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A REVIEW ARTICLE ON ROLE OF ION CHANNELS IN NEUROLOGICAL DISORDERS

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ABSTRACT

Ion channels are fundamental to neuronal excitability, synaptic transmission, and overall neurophysiological balance. Alterations in their function—whether due to genetic mutations, post- translational modifications, or pathological insults—are central to the onset and progression of numerous neurological disorders. This review discusses the physiological and pathological significance of four major classes of ion channels: sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-). Sodium channel dysfunction contributes to excitotoxicity and neuronal hyperexcitability observed in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Potassium channel alterations disrupt neuronal repolarization and glial homeostasis, influencing neuroinflammation and excitability in PD, AD, and epilepsy. Aberrant calcium signaling through voltage-gated calcium channels mediates oxidative stress, excitotoxic damage, and glial activation, thereby exacerbating neurodegenerative processes. Finally, impaired chloride homeostasis—primarily due to altered KCC2 or NKCC1 function—leads to a loss of inhibitory control and increased network hyperexcitability in epilepsy and AD. Understanding the mechanisms underlying ion channel dysfunction provides crucial insights into neurodegenerative pathophysiology and highlights novel therapeutic strategies targeting ion channel modulation for the prevention and management of neurological diseases.

KEYWORDS: Ion Channels, Neuronal Excitability, Channelopathies, Neurodegenerative Disorders, Therapeutic Modulation.

1.0 INTRODUCTION

Ion channels play a fundamental role in regulating neuronal excitability and synaptic communication by mediating the selective transmembrane passage of ions, thereby facilitating the generation and transmission of electrical signals within and among neurons.[1,2] Abnormalities in these channels, arising either from inherited mutations (channelopathies) or secondary pathological alterations, can disrupt normal neuronal activity and synaptic function, contributing significantly to the pathogenesis of various neurological disorders.[3] Given their critical role in neural signaling, ion channels have emerged as promising targets for pharmacological modulation and therapeutic intervention.[4]

Neurological disorders encompass a wide range of conditions that impair the central and peripheral nervous systems, leading to neurodevelopmental, sensory, motor, or cognitive dysfunctions, with etiologies that may be genetic or idiopathic in nature.[5] Many neurodegenerative and neurodevelopmental disorders are associated with altered neuronal excitability due to structural or functional perturbations in ion channels.[6]

Neurons transmit information through rapid electrical signaling that underlies sensation, movement, cognition, and emotion. Ion channels facilitate the selective conductance of sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) ions, thereby establishing the

resting membrane potential, shaping action potentials, and regulating intracellular calcium signalling.[7] Mutations, pathological insults, or drug-induced effects that compromise these channels can disturb ionic homeostasis and contribute to the onset of neurological diseases. Extensive preclinical and clinical studies have demonstrated that pharmacological regulation of ion channel activity can mitigate neurological symptoms, underscoring their therapeutic relevance.[8]

Neurological disorders represent a major global health challenge, accounting for 11.6% of disability- adjusted life years (DALYs) and 16.5% of total mortality worldwide. Elucidating the mechanisms underlying ion channel dysfunction and developing targeted strategies to restore their function are essential steps toward designing novel interventions to alleviate the burden of these disorders.[9] This review highlights four principal types of ion channels — sodium, potassium, calcium, and chloride — discussing their physiological functions, pathological alterations, and therapeutic implications in neurological diseases.

2.0 MAJOR ION CHANNELS IN NEUROLOGICAL DISORDERS

Four principal classes of ion channels are fundamental to neurological function and are implicated in the pathogenesis of various neurological disorders: sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels.

Mutations in specific sodium channel isoforms give rise to a group of disorders collectively known as channelopathies. Among these, sodium channels hold particular significance in genetic neurological conditions such as epilepsy and migraine. Epilepsy, one of the most prevalent neurological disorders, is characterized by recurrent seizures and may also be accompanied by cognitive, psychological, and social impairments.[10]

Potassium channels represent one of the most diverse and widely distributed ion channel families, expressed across nearly all cell types within the central and peripheral nervous systems. The principal pore-forming subunits of these channels are encoded by more than 90 distinct genes.[11-12]

Calcium channels are transmembrane proteins that open in response to membrane depolarization, allowing Ca^{2+} influx that mediates essential intracellular signaling processes. Their activation triggers a variety of physiological functions, including neurotransmission, muscle contraction, secretion, and gene expression.[13]

Chloride channels play a critical role in sustaining neuronal excitability and maintaining inhibitory neurotransmission. By regulating the flux of Cl^- ions, they modulate the hyperpolarizing actions of GABAergic and glycinergic signals, thereby ensuring a balance between excitatory and inhibitory inputs. Dysregulation or genetic defects in chloride channels and their associated transporters have been implicated in multiple neurological disorders.

3.0 ROLE OF SODIUM (NA^+) CHANNELS NEUROLOGICAL DISORDERS

3.1 Role of Sodium (NA^+) Channels In Alzheimer's Disease

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder characterized by irreversible neuronal and synaptic loss, accompanied by the accumulation of amyloid plaques within the brain. Clinically, AD manifests initially as memory impairment, which gradually progresses to global cognitive decline and the deterioration of multiple mental functions. Neuropathological features include neuronal degeneration in both the cerebral and limbic cortices, reactive gliosis, and extracellular deposition of amyloid aggregates closely associated with dystrophic neurons.

Additionally, activated phagocytic microglia and intracellular aggregates of hyperphosphorylated tau, forming neurofibrillary tangles, are hallmark features of the disease.[14]

Presenilins, which constitute part of the γ-secretase complex responsible for amyloid precursor protein (APP) processing, play a pivotal role in AD pathogenesis. Mutations in presenilin 1 (PS1) account for a significant proportion of familial, early-onset cases of AD, with more than 70 distinct PS1 mutations identified to date.[15]

Moreover, the cytoplasmic tail of APP undergoes various post-translational modifications that influence its cleavage and interaction with other proteins. Notably, phosphorylation at serine, threonine, and tyrosine residues has been proposed as a key regulatory mechanism governing APP processing and associated signaling pathways.[16]

3.2 Role of Sodium (NA^+) Channels in Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor disabilities that affects predominantly the dopaminergic neurons of the substantia nigra causing a decrease in dopamine levels in the striatum.[17] In a rat model of Parkinson's disease induced by 6-hydroxydopamine (6-OHDA), Wang and colleagues reported a dynamic upregulation of Nav1.1, Nav1.3, and Nav1.6 channel expression in the hippocampus at various time points following dopamine depletion.[18]

Administration of phenytoin, a sodium channel blocker that prolongs recovery from inactivation, significantly ameliorated cognitive impairments in these models. Similarly, in MPTP-treated PD mice, Nav1.1 expression was elevated in the external globus pallidus. Nav1.1 is particularly important for sustaining high-frequency

firing, and its modulation has been associated with the reduction of motor deficits and synchronous oscillatory activity, underscoring the therapeutic potential of sodium channel blockers such as phenytoin.[19]

Nav1.3 also appears to contribute to PD pathophysiology; re-expression of Nav1.3 in dopaminergic neurons of the substantia nigra was observed 49 days after 6-OHDA administration.[20]

Safinamide, a dual modulator of sodium and calcium channels, exhibits neuroprotective effects by inhibiting glutamate release triggered by aberrant neuronal activity.[21] Mechanistically, safinamide preferentially interacts with the inactivated state of voltage-gated sodium channels (VGSCs), maintaining them in an inactive configuration and thereby selectively suppressing pathological high-frequency discharges while preserving normal neuronal firing.[22]

3.3 Role of Sodium (Na^+) Channels In Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of unknown etiology, characterized by the progressive degeneration of upper and lower motor neurons.[23] The resulting neuronal loss leads to gradual atrophy of the neuromuscular system, culminating in paralysis and death typically within three to five years of symptom onset.[24] Currently, no treatment effectively halts or reverses the neurodegenerative process. However, two pharmacological agents riluzole and edaravone have been shown to modestly extend survival. Riluzole acts by modulating glutamate release and sodium channel activity, thereby reducing neuronal hyperexcitability and inhibiting the persistent current of voltage-gated sodium channels (VGSCs).[25]

The persistent sodium current arises from rapid activation followed by delayed inactivation of VGSCs, maintaining channels in an active state for several hundred milliseconds.[26] Increased cortical excitability is a prominent early feature of ALS, as demonstrated through transcranial magnetic stimulation studies. Animal models further corroborate this finding, revealing motor cortex hyperexcitability that triggers glutamate-mediated excitotoxic cascades via trans-synaptic mechanisms.[27-28]

Among sodium channel subtypes, Nav1.6 has been identified as a potential therapeutic target. Its expression within the primary motor cortex of G93A transgenic mice fluctuates during disease progression, influencing both neuronal excitability and persistent sodium current.[28] Additionally, sporadic ALS cases have been associated with heterozygous point mutations in SCN4A (encoding Nav1.4), such as Arg672His and Ser1159Pro, which render neurons more susceptible to depolarization-induced excitotoxicity.[30]

Whole-genome sequencing studies have also identified mutations in SCN7A (encoding NaX channels), resulting in loss-of-function alterations, disturbed sodium homeostasis, and enhanced neuronal excitability. Dysfunction of VGSCs thus appears to play a significant role in ALS pathogenesis, and elucidating these mechanisms may facilitate the development of novel therapeutic strategies, including personalized gene-based interventions.[30]

4.0 ROLE OF POTASSIUM (K^+) CHANNEL NEUROLOGICAL DISORDERS

4.1 Role of Potassium (K^+) Channel In Parkinson's Disease

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, is clinically characterized by akinesia and cognitive impairments. Pathologically, it is defined by the progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN) compacta, the intracellular accumulation of misfolded α-synuclein within Lewy bodies, and pronounced reactive microgliosis.[31] Previous studies have demonstrated that activation of microglial Kir6.1 channels mitigates DA neuronal degeneration induced by rotenone, primarily through the suppression of neuroinflammatory processes. Conversely, Kir6.1 deficiency exacerbates DA neuronal loss by promoting excessive microglial activation in PD model mice.[32]

Microglia exhibit two distinct activation states: the proinflammatory M1 phenotype, which releases cytokines contributing to neurotoxicity, and the anti-inflammatory M2 phenotype, which supports tissue repair and neuroprotection. Kir6.1 facilitates M2 polarization, whereas its knockdown shifts microglia toward the detrimental M1 phenotype via activation of the p38 MAPK–NF-κB signalling cascade, thereby accelerating DA neuron degeneration.[33] PD pathology is further associated with marked neuroinflammation, including reactive astrogliosis and elevated levels of proinflammatory cytokines.[33-34]

Among astrocytic ATP-sensitive potassium (KATP) channels, Kir6.1—but not Kir6.2—serves as the primary pore-forming subunit and exhibits anti-inflammatory properties. Astrocytic Kir6.1 channels contribute to neuroprotection by promoting mitochondrial autophagy and preventing DA neuronal degeneration, making them potential therapeutic targets for PD. In astrocytic Kir6.1 knockout mice, DA neuron loss and astrocyte reactivity in the SN compacta were markedly increased compared with controls. The absence of Kir6.1 led to enhanced astroglial NF-κB activation, resulting in extracellular release of complement factor C3, which interacted with neuronal C3a receptors (C3aR) to induce neuronal death. Thus, astrocytic Kir6.1 channels appear to prevent neurodegeneration in PD through astrocyte–neuron crosstalk mediated by NF-κB/C3/C3aR signalling.[35]

4.2 Role of Potassium (K^+) Channel in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cerebral atrophy, extracellular deposition of amyloid-β (Aβ) peptides, formation of neurofibrillary tangles composed primarily of hyperphosphorylated tau protein, and extensive loss of neurons and synapses, leading to dystrophic neurite formation. A key pathological hallmark of AD is the excessive accumulation of Aβ peptides in the extracellular matrix, resulting from an imbalance between their synthesis and clearance.[36]

ATP-sensitive potassium (KATP) channels are widely expressed in neurons, where they function as sensors of cellular energy metabolism. Among their subtypes, Kir6.2-containing KATP channels facilitate Aβ release from neurons, whereas Kir6.1-containing channels do not exhibit this effect. In a high-sucrose diet model, Kir6.2+/+ amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice demonstrated enhanced amyloidogenic APP processing and increased Aβ deposition, indicating the role of Kir6.2 channels in promoting AD-related amyloid pathology.[37]

Neuroinflammation and associated neuronal dysfunction mediated by activated microglia play a critical role in AD pathogenesis. Two potassium channels, KCa3.1 and KV1.3, are key regulators of microglial activation, influencing Ca^{2+} signaling and membrane potential.[38] Elevated KV1.3 expression has been observed specifically in microglia from AD patient brains, identifying KV1.3 as a pathologically relevant target in AD. Experimental studies have shown that KV1.3 is essential for Aβ oligomer-induced microglial proinflammatory activation and neurotoxicity, whereas pharmacological inhibition of KV1.3 in APP/PS1 mice alleviated amyloid burden, improved synaptic plasticity, and restored cognitive function.[39]

KV1.3 channel blockers suppress microglia-mediated neurotoxicity in vitro by downregulating the production of proinflammatory cytokines such as IL-1β and TNF-α through inhibition of the NF-κB and p38 MAPK signaling pathways. Similarly, the microglial KCa3.1 channel has been identified as a promising therapeutic target. The selective KCa3.1 inhibitor TRAM-34 effectively reduced neuroinflammation and provided neuroprotection in preclinical models of AD. Targeting KCa3.1channels can mitigate Aβ oligomer-induced neuronal damage, inhibit p38 MAPK phosphorylation, NF-κB activation, and nitric oxide production, and may also be beneficial in addressing cerebrovascular and traumatic comorbidities associated with AD.[40]

The two-pore domain potassium channel THIK-1 exhibits predominant expression in microglia compared to astrocytes and neurons in human brain tissue. Pharmacological inhibition of THIK-1 using selective modulators reduced IL-1β secretion from microglia, suggesting that THIK-1 may serve as a potential therapeutic target for modulating neuroinflammation in AD. Moreover, KV3.4 channels, which mediate fast-inactivating potassium currents critical for action potential repolarization, display dysregulation in AD. Prolonged exposure of primary astrocytes to Aβ oligomers led to a time-dependent upregulation of KV3.4 expression and channel activity.[41]

4.3 Role of Potassium (K^+) Channel In Epilepsy

The pathophysiology of epilepsy is primarily characterized by an imbalance between excitatory and inhibitory neuronal signaling within the central nervous system (CNS), a phenomenon largely attributed to ion channel dysfunction Among these, the KV7.2 and KV7.3 channels—responsible for generating the neuronal M-current—play a critical role in regulating neuronal excitability and represent important therapeutic targets for epilepsy management. The M-current stabilizes neuronal activity by modulating after-depolarization, resting membrane potential, and spike threshold, thereby influencing burst firing patterns and spike frequency adaptation in pyramidal neurons.[42-43]

Mutations in KCNQ genes, including KCNQ7, have been linked to hereditary forms of epilepsy, while pharmacological enhancement of the M-current demonstrates notable antiepileptic potential. Activators of KV7.2/7.3 channels such as retigabine, levetiracetam, and valproate exhibit therapeutic efficacy; however, some are limited by adverse effects. Emerging agents, including SCR2682 and cannabidiol, have shown promising results in experimental models of epilepsy.[44]

Mutations in KCa4.1 channels result in overactivation, characterized by increased maximal channel opening probability, which contributes to seizure susceptibility. Quinidine has been reported to partially suppress KCa4.1-related epileptic activity, though its clinical application is restricted by cardiotoxicity.[45]

Upregulation of microglial KV1.3 channels has also been implicated in epilepsy, where their activation promotes neuroinflammation via the Ca^{2+}/NF-κB signaling cascade. Pharmacological blockade of KV1.3 attenuates seizure frequency and suppresses proinflammatory cytokine production, suggesting a potential anti-inflammatory therapeutic strategy.[46]

Astrocytic Kir4.1 channels are essential for maintaining extracellular potassium buffering and regulating neuronal excitability. Dysfunction or downregulation of Kir4.1, or mutations in the KCNJ10 gene encoding this channel, impair K^+ and glutamate clearance, leading to neuronal hyperexcitability and seizure generation.[47] Decreased Kir4.1 expression has further been shown to upregulate brain- derived neurotrophic factor (BDNF) through activation of the Ras/Raf/MEK/ERK signaling pathway, thereby promoting epileptogenesis.[48] Restoration of astrocytic Kir4.1 expression during early epileptogenic

stages may thus serve as a promising therapeutic strategy for seizure prevention.[49]

5.0 ROLE OF CALCIUM (CA^{2+}) CHANNELS NEUROLOGICAL DISORDERS

5.1 Role of Calcium (Ca^{2+}) Channels Parkinson's Disease

In addition to the potassium channels involved in PD, calcium channels are also reported to have a close relationship with this disorder.[50] Aβ and tau aggregates in AD, α-synuclein contributes to Ca2+ dysregulation, which can lead to α-synuclein aggregation.[51]

Excessive L-type CaV activity in the substantia nigra (SN) renders neurons vulnerable to toxicity, and patients taking L-type CaV antagonists have a reduced incidence of PD.[52] Adult SN dopaminergic neurons are Ca^{2+}-dependent, and their basal activity is intrinsically driven by L-type CaV channels.[53] The CaV1.3 antagonist dihydropyridine can protect SN neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-mediated degeneration.[54]

Ca^{2+} entry through CaV1.3 elevates mitochondrial oxidant stress in SN compacta DA neurons.[55] The metabolic burden of removing cytosolic Ca^{2+} via ATP-dependent mechanisms contributes to oxidative stress.[56] Ca2+ during aging, resulting in older individuals becoming more vulnerable to neurotoxicity, but this can be modulated by CaV1.3 antagonists.[57]

Microgliosis occurs early in PD, and nimodipine (CaV1.2/CaV1.3 antagonist) protects neurons from inflammatory and toxic insults in a microglia-dependent manner.[58] Microglial CaV1.2 channels inhibit M1 activation and promote M2 activation, contributing to neuroprotection.[59] Knockdown of microglial CaV2.2 reduces microglia accumulation around the SN and improves functional deficits in PD models.[60]

5.2 Role of Calcium (Ca^{2+}) Channels Alzheimer's Disease

The "calcium hypothesis of AD" links age-associated intracellular Ca^{2+} dysregulation and the amyloidogenic pathway to cognitive dysfunction and neurodegeneration in AD.[61] Intracellular Ca^{2+} dysregulation is observed near Aβ plaque deposits in neurons, astrocytes, and microglia.[62–63]

Increased intracellular Ca^{2+} can interfere with synaptic plasticity and participate in excitotoxicity in neurons, dysregulate astrocyte-mediated hemodynamics, and perturb microglial responsiveness.[64–65] The AHP, which controls the threshold for LTP, is driven by L-type calcium channels, specifically CaV1.3.[66]

CaV1.2 knockout mice show decreased LTP in CA1 hippocampal neurons, while CaV1.3 knockout mice show impairments in amygdala neurons.[67-68] Aβ25–35 fragments upregulate CaV1.2, CaV2.1, and CaV2.2 mRNA and proteins in a time-dependent manner.[69] Surface protein levels of CaV1.3 are significantly increased by Aβ25–35, resulting in increased calcium entrance into the cell.[70]

CaV1.2 and CaV1.3 channels are detected in rodent cortical astrocytes, with increased expression in reactive astrocytes surrounding Aβ-positive plaques.[71] Expression of CaV1.2 α1-subunits in reactive astrocytes correlates with Aβ load in plaques, suggesting their involvement in AD pathology.[72]

5.3 Role of Calcium (Ca^{2+}) Epilepsy Disease

Temporal lobe epilepsy (TLE) represents the most prevalent form of drug-resistant epilepsy and is closely associated with pathological alterations in the neurons than the CA1 region, with nearly 95% of them exhibiting intrinsic burst-firing properties. These bursting neurons are highly excitable and play a pivotal role in seizure generation. Furthermore, CA3 neurons form direct synaptic connections with glial cells, suggesting that neuron-to-glia communication may contribute to epileptogenesis.[73-75]

Experimental evidence indicates a strong association between astrocytic calcium dynamics and seizure activity. Elevated intracellular Ca^{2+} levels in astrocytes have been correlated with the onset of seizure- like discharges in rat models. Similarly, spontaneous Ca^{2+} elevation has been observed in astrocytes cultured from patients with intractable epilepsy, reinforcing the link between astrocytic calcium dysregulation and epileptic activity.[77]

Notably, following pilocarpine-induced status epilepticus, upregulation of CaV1.3—but not CaV1.2—has been detected in reactive astrocytes within the hippocampal CA3 region. This finding suggests that CaV1.3 channels may mediate calcium oscillations in astrocytes, potentially contributing to the initiation, propagation, and maintenance of seizure activity. Additionally, the redistribution of CaV1.3 channels between the somatic and dendritic compartments of CA3 neurons may influence firing patterns, thereby modulating epileptic network excitability.[78] However, the mechanistic role of astrocytic CaV1.3 upregulation in epilepsy pathogenesis remains incompletely understood and warrants further investigation to elucidate its contribution to seizure dynamics.[79]

6.0 ROLE OF CHLORIDE (CL^-) CHANNELS NEUROLOGICAL DISORDERS

6.1 Role of Chloride (Cl^-) Channels in Epilepsy Disease

Epilepsy, a chronic neurological disorder marked by recurrent seizures, has been strongly associated with disturbances in chloride (Cl^-) homeostasis. Genetic mutations affecting genes that encode Cl^- channels (such as CLCN1, CLCN2, CLCN3, CLCN4, and CLCN6) and Cl^- transporters (including KCC2) have been directly

implicated in various epileptic syndromes, particularly in severe early-onset forms such as infantile migrating focal seizures. Both gain- and loss-of-function mutations in the CLCN2 gene, which encodes the ClC-2 channel, have been proposed to contribute to, though not solely cause, idiopathic epilepsy.[80]

Impaired function or altered expression of the Cl− cotransporters KCC2 and NKCC1 are frequently observed in epilepsy.[81-82] A reduction in KCC2 activity or expression, or an increase in NKCC1 activity, can lead to an accumulation of intracellular Cl−, resulting in a depolarizing shift in EGABA and a switch from inhibitory to excitatory GABAergic signaling, thus increasing neuronal excitabilityand promoting seizure generation.[83-84]

During periods of high neuronal activity, such as during a seizure, the influx of Cl− through activated GABAA receptors can overwhelm the extrusion capacity of KCC2, leading to an activity-dependent accumulation Of intracellular Cl−, which can further exacerbate neuronal hyperexcitability and contribute to the propagation and maintenance of seizure activity.[85] The consequent shift toward depolarizing GABAergic signaling, combined with a lowered action potential threshold, promotes synchronous neuronal firing and persistent hyperexcitability, ultimately driving seizure activity.[86]

6.2 Role of Chloride (Cl^-) Channels in Alzheimer's Disease

Mouse models harboring Alzheimer's disease (AD)-associated mutations demonstrate an early, pre-symptomatic reduction in the neuronal potassium–chloride cotransporter KCC2 within the hippocampus and prefrontal cortex. This loss compromises GABAergic inhibitory signaling and disrupts intracellular chloride (Cl^-) homeostasis. The degree of KCC2 reduction inversely correlates with age-dependent accumulation of amyloid-β42 (Aβ42), while acute Aβ42 administration has been shown to decrease membrane-bound KCC2, thereby impairing Cl^- extrusion and inducing network hyperexcitability.[87]

Although some studies report no significant change in overall KCC2 levels following Aβ42 exposure, prolonged treatment has been found to increase expression of the sodium–potassium–chloride cotransporter NKCC1, resulting in elevated intracellular Cl^- concentration ($[Cl^-]i$) and weakened inhibitory tone.[88] Pharmacological enhancement of KCC2 function, such as with CLP290, has been shown to restore spatial memory and social behavior in AD mouse models. Conversely, inhibition of KCC2 using VU0463271 impairs cognitive performance, underscoring the critical role of efficient Cl^- extrusion in maintaining synaptic and behavioral integrity.[89]

The amyloid precursor protein (APP) also serves as an endogenous regulator of KCC2 expression. Genetic deletion or knockdown of APP reduces KCC2 mRNA and protein levels, shifts the GABA reversal potential EGABA toward depolarized values, and increases neuronal excitability.[90]

Restoration of APP or exogenous administration of soluble APP-α rescues KCC2 expression and reinstates inhibitory signalling.[90] Mechanistically, APP modulates KCC2 expression both transcriptionally—via the APP intracellular domain (AICD)-dependent regulation of SLC12A5—and post-translationally, by stabilizing KCC2 at the plasma membrane.[91-92]

Oligomeric Aβ species and aberrant APP processing disrupt these regulatory mechanisms, leading to impaired KCC2 stability, reduced Cl^- extrusion, and diminished inhibitory synaptic strength.[108]

Augmenting KCC2 expression or activity has been shown to normalize EGABA and improve both synaptic and behavioral outcomes in preclinical models of AD.[93] Collectively, early neuronal hyperexcitability in AD appears primarily driven by KCC2 dysfunction, although NKCC1 upregulation may also contribute under certain pathological contexts. Elucidating the relative contributions and regulation of KCC2 and NKCC1 by Aβ and related molecular signals remains crucial for developing targeted neurotherapeutic interventions.[94]

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