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TOPICAL REVIEW

Role of Ion Channels in Alzheimer's Disease Pathophysiology

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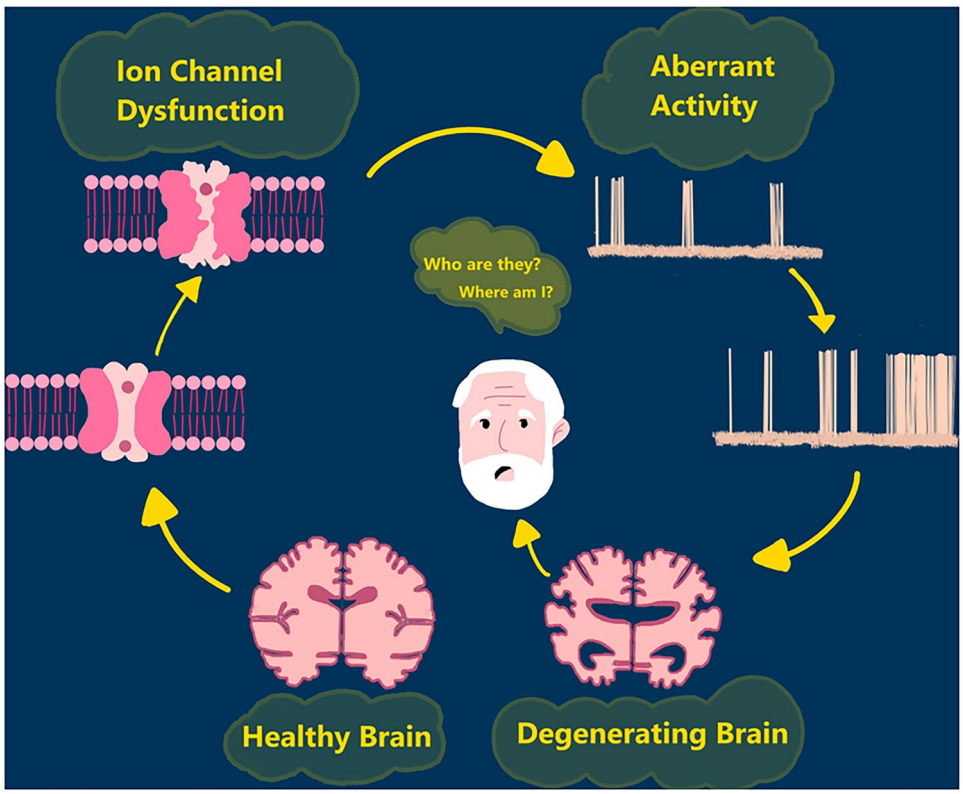
Abstract

Ion channels play an integral role in the normal functioning of the brain. They regulate neuronal electrical properties like synaptic activity, generation of action potentials, maintenance of resting membrane potential and neuronal plasticity, and modulate the physiology of non-neuronal cells like astrocytes and microglia. Dysregulation of ionic homeostasis and channelopathies are associated with various neurological disorders, including Alzheimer's disease (AD). Several families of ion channels are associated with AD pathophysiology and progression. In this review, we outline the current research centered around ion channel dysregulation during AD and discuss briefly the possibility of using ion channels as therapeutic targets.

Graphical Abstract



Keywords Ion channels · Alzheimer's disease · Hyperexcitability

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, multifactorial and identified by the accumulation of Aβ plaques and neurofibrillary tangles in the cerebral cortex and hippocampus (Selkoe 1991). Improper cleavage of APP (Amyloid Precursor Protein) by a complex family of enzymes consisting of γ-secretase and ß-secretase leads to the formation of neurotoxic Aß oligomers (Masters et al. 2015). On the other hand, hyperphosphorylated tau protein has been shown to accumulate intracellularly in neurons as tangles, another hallmark of AD. A third factor that has been linked to AD is the APOE gene, such that APOE4 carriers have been shown to increase AD risk and decrease Aß clearance. All these three main elements are linked with the neurotoxicity of AD. Although late stages of AD manifest excessive neuronal loss and decreased function, leading to cognitive decline and memory impairment, the early stages exhibit neuronal hyperexcitability, leading to metabolic stress and neuronal death, translating to cognitive decline at later stages of the disease (Holtzman 2001; Masters et al. 2015). Beyond the neuronal perspective of AD, astrocytes and microglia are also involved in the pathophysiology of AD (Kim et al. 2024). Astrocytes play an important role in maintaining homeostasis by uptaking neurotransmitters and, re-packing them into vesicles and sending them back to the neurons for the subsequent transmission. Disruption of this mechanism is hypothesized to be one of the earliest defects during AD (Kim et al. 2024; Morquette et al. 2015; Siracusa et al. 2019). Recently, neuroinflammation in AD has been observed in several studies involving AD patients and mouse models, such that activated microglia, immunoglobulins, and complement components were found to be closely associated with Aβ deposits in brains from AD patients and mouse models.

Ion channels play a crucial role in maintaining normal physiology in the CNS in various processes such as action potential generation, neurotransmitter release, synaptic plasticity, membrane potential, memory formation, and more (Shah et al. 2010; Südhof 2012). In various neurological diseases, ion channel dysregulation plays a vital role in the pathophysiology and is an attractive therapeutic target (Chen & Majdi 2009; Li & Lester 2006; Pietrobon 2002; Wang et al. 2022). In AD, ion channel pathophysiology also plays an important role, and this review will encompass the current literature on ion channel pathophysiology in AD (Wang et al. 2022).

Voltage-Gated Sodium Channels

In electrically excitable cells, voltage-gated sodium channels are crucial in generating electrical signals. In neurons, they are the primary ion channels responsible for generating action potential and maintaining excitability. The mammalian system consists of Nav1.1-Nav1.9 and Nav X, and they play a vital role in cellular physiology (Bagnéris et al. 2014; De Lera Ruiz & Kraus 2015a; J. Wang et al. 2017). The following section will attempt to encompass the role of voltage-gated sodium channels in the pathogenesis of AD.

Nav1. 1

Given its prominence in AD, the hippocampus has been extensively studied, with several studies reporting the distribution of Nav1.1 in this brain region (Guo et al. 2008; W. Wang et al. 2011). J20 mice displayed neuronal network hypersynchrony. Transplanting Nav1.1-overexpressing interneurons derived from embryonic MGE (medial ganglionic eminence) cells and MGE WT cells into the cortex and hippocampus reduced hypersynchrony, decreased hyperactivity, and improved behavioral performance. (Martinez-Losa et al. 2018). In BACE1 (beta-secretase 1 that cleaves amyloid precursor protein) null mice, which exhibit AD-related cognitive and behavioral abnormalities, studies found a 57% decrease in the level of Nav1.1 in the whole brain and the hippocampus, with a 37% reduction in surface expression of Nav1.1. as compared to age-matched wild type mice (Kim et al. 2011). GABAergic neurons regulate the firing of excitatory neurons, ensuring coordination in neuronal network activity in the brain. However, any changes in the inhibitory neurons or excitatory neurons can lead to excitatory/inhibitory (E/I) imbalance that has been reported in AD patients, transgenic murine models of AD, hiPSC derived neuronal cultures and cerebral organoids bearing AD mutations (Ghatak et al. 2019; Ambrad Giovannetti and Fuhrmann 2019; Hijazi et al. 2020; Schmid et al. 2016; Styr and Slutsky 2018; Zott et al., 2019). Among them, several studies have suggested an AD-related interneuron or GABAergic dysfunction and loss to be responsible to a great extent for the observed E/I imbalance and hyperexcitability. Interestingly, these GABAergic neurons highly express Nav1.1 ion channels (Ogiwara et al. 2007; Westenbroek et al. 1989) and their levels are altered in AD mice models like hAPP mice. Additionally, when Nav1.1 levels were increased in the Parvalbumin-positive interneurons, APP-J20 mice exhibited less network hypersynchrony and epileptic activity, suggesting a role of these ion channels in AD-related neuronal hyperexcitability, network asynchrony (Verret et al. 2012). Targeted activation of Nav1.1 also improved memory performance in hAPP mice (Martinez-Losa et al. 2018). In Dravet syndrome, characterized by hyperexcitability and cognitive dysfunction similar to that observed in AD, the primary cause is the inactivation of Nav 1.1, and a decrease in Nav 1.1 levels has been shown to alter hippocampal rhythms,

such as the theta rhythm (Bender et al. 2016; Richards et al. 2018).

Nav1. 2, Nav1. 3, Nav1. 4

The roles of Nav1.3 and Nav1.4 in various neurological disorders, characterized by cognitive decline and hyperexcitability, remain unknown (Barbieri et al. 2023). Nav1.2, primarily expressed in excitatory neurons (Goodchild et al. 2024; Ye et al. 2018), shows increased hippocampal surface levels Nav1.2 in BACE1 null mice and AD-related mice model (Kim et al. 2011; Fukumoto et al. 2002). Apart from Nav1.1 and Nav1.2, spinal cord injuries cause dorsal horn neurons to exhibit hyperexcitability and manifest increased Nav1.3 levels (Hains et al. 2003). Hence, a potential link between these channels and the pathophysiology during AD should not be ignored.

Nav1. 5

In multiple sclerosis (MS), where immune cells attack and damage the myelin sheath, astrocytes become reactive and show upregulation of Nav1.5 (Black et al. 2010). Several studies reported hyperexcitability in MS (Rivel et al. 2021; Yousuf et al. 2019; Zanette et al., n.d.). Patients with MS display hyperexcitability in the cortical region, along with increased glutamate transmission and increased neurotoxicity (Rossi et al. 2012). Another study also suggests the presence of Nav 1.5 in the membrane of macrophages within active MS lesions (Black et al. 2013). However, there is a lack of studies demonstrating the role of Nav 1.5 in AD. Similar to AD, MS also shows hyperexcitability, increased neurotransmitter release, neurotoxicity and reactive astrocyte phenotype. It will be an interesting topic for future research to look into the role of this channel in AD.

Nav1. 6

Nav1.6 is one of the major voltage-gated sodium channels in the brain and plays a role in action potential generation (Royeck et al. 2008; J. Wang et al. 2017). The function and expression of Nav1.6 change in various neurological disorders, including AD. Studies have shown that reduction of Nav1.6 activity leads to decreased neuronal excitability, whereas gain-of-function mutations enhance it (O'Brien & Meisler 2013). A study using the APP/PS1 mouse model of AD reported elevated levels of Nav1.6. In their experiments, they knocked down Nav1.6, which attenuated cognitive deficits and reduced neuronal hyperexcitability. Moreover, the authors reported decreased Aβ accumulation and decreased BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) transcription (Yuan et al. 2022). Increased Nav1.6 expression was observed in the hippocampus of 3-month-old Tg2576 AD mice, along with an increase in both the expression and activity of Nav1.6 in primary neuron cultures exposed to external Aβ1–42 (Ciccone et al. 2019). A similar study reported that the hyperexcitability observed in primary cortical neuron cultures after applying Aβ1–42 is due to increased Nav currents. They also noted hyperexcitability in APP/PS1 AD mice, associated with increased Nav1.6 expression (X. Wang et al. 2016). Nav1.6 plays an important role in regulating astrocyte function during AD, and knocking down astrocytic Nav1.6 reduces Aβ plaque formation in the hippocampus and cortex of APP/PS1 mice, thereby decreasing amyloidosis in AD mice. The study further reported reductions in glial cell activation with improved synaptic plasticity, spine density, and protection against abnormal network activity (X. Wang et al. 2024).

Nav1. 7, Nav1. 8, Nav1. 9

The expression of voltage-gated sodium channels Nav1.7, Nav1.8, and Nav1.9 is greatly confined to the peripheral nervous system and is limited in the central nervous system (De Lera Ruiz & Kraus 2015b). Consequently, researchers often do not report their regulation of neurological disorders. However, several studies support the role of Nav 1.7 in acute and chronic neuropathic and inflammatory pain (Dib-Hajj et al. 2007; Nassar et al. 2004).

Several studies have shown that the main changes in expression and activity in AD occur in Nav1.1 and Nav1.6. Nav 1.1, highly expressed in interneurons, shows a reduction in its expression levels in AD (Kim et al. 2011; Yuan et al. 2022). The above results indicate that a decrease in the levels of Nav 1.1 increases excitability in excitatory neurons and promotes AD pathogenesis. In addition, the fact that Nav 1.6 is highly expressed in the CNS and upregulated in AD implicates its role in hyperexcitability, thus contributing to AD progression.

Potassium Channels

Each type of channel has unique electrophysiological and pharmacological properties. Based on the structure and function of the various K^+ channel subunits, it is possible to classify them into four classes: Inwardly rectifying K^+ channels (Kir channels); tandem pore domain K^+ channels (K2P channel); Ca^{2+} activated channels (KCa channels: BKCa, IKCa, and SKCa) and voltage-gated K^+ channels (Kv).

Voltage-Gated Potassium Channels (VGKCs)

Voltage-gated potassium channels (VGKCs) are ion channels that control cellular excitability (Johnston et al. 2010). These channels are responsible for repolarizing neuronal membrane after an action potential by sensing the membrane

voltage changes (Kim and Nimigean 2016; Bachmann et al. 2020). Structurally, Kv channels consist of six transmembrane helices S1–S6, with both the amino and carboxyl termini on the intracellular side (Kim and Nimigean 2016). Helices S1–S4 act as the voltage sensor, whereas helices S5 and S6 form the channel pore. Recent studies suggested that increasing the activity of VGKC might have a neuroprotective role by inhibiting Aβ production. The molecular mechanism that gives rise to this neuroprotective effect is currently unknown and will be an interesting topic to look into for future research.

VGKC Changes in AD

Evidence suggests that Aβ31–35 and Aβ25–35 peptides reduce the activity of delayed rectifying K^+ channels in hippocampal neurons, potentially leading to neurotoxic effects by prolonging action potentials and increasing Ca^{2+} influx (Qi et al. 2004). Research utilizing whole-cell voltage-clamp techniques indicates that Aβ induces a reversible, voltage-dependent reduction in membrane conductance. Specifically, Aβ selectively inhibits fast-inactivating K^+ currents and affects delayed rectifying currents at higher concentrations, resulting in prolonged neuronal depolarization and increased Ca^{2+} influx (Good et al. 1996).

Furthermore, a study employing the Aβ25–35 peptide, known for its neurotoxic properties, involved its intracerebroventricular injection in rats to induce memory impairment. Following 96 h, these rats exhibited significant spatial memory deficits in the water maze. Researchers assessed the mRNA expression levels of key Kv channel subunits (Kv1.5, Kv2.1, Kv1.4, Kv4.2, and Kv4.3) using reverse transcription-polymerase chain reaction (RT-PCR). These experiments demonstrated significant increases in mRNA levels of Kv2.1 and Kv1.4 in the hippocampus and Kv4.2 in the cortex. Increased protein levels for Kv2.1 and Kv1.4 in the hippocampus and Kv4.2 in the cortex were confirmed by Western blotting (Pan et al. 2004). However, it is still unclear how the upregulated potassium channels contribute to neurotoxic or neuroprotective effects in AD pathology.

Kv1.1

Aβ(1–42) has been shown to inhibit Kv1.2 and heteromeric Kv1.1/1.2 channels, thereby prolonging action potentials and increasing calcium influx, possibly causing synaptic and neurotoxicity (Jamshidi et al. 2023). In AD, these findings indicate their crucial role in causing neuronal hyperexcitability.

Another study showed decreased levels of Kv1.1 mRNA and protein levels in hAPP-J20 mice and human AD tissue in the somatosensory cortex, affecting both pyramidal cells and GABAergic interneurons (Addo-Osafo et al. 2022). This reduction in Kv1.1 levels contributed to AD-related pathophysiology. For instance, a decrease in Kv1.1 mRNA and protein added to an increase in Aβ(1–42), which resulted in cognitive impairment and hyperexcitability that eventually led to premature death (Addo-Osafo et al. 2022).

Kv1.3, Kv1.5

AD also affects outward-rectifying potassium channels such that upon exposure to Aβ peptides, outward-rectifying potassium channels' current density increases in neurons (Yu et al. 1998; Zhang and Yang 2006). Kv1.3 and Kv1.5 current density in rat microglia and potassium current density in SN56 cells after Aβ treatment significantly increased (Chung et al. 2001; Colom et al. 2002).

Abnormalities in potassium channels, specifically Kv1.3, are detected in AD. In the brains of AD patients, activated microglia exhibits upregulation of Kv1.3 channels, especially close to amyloid plaques, which mediate amyloid-induced priming and Reactive oxygen species (ROS) production (Schilling et al. 2000; Rangaraju et al. 2015). Kv1.3 blockade in AD models reduced Aβ levels, increased synaptic proteins and switched microglial gene expression toward protective and phagocytic phenotypes, thereby suggesting a possibility of an immune modulatory target for use in immunomodulation against AD (Maezawa et al. 2018; Ramesha et al., n.d.). Impaired group II mGluRs (metabotropic glutamate receptors) in T lymphocytes of AD patients cause abnormal glutamate-dependent modulation of Kv1.3, resulting in enhanced Kv1.3 channel activity (Poulopoulou et al. 2010).

Kv2.1

Studies have reported overexpression of Kv2.1 in hippocampal neurons in Tg2576 AD mice, which was surprisingly associated with decreased delayed rectifier K^+ currents (IDR) caused by increased clustering of the channel leading to loss of activity (Piccialli et al. 2022). Restoring IDR levels by glutamate-induced declustering of Kv2.1 further suggests its participation in AD-related excitability changes (Piccialli et al. 2022). Additionally, this dysfunction is exacerbated by oxidative stress, increasing oligomerization of Kv2.1 channels, leading to reduced activity and elevated neuronal excitability in 3xTg-AD mice (Frazzini et al. 2016). Meanwhile, with oxidative stress being a primary culprit for neuronal dysfunction as observed in AD, there is a need for antioxidants such as N-Acetyl-Cysteine and Trolox that can restore Kv2.1 activity, thus reducing its sensitivity (Frazzini et al. 2016). Also, the mutant KCNB1(Kv2.1) variant (C73A) resistant to oxidation was neuroprotective. In AD models, including mice and Caenorhabditis elegans, this variant protects neurons from apoptosis induced by Aβ1–42 (Cotella

et al. 2012). Another study shows KCNB1 oxidation and subsequent FAK and Src kinase phosphorylation are higher in AD brains than in controls (Wei et al. 2018). Decreased Kv2.1-dependent Ik current densities in 3xTg-AD mice led to altered synaptic activity and increased spike frequency. This was accompanied by Kv2.1 channel clustering among hippocampal neurons. These changes indicate that Kv2.1 channels contribute to AD-related hyperexcitability, primarily through disrupted cell-to-cell communication. (Piccialli et al. 2022).

Kv3.1

More recent work has shed light on how Kv3 channels affect AD. In young 5xFAD mice, changes in the biophysical properties of Kv3 channels, not changes in their genes or proteins, made nerve cells less excitable. These changes also caused too much activity in brain networks at gamma frequencies. This suggests that fixing how Kv3 channels work could be a new way to treat early brain problems in AD (Olah et al. 2022).

Supporting these studies, experiments performed on the APP/PS1 mouse model showed that Kv3.1, Kv3.2, and Kv3.4 subunits play a significant role during embryo growth, which indicates this new role in development. After birth, the expression of Kv3 subunits increased and stabilized in adult mice, further indicating the role these subunits play in the postnatal maturation of the nerve cell. However, in older APP/PS1 mice, researchers saw less Kv3.1 in the neocortex than in normal mice. This drop in Kv3 currents might explain why thinking skills worsen in AD (Boda et al. 2012). Kv3.1 expression levels in human microglia are increased after Aβ treatment (Franciosi et al. 2006).

Kv3.4

Astrocytes showed greater Kv3.4 levels and activity when exposed to Aβ. Tg2576 mice had increased Kv3.4 expression in their cerebral cortex, hippocampus, and cerebellum in astrocytes near Aβ plaques (Boscia et al. 2017). At 12 months, astrocytes around plaques displayed significant Kv3.4 expression, and a Kv3.4 knockdown led to lower glial fibrillary acidic protein expression (GFAP) and Aβ trimers, suggesting its effect on astrocytes reactivity and its response to Aβ plaque (Boscia et al. 2017).

Additionally, it has been shown that Kv3.4, which regulates delayed rectifier currents, is highly expressed in the cerebral cortex during the early stages of AD and remains elevated in the brain areas affected by neurodegeneration as observed in samples from AD patient brains and mice with APP mutations (Angulo et al. 2004). The increased expression was associated with amyloid pathology and not due to plaque deposition (Angulo et al. 2004).

Aβ42 increased Kv3.4 channels in both hippocampal neurons and NGF-differentiated PC-12 cells via NF-κB-related signaling pathways, which were inhibited by SN-50, preventing both the rise in Kv3.4 expression and Aβ-induced neurodegeneration. Additionally, blocking Kv3.4 with blood depressing substance-I (BDS-I) reduced Aβ-induced neuronal damage. This suggests that Kv3.4 channels could be a good target for treating AD (Pannaccione et al. 2007).

In the APP/PS1 mouse model, lowering Kv3.4 expression improved dendritic spine loss and shape. While Kv3.4 mRNA levels decreased in response to Aβ, which could indicate a compensatory mechanism, all other findings suggest reducing Kv3.4 expression might be used as a protective mechanism against Aβ-induced synaptic damage in AD (Yeap et al. 2022).

Kv4.2

Patch-clamp recordings obtained in dendrites demonstrated dendritic hyperexcitability in CA1 pyramidal neurons in AD mouse hippocampus caused by a lack of Kv4.2. Kv4.2 plays significant roles in both dendritic excitability and synaptic plasticity. Interestingly, the anti-epileptic drug levetiracetam blocked Kv4.2 loss. This effect was also tau-dependent, as the absence of tau prevented the loss of Kv4.2 and decreased dendritic hyperexcitability. Aβ and Tau-dependent Kv4.2 deficiency enhanced dendritic excitability exacerbated behavioral deficits, and induced epileptiform activity, indicating that changes in ion channels like Kv4.2 may contribute to early AD-related neuronal dysfunction (Hall et al. 2015).

Inward Rectifying Potassium Channels—Kir

Inward rectifying potassium channels contribute to sustaining resting K^+ conductance in a wide variety of cells, including neurons, such that they allow K^+ entry into the cells only during hyperpolarization (Matsuda et al. 1987). The fundamental unit of Kir consists of two transmembrane helices with cytoplasmic NH_2 and COOH ends, along with an extracellular loop that bends back to create the ion selectivity filter lining the pore. Internal substances like Mg^{2+} and polyamines cause inward rectification by blocking the channel pore. Ions, phospholipids, and binding proteins regulate Kir activity. The classification of inward rectifying potassium channels yields four functional groups, each containing specific subsets, classical Kir (Kir2.x), which are fundamentally active; G protein-gated Kir channels (Kir3.x) governed by G-protein coupled receptors; ATP-sensitive K^+ channels (Kir6.x), dedicated to cellular metabolism, and K^+ transport channels (Kir1.x, Kir4.x, Kir5.x, and Kir7.x) (Hibino et al. 2010).

Researchers observed increased hippocampal interstitial fluid (ISF) Aβ levels in APP/PS1 mice under hyperglycemic conditions, which could be reversed by opening K_{ATP} channels (composed of Kir6.1 or Kir6.2 subunits). It lowered neuronal activity in the hippocampus of the mice (Macauley et al. 2015). In moderate to severe conditions of cerebral amyloid angiopathy, levels of Kir4.1 and BK, a calcium-sensitive large conductance potassium channel, were low in autopsied human AD brain tissues (Wilcock et al. 2009). Evidence shows that Kir channel (Kir2.x) function in the endothelium of posterior cerebral arteries of 3xTg-AD mice decreases by 50% in AD conditions compared to pre-AD young mice, regardless of sex (Hakim and Behringer 2020, 2023). Pyramidal neurons manifest altered morphology and increased Kir current under hyperphosphorylated conditions in aged tau transgenic mice (Muller-Thomsen et al. 2020). K_{ATP} positively correlated with increased uptake of 11C-Pittsburgh compound that is used to trace cortical amyloid β plaques in AD patients (Aso et al. 2021; Klunk et al. 2004). Exogenous administration of phosphatidylinositol 4,5-bisphosphate (PIP2) restored Kir2.1 current density (significantly decreased in AD) in capillary endothelium, helping to alleviate AD (Mughal et al. 2021; Fang et al. 2023). In contrast to the above finding, other Kirs, like the Kir4.1 function, were not affected, though there were noticeable changes in Kir4.1 protein expression. Astrocytes in the dentate gyrus of APP/PS1 mice were shown to rebalance the K^+ ionic imbalance by localized upregulation of astrocytic Kir4.1 protein expression (Huffels et al. 2022). Interestingly, closing Kir2 channels on memory engram cells through optogenetic manipulation of serotonin nuclei helped retrieve the lost memory in AD (Bostancıklıoğlu 2019).

Considering G-protein gated inwardly rectifying potassium (GirK) channels, Aβ downregulates GirK1,2,3, and 4 channel expression (Sánchez-Rodríguez et al. 2017; Mayordomo-Cava et al. 2015) and its subcellular localization in the hippocampus (Alfaro-Ruiz et al. 2021; Djebari et al. 2021). Aβ disrupts GirK channel conductance in CA3 pyramidal neurons, which could lead to septohippocampal activity dysfunction (Nava-Mesa et al. 2013). Along with GirK1 and GirK2, a significant reduction in the levels of $GABA_B$ was observed in APP/PS1 mice, and studies suggest that $GABA_B$ signaling modulates GirK channels (Martín-Belmonte et al. 2022). Efforts to activate GirK successfully rescued all hippocampal deficits, like long-term synaptic depression and memory deficits, which were induced by Aβ. The same group also established that GirK has the potential to control excess excitability by strengthening LTP in GABA and GirK-mediated inhibitory post-synaptic responses in vivo (Sánchez-Rodríguez et al. 2019, 2020). Spatial memory training normalized GirK2 expression levels in 6-month-old $APP_{Sw,\ Ind}$ J9 mice, matching those of healthy control mice and abnormal Girk2 expression is also shown to be involved in excitatory/inhibitory imbalance generally found in AD (Temprano-Carazo et al. 2022).

$Ca.^{2+}$ Dependent Potassium Channels (KCa)

Ca^{2+}-activated potassium channels are a large family of potassium channels activated by an increase in cytosolic calcium. The three main subfamilies of calcium-activated K^+ channels include large conductance, BK or KCa 1.1; intermediate conductance, IK or KCa 3.1; and small conductance, SK or KCa 2.1, KCa 2.2, KCa 2.3. Structurally, they are made up of alpha and beta subunits. The alpha subunit is a tetramer, which forms the voltage sensor, the channel pore and the calcium-sensing region. The alpha subunit consists of seven transmembrane units and a large intracellular region. The S4 transmembrane region forms the voltage sensor, and the linker between the S5 and S6 transmembrane regions forms the channel pore. Each type makes distinctive contributions to the fine-tuning of neuronal activity and has been implicated in various neurological processes and disorders (Trombetta-Lima et al. 2020).

BK

BK channels are implicated in AD such that Transcranial Magnetic Stimulation (TMS) benefits AD patients by enhancing the activity of BK channels in 3xTg mice in a frequency-dependent manner. The enhancement was associated with increased expression of the scaffold protein Homer1a, which further increases the activity of BK channels (Yamamoto et al. 2011) (F. Wang et al. 2015a, b). Additionally, ventricular injection of the BK channel activator isopimaric acid (ISO) in 3xTg mice improved non-spatial memory, as evidenced by the novel object recognition (NOR) test and spatial memory, as shown by the Morris water maze probe test. Electrophysiological studies revealed that ISO treatment normalized synaptic transmission and partially restored long-term potentiation (LTP) at hippocampal CA1 synapses. Furthermore, ISO treatment reduced Aβ1–42 levels in the hippocampal tissue of 3xTg mice (L. Wang et al. 2015a, b).

IK/KCa3.1 and SK

Microglia from both 5xFAD mice and AD patients manifest increased expression and activity of KCa3.1 channels. Aβ oligomer ($Aβ_O$) treatment elevated the expression and activity of these channels in hippocampal slices. At the same time, their inhibition reduced the pro-inflammatory effects and LTP impairment caused by $Aβ_O$ (Jin et al. 2019).

In the 3xTg-AD mouse model of AD, reduced SK channel activity drives dopaminergic neuronal (DA) hyperexcitability and disrupts firing. RNA sequencing of single patch-clamped DA neurons revealed an upregulation of the

modulatory enzyme casein kinase2 (CK2) for SK channels. Pharmacological CK2 inhibition restored normal SK channel activity and firing in these neurons. (Blankenship et al. 2023). In the TgCRND8 mouse model, impaired cholinergic excitation in prefrontal cortex neurons affects attention. Excessive calcium-activated potassium conductance caused the issue. Blocking SK channels improved this excitation, suggesting a potential treatment target for cognitive issues in Alzheimer's (Proulx et al. 2015; Jhamandas et al. 2001). A newly identified shorter form of SK2 isoform (SK2-sh) mRNA is also elevated in the cortical tissue of AD patients (Murthy et al. 2008).

Two Pore Domain Leak Potassium Channels

In the context of AD, the number of studies exploring the role of two-pore domain leak potassium channels (K2P) is significantly less. These potassium channels play a significant role in maintaining negative membrane potential, which is necessary to prevent the neuron from getting hyper-excited (Braun 2012). TREK1 activation improved cognitive deficits, upregulated the levels of glutamate transporter-1, and downregulated the levels of glutamate and N-methyl-D-aspartate receptor (NMDAR) alongside rescuing damaged neurons and astrocytes in an AD model. Further, TREK1 expression was shown to be increased in 3-month-old AD mice, which eventually started declining with increasing age of the animal. This rise in expression in the early stages of AD might have neuroprotective capabilities (Li et al. 2022). Supporting this, another research group observed a massive increase in the upregulation of gene marker KCNK13, which codes for the THIK1 K2P ion channel. Interestingly, the downregulation of DNA methylation on KCNK13 in AD explained the observations (Tang et al. 2023). Researchers in both studies observed an upregulation of K2P channels in AD conditions. Studies suggest that upregulated expression of K2P like TREK1 and THIK1 in AD drove the neural tissue toward better neuronal health, but the mechanisms underlying their upregulation and their involvement in AD are largely unknown.

Voltage-Gated Calcium Channels

Voltage-gated calcium Channels (VGCCs) are important calcium channels on the plasma membrane of excitable cells that regulate Ca^{2+} by changes in membrane potential. (Heck et al. 2021) VGCCs can be categorized broadly into high voltage-activated (L-Type, N-Types, P/Q-types, and R-types) and low voltage-activated (T-Type) (Catterall 2011). VGCCs are formed from a pore-forming α1 subunit in association with different β subunits and other regulatory subunits and scaffolding proteins. α_1 subunit contains four homologous domains (labeled I–IV), each containing six transmembrane helices (S1–S6) that consist of the voltage-sensing domain and drug/toxin binding sites. This arrangement is analogous to a homo-tetramer formed by voltage-gated potassium channels (each contain 6 TM helices). Functionally, they play an essential role in regulating neurotransmitter release and synaptic plasticity by regulating long-term potentiation (LTP) and long-term depression (LTD), initiating various molecular cascades by transient influx of Ca^{2+} and controlling the release of Ca^{2+} from the ER internal stores to name a few (Dittmer et al. 2017; McElligott & Winder 2008; Weisskopf et al. 1999; Yang et al. 2009). Dysregulation of VGCCs plays an important role in the development of neurological and psychiatric conditions, such as autism, schizophrenia, epileptic phenotypes, and chronic pain (Nelson et al. 2006; Vossel et al. 2017). During the early stages of Alzheimer's, Ca^{2+} dysregulation has been indicated as one of the first defects that occur during pathogenesis, leading to the activation of programmed cellular death pathways through metabolic stress and excitotoxicity (Berridge 2014). Due to the wide variety of functions they can regulate, VGCCs play a significant role in the pathophysiology of AD (Dittmer et al. 2017; McElligott & Winder 2008; Weisskopf et al. 1999).

L Type

LTCCs (L-type calcium channels) form the largest group of VGCCs and consist of four isoforms (Cav1.1, Cav1.2, Cav1.3, and Cav1.4), of which the heart and brain primarily consist of Cav1.2 and Cav1.3 (Crossley et al. 2023). Most LTCCs found in the hippocampus are of the Cav1.2 isoform and might play an important role in the pathophysiology of AD and as a future therapeutic target (Crossley et al. 2023). The localization of LTCCs within the hippocampus is not uniform, as shown in the 3xTG mice, where LTCC enrichment was significant at the CA1 region. At the same time, CA3 and DG regions had negligible amounts (Crossley et al. 2023). During aging, the total protein concentration of Cav1.2 and Cav1.3 does not increase, but the surface density of these ion channels on the plasma membrane increases, followed by increased Ca^{2+} current (Campbell et al. 1996; Núñez-Santana et al. 2014; Thibault and Philip 1996). These results imply that neurons become more susceptible to degeneration as they age, leading to cognitive decline. When exposed to Aβ (25–35), Ca^{2+} influx initiates through LTCCs in cortical and hippocampal neuronal cultures. In contrast, there was no such influx through the P/Q or N-type channels (Ueda et al. 1997). Bis(7)-tacrine, a novel Ache (Acetylcholinesterase) inhibitor, showed that neuronal apoptosis by Aβ decreased after inhibiting the extracellular influx of Ca^{2+} through LTCCs (Fu et al. 2006). PS1(delta)E9 mutation, a mutation that attenuates gamma-secretase activity but does not abolish it, mimics the phenotype of familial AD and leads to increased expression of LTCCs, especially

Cav1.2 (Skobeleva et al. 2022). Studies done on the SH-SY-5Y neuroblastoma cell line indicated that the increased influx of Ca^{2+} through L-Type channels might be due to the phosphorylation of the channel by MAP kinase (Ekinci et al. 1999). Due to the increase of LTCCs after exposure to Aβ, dysregulation of LTP leads to improper memory formation and storage. The exact mechanism by which memory storage gets disrupted is still unknown, but specific mechanisms involving memory erasure at inappropriate times have been hypothesized (Berridge 2014). Interestingly, a correlation between AD and Vitamin D deficiency exists, and patients have reduced expression of Vitamin D receptors along with an increase in LTCCs. Treatment with Vitamin D3 causes an increase in Vitamin D receptors and a decrease in LTCCs in cultured hippocampal neurons, indicating a potential therapeutic property of Vitamin D (Brewer et al. 2006). LTCCs have a unique role beyond the initial Ca^{2+} influx and even regulate the internal Ca^{2+} stores. After the initial Ca^{2+} influx, the ER stores release Ca^{2+}, thus depleting the luminal stores and leading to the activation of the STIM1 protein, which can interact directly with LTCCs, further inhibiting Ca^{2+} through the plasma membrane (Park et al. 2010). Post-synaptic activation of LTCCs has also been indicated in increased ER content (Dittmer et al. 2017). Since dysregulation of STIM1 is known to play a role in the pathogenesis of AD, it would be interesting to see if modulating LTCCs can reduce the pathological phenotype in a STIM1-dependent manner (Pascual-Caro et al. 2018).

T Type

Unlike the extensive literature on LTCCs, information about the other VGCCs is ambiguous. However, they still play an essential role in regulating various functions in the CNS, and some of them are involved in the pathogenesis of AD. T-type calcium channels (TTCCs) are involved with various neurological disorders such as autism epilepsy (Nelson et al. 2006; Powell et al. 2014) ST101 is an activator of TTCCs, and treating 3xTG mice with this compound causes a novel cleavage of APP protein, which is independent of the alpha-secretase or gamma-secretase pathway and, therefore, reduces the amount of Aβ present in the brain and also improves cognitive function (Green et al. 2011). TTCCs play an important role in memory erasure mechanisms during non-rapid eye movement (NREM) and actively participate in maintaining the UP state in slow oscillations. Therefore, a TTCC dysfunction might be able to explain certain cognitive defects that occur during AD (Berridge 2014). In rat cortical slices, LTP and CaMKII autophosphorylation were enhanced by ST101, indicating that activation of these channels might also improve cognitive ability. Interestingly, inhibiting TTCCs inhibited LTP, while blocking other VGCCs had no such effect in this system (Moriguchi et al. 2012).

P/Q Type

P/Q-Type calcium channels have been indicated to play a role in AD pathology by disrupting synaptic plasticity (Nimmrich et al. 2008; Nimmrich & Gross 2012). In certain studies, Aβ (8 nM) inhibited P/Q currents, thus inhibiting the release of synaptic vesicles, and an enhancer of P/Q current reversed this phenotype (Nimmrich et al. 2008). However, in other studies, contrary to the previous finding, incubation with 1μM Aβ caused an increase in various Ca^{2+} currents, including P/Q currents (Ramsden et al. 2002). In the heterologous system of Xenopus oocyte, Aβ (200 nM) oligomers increased P/Q currents in a dose-dependent manner. At the same time, it did not affect NMDAR currents, indicating that P/Q currents might play an important role in excitotoxicity in AD patients (Mezler et al. 2012).

N Type

N-type calcium currents increase after the application of 1μM Aβ on cultured neurons and synaptosomes, leading to neuronal apoptosis. Interestingly, the application of interleukin 1β attenuated this effect and decreased apoptosis by regulating Ca^{2+} homeostasis (MacManus et al. 2000). Further supporting the role of N-type channels in causing neurotoxicity, incubating Aβ42 at nerve endings was shown to cause the release of glutamate and noradrenaline due to increased Ca^{2+} current via the Cav2.2 channel (Bobich et al. 2004).

R Type

R-type calcium channels play an important role in neuronal function, such that they are associated with synaptic functions and are involved in sleep architecture (Cohen & Atlas 2004; Murphy et al. 2022; Siwek et al. 2014). However, there is a lack of studies exploring the role of R-type channels in AD. Nonetheless, it is important to note that R-type channels are associated with various other neurological disorders and are involved in convulsive and non-convulsive seizure-like activity (Wormuth et al. 2016). Seizure activity is also associated with AD, making these channels important candidates for their possible role in AD pathogenesis (Kamondi et al. 2024; Pandis & Scarmeas, n.d.; Vossel et al. 2017).

Hyperpolarization-Activated and Cyclic Nucleotide-Gated Channels

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are cation channels activated by hyperpolarization,

permeable to Na^+ and K^+ ions, and crucial for rhythmic activity in the heart and brain (Gauss et al. 1998; Männikkö et al. 2002; Ramentol et al. 2020; Sartiani et al. 2017).

In AD, elevated Aβ42 levels were observed in the cortex of HCN1-deficient ($HCN1^{-/-}$) mice compared to wild-type controls (Saito et al. 2012; Zhang et al. 2024). Glial activation, a hallmark of AD, appears to be influenced by functional HCN channels, which are essential for microglial activation and polarization (Miao et al. 2023; Vay et al. 2020; Zhang et al. 2024). HCN channels have been implicated in several mice models of AD including 3xTg, 5xFAD, J20, ARTE10, rTg4510, Tau35 mice (Booth et al. 2016; Crimins et al. 2012; Goniotaki et al. 2024; Musial et al. 2018).

HCN channels also play distinct roles in learning and memory. $HCN1^{-/-}$ mice exhibit motor learning and memory deficits due to HCN1 loss in cerebellar Purkinje cells (Nolan et al., 2003, 2004). However, these mice also display enhanced spatial learning and memory, suggesting region-specific functions of HCN1 and therefore their role in AD (Chang et al. 2019; Nolan et al., 2003, 2004).

Ligand-Gated Ion Channels/ Receptors

In AD, ligand-gated ion channels (LGICs) or receptors play a crucial role in synaptic dysfunction. Aβ-induced alterations are evident in several types of receptors. Some of the major LGICs known to be affected in AD are NMDARs (N-methyl-D-aspartate receptors), AMPARs (α- amino-3-hydroxy- 5-methyl- 4- isoxazolepropionic acid receptor), Kainate, AChRs (Acetylcholine receptors), Purinergic receptors, and GABARs (gamma-aminobutyric acid receptors). The body of literature which has effectively studied the expression, function, and regulation of these LGICs in the context of AD is huge and has been covered extensively in several exceptional review articles (Babaei 2021; Bordji et al. 2011; Chałupnik and Szymanska 2023; Chang et al. 2012; Chohan and Iqbal 2006; Henley and Wilkinson 2016; Kocahan & Doğan 2017; Liu et al. 2019; Malinow 2012; Mota et al. 2014; Ning et al. 2024; Olney et al. 1996; Rissman et al. 2007; Zhang et al. 2016). Here we aim to briefly describe the overall changes in them. Synaptic NMDAR subunits have been shown to decrease in AD, while extrasynaptic NMDARs were upregulated (Alfaro-Ruiz et al. 2024; Babaei 2021; Bordji et al. 2010, 2011; Chohan & Iqbal 2006; Escamilla et al. 2024; Goussakov et al. 2010; Hanson et al. 2020; Kessels et al. 2013; Kocahan & Doğan 2017; Liu et al. 2019; Malinow 2012; Mota et al. 2014; Olney et al. 1996; Ortiz-Sanz et al. 2022; Snyder et al. 2005; Wang & Reddy 2017; Zhang et al. 2016). Extrasynaptic NMDAR current increases in hAPP-J20 AD transgenic mice as well as in hiPSC derived neurons which is caused due to accumulation of oligomeric Aβ (Talantova et al. 2013; Ghatak et al. 2021a, b).

Aβ also promotes the endocytosis of synaptic NMDARs (Kurup et al. 2010). Additionally, there is a loss of extrasynaptic inhibitory glycine receptors (Chumakov et al. 2015; Jin et al. 2024; Kuhse et al. 2023). Furthermore, Aβ oligomers mediate the ubiquitination and removal of AMPAR (α- amino- 3-hydroxy- 5-methyl- 4- isoxazolepropionic acid receptor) from the membrane, resulting in a decrease in synaptic AMPARs and cognitive decline (Babaei 2021; Chang et al. 2012; E. H. Chang et al. 2006; Guntupalli et al. 2016, 2017; Henley & Wilkinson 2016; Hettinger et al. 2018; Kadriu et al. 2021; Lee et al. 2016; Madsen et al. 1994; Martín-Belmonte et al. 2020; Ning et al. 2024; Qu et al. 2021; Reinders et al. 2016; Whitehead et al. 2017). A selective reduction in kainate receptors is observed in APP/PS1 mice (Barthet et al. 2022; Chałupnik & Szymańska 2023; Dewar et al. 1991; Matute 2011; Ourdev et al. 2019). Additionally, an age-dependent decline in GABA (gamma-aminobutyric acid) currents and faster desensitization is seen, associated with lower mRNA and protein levels of GABA receptors (Jiménez-Balado & Eich 2021; Kwakowsky et al. 2018a, ba, b, 2018a, ba, b; Leisgang Osse et al. 2023; Limon et al. 2012; Rissman et al. 2007). Postmortem studies in AD patients show reduced nicotinic AChRs (Pimlott et al. 2004; Rinne et al. 1991; Wevers et al. 2000) and serotonin receptor densities (Garcia-Alloza et al. 2004; Lorke et al. 2006; Solas et al. 2021) in the frontal and temporal cortex. Studies show that purinergic receptors like P2X7 can regulate Aβ formation and are linked to chronic neuroinflammatory processes, tau hyperphosphorylation, oxidative stress and other pathological processes in AD. Additionally their expression levels were upregulated in Tg2576 AD transgenic mice in non-neuronal cells like microglia (Huang et al. 2024; McLarnon et al. 2006; Parvathenani et al. 2003).

Conclusion

In this review, we outline the roles that different ion channels play in AD pathology and progression (Fig. 1). With some of the ion channels, contradictory results exist, and it will be important to investigate the mechanisms that lead to such behavior. The same ion channel might have varying and potentially opposite effects depending on the brain region and neuronal cell type and non-neuronal cell type in the brain (Table 1). An understanding of the ion channel physiology in AD will provide insight into the various aspects of the disease and can potentially uncover therapeutic targets early in the disease. Since AD is a highly debilitating progressive neurodegenerative disease, early interventions will not only help in slowing progression but may also reverse the disease. Therefore, it is important to target the ion channels that can act as disease-modifying therapies at the early stages of AD.

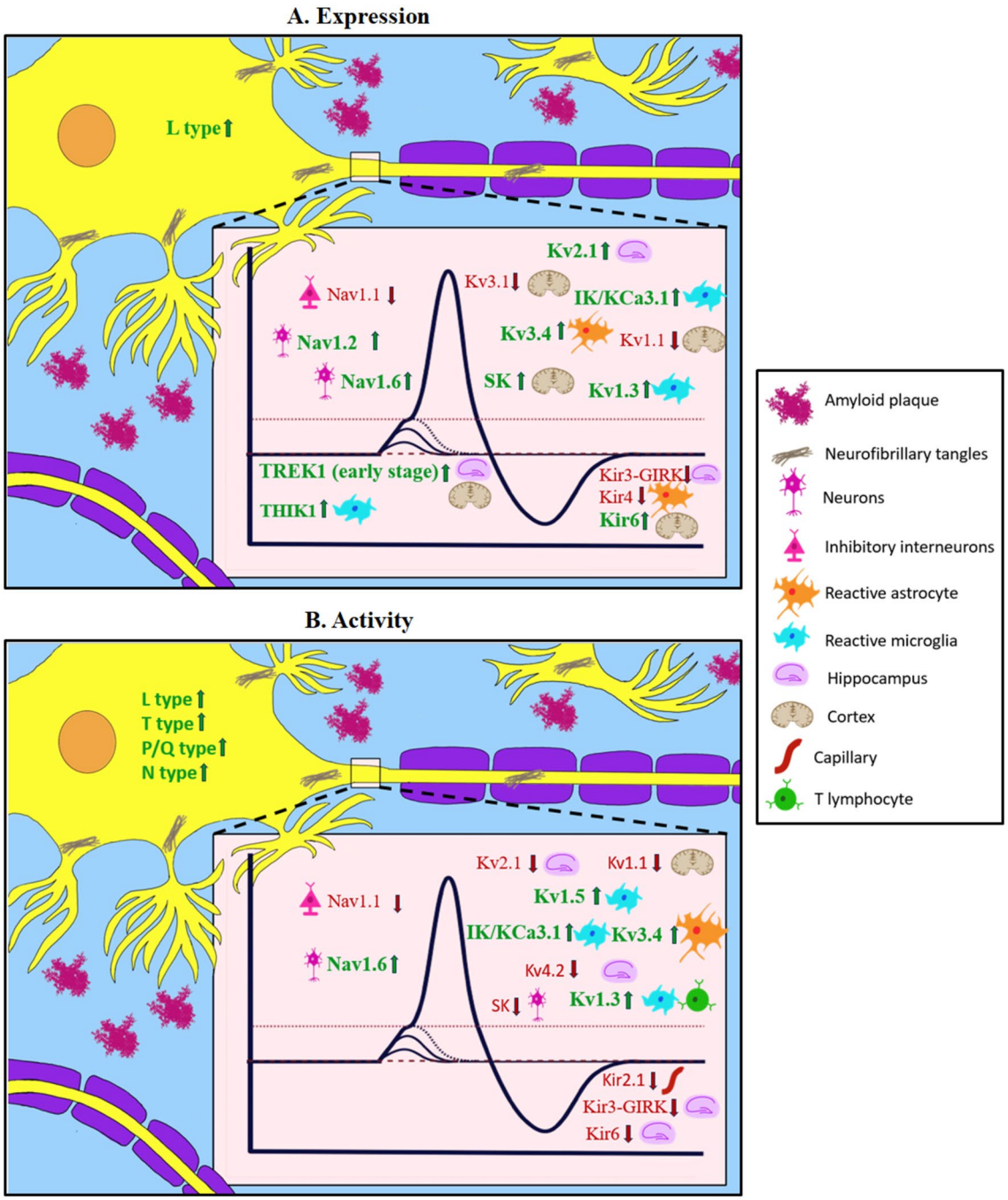

Fig. 1 Ion Channel Dysregulation in AD. **A** Ion Channel Expression Changes in AD: The schematic illustrates the changes in ion channel expression across neurons, inhibitory interneurons, reactive astrocytes, and microglia. Increases are observed in Nav1.2, Nav1.6, TREK1, THIK1, Kv1.3, Kv3.4, Kv2.1, IK/KCa3.1, Kir6, SK, and L type calcium channel while decreases are noted in Nav1.1, Kv1.1, Kv3.1, Kir3-GIRK, and Kir4. **B** Ion Channel Activity Changes in AD: The diagram represents the ion channel activity changes during the AD. Increased activity is seen in Nav1.6, Kv1.5. Kv3.4, Kv1.3, IK/KCa3.1 and also L type, T type, P/Q type, N type voltage-gated calcium channels, with reduced activity in Nav1.1, Kv1.1, Kv2.1, Kv4.2, Kir3-GIRK, Kir2.1, Kir6, and SK

Since plaque and neurofibrillary tangle formation occurs at much later stages, it will be important to target early defects such as dysregulation of calcium activity, dysregulation of neurotransmitter homeostasis and hyperexcitability rather than targeting plaques and tangles. Lecanemab (Leqembi®) and aducanumab (Aduhelm® are two anti-amyloid monoclonal antibodies (MABs) that have been approved by the FDA for the treatment of AD. Anti-amyloid monoclonal antibodies have disease-modifying abilities that can slow down clinical decline. However, the reduction in

Table 1 Ion channel dysregulation associated with AD

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
Voltage-Gated Na^+ Channel (Nav)	**Nav1.1**	hAPP-J20 BACE1-null mice	4–7 Months 3 months	Suppresses excitatory neuron firing	-Decreased expression and activity levels in interneurons. -Improved network function and memory with targeted activation.	Martinez-Losa et al. 2018; Kim et al. 2011; Verret et al. 2012
	Nav1.2	BACE1-null mice	3 months	Action potential generation	-Increased hippocampal surface level expression was observed in AD-modeled BACE1 null mice.	Kim et al. 2011
	Nav1.6	APP/PS1C57B L/6J as control Postnatal day 0–1 primary cortical cultures Tg2576 Embryonic day 15 Tg2576 mouse Primary hippocampal neuron culture Postnatal day 0 APP/PS1 mouse primary neuron culture	5–8 months 7 DIV 3 months 8–12 DIV 12 DIV	Action potential generation	-Decreased level of expression and activity. -Elevated levels in APP/PS1 mice, reduced cognitive deficits and hyperexcitability with knockdown. -Increased expression in primary neuron cultures with external Aβ1–42 exposure.	Yuan et al. 2022; Ciccone et al. 2019; X. Wang et al. 2016; X. Wang et al. 2024
Voltage-Gated K^+ Channels (Kv)	**Kv1.1**	hAPP-J20 mice Xenopuslaevis oocytes injected with Kv1.2 cRNA treated with Aβ 42	4-6 months	Regulates action potential duration and neuronal excitability.	-Reduced mRNA and protein levels. -Inhibited by Aβ(1–42), prolongs action potentials and increases calcium influx.	Addo-Osaf o et al. 2022; Jamshidi et al. 2023
	Kv1.3	AD patients, activated microglia Tg6799 5xFAD mice T lymphocytes of AD patients	71.5±3.6 years AD patients 4, 6, and 10 month-old 5XFAD mice Late-onset (>65 years) AD	Modulates microglial activation and inflammation.	-Upregulated in activated microglia. -Kv1.3 blockade reduces Aβ levels and improves microglial activity. -Increased Kv1.3 activity promotes inflammation and oxidative stress.	Rangaraju et al. 2015; Maezawa et al. 2018; Poulopoulou et al. 2010

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
	Kv1.5	Sprague Dawley rat microglia and astrocytes co-culture	14 days DIV	Regulate membrane potential and inflammatory responses.	-Current density increased.	Chung et al. 2001
	Kv2.1	Tg2576 3xTg-AD cultured hippocampal neurons	3 months Between 14 and 19 DIV	Contributes to delayed rectifier K+ currents and neuronal excitability.	- Overexpressed. -Decreased K+ currents and increased neuronal excitability. -Elevated expression leads to impaired K+ current regulation and increased excitability in neurons.	Piccialli et al. 2022; Frazzini et al. 2016
	Kv3.1	5xFAD mice APP/PS1 mouse	7–8 weeks old 5XFAD; 12 months of APP/PS1	Regulates high-frequenc y firing and neuronal excitability.	-Decreased levels in older AD mice. -Changes in function reduce neuronal excitability.	Olah et al. 2022; Boda et al. 2012
	Kv3.4	Tg2576; AD patient brains APP/PS1 Wistar Rat Hippocampal Neuronal Cultures	12 and 16 months of Tg2576; Sporadic late-onset AD patients; 7 months of APP/PS1; 8DVI	Modulates astrocytic activity and dendritic spine structure.	-Elevated in astrocytes near Aβ plaques. -Elevated activity -Knockdown reduces Aβ trimers and improves dendritic spine morphology.	Boscia et al. 2017; Angulo et al. 2004; Yeap et al. 2022; Pannaccione et al. 2007
	Kv4.2	hAPPJ20 mice	4.5–7 months	Regulates dendritic excitability and synaptic plasticity	-Depletion of Kv4.2. -Restoring Kv4.2 levels reduces hyperexcitability and improves behavior.	Hall et al. 2015
Inward Rectifyin g K^+ Channels (KIR)	**KIR2**	3xTg-AD B6129SF2/J-Control 5xFAD	4 groups were categorized based on their age: 1–2, 4–5, 6–8, and 12–15 months 12–13 month	They trigger hyperpolarizing signals from capillaries to arterioles, increasing cerebral blood flow	-Diminished capillary Kir2.1 channel activity. -Exogenously administered PIP2 rescued Kir2.1 currents. -Closing Kir2 channels on memory engram cells helped retrieve lost memory in AD.	Bostancıklıoğlu et al., 2019; Hakim et al. 2020; Mughal et al. 2021

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
	KIR3 - GIRK	P301S mice APP/PS1 mice Wistar rats C57BL/6 male mice C57BL/6 male mice $APP_{Sw;Ind}$ J9 mice-AD	3 and 10 months 12 months 23–33 days after birth (P23-33) 3–5 months 3–10 weeks 6 and 12–18 months	Key effector in inhibitory signaling pathways	-Significant reduction in gene expression of GirK1,2,3,4 subunits. -Aβ meddles with GirK channel conductance in CA3 pyramidal neurons. -$GABA_B$ signaling modulates GirK channels. -Girk2 could be responsible for excitatory/ inhibitory imbalance. -GIRK strengthens LTP in GABA receiving post synapses.	Alfaro-Ruiz et al. 2021 Luján et al. 2014; Martín-Belmont e et al. 2022; Mayordomo-Cav a et al. 2015; Nava-Mesa et al. 2013; Sánchez-Rodrígu ez et al. 2017, 2019, 2020; Temprano-Caraz o et al. 2022
	KIR4	APP/PS1 mice APP_{Sw} (Tg2576), NOS2-/-, APPSw/NOS2-/- , APP_{Sw}DI, APPSwDI/NOS2-/- mice	3, 9 and 15 months 52 - 56 weeks	Kir4.1 is essential in clearing and redistributing extracellular K^+ in astrocytes	-Reduced levels of Kir4.1 in autopsied human brain AD samples. -Kir4.1 conductance was not affected at all. -Astrocytes in AD mice coped by upregulating Kir4.1 protein expression.	Huffels et al. 2022; Wilcock et al. 2009
	KIR6	APP/PS1 mice Humans with amnestic mild cognitive impairment	3 and 18 months Elderly individuals	Link between cellular energetics and electrical excitability (Nichols 2006)	-High ATP levels in AD-like conditions close KATP channels, boosting gene expression. -Opening of KATP channels led to decreased ISF Aβ levels and lowered neuronal activity in the hippocampus.	Macauley et al. 2015; Aso et al. 2021

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
Two Pore Domain Leak K^+ Channels (K2P)	**TREK1**	SAMP8 - AD mice SAMR1 - Control mice	3 and 6 months	It helps regulating neuronal excitation by modulating membrane potential	-Increased levels in the early stages of AD and began to decrease after that. -TREK1 activation enhances cognition, upregulates GLUT-1, and reduces glutamate and NMDAR levels.	Li et al. 2022
	THIK1	Lister hooded rats (female) Human AD postmortem brain tissue samples	8 weeks	It helps in upstream regulation for activating NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome	Increased gene expression levels. -Decrease in DNA methylation on KCNK13 (THIK1 gene) is observed.	Tang et al. 2023
Calcium-Activated K+ Channels (KCa)	**BK Channels**	3xTg mice Male 3xTg mice	4-monthold 3xTg and at P16–P18 4 to 5 months	Modulates neuronal firing and synaptic function. Improves memory and reduces Aβ levels.	-Enhanced activity following TMS treatment. -Increased BK channel activity helps ameliorate AD symptoms and promotes cognitive function.	Yamamoto et al. 2011; F. Wang et al. 2015; L. Wang et al. 2015
	IK/KCa 3.1	Tg6799 5xFAD mice hippocampal slices	4 and 10 months	Regulates microglial activation and synaptic plasticity.	-Increased expression -Increased activity in microglia, exacerbated by Aβ oligomers. -Inhibition reduces inflammation and LTP impairment.	Jin et al. 2019
	SK Channels	3xTg-AD mice brain slices TgCRND8 mice brain slices Human brain tissue	12-month 3–4 months Range 73–85 years, average 81 years	Modulates neuronal firing and excitability.	-Reduced activity drives dopaminergic neuronal hyperexcitability. -Elevated mRNA level. -Inhibition of CK2 restores SK channel function and normalizes firing in DA neurons.	Blankenship et al. 2023; Proulx et al. 2015; Murthy et al. 2008

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
Voltage Gated Ca^{2+} Channels	**L-Type**	Fischer 344 rat hippocampa l slices Mouse embryonic corti-cal neurons treated with Aβ 3xTG hippocampa l slices	24–27 months 3 days DIV Young(1 month old), middle-age d(6–9 month old), old(12–16 month old)	Regulates neuronal excitability, plasticity and calcium dependent gene transcription.	-Increased membrane localization during AD but expression remains unchanged. -Increased Activity in AD. -Increased Activity in the presence of Aß, leading the increased neuronal apoptosis.	Crossley et al. 2023
	T-Type	3xTg brain slices	2 months old	Regulates neuronal firing, nociception, neurotransmitter release, electrical automaticity	T-Type activator(ST101) reduces B-Amyloid content in 3xTg mice.	Green et al. 2011; Berridge 2014; Moriguchi et al. 2012
	P/Q-Type	Primary hippocampa l cultures from winstar rat E19 embryo Primary rat cerebellar granule and cortical neuron cultures	10–12 DIV 14 DIV	Regulates presynaptic vesicle release and regulates E/I balance	-Decreases P/Q currents when exposed to nanomolar range of Aβ in some models leading to decreased synaptic release. -Increases P/Q currents when exposed to Aβ at the micromolar range in some models	Nimmrich et al. 2008; Ramsden et al. 2002
	N-Type	Synaptosomes of cortices of Winstar rats (200-250g) Primary culture of rat cortical neurons Nerve endings of Win-star, Sprague Dawley and Long Evans rats	5–12 DIV 5 weeks old	Involved in neurotrans-mitter release and plays an important role in dendritic calcium influx	-Increased activity lead-ing to neuronal apopto-sis when exposed to Aβ -Exposing nerve endings to Aβ leads to increased glutamate release	MacManus et al. 2000 Bobich et al. 2004

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
Hyperpolar ization-acti vated and cyclic nucleotide-g ated (HCN) channels		Frozen human hip- pocampi from AD HCN1$^{-/-}$Mice	Brain Network Europe (BNE) stage VI 4 months old	Regulate neuronal excitability, and synaptic integration by controlling the flow of positively charged ions.	-Increased HCN channel expression, reduced dendritic branching, decreased synapse density, and vesicle clustering -Elevated Aβ42 levels in the cortex of HCN1-deficient mice -Activation of glial cells	Goniotaki et al. 2024; Saito et al. 2012; Zhang et al. 2024
Ligand-Gat ed Ion Channels	**N-methyl-Daspartate receptors (NMDAR)**	Hippocampus of 3xTg-AD mice	6-monthold	Mediates excitatory neurotransmission, syn- aptic plasticity, and	- Reduction in gluN2A and gluN2B subunits in synaptic NMDARs	Ortiz-Sanz et al. 2022; Alfaro-Ruiz et al. 2024
		CA1 and CA3 and the DG of the hippocampus in APP/PS1 mice Tg2576 cortex hAPP-J20 hiPSC derived neurons	12-month-old 12 month 12-month and 20- to 24-month old male and femalemice	Memory Formation	- Upregulation of these subunits in extrasyn- aptic NMDARs - Promotes endocytosis of synaptic NMDARs -Extrasynaptic NMDAR current increases in hAPP-J20 AD transgenic mice as well as in hiPSC derived neurons which is caused due to accumula- tion of oligomeric Aβ	Kurup et al. 2010; Talantova et al.2013; Ghatak et al. 2021
	α- amino- 3-hydroxy- 5-methyl- 4- isoxa- zolepro pionic acid receptor (AMPAR)	Cultured cortical neurons treated with 5 µM Aβ Double knockin (2×KI) mice, carrying human mutations in APP and PS-1	13 DIV 6 months	Mediates fast excitatory synaptic transmission	- Aβ oligomers medi- ate ubiquitination and removal from membrane - Decrease in synaptic AMPARs and cognitive decline	Guntupalli et al., 2016, 2017; E. H. Chang et al. 2006

Table 1 (continued)

Channel Type	Channel Subtype	Model System	Age Group/ Days in vitro of Cultures	Channel Function	Findings in AD	References
	Kainate receptors	Postmortem Human Brain APP/PS1 Transgenic Mice Astrocyte Culture	Average age 82 ± 3 years 6 month old 24 hr	Mediates excitatory Neurotransmission	-Significant reduction in AMPA, kainate, and metabotropic glutamate binding correlated with neuronal loss Synaptic KARs are selectively downregulated at mossy fiber–CA3 synapses. -Activation with kainic acid increases production of toxic APP breakdown products (Aβ1–40 and Aβ1–42).	Dewar et al. 1991 Barthet et al. 2022 Ourdev et al. 2019
	Gamma-ami nobutyric acid (GABA)	Human postmortem tissue of AD brain Micro transplanted cell membranes, isolated from temporal cortices of control and AD brains, into *Xenopus* oocytes	65–90 y	Inhibitory neurotransmission	- Age-dependent decline in GABA currents. - Faster desensitization and lower mRNA/ protein levels of GABA receptors.	Limon et al. 2012
	Glycine receptors	Hippocampus of 5×FAD mouse model Hippocampus of APP/ PS1 mice	4 months old 12-month-old	Inhibitory neurotransmission	- Loss of extrasynaptic inhibitory glycine receptors.	Jin et al. 2024; Kuhse et al. 2023
	Nicotinic acetylcholine	Postmortem Human Brain Tissue	80.6±8.0 years	Modulates cognitive Function, attention, and memory	- Reduced receptor density in frontal and temporal cortex in AD patients.	Pimlott et al. 2004; Rinne et al. 1991; Wevers et al. 2000
	Serotonin receptor	Postmortem Human Brain Tissue	80.2 ± 10.0 years	Regulates mood, anxiety, and cognitive functions	- Reduced receptor density in frontal and temporal cortex in AD patients.	Garcia-Alloz a et al. 2004; Lorke et al. 2006; Solas et al. 2021
	Purinergic receptor	Cultured adult human microglia treated with Aβ 42 Tg2576 mice hippocampi	10 to 14 days 19 and 24 months old	P2X7 receptor regulates cellular responses, immune response, inflammation, and cell death	-Upregulated Expression of Purinergic P2X7	McLarnon et al. 2006; Parvathenani et al. 2003

Bolded text indicates specific ion channel subtypes that have been studied in relation to Alzheimer's disease models

clinical decline is modest at about 30% (Cummings et al. 2023), indicating that further research is required for the development of effective therapies.

Receptor-based drugs like FDA-approved memantine, which act on NMDA receptors, have been shown to be efficacious in slowing the progression of moderate-to-severe Alzheimer's disease (Lipton, Curr Drug Targets 2007; Ghatak et al., Annual Review of Pharmacology and Toxicology 2021). However, their efficacy early on in the disease is low. Therefore, an understanding of ion channels affecting early AD is important.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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