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The Therapeutic Potential of Small-Conductance KCa2 Channels in Neurodegenerative and Psychiatric Diseases

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Abstract

Introduction—KCa2 or small-conductance Ca^{2+} -activated K^+ channels (SK) are expressed in many areas of the central nervous system where they participate in the regulation of neuronal afterhyperpolarization and excitability, and also serve as negative feedback regulators on the glutamate -NMDA pathway.

Areas covered—This review focuses on the role of KCa2 channels in learning and memory and their potential as therapeutic targets for Alzheimer's and Parkinson's disease, ataxia, schizophrenia, and alcohol dependence.

Expert opinion—There currently exists relatively solid evidence supporting the use of KCa2 activators for ataxia. Genetic KCa2 channel suppression in deep cerebellar neurons induces ataxia, while KCa2 activators like 1-EBIO, SKA-31 and NS13001 improve motor deficits in mouse models of episodic ataxia (EA) and spinal cerebellar ataxia (SCA). Use of KCa2 activators for ataxia is further supported by a report that riluzole improves ataxia in a small clinical trial. Based on accumulating literature evidence, KCa2 activators further appear attractive for the treatment of alcohol dependence and withdrawal. Regarding Alzheimer's disease, Parkinson's and schizophrenia further research, including long-term studies in disease relevant animal models, will be needed to determine whether KCa2 channels constitute valid targets and whether activators or inhibitors would be needed to positively affect disease outcomes.

Keywords

Afterhyperpolarization; alcohol dependence and withdrawal; Alzheimer's disease; ataxia; apamin; calcium-activated potassium channel; 1-EBIO; learning and memory; KCa2; NS13001; NS309; Parkinson's disease; riluzole; schizophrenia; small-conductance; SKA -31

1. Introduction

Calcium-activated potassium channels (KCa) play an important physiologic role in diverse cell types through their modulation of membrane potential and calcium signaling, thereby indirectly regulating downstream signaling pathways and cellular processes. The human genome contains eight ion channels classified as KCa channels (Figure 1), which are divided into two distinct groups based on their genetic relationship to each other, their single channel conductances, and their calcium-sensing mechanisms [1]. The first group comprises KCa1.1, KCa5.1, KCa4.1 and KCa4.2, all of which have relatively large single channel conductances. KCa1.1, also known as BK or Maxi-K, is activated by both membrane depolarization and increases in cytosolic calcium. KCa4.1, KCa4.2, and KCa5.1 are not activated by calcium, but have been grouped with the other KCa channels based on sequence

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and structural homology. The second group consists of KCa2.1, KCa2.2, KCa2.3, and KCa3.1. In contrast to the first group, the KCa2/3 channels are voltage-independent, have small single channel conductances and are accordingly commonly referred to as small-conductance (SK) channels. KCa3.1 has an intermediate single channel conductance and has therefore been termed intermediate-conductance (IK) channel, but is sometimes referred to as SK4. This article will focus on the small-conductance KCa2 channels, their role in learning and memory, and their potential as therapeutic targets for neurologic and psychiatric diseases.

Like other K^+ channels, functional KCa2 channels are tetramers [2] with six transmembrane segments per subunit and in this case an intracellular C terminus that is bound to the Ca^{2+} -binding protein calmodulin (Figure 2A). Calcium binding to calmodulin causes a conformational change that opens the channel [3] to allow K^+ efflux (Figure 2B). KCa2 channels are widely expressed throughout the body, being present in the adrenal glands, the heart, the kidneys, the liver, the prostate, the small intestine, the omentum, the myometrium, skeletal muscle, and even testes and ovaries [4]. In addition to their expression in these peripheral tissues, KCa2 channels are also found throughout the central nervous system. KCa2.1 and KCa2.2 are oftentimes co-expressed in neurons of the neocortex, the hippocampal formation, the amygdala, the cerebellum, and the brainstem, while KCa2.3 is present in the midbrain, the thalamus and hypothalamus, as well as subcortical regions [5–7]. All three KCa2 subtypes have also been found in the dorsal root ganglia and the spinal cord of rats, where they are thought to contribute to both nociceptive processes and motoneuron function [8,9]. KCa2 channel opening and the subsequent K^+ efflux have been shown to play an important role in many neuronal processes, such as afterhyperpolarization, as well as dendritic excitability and synaptic function and plasticity [10,11].

Regulation of KCa2 activity can be achieved in a variety of ways, including modulation of channel trafficking to the surface of the postsynaptic membrane, and modulation of the Ca^{2+} sensitivity of the C-terminal bound calmodulin. For example, protein kinase A (PKA) phosphorylates a serine residues on the C-terminus of the KCa2 channels, and phosphorylated KCa2 channels are thought to be trapped within the endoplasmic reticulum [12,13]. Alternatively, the Ca^{2+} sensitivity of the C-terminal bound calmodulin can also be modulated to regulate KCa2 activity. KCa2 channels have constitutively bound protein kinase CK2 and protein phosphatase 2A (PP2A), which function to phosphorylate and dephosphorylate KCa2-bound calmodulin, respectively [14,15]. CK2 phosphorylates calmodulin at threonine 80, reducing the apparent Ca^{2+} sensitivity approximately 5-fold, while PP2A dephosphorylates the calmodulin and augments the Ca^{2+} sensitivity. And since a total of four calmodulins are associated with a tetrameric KCa2 channel, it is of course possible to have partial phosphorylation thus permitting exquisite and dynamic regulation of the Ca^{2+} sensitivities of KCa2 channels in order to fine tune neuronal excitability.

2. Pharmacology

Similar to most other ion channels, KCa2 channels have not been crystallized, making structure-based drug design a difficult, if not impossible task. However, despite this impediment, KCa2 channels have a relatively well-developed pharmacology [16–18], and the existing arsenal of pharmacological tool compounds has been instrumental to understanding of the normal physiological as well as the pathophysiologic roles of KCa2 channels. The most well-known and widely used KCa2 blocker is the bee venom toxin apamin which inhibits the channel through an allosteric mechanism [19] by interacting with an outer pore histidine residue common to all KCa2 subtypes [19,20]. Other, less commonly used blockers, include but are not limited to, the scorpion toxins leiurotoxin I (also called

scyllatoxin) [21,22] and tamapin[23], and the bis-quinolinium cyclophanes UCL1684 and UCL1848 [24](Figure 3).

In addition to these blockers, KCa2 channels also have positive and negative gating modulators, which left-shift or right-shift the Ca^{2+} -response curve of these Ca^{2+} /calmodulin-gated channels, making the channels more or less Ca^{2+} sensitive [25]. The most commonly used positive gating modulators are 1-EBIO [26], NS309 [27], and SKA-31 [28], which activate all three KCa2 channels with equal potency. Examples of subtype specific KCa2 activators are CyPPA [29] and its recently published derivative NS13001, which activate KCa2.2 and KCa2.3 with EC_{50} values of 5.6 μM and 140 nM, respectively, but have no effects on KCa2.1 [30]. The carbamate GW542573X (Figure 3) in contrast selectively activates KCa2.1 channels, and has been termed “a true activator” because it can activate KCa2.1 even in the absence of Ca^{2+} [31,32].

1-EBIO, the oldest KCa2 activator, has been reported to have EC_{50} values ranging from 300 to 700 μM [16]. Despite its low potency, 1-EBIO reduces seizures induced by electroshock and subcutaneous metrazol (scMET) at concentrations of 10–80 mg/kg in mice, but causes profound sedation at 80 mg/kg [33]. The structurally related indolinone NS309 is significantly more potent than 1-EBIO, activating KCa2 channels at submicromolar concentrations [27]. However, NS309 has an extremely short half-life and blocks the cardiac K^{+} channel Kv11.1 (HERG) at a concentration of 1 μM , which prohibits its *in vivo* use [27]. More recently, riluzole was used as a starting point in a structure activity relationship study which lead to the identification of SKA-31 [28], a nonselective KCa channel activator, activating the intermediate-conductance KCa3.1 channel at 250 nM and all three KCa2 channels at 2 μM .

Similar to the positive gating modulators, negative gating modulators can also be nonspecific or subtype specific. NS8593, inhibits all three KCa2 channels at submicromolar concentrations [34], while the more recently described (–)+CM-TMPF and the structurally related (–)B-TMPF act as KCa2.1-selective positive and negative gating modulators with EC_{50} or IC_{50} values of 24 and 31 nM, respectively[35].

3. Therapeutic Potential of KCa2 Modulation

3.1 Learning and Memory

Learning and memory are based on changes in the number and strength of neural connections and involve new protein synthesis, morphologic changes in the cytoskeleton, and changes in trafficking of receptors and channels to and from the cell membrane [36]. Long term potentiation (LTP) is one of the best studied processes underlying learning and memory, in which repetitive stimulation of neurons leads to a lasting increase in synaptic strength [37,38], as seen in CA1 pyramidal neurons of the hippocampus. The two ionotropic glutamate receptors AMPA and NMDA are both excitatory receptors on postsynaptic membranes with a known role in LTP. Following glutaminergic stimulation, AMPA receptors open to allow influx of Na^{+} and depolarization of the cell. NMDA receptors, like AMPA receptors, are glutamate-gated, but are blocked by Mg^{2+} at resting membrane potentials [39,40]. The depolarization following Na^{+} influx through AMPA removes the Mg^{2+} block and allows extracellular Na^{+} and Ca^{2+} to flow into the cell and induce an excitatory postsynaptic potential (EPSP). In the hippocampus and amygdala, NMDA receptors are expressed on dendritic spines in proximity to KCa2 channels [41]. Studies by Ngo-Anh et al. using the Ca^{2+} chelators BAPTA and EGTA estimated the distance between the NMDA receptors and KCa2 channels to be in the range of 20–50 nm [42]. The influx of Ca^{2+} activates KCa2 channels, which then repolarize the cell through K^{+} efflux (Figure 4). The KCa2-induced repolarization then re-establishes the Mg^{2+} block in NMDA, thereby

acting as a negative feedback on the EPSP underlying the induction of LTP [41,43,44]. As noted above, in potentiated synapses, PKA phosphorylation of KCa2 channels inhibits trafficking of channels to the membrane, thereby down-regulating KCa2 activity to allow induction of LTP.

KCa2 channels can also affect learning and memory through their role in the medium afterhyperpolarization (mAHP) [2]. In many neurons, action potentials end with an AHP, which is a hyperpolarization phase that follows repolarization, and during which the membrane potential drops below the neuron's normal resting membrane potential. In most neurons the AHP can be divided into a fast, medium, and slow component. The medium AHP has been demonstrated in many neurons to be apamin-sensitive [45–56], therefore identifying KCa2 channels as one of the main mediators of the medium AHP. AHPs affect the neuron's firing frequency and can also cause a phenomenon called spike frequency adaptation, where bursts of action potentials lead to a summation of AHP that ultimately prevents further firing of action potentials [57]. Learning, is in part characterized by changes in the rate of hippocampal neuronal firing [58,59] as a result of reduced postburst AHP [60]. KCa2 channel activators like 1-EBIO and NS309 amplify the magnitude of the medium AHP and thus decrease the firing rate of CA1 pyramidal neurons [25,61]. In contrast, KCa2 blockers like apamin dampen the AHP and increase neuronal firing rates [25]. In a recent study of rats and mice learning the hippocampus-dependent trace eye-blink conditioning task, CA1 pyramidal and somatostatin-positive inhibitory neurons (SOMs) showed an increase in intrinsic excitability as a result of reduction in KCa2 channel mediated AHP [62]. In other words, KCa2 channels affect the intrinsic neuronal excitability through their role in afterhyperpolarization, and this reduction in KCa2-mediated AHP is associated with learning. It is, however, important to note that complete block of the mAHP with apamin can induce seizures and chronic infusion of apamin can cause Purkinje cell degeneration [63], and therefore, should KCa2 blockers ever be used therapeutically, dosing will be critical to prevent seizures and neurodegeneration.

Consistent with the underlying molecular biology described above regarding the role of KCa2 channels in learning and memory, KCa2.2 and KCa2.3 expression appears to be transiently depressed during the early stages of a spatial learning task [64], while several studies have shown that KCa2 blockers do indeed facilitate learning. Studies in mice and rats have demonstrated that apamin treated animals perform better in object recognition tasks [65,66], supporting the hypothesis that KCa2 blockade facilitates encoding of object memory. Apamin treatment also accelerates learning during training trials in the Morris water maze, with apamin treated mice requiring fewer trials to learn the location of a hidden platform [66]. Apamin has also been shown to mitigate scopolamine induced memory deficits [67]. These results all suggest that KCa2 blockade facilitates hippocampus-dependent spatial memory encoding.

The effects of KCa2 blockade on amygdala-dependent learning are more complex. Amygdala-dependent learning can be tested by the appetitive motivated response, as well as by through the passive avoidance test and the discrimination avoidance task. In a study by Messier et al. that tested the appetitive motivated response in mice, apamin at doses of 0.1 mg/kg, 0.2 mg/kg or 0.4 mg/kg was administered at three different time points: pre-training, post-training, and a delayed 3-hour post-training time point [68]. When given prior to training, apamin hastened the development of the bar-pressing response and increased bar-pressing rates, with the 0.4 mg/kg pre-training apamin group having the fastest response acquisition. This result would support the hypothesis that apamin accelerates memory acquisition, which then leads to increased behavioral activity. During the retention test, the animals that received 0.2 mg/kg apamin administered either pre-training or post-training had significantly more reinforced responses than the control animals, suggesting that apamin

also helps with memory retention. However, the group that received the higher dose of 0.4 mg/kg of pretraining apamin had significantly less reinforced responses than the control animals, but as was noted by the authors, the 0.4 mg/kg dose of apamin also caused behavioral changes, such as loss of equilibrium and total stretching, and alternating episodes of tonic-clonic seizures with periods of prostration, making the retention test results for the 0.4 mg/kg group difficult to interpret. Further complicating this story of KCa2 channel function on amygdala-dependent learning, Deschaux et al. tested the habituation and passive avoidance response in rats treated with apamin [69]. Interestingly, apamin had no effect on the performance of rats in a passive avoidance test, but in the habituation test, apamin, when injected before the memory acquisition stage, decreased exploratory activity (i.e. distance travelled and rearing), suggesting improved memory acquisition. These results suggest that apamin's effect on memory, are task dependent. Apamin does improve memory acquisition, but only in non-stressful situations like the habituation test. It does not appear useful in stressful situations like the passive avoidance test. Finally, it should also be noted that the effect of KCa2 blockade on memory retention is being debated with mixed research results. As has just been discussed, Messier et al. found that apamin at moderate doses improves memory retention. However, in a study using a discrimination avoidance task in young chicks, Baker et al. found that apamin treatment caused a persistent impairment of long-term memory [70]. Taken together, these studies on amygdala-dependent learning suggest that KCa2 blockade by apamin does help with memory acquisition in non-stressful situations, but apamin's effects on long term memory retention are still unclear.

In contrast to the studies mentioned above, which suggest that KCa2 blockade in certain situations, enhances memory acquisition and processing, studies evaluating KCa2 activation found that promoting KCa2 activity impairs learning. KCa2-overexpressing mice failed to learn the platform location in the Morris water maze even after extensive training [44]. It should also be noted that there is an increase in KCa2.3 expression in the hippocampus of aged mice which is possibly contributing to the age-related decline in LTP and performance in learning tasks [71]. The KCa2 channel activators NS309, 1-EBIO and CyPPA have further been shown to negatively impact certain memory processes. NS309 impaired trace eye-blink conditioning in an associative learning model in rats [72], and 1-EBIO and CyPPA have been shown to impair memory encoding in a spontaneous object recognition task [73]. As these studies have demonstrated, KCa2 channel activators appear to impair certain memory processes, and consequently, KCa2 channel activators have been proposed as a potential treatment of posttraumatic stress disorder (PTSD). PTSD is known to lead to amygdala hyperactivity in humans [74], and KCa2 channels play a role in regulating excitatory synaptic transmission and plasticity in the lateral amygdala [75]. Atchley et al. further demonstrated that KCa2 activators ameliorate the stress-induced neuronal hyperexcitability associated with basolateral amygdala-dependent fear memory [76].

Given how learning and memory is affected in many disease processes, we will now further delve into the potential of using KCa2 channels as a therapeutic target in conditions such as neurodegenerative diseases, ataxia, alcohol addiction, and schizophrenia.

3.2 Neurodegenerative Diseases

Many neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), can cause dementia in addition to other symptoms. Dementia is characterized by a significant decline in cognitive function, as found in a patient's medical history and mental status exam, with major impairments in learning and memory, in addition to one or more possible impairments in handling complex tasks, reasoning abilities, spatial and orientation abilities, and language [77,78]. Dementia is not the normal cognitive decline seen with aging, which is characterized by non-progressive, mild changes in memory and information processing.

AD is by far the most common cause of dementia [79] and has a significant morbidity associated with it. As the disease progresses, patients can become increasingly angry or passive. Other late changes seen with AD include hallucinations or delusions, disorientation, and bowel and bladder incontinence. Patients will eventually require help with basic everyday tasks like eating, dressing, and bathing. Treatments for AD include the cholinesterase inhibitors donepezil (Aricept®), rivastigmine (Exelon®), and galatamine (Razadyne®), which work to offset the drop in acetylcholine levels seen in AD (Table 1). The other alternative is memantine (Namenda®), an NMDA receptor blocker, which is typically used in combination with cholinesterase inhibitors. These medications are usually started as an eight week trial with routine monitoring of response and side-effects. Medications are stopped if there is no improvement or if intolerable side-effects occur. It is important to note that none of these medications offer a cure for AD and patients and their family can sometimes be disappointed with the results as the patient continues to worsen over time despite the medications. There is therefore a need for continued research in AD and dementia with the hopes of finding a better therapy.

KCa2 channels are a possible therapeutic target. AD and other neurodegenerative diseases exhibit alterations in Ca^{2+} signaling that affect neuronal signaling processes. For example, endoplasmic reticulum Ca^{2+} signaling is integral to synaptic function, and appears to be disrupted in many neurodegenerative diseases. In AD, presenilin (PS) mutations enhance ER Ca^{2+} release, causing Ca^{2+} dysregulation in the presynaptic terminals and dendritic spines, which consequently alters synaptic transmission [80–82]. Memory loss in AD models in fact correlates best with the degree of synaptic dysregulation, and the disruptions in normal Ca^{2+} balance occurs even before the amyloid and tau pathology is noticeable [83]. Interestingly, in 3xTg-AD mice that serve as an animal model of AD, there is an up-regulation of ryanodine receptor (RyR) activity. The consequent increase in RyR-mediated Ca^{2+} release from the ER appears to be compensated by an up-regulation of postsynaptic KCa2 channel activity [83]. Furthermore, abnormal increases in Ca^{2+} concentrations along with overstimulation of glutamate receptor-coupled Ca^{2+} channels, like the NMDA receptors, are well-recognized hallmarks of neuronal cell death [84]. This explains how the NMDA receptor blocker memantine might work in the treatment of AD, and suggests that targeting KCa2 channels might have therapeutic value by modulating their effects on Ca^{2+} signaling and NMDA receptors.

Interestingly, there is a notable increase in the inflammatory cytokine tumor necrosis factor- α (TNF- α) in brain tissue, cerebrospinal fluid and plasma of patients with AD, as well as in patients with other CNS diseases, and this increase in TNF- α appears to increase the expression of KCa2.2 channels in cortical neurons [85]. It is thought that the increase in KCa2.2 expression is a neuroprotective mechanism. TNF- α was shown in an *in vitro* model to be neuroprotective against glutamate-induced cell death, but its neuroprotective effects were neutralized by apamin blockade of KCa2 [86]. This data correlates with clinical data that demonstrated an improvement of neurologic symptoms in patients with multiple sclerosis (MS) who are taking riluzole (Rilutek®) [87,88], a compound that blocks sodium channels, activates KCa2 channels and inhibits glutamate release [89]. Similar neuroprotection has been found *in vitro* with NS309 [84] and with NS309 and 1-EBIO *in vivo* in experimental stroke models [43]. However, in an animal model of AD, in mice with partial hippocampal lesions and impairments in spatial reference and working memory, apamin treatment showed improvement of symptoms [90]. Therefore, although KCa2 channels clearly play an important role, further research is required to determine what exact effects KCa2 modulators will have on AD pathology and progression. It appears that activators of KCa2 channels may be neuroprotective, but as was discussed in the previous section on Learning and Memory, activation of KCa2 channels can worsen memory (Table

2). In contrast, KCa2 blockers alleviate memory deficits, but may not be neuroprotective (Table 2).

PD is another progressive neurodegenerative disease that, like AD, is associated with significant morbidity [91] and currently has no curative treatment. It is estimated to affect over 1 million people in North America [92]. The most prominent findings in PD are resting tremors, bradykinesia, rigidity, and in late disease, postural instability. Dementia is also a common finding in PD, and serves as an independent predictor of mortality [93]. PD is characterized by loss of dopaminergic neurons in the substantia nigra. Treatment therefore targets the dopaminergic pathway with levodopa, MAO B inhibitors such as selegiline (Eldepryl®), dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, anticholinergic agents, and amantadine (Symmetrel®) (Table 1). Levodopa is the most effective symptomatic treatment for PD, but it can cause dyskinesia and there are concerns that it may be neurotoxic. MAO B inhibitors may be neuroprotective, but only have modest effectiveness in symptomatic management. KCa2 channel modulators may offer some therapeutic hope. KCa2.3 channels are present in dopaminergic neurons of the substantia nigra based on their overlap in expression with dopamine synthesizing enzymes [94] and have been shown to modulate AHP and thus regulate the frequency of spontaneous neuronal firing and catecholamine release [95,96]. The KCa2 channel activator CyPPA decreases spontaneous firing rates and inhibits current-evoked action potentials in dopaminergic neurons in an activity dependent manner. CyPPA also decreases dopamine release and can offset the dopaminergic effects of methylphenidate, which is a dopamine and norepinephrine reuptake inhibitor [97]. Interestingly, in the rodent 6-hydroxy-DA (6-OHDA) model of PD, there is a phenotypic shift in the substantia nigra pars compacta (SNc) neurons from being tyrosine hydroxylase-positive (TH⁺) to being TH⁻ following administration of the neurotoxin 6-OHDA. This initial phenotypic shift is followed by a partial recovery of TH⁺ expression. A look at the electrophysiology of these TH⁺ and TH⁻ cells revealed that KCa2 inhibition shifts the TH⁺ phenotype to TH⁻, and conversely, KCa2 channel activation changes TH⁻ phenotype into TH⁺ [98]. These results all highlight both the importance of KCa2 channels in dopaminergic neurons and the difficulty in predicting the exact role KCa2 channel modulators will play in the treatment of PD, given the interesting and seemingly contradicting roles KCa2 channels play in modulating dopamine levels. As the study using the 6-OHDA PD model shows [98], positive modulation of KCa2 channels may potentially increase the number of dopamine synthesizing neurons and/or protect them from AMPA-receptor induced excitotoxicity [141]. On the other hand, KCa2 channel blockers increase dopamine release. More research will be required to further elucidate the potential of KCa2 channel modulators in treatment of PD (Table 2).

3.3 Cerebellar Ataxias

Ataxia is characterized by incoordination of muscle movement with abnormalities in gait, speech, and posture. Hereditary spinocerebellar ataxia (SCA) is the most common form of ataxia, with 31 SCA types, numbered from SCA1 to SCA36, out of which, SCA3 is the most common worldwide. There are many mutations associated with ataxia, and diagnosis is usually established by genotyping the patient [99]. For example, SCA3 is characterized by an expansion of the poly-CAG sequence in the ATXN3 gene, which codes for the ataxin-3 protein. Clinical presentation of SCAs is multifactorial with symptoms mostly resulting from damage to the cerebellum and its neuronal connections. No effective treatment is available, but small studies have investigated a variety of agents for treatment. For example, one report described transient improvement in cerebellar symptoms with zolpidem 10 mg in SCA2 [100], and an eight-week placebo-controlled trial of 20 patients with SCA3 found that varenicline led to improvement in some, but not all, measures of cerebellar dysfunction [101].

There has also been evidence suggesting the potential of KCa2 channel activators for the treatment of ataxia. KCa2 channels are expressed in the deep cerebellar nuclei (DCN) neurons, where Aizenman and Linden demonstrated that apamin can convert the normal regular firing into spontaneous burst firing [102], suggesting that KCa2 channels are important in regulating DCN excitability. Using transgenic mice that expressed a GFP-tagged dominant-negative alternative transcript of KCa2.3 (SK3-1B), Shakkottai et al. suppressed KCa2 channel expression in DCNs and produced mice that exhibited the classical symptoms of SCA [103]. The authors further showed that the changes in DCN firing rates occurred in the absence of any signs of neurodegeneration in the cerebellar cortex, particular Purkinje neurons, or other brain regions, suggesting that hyperexcitability of DCNs alone can cause ataxia. The same authors later used a mouse model of SCA3, which is characterized by Purkinje neuron hyperexcitability to test whether KCa2 activators could potentially improve motor deficits in ataxia as suggested by the observation that suppressing KCa2 channels in DCNs induces ataxia. Purkinje neurons, which are found to be degenerated in many SCAs, project inhibitory inputs onto the DCNs and thus reduce their spontaneous firing rates. In this later study, administration of the KCa2 activator SKA-31 partially corrected the abnormal Purkinje cell firing and improved motor function in the ataxic mice [104]. In another study, oral delivery of NS13001 alleviated both motor deficits and prevented Purkinje neuron degeneration in SCA2 transgenic mice [30], suggesting that KCa2 activators might not only acutely improve motor deficits but might actually be neuroprotective and prevent further neurodegeneration. KCa2 activation therefore holds definitive promise as a potential therapeutic approach for the treatment of SCA2 and SCA3 and possibly other cerebellar ataxias like episodic ataxia (EA). Episodic ataxia type-2 (EA2) is caused by mutations in the Cav2.1 α -subunit of P/Q-type voltage-gated Ca^{2+} channels, which are expressed at high densities in Purkinje cells. The mutations, which either decrease or increase channel activity, result in diminished precision of Purkinje cell pacemaking and KCa2 activators like 1-EBIO and chlorzoxazone have been shown to restore Purkinje cell pacemaking and to improve motor performance in EA2 mouse models [142–144].

In this context it should further be mentioned that riluzole (Rilutek®) has been found to reduce the ICARS score (International Cooperative Ataxia Rating Scale) in a small, randomized, double-blind, placebo controlled clinical trial evaluating its therapeutic potential in the management of cerebellar ataxia [105]. As mentioned before, riluzole is an interesting drug that exhibits various pharmacological activities [106], the most prominent of which are inhibition of neuronal voltage sodium channels at concentrations of 1–50 μM and activation of KCa2 channels with EC_{50} values of 20 μM . It therefore can be speculated that riluzole derives its potential benefits in ataxia at least in part from its KCa2 activation.

3.4 Schizophrenia

Ranked by the World Health Organization as among the top ten diseases contributing to global disease burden [107], schizophrenia is a psychiatric condition involving chronic or recurrent episodes of psychosis. Associated with impairments in social and occupational functioning, it is a highly disabling disorder. It is also medically costly, with an estimated overall cost of approximately \$63 billion in the United States in 2002 [108]. Occurring all over the world, schizophrenia's total prevalence is close to one percent with an incidence of 1.5 per ten thousand new cases per year [109]. Manifestations of schizophrenia include positive and negative symptoms. Positive symptoms depict amplification of normal processes [110] and typically include hallucinations or delusions and disorganized speech, while negative symptoms include flat affect or poverty of speech, and impairments in cognition including attention, memory and executive functions. Diagnosis is based on the presence of such symptoms, as well as social or occupational dysfunction for at least six months [111].

There are several neurotransmitter systems involved in the pathology of schizophrenia, including dopamine, glutamate, GABA, and acetylcholine. Excess dopamine in the mesolimbic tract has been hypothesized to cause the positive psychotic symptoms of schizophrenia, while reduction in dopamine in the prefrontal cortex is associated with the cognitive and negative symptoms [112]. Glutamate is the major central nervous system excitatory neurotransmitter, and having a hypoactive N-methyl-D-aspartate (NMDA) glutamate receptor has been hypothesized to contribute to the pathology of schizophrenia [113]. Gamma-amino-butyric acid (GABA) is the major central nervous system inhibitory neurotransmitter. GABA-ergic interneurons are essential in regulating prefrontal cortical function, via their modulation of glutamatergic pyramidal cells. There is evidence suggesting that these interneurons are dysfunctional in people with schizophrenia [114–116]. Derangements in acetylcholine are also hypothesized to contribute to schizophrenia's pathology as schizophrenic patients treated with nicotine or nicotinic cholinergic drug showed normalization of eye-tracking and EEG abnormalities [117–119]. However, since nicotinic acetylcholine receptors are capable of affecting many other neurotransmitter systems, it is not clearly understood whether there is primary disruption in the cholinergic system in schizophrenia or if the disruption is secondary to other pathological characteristics of the illness.

As mentioned above, the neurotransmitters dopamine, glutamate, GABA and acetylcholine play a role in the pathogenesis of schizophrenia, and currently these neurotransmitters represent the targets for pharmacological intervention for this disorder (Table 1). Drugs targeting these neurotransmitter systems have been shown in clinical trials to be effective in treating symptoms and behaviors associated with the disorder, but they are associated with significant side effects that can lead to non-compliance and discontinuation of the medications. There is therefore significant interest in evaluating other pharmacologic targets including KCa2 channels.

KCa2 channels can be found abundantly in the brain regions involved in schizophrenia, including the hippocampus, midbrain, and the limbic system [120–122]. In rat dopaminergic neurons, KCa2 channels work as the intrinsic pacemaker [95], and pharmacological blockade of KCa2 channels eliminates the medium AHP, resulting in bursting action potentials and increased release of dopamine [25,52,123–126]. As dopamine excess is one of the hypothesized underlying causes of schizophrenia, KCa2 channel activators may potentially benefit schizophrenic patients by reducing the hyperactive dopaminergic activity [16]. On the other hand, KCa2 channels play an important role as the negative feedback control on the glutamate-NMDA excitatory pathway. As we have just discussed, another suspected underlying pathology of schizophrenia is having hypoactive NMDA receptors [113]. So an interesting question is whether KCa2 channel activators will further depress NMDA receptor activity to worsen schizophrenic symptoms or whether KCa2 channel activators will improve symptoms by mitigating a hyperactive dopaminergic pathway.

3.5 Alcohol Dependence and Abuse

The Joint Committee of the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine defined alcoholism as a “primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal” [127]. In 2004, the World Health Organization estimated that 76.3 million had alcohol-use disorders. In the United States, the 2008 National Survey on Drug Use and Health revealed that more than 23.3 percent of the population had participated in binge drinking in the 30 days prior to the survey (58.1 million people) and 6.9 percent (17.3 million) reported heavy drinking. While the average American's alcohol intake has decreased over the past 50 years, the incidence of alcohol use disorders has not changed [128].

The common characteristics of alcohol dependence include loss of control over drinking, increased desire to consume alcohol, continued use despite adverse consequences, and denial. Alcohol use disorders are associated with tremendous health, economic and social adverse consequences [129,130]. Alcohol can be a significant contributing factor to various medical conditions involving the liver, lungs, pancreas, heart, central and peripheral nervous system [131] and is also associated with cancers of the mouth, esophagus, pharynx, larynx, and breast [132]. Several psychiatric disorders, including depression, eating disorders, and anxiety disorders are also associated with alcohol use [133]. Although effective psychosocial interventions are available, medications are still needed to treat alcohol abuse and dependence [134] since as much as 70 percent of individuals relapse after psychosocial treatment alone [135]. Currently, the pharmacologic treatment of alcohol abuse and dependence focuses on altering the reinforcing effects of alcohol by targeting neurotransmitter systems which interact with the corticomesolimbic dopamine (CMDA) pathway (Table 1). The pharmacotherapies used for alcoholism, include the opioid antagonist naltrexone and the glutamate receptor modulator acamprostate, and only have moderate benefits or are only effective for a subset of alcoholics [129].

Given the multiple burdensome health, economic, and societal consequences that can result from alcohol dependence, there is tremendous interest in identifying new pharmacological treatments. Recent studies have outlined the potential of KCa2 channel activators as novel treatments of alcohol abuse. Hopf et al. found that long-term, voluntary alcohol intake is associated with reduced KCa2 channel function and increased excitability in neurons from the nucleus accumbens core [136]. This decrease in KCa2 channel function with an associated enhanced spike firing is thought to underlie the motivation to seek alcohol during abstinence. Hence, direct 1-EBIO infusion, which inhibits neuronal firing, reduces alcohol seeking behavior during abstinence in rats [140]. In another study the FDA-approved muscle relaxant chlorzoxazone, which activates KCa2 channels at high micromolar concentrations, was found to dose dependently reduce excessive alcohol intake in rats with intermittent access to alcohol [137]. It should be noted that KCa2 activators seem to only reduce intake of rewards (including alcohol) under conditions where there is reduced KCa2 function, which could represent a selective intervention to decrease alcohol consumption. An important complication of excessive use of alcohol is alcohol withdrawal. Alcohol withdrawal symptoms can range from minor tremulousness, anxiety, headache, to major palpitations, delirium tremens, and life threatening grand mal seizures [138]. These symptoms can begin within four to twelve hours after alcohol cessation, but can appear as late as a few days later. The current treatment of alcohol withdrawal involves benzodiazepines, but their use is associated with increased severity of withdrawal and relapse rates [139]. Therefore, there is a need for identifying novel pharmacological targets for the treatment of alcohol withdrawal. Recent data have shown that the KCa2 channel activators 1-EBIO and chlorzoxazone counter the reduction in KCa2 channel function caused by continuous alcohol exposure in a mouse model of alcohol dependence [140]. Furthermore, the results demonstrated that KCa2 channel activators attenuated acute withdrawal-related epileptiform burst firing and neurotoxicity, suggesting that restoring KCa2 channel activity can prevent the deleterious consequences of alcohol withdrawal (Table 2).

4. Conclusion

KCa2 channels are expressed throughout the central nervous system, including the hippocampus, amygdala, cerebellum and substantia nigra and play crucial roles in neuronal afterhyperpolarization, negative feedback regulation on NMDA induced long term potentiation, and controlling intrinsic neuronal excitability. These multiple roles are intriguingly complex and hold much untapped therapeutic potential for the management of

neurodegenerative and psychiatric diseases. This complexity is highlighted by the many, varied effects modulation of KCa2 channels has on neuronal function. At the basic level, KCa2 activators reduce neuronal excitability and appear to be neuroprotective, while KCa2 inhibitors increase excitability and seem to be able to improve learning and memory. However, since KCa2 channels are powerful regulators of neuronal excitability, both KCa2 inhibitors and activators need to be dosed carefully, otherwise they are prone to induce seizures in the case of the inhibitors and sedation in the case of the activators. This careful dosing is of course no different from many other currently used CNS drugs, and the more challenging task is to get a clearer understanding of the therapeutic potential KCa2 modulators hold for the management of neurologic and psychiatric diseases such as Alzheimer's disease, Parkinson's disease, ataxia, alcohol dependence, and schizophrenia, and to determine whether KCa2 activators or inhibitors are more beneficial for the particular disease or condition.

5. Expert Opinion

In our opinion, there currently exists relatively solid evidence supporting the use of KCa2 activators for the symptomatic treatment of ataxia. As discussed above, genetic KCa2 channel suppression in the DCNs induces ataxia in mice [103], while pharmacological KCa2 channel activation with KCa2 activators from two different chemotypes improves motor deficits in SCA2 [30] and SCA3 [104] mice suggesting that KCa2 activators might be useful for the treatment of these two types of ataxias and potentially also for other ataxias associated with Purkinje neuron degeneration and uncontrolled DCN firing. This therapeutic hypothesis is further supported by the findings that 1-EBIO and chlorzoxazone improve motor performance in models of episodic ataxia [142–144] and that riluzole, a mixed sodium channel blocker and KCa2 channel activator, which however also has other pharmacological actions, has been reported to alleviate the symptoms of diverse forms of ataxia in a small, double-blind, placebo-controlled clinical trial in Italy [105]. Taken together, the animal and human trial data are very suggestive and we therefore believe that a selective KCa2 activator like the recently reported NS13001 should be tested in ataxia, especially since this compound also appears to have been neuroprotective in SCA2 mice and to have prevented further Purkinje neuron degeneration [30], raising the hope that KCa2 channel activators might potentially be able to delay the progression of ataxia and not only provide symptomatic relieve to patients. A remaining concern for the therapeutic use of KCa2 activators is of course their potential negative effect on learning and memory (Table 2), which for a devastating and severely disabling disease like ataxia, is probably less of a concern, than for other potential indications.

Another condition, for which it is increasingly becoming clear that KCa2 activators might be therapeutically useful, is alcohol abuse. Alcohol dependence in rodents is clearly associated with reduced KCa2 activity in the nucleus accumbens [136]. However, so far only KCa2 activators of relatively low potency and selectivity like 1-EBIO or chlorzoxazone have been shown to reduce excessive alcohol seeking in rodents, and it therefore would be desirable if more potent and selective KCa2 activators could be shown to reduce alcohol seeking and ease the symptoms of alcohol withdrawal.

There also is quite a substantial body of evidence supporting the use of KCa2 inhibitors to improve learning and memory. Apamin clearly facilitates hippocampus-dependent spatial memory encoding and seems to help with amygdala-dependent memory acquisition in non-stressful situations. However, the effect of KCa2 channel inhibition on long term memory retention currently remains unclear. It should of course again be pointed out in this context, that KCa2 blockers like apamin are prone to induce seizures and that memory enhancement with KCa2 blockers accordingly has a narrow therapeutic window.

As highlighted in this review, KCa2 channels are also being discussed as potential targets of AD, PD and schizophrenia because of their involvement in long-term potentiation and regulation of neuronal excitability. However, for all three diseases it currently is not clear what effects KCa2 modulators will have on AD and PD pathophysiology and progression and further research, including long-term studies in disease relevant animal models, will be needed to determine whether KCa2 channels constitute potential targets and whether activators or inhibitors would be needed to positively affect disease outcomes. For example, in AD it currently seems likely that KCa2 channel activators might be beneficial by being neuroprotective, but could potentially worsen memory. In contrast, KCa2 blockers might potentially alleviate memory deficits, but may not be neuroprotective and conversely even further accelerate neurodegeneration (Table 2). Similar in PD, positive modulation of KCa2 channels may potentially increase the number of dopamine synthesizing neurons, while KCa2 inhibition seems to increase dopamine release. So, in these cases, the field currently faces an interesting dilemma as both KCa2 activators and blockers could potentially be useful and harmful, or perhaps both types of modulations might be beneficial, but in different stages of these long-term diseases.

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Highlights

- KCa2 channels are expressed throughout the central nervous system and play crucial roles in controlling neuronal excitability, afterhyperpolarization, and long term potentiation.
- At the basic level, KCa2 activators reduce neuronal excitability and appear to be neuroprotective, while KCa2 inhibitors increase excitability and seem to be able to improve learning and memory.
- KCa2 activators are therapeutically attractive for the treatment of ataxia based on the facts that KCa2 channel suppression in deep cerebellar neurons induces ataxia, while KCa2 activators like 1-EBIO, SKA-31 and NS13001 improve motor deficits in mouse models of episodic ataxia (EA) and spinal cerebellar ataxia (SCA).
- Riluzole, a drug that in addition to engaging other targets activates KCa2 channels, has been reported to improve the symptoms of ataxia in a clinical trial.
- Based on rodent models of alcohol dependence and withdrawal KCa2 activators constitute promising drug candidates for the treatment of alcohol dependence.
- KCa2 channels have been suggested as possible targets for Alzheimer's disease, Parkinson's and schizophrenia, but further research will be needed to determine whether KCa2 channels constitute valid targets and whether blockers or activators will be beneficial.

	Channel Topology	γ [pS]	Gating	Expression	Function
KCa1.1 (BK, Slo, Slo1, maxi K, KCNA1)		260	Voltage $\mu\text{M Ca}^{2+}$ $\mu\text{M Mg}^{2+}$	CNS, skeletal and smooth muscle, adrenal cortex, cochlear cells, pancreatic islets	Fast AHP in neurons; Ca^{2+} sparks in smooth muscle
KCa5.1 (Slo3, KCNU1 KCNMC1)		106	Voltage and alkalization	Testis, spermatocytes	pH-triggered membrane hyperpolarization during sperm capacitation
KCa4.1 (Slack, Slo2.2, KCNT1)		60-165	Voltage, $\mu\text{M Na}^+$ and Cl^-	CNS, kidney, testis	Fast AHP in MNTB neurons; slow AHP; assists Na^+ and Cl^- absorption in Henle's loop
KCa4.2 (Slack, Slo2.1, KCNT2)		141	Voltage, $\mu\text{M Na}^+$ and Cl^-	CNS, heart, kidney, testis, lung, liver	Slow AHP; adaptation of firing rates
KCa3.1 (SK4, IK1, IKCa1, KCNN4, Gardos channel)		11-40	Ca^{2+} via CaM	T and B cells, lung, pancreas, colon, spleen, lymph node, erythrocytes, fibroblasts, proliferative vascular smooth muscles, vascular endothelium	Volume regulation in erythrocytes; Ca^{2+} signal in T cells; proliferation; fluid secretion; EDH response
KCa2.1 (SK1, SKCa1, KCNN1)		2-9	Ca^{2+} via CaM	CNS, enteric neurons, dorsal root ganglia, heart	Medium AHP in neurons
KCa2.2 (SK2, SKCa2, KCNN2)		2-9	Ca^{2+} via CaM	CNS, adrenal glands, liver, heart, skeletal muscle, Jurkat T cells	Medium AHP in neurons
KCa2.3 (SK3, SKCa3, KCNN3)		2-9	Ca^{2+} via CaM	CNS, skeletal muscle, liver, pituitary, myometrium, prostate, vascular endothelium	Medium AHP in neurons; EDH response

Figure 1.

KCa channel topology, properties, expression and physiological function. Residues involved in apamin binding are highlighted in the S3–S4 loop of KCa2.1, KCa2.2 and KCa2.3.

Figure 2.

KCa2 channels are Ca²⁺-activated K⁺ channels. (A) KCa2 channel monomer with 6 transmembrane segments (S1–6). The CK2 binding site is on the intracellular N-terminus, while the calmodulin (CaM) and PP2 binding sites are on the intracellular C-terminus. The pore forming loop is between S5 and S6. (B) Ca²⁺ binding to calmodulin promotes opening of the channel to allow K⁺ efflux. Sources of Ca²⁺ include Ca²⁺ influx through Ca²⁺ channels and Ca²⁺ release from the endoplasmic reticulum.

Subtype	Positive Gating Modulators	Negative Gating Modulators	Blockers
KCa2.1	1-EBIO, NS309, SKA-31, GW542573X, (-)-CM-TMPF	NS8593, (-)-B-TMPF	apamin, UCL1684, UCL1848, tamapin, leiurotoxin-I, bicuculline, (+)-tubocurarine, dequalinium
KCa2.2	1-EBIO, NS309, SKA-31, CyPPA, NS13001	NS8593	apamin, UCL1684, UCL1848, tamapin leiurotoxin I, Lei-Dab ⁷ , bicuculline, (+)-tubocurarine, dequalinium
KCa2.3			apamin, UCL1684, UCL1848, tamapin, leiurotoxin I, (+)-tubocurarine,

UCL1684

UCL1848

Bicuculline

1-EBIO

NS309

SKA-31

NS8593

NS13001

CyPPA

GW542573X

CM-TMPF

B-TMPF

Figure 3.

Figure 4.

KCa2 channels provide negative feedback regulation on the glutamatergic-NMDA pathway. Glutamate binding opens AMPA receptors to allow cation influx. However, NMDA receptors are initially blocked by Mg^{2+} , and so despite glutamate binding, there is no Ca^{2+} influx through the NMDA receptor. The influx of cations through AMPA depolarizes the membrane and removes the Mg^{2+} block on the NMDA receptor, allowing Ca^{2+} influx. Responding to the increase in Ca^{2+} concentration, KCa2 channels open to allow K^+ efflux, which repolarizes the membrane and reestablishes Mg^{2+} block of the NMDA receptors

Table 1

Examples of available treatment for AD, PD, alcohol dependence and abuse, and schizophrenia

Condition	Examples of available treatments	Mechanism of action
Alzheimer's Disease	Donepezil, Rivastigmine, Galatamine	Cholinesterase inhibitor
	Memantine	NMDA receptor antagonist
Parkinson's Disease	Levodopa	Dopamine precursor
	Selegiline, Amantadine	MAO B inhibitor
	Tolcapone, Entacapone	Catechol-O-methyl transferase (COMT) inhibitors
	Trihexyphenidyl, Benztropine	Anticholinergic agents
	Bromocriptine, Pramipexole, Ropinirole, Rotigotine, Apomorphine	Dopamine agonists
Alcohol Dependence/Abuse	Naltrexone	Blockade of μ -opioid receptors
	Acomprostate	Modulates glutamate receptors
	Disulfiram	Inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde
Schizophrenia	First generation/typical agents	Block receptors in the brain's dopamine pathways *Loxapine has anti-serotonin 5HT ₂ activity **Thiothixene has anti- cholinergic and α -blocking effects
	Chlorpromazine, Fluphenazine, Haloperidol, Loxapine*, Perphenazine, Pimozide, Thiothixene**, Thioridazine, Trifluoperazine	
	2nd generation/atypical agents	Block receptors in the brain's dopamine and serotonin pathways
	Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone	

Table 2

Summary of the therapeutic potential of KCa2 modulators

Condition or Disease	Physiological Role of KCa2 Channels and Effect of Modulation	Potential Therapeutic Benefits and Problems
Learning and Memory	<ul style="list-style-type: none"> KCa2 channels are involved in LTP and mAHP [2, 41, 43,44] KCa2 blockers increase neuronal firing frequency [25] and strengthen LTP KCa2 activators reduce neuronal firing [26,61] 	<ul style="list-style-type: none"> KCa2 blockade with apamin improves hippocampus dependent learning in rodents [65–67] <i>Higher doses of KCa2 blockers induce seizures and possibly neurodegeneration [63]</i> KCa2 activators reduce fear memory in mice suggesting KCa2 activators for PTSD [75,76] <i>KCa2.2 overexpression [44] and KCa2 activators [72,73] affect performance in memory tasks</i>
Alzheimer's Disease	<ul style="list-style-type: none"> AD and mouse models associated with Ca²⁺ dysregulation [80–83] Increased KCa2.2 expression thought to be a neuroprotective counter-regulation [85,86]; KCa2 activators are neuroprotective [43,89] Apamin improves memory in an AD model [90] 	<ul style="list-style-type: none"> KCa2 activators might be useful in AD as neuroprotectants <i>KCa2 activation could affect learning and memory [44,72,73]</i> KCa2 blockers could improve memory <i>KCa2 blockers might induce neurodegeneration</i>
Parkinson's Disease	<ul style="list-style-type: none"> KCa2 channels modulates firing and catecholamine release in dopaminergic neurons [94–96] KCa2 activators reduce DA release [97] but shift the phenotype of TH⁻ into TH⁺ neurons [98] 	<ul style="list-style-type: none"> Currently not clear whether KCa2 channels are targets and whether blockers or activators are needed
Ataxia	<ul style="list-style-type: none"> KCa2 channels regulate firing in DCNs [102] and genetic KCa2 suppression in DCNs induces ataxia in mice [103] KCa2 activators restore Purkinje cell pacemaking in SCA and EA mouse models [104, 142–144] 	<ul style="list-style-type: none"> KCa2 activators proposed for treatment of ataxia since they improve motor deficits [104, 142–144] and prevent Purkinje cell degeneration [30] in SCA and EA mouse models Riluzole alleviated ataxia symptoms in a clinical trial [105]
Schizophrenia	<ul style="list-style-type: none"> KCa2 channels modulates firing and catecholamine release in dopaminergic neurons [94–96] 	<ul style="list-style-type: none"> Currently not clear whether KCa2 channels are targets and whether blockers or activators are needed
Alcohol Dependence	<ul style="list-style-type: none"> long-term alcohol intake associated with reduced KCa2 channel function in rodents [136] 	<ul style="list-style-type: none"> KCa2 activators reduce alcohol seeking and withdrawal symptoms in rodents [137,140] suggesting KCa2 activators for the treatment of alcohol dependence