilova, S.; Sano, M.; Thomas, R.G.; Aisen, P.S.; O Bachurin, S.; Seely, L.; Hung, D. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: A randomised, double-blind, placebo-controlled study. *Lancet* 2008, 372, 207–215. [CrossRef]
- Moriguchi, S.; Shioda, N.; Yamamoto, Y.; Tagashira, H.; Fukunaga, K. The T-type voltage-gated calcium channel as a molecular target of the novel cognitive enhancer ST101: Enhancement of long-term potentiation and CaMKII autophosphorylation in rat cortical slices. J. Neurochem. 2012, 121, 44–53. [CrossRef]
- Deshpande, L.S.; Sun, D.A.; Sombati, S.; Baranova, A.; Wilson, M.S.; Attkisson, E.; Hamm, R.J.; DeLorenzo, R.J. Alterations in neuronal calcium levels are associated with cognitive deficits after traumatic brain injury. *Neurosci. Lett.* 2008, 441, 115–119. [CrossRef] [PubMed]
- 192. Mallmann, R.T.; Elgueta, C.; Sleman, F.; Castonguay, J.; Wilmes, T.; Maagdenberg, A.V.D.; Klugbauer, N. Ablation of CaV2.1 Voltage-Gated Ca2+ Channels in Mouse Forebrain Generates Multiple Cognitive Impairments. *PLoS ONE* **2013**, *8*, e78598. [CrossRef]
- 193. Micale, V.; Cristino, L.; Tamburella, A.; Petrosino, S.; Leggio, G.M.; Di Marzo, V.; Drago, F. Enhanced cognitive performance of dopamine D3 receptor "knock-out" mice in the step-through passive-avoidance test: Assessing the role of the endocannabi-noid/endovanilloid systems. *Pharmacol. Res.* **2010**, *61*, 531–536. [CrossRef] [PubMed]
- 194. Van Vliet, P.; Oleksik, A.M.; Mooijaart, S.P.; De Craen, A.; Westendorp, R.G. APOE genotype modulates the effect of serum calcium levels on cognitive function in old age. *Neurology* **2009**, *72*, 821–828. [CrossRef]
- 195. Cui, P.-J.; Zheng, L.; Cao, L.; Wang, Y.; Deng, Y.-L.; Wang, G.; Xu, W.; Tang, H.-D.; Ma, J.-F.; Zhang, T.; et al. CALHM1 P86L Polymorphism is a Risk Factor for Alzheimer's Disease in the Chinese Population. J. Alzheimer's Dis. 2010, 19, 31–35. [CrossRef]
- 196. Shilling, D.; Müller, M.; Takano, H.; Mak, D.-O.D.; Abel, T.; Coulter, D.A.; Foskett, J.K. Suppression of InsP3 Receptor-Mediated Ca2+ Signaling Alleviates Mutant Presenilin-Linked Familial Alzheimer's Disease Pathogenesis. J. Neurosci. 2014, 34, 6910–6923. [CrossRef]
- 197. Jaworska, A.; Dzbek, J.; Styczynska, M.; Kuznicki, J. Analysis of calcium homeostasis in fresh lymphocytes from patients with sporadic Alzheimer's disease or mild cognitive impairment. *Biochim. Biophys. Acta BBA Bioenerg.* 2013, 1833, 1692–1699. [CrossRef]
- 198. Lü, N.; Lü, B.-C.; Cheng, L.-Z.; Zhang, Y.-Q.; Li, Y.-Q.; Zhao, Z.-Q. Involvement of ryanodine receptors in tetanic sciatic stimulationinduced long-term potentiation of spinal dorsal horn and persistent pain in rats. *J. Neurosci. Res.* 2012, *90*, 1096–1104. [CrossRef]
- 199. Matsuo, N.; Tanda, K.; Nakanishi, K.; Yamasaki, N.; Toyama, K.; Takao, K.; Takeshima, H.; Miyakawa, T. Comprehensive behavioral phenotyping of ryanodine receptor type3 (RyR3) knockout mice: Decreased social contact duration in two social interaction tests. *Front. Behav. Neurosci.* **2009**, *3*, 3. [CrossRef]
- Alkon, D.L.; Nelson, T.J.; Zhao, W.; Cavallaro, S. Time domains of neuronal Ca2+ signaling and associative memory: Steps through a calexcitin, ryanodine receptor, K+ channel cascade. *Trends Neurosci.* 1998, 21, 529–537. [CrossRef]
- 201. Tong, B.C.-K.; Lee, C.S.-K.; Cheng, W.-H.; Lai, K.-O.; Foskett, J.K.; Cheung, K.-H. Familial Alzheimer's disease–associated presenilin 1 mutants promote γ-secretase cleavage of STIM1 to impair store-operated Ca2+entry. *Sci. Signal.* 2016, 9, ra89. [CrossRef]
- 202. Emptage, N.J.; Reid, C.; Fine, A. Calcium Stores in Hippocampal Synaptic Boutons Mediate Short-Term Plasticity, Store-Operated Ca2+ Entry, and Spontaneous Transmitter Release. *Neuron* 2001, *29*, 197–208. [CrossRef]
- Shoshan-Barmatz, V.; Nahon-Crystal, E.; Shteinfer-Kuzmine, A.; Gupta, R. VDAC1, mitochondrial dysfunction, and Alzheimer's disease. *Pharmacol. Res.* 2018, 131, 87–101. [CrossRef]
- Kon, N.; Murakoshi, M.; Isobe, A.; Kagechika, K.; Miyoshi, N.; Nagayama, T. DS16570511 is a small-molecule inhibitor of the mitochondrial calcium uniporter. *Cell Death Discov.* 2017, *3*, 17045. [CrossRef]
- Kon, N.; Satoh, A.; Miyoshi, N. A small-molecule DS44170716 inhibits Ca2+-induced mitochondrial permeability transition. *Sci. Rep.* 2017, 7, 3864. [CrossRef]
- Sakurai, Y.; Kolokoltsov, A.A.; Chen, C.-C.; Tidwell, M.W.; Bauta, W.E.; Klugbauer, N.; Grimm, C.; Wahl-Schott, C.; Biel, M.; Davey, R.A. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment. *Science* 2015, 347, 995–998. [CrossRef]
- 207. Pickford, F.; Masliah, E.; Britschgi, M.; Lucin, K.; Narasimhan, R.; Jaeger, P.A.; Small, S.; Spencer, B.; Rockenstein, E.; Levine, B.; et al. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice. *J. Clin. Investig.* 2008, 118, 2190–2199. [CrossRef]

- 208. Birks, J.; López-Arrieta, J.; López-Arrieta, J.M. Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst. Rev.* 2002, 2002, CD000147. [CrossRef]
- Hopp, S.C.; D'Angelo, H.M.; E Royer, S.; Kaercher, R.M.; Crockett, A.M.; Adzovic, L.; Wenk, G.L. Calcium dysregulation via L-type voltage-dependent calcium channels and ryanodine receptors underlies memory deficits and synaptic dysfunction during chronic neuroinflammation. J. Neuroinflamm. 2015, 12, 56. [CrossRef]
- 210. Luengo, E.; Buendia, I.; Fernández-Mendívil, C.; Trigo-Alonso, P.; Negredo, P.; Michalska, P.; Hernández-García, B.; Sánchez-Ramos, C.; Bernal, J.A.; Ikezu, T.; et al. Pharmacological doses of melatonin impede cognitive decline in tau-related Alzheimer models, once tauopathy is initiated, by restoring the autophagic flux. *J. Pineal Res.* 2019, 67, e12578. [CrossRef]
- Mattson, M.P.; Partin, J.; Begley, J. Amyloid β-peptide induces apoptosis-related events in synapses and dendrites. *Brain Res.* 1998, 807, 167–176. [CrossRef]
- 212. Jin, Y. Synaptogenesis: Insights from worm and fly. Curr. Opin. Neurobiol. 2002, 12, 71–79. [CrossRef]
- 213. Mattson, M.P.; Chan, S.L. Dysregulation of Cellular Calcium Homeostasis in Alzheimer's Disease: Bad Genes and Bad Habits. *J. Mol. Neurosci.* **2001**, *17*, 205–224. [CrossRef]
- 214. Chan, S.L.; Furukawa, K.; Mattson, M.P. Presenilins and APP in Neuritic and Synaptic Plasticity: Implications for the Pathogenesis of Alzheimer's Disease. *NeuroMol. Med.* 2002, 2, 167–196. [CrossRef]
- 215. Nalbantoglu, J.; Tirado-Santiago, G.; Lahsaïni, A.; Poirier, J.; Goncalves, O.; Verge, G.; Momoli, F.; Welner, S.A.; Massicotte, G.; Julien, J.-P.; et al. Impaired learning and LTP in mice expressing the carboxy terminus of the Alzheimer amyloid precursor protein. *Nat. Cell Biol.* **1997**, 387, 500–505. [CrossRef] [PubMed]
- Nelson, O.; Supnet, C.; Liu, H.; Bezprozvanny, I. Familial Alzheimer's Disease Mutations in Presenilins: Effects on Endoplasmic Reticulum Calcium Homeostasis and Correlation with Clinical Phenotypes. J. Alzheimer's Dis. 2010, 21, 781–793. [CrossRef] [PubMed]
- 217. Tonkikh, A.; Janus, C.; El-Beheiry, H.; Pennefather, P.S.; Samoilova, M.; McDonald, P.; Ouanounou, A.; Carlen, P.L. Calcium chelation improves spatial learning and synaptic plasticity in aged rats. *Exp. Neurol.* **2006**, *197*, 291–300. [CrossRef]
- 218. Winder, D.G.; Mansuy, I.M.; Osman, M.; Moallem, T.M.; Kandel, E.R. Genetic and Pharmacological Evidence for a Novel, Intermediate Phase of Long-Term Potentiation Suppressed by Calcineurin. *Cell* **1998**, *92*, 25–37. [CrossRef]
- Foster, T.C.; Sharrow, K.M.; Masse, J.R.; Norris, C.M.; Kumar, A. Calcineurin links Ca2+ dysregulation with brain aging. *J. Neurosci.* 2001, 21, 4066–4073. [CrossRef]
- Yamin, G. NMDA receptor-dependent signaling pathways that underlie amyloid β-protein disruption of LTP in the hippocampus. J. Neurosci. Res. 2009, 87, 1729–1736. [CrossRef]
- 221. Raymond, C.R.; Redman, S.J. Spatial segregation of neuronal calcium signals encodes different forms of LTP in rat hippocampus. *J. Physiol.* **2006**, 570, 97–111. [CrossRef]
- 222. Sanderson, J.L.; Gorski, J.A.; Dell'Acqua, M.L. NMDA Receptor-Dependent LTD Requires Transient Synaptic Incorporation of Ca 2+ -Permeable AMPARs Mediated by AKAP150-Anchored PKA and Calcineurin. *Neuron* **2016**, *89*, 1000–1015. [CrossRef]
- 223. Jia, Z.; Agopyan, N.; Miu, P.; Xiong, Z.; Henderson, J.; Gerlai, R.; A Taverna, F.; Velumian, A.; MacDonald, J.; Carlen, P.; et al. Enhanced LTP in Mice Deficient in the AMPA Receptor GluR2. *Neuron* 1996, 17, 945–956. [CrossRef]
- 224. Plant, K.; A Pelkey, K.; A Bortolotto, Z.; Morita, D.; Terashima, A.; McBain, C.J.; Collingridge, G.L.; Isaac, J.T.R. Transient incorporation of native GluR2-lacking AMPA receptors during hippocampal long-term potentiation. *Nat. Neurosci.* 2006, *9*, 602–604. [CrossRef]
- Fortin, D.A.; Davare, M.A.; Srivastava, T.; Brady, J.D.; Nygaard, S.; Derkach, V.A.; Soderling, T.R. Long-Term Potentiation-Dependent Spine Enlargement Requires Synaptic Ca2+-Permeable AMPA Receptors Recruited by CaM-Kinase I. J. Neurosci. 2010, 30, 11565–11575. [CrossRef]
- 226. Chowdhury, D.; Hell, J.W. Ca2+/Calmodulin Binding to PSD-95 Downregulates Its Palmitoylation and AMPARs in Long-Term Depression. *Front. Synaptic Neurosci.* 2019, 11. [CrossRef]
- Huber, K.M.; Mauk, M.D.; Kelly, P.T. LTP induced by activation of voltage-dependent Ca2+ channels requires protein kinase activity. *NeuroReport* 1995, 6, 1281–1284. [CrossRef]
- 228. White, J.A.; McKinney, B.C.; John, M.C.; Powers, P.A.; Kamp, T.J.; Murphy, G.G. Conditional forebrain deletion of the L-type calcium channel CaV1.2 disrupts remote spatial memories in mice. *Learn. Mem.* **2008**, *15*, 1–5. [CrossRef]
- Li, H.-B.; Mao, R.-R.; Zhang, J.-C.; Yang, Y.; Cao, J.; Xu, L. Antistress Effect of TRPV1 Channel on Synaptic Plasticity and Spatial Memory. *Biol. Psychiatry* 2008, 64, 286–292. [CrossRef]
- Gerdeman, G.L.; Ronesi, J.; Lovinger, D.M. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nat. Neurosci.* 2002, 5, 446–451. [CrossRef]
- Chávez, A.E.; Chiu, C.Q.; Castillo, P.E. TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. *Nat. Neurosci.* 2010, 13, 1511–1518. [CrossRef]
- 232. James, E.O.; Clevenger, A.C.; Dietz, R.M.; Patsos, O.P. A Novel Peptide Inhibitor Of Trpm2 Channels Reduces Memory Deficits And Improves Ltp Following Traumatic Brain Injury In Mice. *J. Neurotrauma* 2018. Available online: https://www.google. com/search?tbm=bks&q=104.+232.+Orfila%2C+James%2C+E.%2C+Clevenger%2C+Amy%2C+C.%2C+Dietz%2C+Robert% 2C+M.%2C+Patsos+%282018%29+A+NOVEL+PEPTIDE+INHIBITOR+OF+TRPM2+CHANNELS+REDUCES+MEMORY+ DEFICITS+AND+IMPROVES+LTP+FOLLOWING+TRAUMATIC+BRAIN+INJURY+IN+MICE.+Journal+of+Neurotrauma (accessed on 13 March 2021).

- 233. Menigoz, A.; Ahmed, T.; Sabanov, V.; Philippaert, K.; Pinto, S.; Kerselaers, S.; Segal, A.; Freichel, M.; Voets, T.; Nilius, B.; et al. TRPM4-dependent post-synaptic depolarization is essential for the induction of NMDA receptor-dependent LTP in CA1 hippocampal neurons. *Pflügers Arch. Eur. J. Physiol.* 2016, 468, 593–607. [CrossRef]
- 234. Miyata, M.; Finch, E.A.; Khiroug, L.; Hashimoto, K.; Hayasaka, S.; Oda, S.-I.; Inouye, M.; Takagishi, Y.; Augustine, G.J.; Kano, M. Local Calcium Release in Dendritic Spines Required for Long-Term Synaptic Depression. *Neuron* **2000**, *28*, 233–244. [CrossRef]
- 235. A Cummings, J.; Mulkey, R.M.; A Nicoll, R.; Malenka, R.C. Ca2+ Signaling Requirements for Long-Term Depression in the Hippocampus. *Neuron* **1996**, *16*, 825–833. [CrossRef]
- 236. Kato, H.K.; Kassai, H.; Watabe, A.M.; Aiba, A.; Manabe, T. Functional coupling of the metabotropic glutamate receptor, InsP3receptor and L-type Ca2+channel in mouse CA1 pyramidal cells. *J. Physiol.* **2012**, *590*, 3019–3034. [CrossRef] [PubMed]
- 237. Shimuta, M.; Yoshikawa, M.; Fukaya, M.; Watanabe, M.; Takeshima, H.; Manabe, T. Postsynaptic Modulation of AMPA Receptor-Mediated Synaptic Responses and LTP by the Type 3 Ryanodine Receptor. *Mol. Cell. Neurosci.* 2001, 17, 921–930. [CrossRef] [PubMed]
- Chakroborty, S.; Kim, J.; Schneider, C.; Jacobson, C.; Molgó, J.; Stutzmann, G.E. Early Presynaptic and Postsynaptic Calcium Signaling Abnormalities Mask Underlying Synaptic Depression in Presymptomatic Alzheimer's Disease Mice. J. Neurosci. 2012, 32, 8341–8353. [CrossRef]
- 239. Zhang, C.; Wu, B.; Beglopoulos, V.; Wines-Samuelson, M.; Zhang, D.; Dragatsis, I.; Südhof, T.C.; Shen, J. Presenilins are essential for regulating neurotransmitter release. *Nat. Cell Biol.* **2009**, *460*, 632–636. [CrossRef]
- Majewski, Ł.; Maciag, F.; Boguszewski, P.M.; Wasilewska, I.; Wiera, G.; Wójtowicz, T.; Mozrzymas, J.; Kuznicki, J. Overexpression of STIM1 in neurons in mouse brain improves contextual learning and impairs long-term depression. *Biochim. Biophys. Acta BBA Bioenerg.* 2017, 1864, 1071–1087. [CrossRef] [PubMed]
- Weeber, E.J.; Levy, M.; Sampson, M.J.; Anflous, K.; Armstrong, D.L.; Brown, S.E.; Sweatt, J.D.; Craigen, W.J. The Role of Mitochondrial Porins and the Permeability Transition Pore in Learning and Synaptic Plasticity. *J. Biol. Chem.* 2002, 277, 18891–18897. [CrossRef]
- 242. Mulkey, R.M.; Malenka, R.C. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* **1992**, *9*, 967–975. [CrossRef]
- 243. Obenaus, A.; Mody, I.; Baimbridge, K.G. Dantrolene-Na (Dantrium) blocks induction of long-term potentiation in hippocampal slices. *Neurosci. Lett.* **1989**, *98*, 172–178. [CrossRef]