



K_{Ca}2 and K_{Ca}3 channels in learning and memory processes, and neurodegeneration

Els F. E. Kuiper¹, Ad Nelemans^{1*}, Paul Luiten¹, Ingrid Nijholt¹, Amalia Dolga² and Uli Eisel¹

¹ Molecular Neurobiology, University of Groningen, Groningen, Netherlands

² Institut für Pharmakologie und Klinische Pharmazie, Philipps-Universität Marburg, Marburg, Germany

Edited by:

Nick Andrews, Pfizer, UK

Reviewed by:

Alasdair Gibb, University College London, UK

Mariela Fernanda Perez, Universidad Nacional de Cordoba, Argentina

*Correspondence:

Ad Nelemans, Department of Molecular Neurobiology, University of Groningen, Nijenborgh 7, 9747 AG Groningen, Netherlands.
e-mail: s.a.nelemans@rug.nl

Calcium-activated potassium (K_{Ca}) channels are present throughout the central nervous system as well as many peripheral tissues. Activation of K_{Ca} channels contribute to maintenance of the neuronal membrane potential and was shown to underlie the afterhyperpolarization (AHP) that regulates action potential firing and limits the firing frequency of repetitive action potentials. Different subtypes of K_{Ca} channels were anticipated on the basis of their physiological and pharmacological profiles, and cloning revealed two well defined but phylogenetic distantly related groups of channels. The group subject of this review includes both the small conductance K_{Ca}2 channels (K_{Ca}2.1, K_{Ca}2.2, and K_{Ca}2.3) and the intermediate-conductance (K_{Ca}3.1) channel. These channels are activated by submicromolar intracellular Ca²⁺ concentrations and are voltage independent. Of all K_{Ca} channels only the K_{Ca}2 channels can be potently but differentially blocked by the bee-venom apamin. In the past few years modulation of K_{Ca} channel activation revealed new roles for K_{Ca}2 channels in controlling dendritic excitability, synaptic functioning, and synaptic plasticity. Furthermore, K_{Ca}2 channels appeared to be involved in neurodegeneration, and learning and memory processes. In this review, we focus on the role of K_{Ca}2 and K_{Ca}3 channels in these latter mechanisms with emphasis on learning and memory, Alzheimer's disease and on the interplay between neuroinflammation and different neurotransmitters/neuromodulators, their signaling components and K_{Ca} channel activation.

Keywords: small conductance calcium-activated potassium channels, SK channels, learning and memory, neurodegeneration

INTRODUCTION

It is widely accepted that the trigger for neurotransmitter release is the entry of calcium ions (Ca²⁺) into the presynaptic terminal (Ghosh and Greenberg, 1995). Because of this role of Ca²⁺ in neurotransmitter release, many neuronal functions are dependent on dynamics of Ca²⁺ signaling. Resting levels of intracellular free Ca²⁺ ([Ca²⁺]_i) in neurons are maintained at very low levels, but can be increased by influx of extracellular Ca²⁺ through voltage-, receptor-, or store-operated channels on the plasma membrane or by release from intracellular Ca²⁺ stores, predominantly the ryanodine receptor and inositol trisphosphate (IP₃) receptor dependent endoplasmic reticulum (ER). Most Ca²⁺ signals are delivered as brief transients with spatial and temporal properties. The frequency of the repetitive transients and the [Ca²⁺]_i obtained encode information to control cellular processes. Also the localization of these events at specific regions of the cell (Ca²⁺ microdomains), for instance at the plasma membrane or ER, contribute to the regulation of these cellular processes (Berridge, 2006). The regulation of these dynamics of the [Ca²⁺]_i at the Ca²⁺ microdomain level is critical for proper neuronal activity, because insufficient levels of [Ca²⁺]_i can lead to impaired functioning whereas excessive cytosolic [Ca²⁺]_i levels can cause overstimulation and ultimately cell death (Berridge et al., 1998).

One way to maintain appropriate intracellular [Ca²⁺]_i is repolarization of the membrane potential by initiating K⁺ efflux from the cell. Increased K⁺ permeability in response to elevated cytosolic [Ca²⁺]_i was first described in human erythrocytes (Gardos, 1958). Slow hyperpolarizing effects observed after stimulation of adrenergic, cholinergic, or purinergic pathways in smooth muscles of the gastrointestinal tract were caused by such an increase in K⁺ permeability as detected by the use of apamin (Banks et al., 1979; Maas and Den Hertog, 1979; Shuba and Vladimirova, 1980; Den Hertog, 1982). This neurotoxic polypeptide was isolated from bee-venom and, when injected in rodents in purified form, exerted severe uncoordinated movements of the skeletal musculature increasing to spasms and convulsions of apparently spinal origin after a dose-dependent lag time (Habermann, 1984). Apamin specifically blocks Ca²⁺-activated K⁺ channels and turned out to be the archetypical blocker for these channels. Such a specific blockade was demonstrated for the first time in guinea-pig taenia caeci in which changes in membrane potential and muscle contraction were measured using the sucrose-gap method in combination with ⁴²K⁺ efflux (Den Hertog, 1981) and in differentiating neuroblastoma cells using voltage-clamp electrophysiology (Hugues et al., 1982). Voltage-insensitive Ca²⁺-activated K⁺ channels of the small conductance-type (K_{Ca}) were later identified to carry these apamin-sensitive currents (Blatz and Magleby, 1986).

PHARMACOLOGICAL AND MOLECULAR PROPERTIES

Based on their pharmacological and molecular properties a number of different Ca²⁺-activated K⁺ channels can be identified. The International Union of Pharmacology has put the Ca²⁺-activated K⁺ channels into one family which can be subdivided into two functionally defined, but genetically unrelated groups (Wei et al., 2005). The first group consists of four voltage-insensitive Ca²⁺-activated K⁺ channels (Köhler et al., 1996; Ishii et al., 1997; Joiner, 1997) of which K_{Ca}3.1 (formerly called Gardos channel or intermediate-conductance channel IK1) has a single channel conductance of 11 pS and is not blocked by apamin. The other three members of this phylogenetic tree, the K_{Ca} channels K_{Ca}2.1, K_{Ca}2.2, and K_{Ca}2.3, also known as SK1, SK2, and SK3, with a smaller conductance of 8–10 pS, are specifically blocked by apamin in the nM range (Wei et al., 2005). The other group consists of four members of which the large conductance Ca²⁺-activated K⁺ channel (K_{Ca}1.1, also known as BK channel) is functionally related to the former group. It is voltage-dependent with a single channel conductance of 260 pS. The three other members of this group are structurally related channel-types which are surprisingly not activated by intracellular Ca²⁺.

K_{Ca} channels resemble the serpentine transmembrane topology of voltage-activated K⁺ channels consisting of six transmembrane domains and a P loop region between domain S5 and S6, containing the K⁺-selective filter, and intracellular N and C termini (Faber, 2009). Apamin has different affinities for the K_{Ca}2 channel subtypes. The toxin is most potent at K_{Ca}2.2 channels (IC₅₀ ~ 70 pM) followed by K_{Ca}2.3 channels (IC₅₀ ~ 0.63–6 nM) and the human isoform of K_{Ca}2.1 channels (IC₅₀ ~ 1–8 nM; Köhler et al., 1996; Nolting et al., 2007; Lamy et al., 2010; Weatherall et al., 2010). Interestingly, the rat isoform of K_{Ca}2.1 channel is apamin insensitive (D'Hoedt et al., 2004). Apamin does not simply obstruct the pore, but blocks by an allosteric mechanism in which outer pore residues are involved (Lamy et al., 2010). However, apamin must bind to both the S3–S4 extracellular loop and the outer pore to block K_{Ca}2 channel current by an allosteric mechanism. A three-amino-acid motif in the S3–S4 loop is a crucial determinant of the sensitivity of the apamin blockade. Since the motif SYA in K_{Ca}2.2 channels, SYT in K_{Ca}2.3 channels and TYA in human K_{Ca}2.1 channels is required for binding and block by apamin, this suggests that a change in pore shape underlies the allosteric block (Weatherall et al., 2011). Rat K_{Ca}2.1 channels display SLV in the S3–S4 loop that prevents binding of apamin, despite having the same pore sequence as the other isoforms (Weatherall et al., 2011). Functional K_{Ca}2 channels assemble as homomeric tetramers (Köhler et al., 1996), but could also co-assemble different subunits into heteromeric channels (Strassmaier et al., 2005; Weatherall et al., 2011). Recently, it was proposed that in heteromeric channels the binding site for apamin is formed by two adjacent subunits, the outer pore region of one and the S3–S4 loop of the other subunit (Weatherall et al., 2011; **Figure 1B**). The relative abundance of heteromeric or homomeric channel assembly and their physiological relevance for signal transduction is not understood at the moment.

Calmodulin (CaM) is constitutively bound to the C terminus of the channel (Xia et al., 1998; Schumacher et al., 2001). Binding of

Ca²⁺ to CaM leads to a conformational change enabling opening of the channel and K⁺ efflux (**Figure 1A**). Direct modulation of the channel can be obtained by phosphorylation, since the protein has multiple predicted phosphorylation sites (Köhler et al., 1996). For example, phosphorylation by cAMP-dependent protein kinase reduces the plasma membrane localization of K_{Ca}2 channels and contributes in this way to long-term potentiation (LTP; Faber et al., 2005; Ren et al., 2006; Lin et al., 2008). Modulation of channel activity can also be achieved by constitutively bound protein kinase CK2 (Casein Kinase 2) and protein phosphatase 2A. CK2 phosphorylates channel-bound CaM in the closed channel state thereby reducing the apparent Ca²⁺ sensitivity. In the open state, dephosphorylation of CaM by protein phosphatase 2A increases the Ca²⁺ sensitivity of the channel (Allen et al., 2007). Therefore, Ca²⁺ sensitivity is dependent on the intracellular Ca²⁺ levels enabling K_{Ca} channels to closely follow neuronal activity. Recently, these aspects of K_{Ca} channel signaling have been excellently reviewed (Adelman et al., 2012).

K_{Ca}2 channels interact with a large number of pharmacological agents (Faber and Sah, 2007; Pedarzani and Stocker, 2008). Apart from apamin, other peptides, like leiuotoxin I and tamapin were found to block the channels at the nanomolar range. Most of the organic blockers and inhibitors are needed in micromolar concentrations to block the channels, except for UCL1684 and UCL1848, which also block at the nanomolar range (Shah and Haylett, 2000; Strobaek et al., 2000; Fanger et al., 2001; Hosseini et al., 2001; Benton et al., 2003). A different set of toxins is available to block K_{Ca}3.1 channels of which maurotoxin and charybdoxin are the most effective (low nanomolar range). In addition, triarylmethane derivatives block K_{Ca}3.1 channels at the nanomolar range (Ghanshani et al., 2000; Visan et al., 2004). Enhancers of channel activity are also available. Most of them work at the micromolar range (Pedarzani and Stocker, 2008), like 1-ethyl-2-benzimidazolinone (1-EBIO) which acts on K_{Ca}2.1, K_{Ca}2.2, and K_{Ca}2.3 channels (Lappin et al., 2005) as well as on K_{Ca}3.1 channels (Jensen et al., 1998; Lappin et al., 2005). The only enhancer with higher affinity is NS309, acting on these channels at the nanomolar range (Strobaek et al., 2004). The positive modulator CyPPA is selective for K_{Ca}2.2 and K_{Ca}2.3 channels at the low micromolar range and virtually inactive toward K_{Ca}2.1 and K_{Ca}3.1 channels (Hougaard et al., 2007).

DISTRIBUTION OF K_{Ca} CHANNELS IN THE PERIPHERY AND THE NERVOUS SYSTEM

K_{Ca} channels are widely distributed throughout peripheral tissues and in the central nervous system. In the peripheral tissues mRNA of the K_{Ca} channels has partially overlapping but clearly distinct distribution patterns. K_{Ca}2.1 channels are only found in low quantities in the ovaries and testes. K_{Ca}2.2 channels are, next to other areas, present in the adrenal glands, heart, kidneys, liver, prostate, and urinary bladder. K_{Ca}2.3 shows distinctive distribution to the small intestine, rectum, omentum, myometrium, and skeletal muscles (Chen et al., 2004). Immunohistochemistry also revealed the presence of K_{Ca}2.3 protein in the cell bodies and processes of cultured rat superior cervical ganglion neurons and K_{Ca}2.3 protein was identified as a major component of the K_{Ca} channels responsible for the afterhyperpolarization (AHP) in these cells

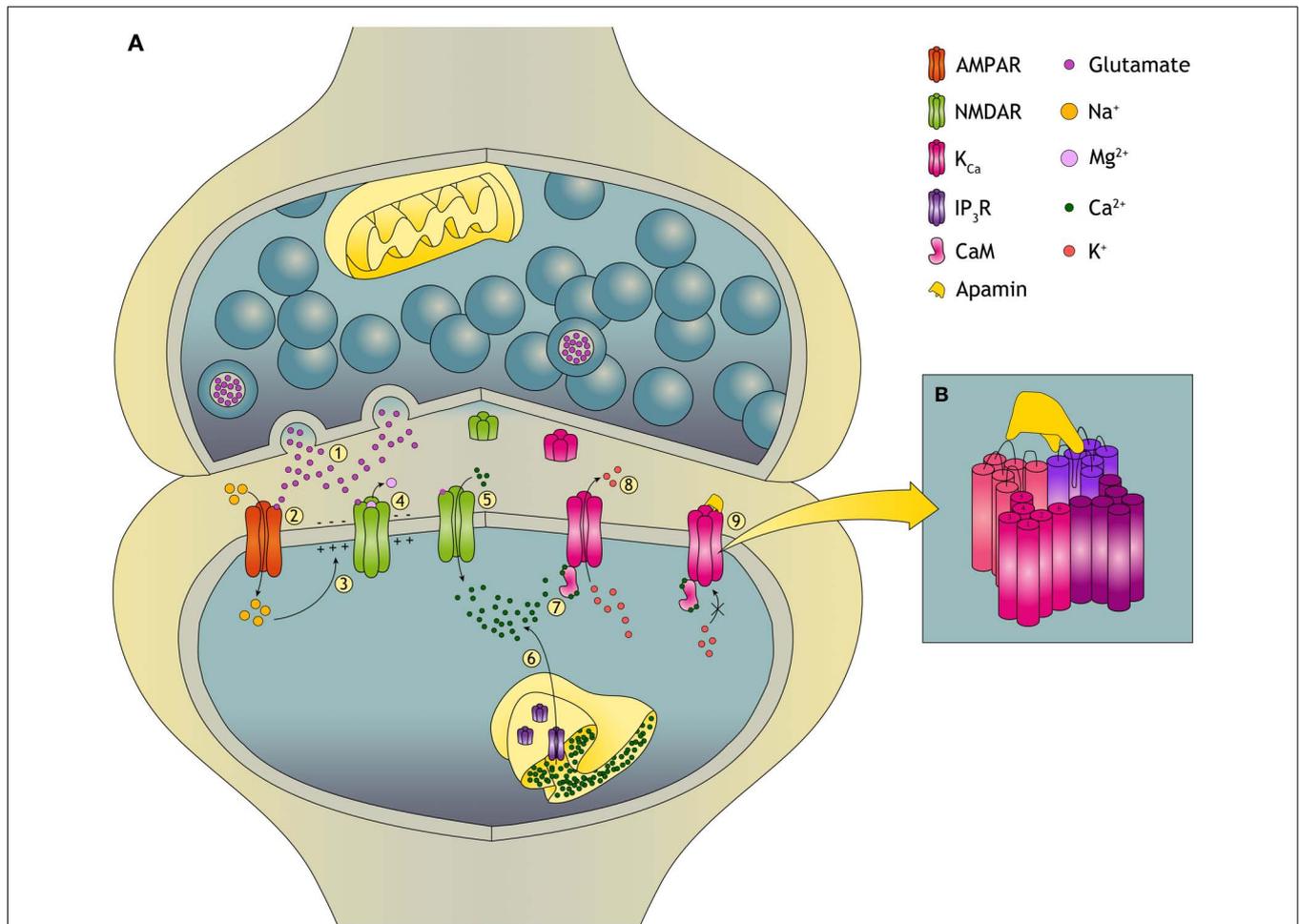


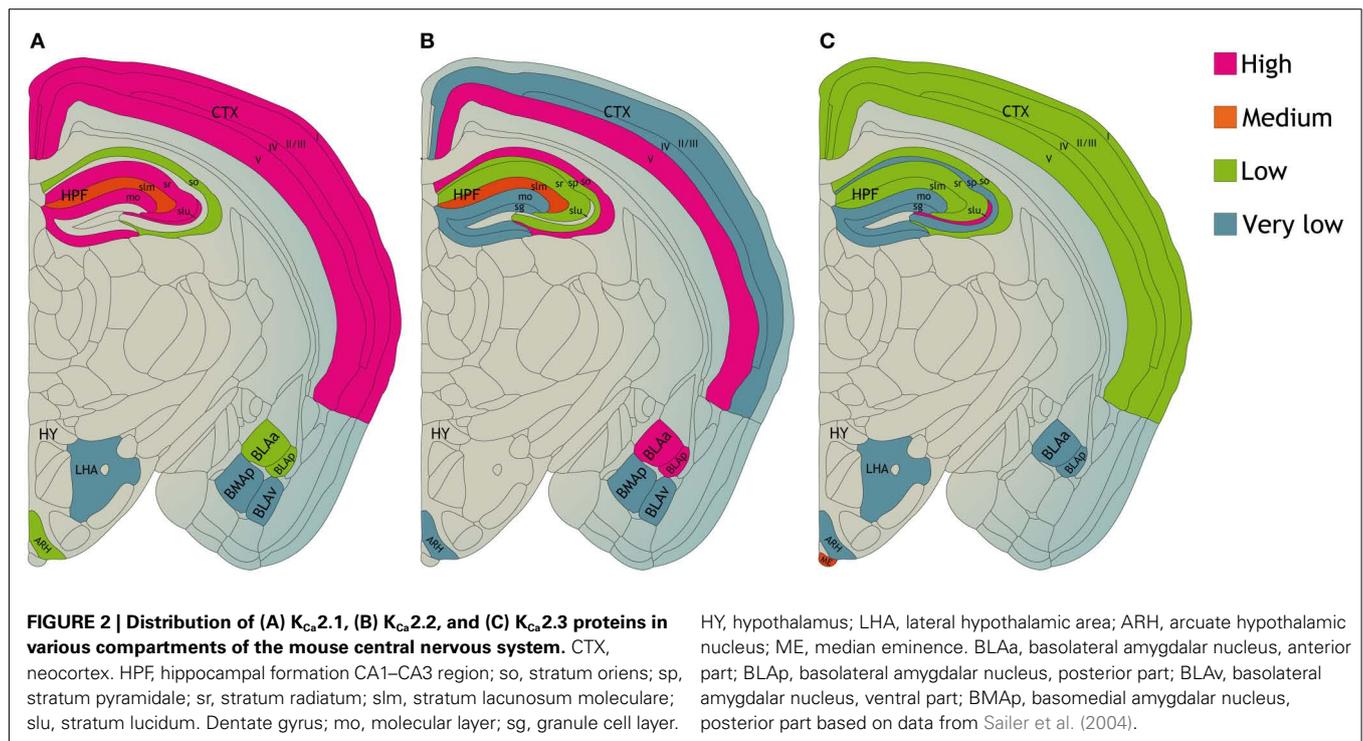
FIGURE 1 | Plasticity in the glutamatergic synapse and the role of K_{Ca} channels. (A) (1) During synaptic transmission, glutamate is released from the presynaptic neuron and acts on the two primary excitatory glutamate receptors: AMPA (α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors and NMDA (*N*-Methyl-D-Aspartate) receptors. (2) Na⁺ flows only through AMPARs and not through NMDARs because the NMDAR is blocked by a voltage-dependent Mg²⁺ block. (3) Influx of Na⁺ causes depolarization of the postsynaptic neuron. (4) The depolarization relieves the Mg²⁺ block of the NMDAR and an excitatory postsynaptic potential (EPSP) is induced. (5) This allows, next to Na⁺, for Ca²⁺ influx into the dendritic spine. Changes in the dendritic spine Ca²⁺ concentration can initiate synaptic plasticity. The dynamics of changes in [Ca²⁺] upon tetanic stimulation determines whether the synapse will undergo long-term potentiation (LTP) or long-term depression (LTD). (6) Ca²⁺ can also be

released from the ER, predominantly dependent on ryanodine receptors and inositol trisphosphate receptors (IP₃R). (7) When intracellular levels of Ca²⁺ increase, K_{Ca} channels are activated through calmodulin (CaM). Ca²⁺ binds to CaM and CaM induces a conformational change that leads to opening of the channel pore. (8) Opening of the K_{Ca} channel leads to K⁺ efflux. K_{Ca} channels also facilitate reestablishment of the Mg²⁺ block of the NMDARs which reduces Ca²⁺ influx. In this way opening of K_{Ca} channels provides a negative feedback on the EPSP through their repolarizing effect. (9) Binding of apamin to the K_{Ca} channel blocks the channel and induces an increased EPSP. **(B)** Apamin does not obstruct the pore of the K_{Ca} channel but blocks it by an allosteric mechanism. The binding site for apamin is formed by two adjacent subunits, the S3–S4 extracellular loop of one and the loops of the outer pore of the other, also providing a block on heteromeric channels.

(Hosseini et al., 2001). K_{Ca}3.1 channels are abundantly distributed in peripheral tissues like lymphocytes (Ghanshani et al., 2000), erythrocytes (Vandorpe et al., 1998), endothelium (Eichler et al., 2003), and smooth muscle cells (Köhler et al., 2003), but they are also present on the placenta, prostate, rectum, salivary glands, trachea, and tonsils (Chen et al., 2004). The different channels have been implicated in various physiological functions like volume regulation of erythrocytes (Brugnara et al., 1996; Vandorpe et al., 1998), vasodilatation (Eichler et al., 2003), and proliferation of lymphocytes (Jensen et al., 1999), proliferation of vascular

endothelial (Grgic et al., 2005), and proliferation of smooth muscle cells (Köhler et al., 2003).

Different subunits of the K_{Ca} channels are widely distributed throughout the brain (Figure 2). K_{Ca}2.1 and K_{Ca}2.2 channels are often expressed in the same neurons, predominantly in the neocortex, hippocampal formation, and cerebellum. In the hippocampal formation K_{Ca}2.1 channel immunolabeling is most pronounced in the neuropil of layers CA1–CA3, in particular in the stratum radiatum. K_{Ca}2.2 channel labeling is strongest in the CA1–CA2 stratum radiatum and stratum oriens (Sailer et al., 2002,



2004). K_{Ca}2.3 subunits are also present in the hippocampal formation, most prominent in the hilus and in the stratum lucidum of CA3. In the rest of the brain K_{Ca}2.3 subunits show a complementary distribution to K_{Ca}2.1 and K_{Ca}2.2 subunits. K_{Ca}2.3 subunits are present in subcortical regions like midbrain nuclei (Rimini et al., 2000; Stocker and Pedarzani, 2000; Tacconi et al., 2001; Sailer et al., 2002, 2004; Chen et al., 2004). In dorsal root ganglia and spinal cord of the rat sensory nervous system, all K_{Ca}2 channel subtypes are expressed. Co-localization of channel expression with calcitonin gene-related peptide and isolectin B4-labeled neurons provides evidence for their presence in nociceptors (Mongan et al., 2005). Their level of expression, however, was not altered following induction of inflammation or nerve injury, suggesting that channel modulation rather than expression contributes to the changes in neuronal excitability observed under these “pathological” circumstances (Mongan et al., 2005).

Within neurons, K_{Ca}2.1 and K_{Ca}2.2 channels are primarily found in somatic and dendritic areas. K_{Ca}2.2 channels have been shown to be present in hippocampal CA1 dendritic spines (Lin et al., 2008). K_{Ca}2.3 channels are associated with fibers extending from layer 5 to layer 1 in the neocortex (Rimini et al., 2000; Stocker and Pedarzani, 2000; Tacconi et al., 2001; Sailer et al., 2002, 2004; Chen et al., 2004). K_{Ca}3.1 channels are present in dorsal root ganglia, spinal cord and on cultured microglial cells from rat and mouse brain (Khanna et al., 2001; Schilling et al., 2002; Mongan et al., 2005; Kaushal et al., 2007). In microglial cells, K_{Ca}3.1 channels are activated by sphingosine-1-phosphate and lysophosphatidic acid and play a role in the respiratory bursts of reactive oxygen species generated after activation of microglia (Khanna et al., 2001; Schilling et al., 2002). The properties of the different channels have been reviewed in detail (Pedarzani and

Stocker, 2008), and in particular as possible targets for therapeutic interventions because in the past few years the role of K_{Ca} channels in disease is becoming more and more clear (Chandy et al., 2004; Wulff and Zhorov, 2008). The distribution of the different K_{Ca} channels gives the channels the ability to play a role in many processes like dendritic excitability, contributing to the AHP that follows an action potential, synaptic functioning, and plasticity (Xia et al., 1998; Ngo-Anh et al., 2005) and thereby modulating firing patterns of action potentials, all processes known for their involvement in learning and memory and in neurodegenerative diseases. The main focus of this review is the role of K_{Ca} channels in neurodegenerative processes, and in learning and memory. However, to place K_{Ca} channel research in a historical perspective first two important peripheral pathways which are under control of K_{Ca} channels will be discussed.

GASTROINTESTINAL TRACT

K_{Ca} channels are important participants in inhibitory neurotransmission in gastrointestinal smooth muscles (Banks et al., 1979; Maas et al., 1980; Shuba and Vladimirova, 1980). Three isoforms of the K_{Ca}2 channel family were cloned from murine and canine proximal colon smooth muscle (Ro et al., 2001). The mRNA of each subunit was expressed at different levels in murine colonic smooth muscles in the following sequence: K_{Ca}2.2 > K_{Ca}2.3 > K_{Ca}2.1 channels. In contrast, no mRNA for these channels could be detected in canine colonic smooth muscle. Immunoreactivity against K_{Ca}2.3 channels was present at the plasma membrane of circular and longitudinal muscle as well as in myenteric ganglia. Variation in the K_{Ca}2 channel expression suggests that they may contribute differentially to inhibitory junction potentials (Ro et al., 2001). A role for K_{Ca}2 channels

in spontaneous motility of the gastrointestinal tract has been suggested. K_{Ca}2.3-immunoreactive cells were positive for *c-kit*, a marker for the interstitial cells of Cajal (ICC), but not for glial fibrillary acidic protein in the ileum and stomach. Immunoelectron microscopic analysis indicates that K_{Ca}2.3 channels are localized on processes of ICC that are located close to the myenteric plexus between the longitudinal and circular muscle layers and within the muscular layers. Because ICC have been identified as pacemaker cells and are known to play a major role in generating the regular motility of the gastrointestinal tract, these findings suggest that K_{Ca}2.3 channels, which are expressed specifically in ICC, play an important role in generating a rhythmic pacemaker current in the gastrointestinal tract (Fujita et al., 2001).

VASCULAR RELAXATION

The endothelium-derived hyperpolarizing factor (EDHF) system is a major vasodilator mechanism (Taylor and Weston, 1988; Féletou and Vanhoutte, 2007, 2009; Edwards et al., 2010). The function of the EDHF system requires activation of endothelial K_{Ca} channels (Edwards et al., 2010), e.g., K_{Ca}3.1 channels (Ishii et al., 1997) and K_{Ca}2.3 channels (Köhler et al., 1996). Contribution of K_{Ca} channels has been implicated in endothelial dysfunction in many experimental models of vascular disease (Féletou and Vanhoutte, 2009), among which are coronary microvascular dysfunction (Gschwend et al., 2003; Feng et al., 2008), hypercholesterolemia (Ding et al., 2005; Morikawa et al., 2005), and diabetes (Dalsgaard et al., 2009; Brøndum et al., 2010; Matsumoto et al., 2010). A possible role for these channels in antihypertensive therapy is emerging (Sankaranarayanan et al., 2009). Newly developed activators were shown to potentiate EDHF-mediated dilations of carotid arteries from K_{Ca}3.1(+/+) mice but not from K_{Ca}3.1(-/-) mice. Administration of these activators lowered mean arterial blood pressure by 4 and 6 mmHg in normotensive mice and by 12 mmHg in angiotensin-II-induced hypertension. These effects were absent in K_{Ca}3.1-deficient mice. In addition, changes in arterial blood flow for 24 h modify the function of the endothelial K_{Ca}2.3 and K_{Ca}3.1 channels before arterial structural remodeling in rat mesenteric arteries. Reduction of blood flow blunts endothelium-dependent relaxation due to a reduction in the EDHF response. An increase in blood flow leads to an enhanced contribution of K_{Ca}3.1 channels to the EDHF relaxation, as indicated by the use of specific blockers (Hilgers et al., 2010). An endothelium-specific antihypertensive therapy based on pharmacological activation of these channels is also supported by recent experiments in dogs showing that activation of K_{Ca}2.3/K_{Ca}3.1 channels produces endothelial hyperpolarization and lowers arterial blood pressure by an immediate electrical vasodilator mechanism (Damkjaer et al., 2012). Apart from their role in cardiovascular, K_{Ca}3.1, K_{Ca}2.2, and K_{Ca}2.3 channels are also functional in endothelium-dependent vasodilatation in porcine retinal arterioles (Dalsgaard et al., 2010), and very important in the regulation of contraction mechanisms of brain (micro)vasculature to maintain homeostasis of the brain (Zhou et al., 2010).

STROKE

K_{Ca}2 and K_{Ca}3.1 channels are expressed in cerebral blood vessels and play a significant role in the regulation of local blood

flow (Marrelli et al., 2003; Faraci et al., 2004; McNeish et al., 2005). The release of K⁺ through the channels accumulates in the myo-endothelial space between the endothelial cells and myocytes of small arteries, causing an increase in the extracellular K⁺ concentration (Edwards et al., 2010). This increased extracellular K⁺ results in hyperpolarization of the myocyte and leads to smooth muscle relaxation and vascular dilation (Weston et al., 2002; Longden et al., 2011). Activity of K_{Ca}2 and K_{Ca}3.1 channels can play an important role in vascular dynamics under pathophysiological conditions, like cerebral ischemia. An EDHF-mediated relaxation mechanism is present in the carotid artery – together with the vertebral arteries the main feed path for blood supply to the brain – as well as in cerebral parenchymal arterioles (McNeish et al., 2006; Leuranguer et al., 2008; Cipolla et al., 2009; Sankaranarayanan et al., 2009). The EDHF component can activate K_{Ca}2 and K_{Ca}3.1 channel activity, regulating cerebral blood flow and contributing to the basal tone of cerebral parenchymal arterioles. Activators of K_{Ca}3.1 channel activity were shown to potentiate EDHF-mediated dilations of rat middle cerebral arteries (Marrelli et al., 2003), the carotid arteries in mouse (Sankaranarayanan et al., 2009) and in guinea-pig which is mediated by stimulation of both K_{Ca}2 and K_{Ca}3.1 channels (Leuranguer et al., 2008). Endothelial K_{Ca}2 and K_{Ca}3 channels regulate rat brain parenchymal arteriolar diameter and basal tone (Cipolla et al., 2009; Hannah et al., 2011) and via these endothelial mechanisms can determine cortical cerebral blood flow as was demonstrated in mice (Hannah et al., 2011). After cerebral ischemia and subsequent reperfusion, EDHF responsiveness was preserved in rat parenchymal arterioles, in contrast to the diminished response to nitric oxide synthase inhibition, providing further support for an important physiological role for K_{Ca}2 and K_{Ca}3.1 channels under pathophysiological conditions (Cipolla et al., 2009). K_{Ca} channels do not only play a role in regulating blood flow to different brain regions, but also in maintenance of the structure of the blood-brain barrier as the activation of K_{Ca}2.2 channels is necessary for ATP-induced proliferation of brain capillary endothelial cells (Yamazaki et al., 2006).

In addition to effects on the (micro)vasculature, K_{Ca} channels are also involved in the pathogenic mechanisms subsequent to the ischemic event. Cerebral ischemia induced in mice by cardiac arrest and cardiopulmonary resuscitation caused hippocampal CA1 pyramidal neuronal cell death associated with delayed and sustained reduction of synaptic K_{Ca}2.2 channel activity (Allen et al., 2011b). Treatment of mice with the K_{Ca} channel activator 1-EBIO 30 min before cardiac arrest prevented ischemia-induced synaptic channel internalization, restored channel activity, and reduced ischemia-induced cell death (Allen et al., 2011b). The brain infarct area obtained after occlusion of the middle cerebral artery of the rat could be reduced by ±50% by blocking K_{Ca}3.1 channels, probably reflecting reduced microglia activity (Chen et al., 2011). During stroke there is strong increase of glutamate release and overstimulation of nerve cells, which goes together with very high calcium levels in neurons and their death. The role of K_{Ca}2 and K_{Ca}3.1 channels in NMDA-mediated neurotoxicity will be addressed in the section “Neurodegenerative diseases.”

LEARNING AND MEMORY

Learning is by definition the result of processes by which experiences produce long-term and lasting changes in the nervous system. Memory formation is derived from those changes (Morgado-Bernal, 2011). Memory formation and persistent memory storage are accompanied by structural changes and synaptic plasticity of dendritic spines. Due to repetitive activation of excitatory glutamatergic synapses, particularly in CA1 pyramidal neurons of the hippocampus, an increase in synaptic strength is established, also known as LTP (Bliss and Collingridge, 1993). LTP is a form of plasticity that has been studied extensively in the hippocampus region of the brain. Plasticity is facilitated by phosphorylation of AMPA receptors and NMDA receptors. These receptors are the two primary excitatory glutamate receptors which can be found at the postsynaptic site of excitatory synapses. NMDARs particularly can be found on almost all neurons in the central nervous system and are ligand-gated non-selective cation channels which facilitate the flow of K⁺, Na⁺, and Ca²⁺ (Debanne et al., 2004; Yamin, 2009; Malenka and Malinow, 2011). In hippocampal CA1 pyramidal neurons, changes in dendritic spine Ca²⁺ concentration can initiate synaptic plasticity via the NMDA receptors (El-Hassar et al., 2011; O'Donnell et al., 2011). K_{Ca}2 channels are able to dampen synaptic plasticity, because K_{Ca}2 channels have been shown to be present in the hippocampal CA1 synaptic membrane of dendritic spines in the postsynaptic density (PSD), where they are colocalized with NMDA receptors (Lin et al., 2008; Allen et al., 2011b). During an excitatory postsynaptic potential (EPSP), Ca²⁺ enters a neuron through NMDARs and nearby K_{Ca}2 channels are activated. Opening of K_{Ca}2 channels has a repolarizing effect and the EPSP is reduced, firstly by providing K⁺ efflux and secondly through modulation of the membrane potential. Opening of K_{Ca}2 channels can facilitate reestablishment of the Mg²⁺ block of the NMDARs which reduces Ca²⁺ influx (Allen et al., 2011b). By regulating Ca²⁺ concentrations, K_{Ca}2 channels can alter the threshold for the induction of hippocampal synaptic plasticity and modulate EPSPs underlying the induction of LTP (Hammond et al., 2006; Lin et al., 2008). In concordance with these results it has been shown that during LTP induction in mouse hippocampus, K_{Ca}2 channels are internalized into the dendritic spine due to PKA phosphorylation of three serine residues in the K_{Ca}2.2 C-terminal domain. Internalization of K_{Ca}2 channels abolishes K_{Ca}2 channel activity in the potentiated synapses and this results in increased EPSP (Lin et al., 2008; **Figure 1**).

Since K_{Ca}2 channels reduce synaptic plasticity, it can be expected that inhibition of K_{Ca}2 channels improves learning. Indeed, the excitability of rat hippocampal neurons can be enhanced by blocking K_{Ca}2 channels with apamin within a nanomolar concentration range (Behnisch and Reymann, 1998). In mice, hippocampal learning and induction of synaptic plasticity can be increased with apamin treatment (Stackman et al., 2002). Blocking K_{Ca}2 channels can remove the negative feedback on NMDARs, while LTP induction can be facilitated by NMDAR-dependent Ca²⁺ signals within dendritic spines in the hippocampal CA1 area (Stackman et al., 2002; Faber et al., 2005; Ngo-Anh et al., 2005; Allen et al., 2011a). The K_{Ca} channel subtype K_{Ca}2.2 especially appears to be involved in regulating CA1 plasticity and

excitability, because genetic deletion of K_{Ca}2.2 channels, but not K_{Ca}2.1 or K_{Ca}2.3, abolishes the effect of apamin (Bond et al., 2004). The K_{Ca}2.2 channel has two isoforms, K_{Ca}2.2-long (K_{Ca}2.2-L) and K_{Ca}2.2-short (K_{Ca}2.2-S), which are coexpressed in CA1 pyramidal neurons. In mice lacking K_{Ca}2.2-L isoform, K_{Ca}2.2-S-containing channels are expressed in the extrasynaptic spine plasma membrane but they are specifically excluded from the PSD of dendritic spines. Due to this exclusion, apamin does not increase EPSPs or LTP in these mice. It is suggested that the K_{Ca}2.2-L isoform directs synaptic K_{Ca}2.2 channel expression and is important for normal synaptic signaling, plasticity, and learning (Allen et al., 2011a).

Many studies on the role of K_{Ca}2 channels in learning and memory consolidation have been performed using various kinds of behavioral tasks and paradigms in rodents. Hippocampal-dependent learning and memory can be tested using spatial learning tasks, like radial arm mazes, Y- or T-mazes and water mazes, avoidance test, fear conditioning, eyeblink conditioning, or using novel object-recognition tasks (Geinisman et al., 2001; Borghot van der et al., 2005; Havekes et al., 2006; Morgado-Bernal, 2011). It was shown that in the early stages of a spatial learning task K_{Ca}2.2 and K_{Ca}2.3 mRNA levels were transiently downregulated, suggesting an endogenous regulation of K_{Ca}2 channels involved in learning (Mpari et al., 2010). In the hippocampus of aged mice an elevated expression of K_{Ca}2.3 channels contributes to an age-related reduction in performance on learning tasks, synaptic plasticity, and LTP (Blank et al., 2003). However, mice lacking K_{Ca}2.3 channels show short-term learning and memory deficits in their performance in an alternation arm maze test (Jacobsen et al., 2009). Mice treated with apamin also demonstrate accelerated hippocampal-dependent spatial and non-spatial memory encoding. Apamin-treated mice require fewer trials to learn the location of a hidden platform in the Morris water maze. In mice, and also rats, apamin facilitates the encoding of object memory in an object-recognition task, as assessed by habituation of exploratory activity. Moreover, apamin improves performance on the novel object-recognition task (Deschaux et al., 1997; Stackman et al., 2002). Amygdala-dependent learning or emotional learning is tested with inhibitory avoidance tests, contextual fear memory tests, and with the appetitive motivated response. Blockade of K_{Ca}2 channels with systemically administered apamin was shown to facilitate memory processes in conditioning for an appetitively motivated bar-pressing response in mice (Messier et al., 1991). Interestingly, apamin did not alter performance in rats when administered at different time points in a passive avoidance test, which might indicate that acquisition, consolidation and retention are not enhanced by apamin (Deschaux and Bizot, 1997). In a discrimination avoidance task in young chicks, blocking K_{Ca}2 channels with apamin resulted even in persistent impairment of retention during the long-term memory stage, which might indicate that K_{Ca}2 channels play a role in long-term memory (Baker et al., 2011). Taken together, these studies indicate that blocking K_{Ca}2 channels results in an LTP increase and in learning improvement. In hippocampus-dependent tasks, the effect of blocking K_{Ca}2 channels is more evident than in amygdala-dependent tasks.

Blocking of K_{Ca}2 channel activity by apamin can also be of interest in alcohol and drug addiction which is associated with long-lasting changes in the activity of neuronal networks. Molecular changes in K⁺ channel function are linked to an enhancement of drug-seeking behavior. In *ex vivo* rat neurons from the core nucleus accumbens (NAcb), a reduction in K_{Ca} channel currents can significantly enhance spike firing after abstinence from alcohol, but not after sucrose abstinence, and facilitates motivation to seek alcohol following protracted abstinence. Inhibition of K_{Ca} channels with apamin produces a greater enhancement of firing in neurons from sucrose- versus alcohol-abstinent animals, indeed indicating reduced K_{Ca} currents. Activation of K_{Ca} channels in NAcb core neurons with the positive modulator 1-EBIO significantly inhibits firing of neurons *ex vivo* and reduces alcohol seeking after abstinence *in vivo*. Apamin can fully reverse the effect of 1-EBIO *ex vivo*, indicating that 1-EBIO depressed firing through K_{Ca} channel activation. Also the positive K_{Ca} channel modulator chlorzoxazone can inhibit firing in NAcb core neurons *ex vivo* and significantly and dose-dependently decrease alcohol intake in rats with intermittent access to alcohol compared to rats with continuous access to alcohol (Hopf et al., 2010, 2011a,b). Chronic exposure to alcohol *in vitro* and *in vivo* also reduces hippocampal CA1 pyramidal neuronal K_{Ca}2 channel function and reduces K_{Ca}2 expression with concomitant increases in NMDAR specifically at synaptic sites. Apamin potentiated EPSPs in control but not in ethanol-treated neurons, suggesting disruption of the K_{Ca}2-NMDAR feedback loop. Increasing channel activity by 1-EBIO decreased alcohol withdrawal hyperexcitability and attenuated ethanol withdrawal neurotoxicity in hippocampus (Mullolland et al., 2011). Endocannabinoid signaling is potentiated by K_{Ca}2 channels resulting in an enhanced AHP current and spike-frequency adaptation, shown by examining the endocannabinoid anandamide in cultured rat hippocampal neurons (Wang et al., 2011). Mice with cannabinoid tolerance, such as observed in drug addiction, show impaired endocannabinoid-induced long-term depression (LTD) and the reversal of LTP in the dorsolateral striatum. *In vivo* modulation of K_{Ca}2 channel activity by apamin can potentiate the endocannabinoid signaling and rescue the deficit in LTD and corresponding behavioral alterations. Striking also is the observation that the K_{Ca} channel stimulator NS309 has the reversed effect (Nazzaro et al., 2012). Stimulation of K_{Ca}2 channels results in a reduction of LTP and learning in both hippocampus- and amygdala-dependent tasks (Hammond et al., 2006). 1-EBIO facilitates K_{Ca}2 channel activation by increasing their sensitivity to Ca²⁺. Systemic administration of 1-EBIO results in impaired motor and cognitive behavior in mice and facilitates object memory encoding but not retrieval. The compound CyPPA, which can selectively activate K_{Ca}2.2 and K_{Ca}2.3 channels, has the same effect as 1-EBIO (Vick et al., 2010). Next to activation, overexpression of K_{Ca}2.2 channels results in deficits in hippocampal contextual memory encoding and synaptic plasticity. However, K_{Ca}2 channels constrain, but do not fully prevent hippocampal synaptic plasticity (Stackman et al., 2008).

NEURODEGENERATIVE DISEASES

With increasing age, memory impairments, and neurodegenerative diseases like Alzheimer's disease occur more frequent and

substantial changes in neuronal signal processing in the hippocampus are observed. Alterations in Ca²⁺ signaling might be one of the underlying cause of changes in signal processing (Norris et al., 1998; LaFerla, 2002; Stutzmann, 2005). It was hypothesized that during aging Ca²⁺ levels may slowly increase, affecting critical Ca²⁺ signaling throughout cells and affecting cellular activity (Toescu et al., 2004; Shetty et al., 2011). Indeed, in neurons from aged rats, elevated levels of [Ca²⁺]_i can lead to a prolonged Ca²⁺-dependent K⁺-mediated AHP, resulting in deleterious effects on neurons (Landfield and Pitler, 1984; Norris et al., 1998). Also an immediate abnormal increase in [Ca²⁺]_i and exacerbated activation of glutamate receptor-coupled Ca²⁺ channels, like NMDA receptors, are established hallmarks of neuronal cell death in acute and chronic neurological diseases (Dolga et al., 2011). Neurons modulate Ca²⁺ signals by regulating the influx into the cell from the extracellular environment or by its release from internal sources such as the ER via IP₃ receptors and ryanodine receptors in the ER membrane (LaFerla, 2002; Stutzmann, 2005). The regulation of the [Ca²⁺]_i is critical, because insufficient levels of [Ca²⁺] can lead to impaired functioning whereas excessive cytosolic [Ca²⁺] levels can cause overstimulation and even cell death (Berridge et al., 1998). Several factors can trigger increases in [Ca²⁺]_i in neurons, like exposure to glutamate, which activates NMDA receptors (Randall and Thayer, 1992; Dolga et al., 2011). In physiological conditions, glutamate receptor-coupled Ca²⁺ channels are responsible for the primary depolarization in glutamate-mediated neurotransmission and changes in dendritic spine Ca²⁺ concentration play a key role in initiating synaptic plasticity (Santos et al., 2009; El-Hassar et al., 2011; O'Donnell et al., 2011).

Next to changes in [Ca²⁺], functional alterations in K_{Ca} channels can play a significant role in the regulation of Ca²⁺ homeostasis in aging and neurodegenerative diseases (LaFerla, 2002). In the hippocampus of aged mice an elevated expression of K_{Ca}2.3 channels contributes to an age-related reduction in performance on learning tasks, synaptic plasticity and LTP (Blank et al., 2003). In patients with multiple sclerosis (MS), K_{Ca}2 channels may significantly contribute to neuroprotection. In MS glutamate receptors are involved in glial activation and pathological changes in axonal processes associated with progressive brain damage. Improvements of symptoms are seen with treatment with riluzole, a neuroprotective agent that inhibits the release of glutamate from nerve terminals, reduces neuronal excitability and activates K_{Ca}2 channel activity, indicating a protective role of K_{Ca}2 channels (Cao et al., 2002; Geurts et al., 2003; Killestein et al., 2005). Neuroprotection can also be promoted by pharmacological positive modulation of K_{Ca}2.2 channels by NS309 *in vitro* by reducing glutamate- and NMDA-induced delayed Ca²⁺ deregulation (DCD), which is responsible for apoptotic neuronal death (Figure 3). Glutamate-induced DCD is paralleled by downregulation of K_{Ca}2.2 channel expression in a time-dependent manner in primary cortical neurons, which may explain the lack of adaptation to extended glutamate receptor stimulation, and the NS309 therapeutic time window. As shown by Dolga et al. (2011), NS309 mediated neuroprotection only when applied up to 3 h after the onset of [Ca²⁺]_i deregulation, an effect that

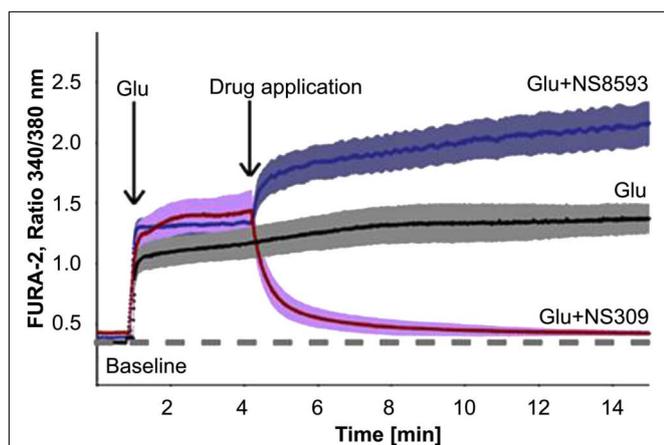


FIGURE 3 | Effect of a negative modulator (NS8593) and an positive modulator (NS309) of K_{Ca} channel activity on the glutamate (Glu)-induced intracellular Ca²⁺ concentrations of primary cortical neurons, seen as changes in fluorescence intensities of the Ca²⁺-sensitive dye FURA-2. Single neurons were stimulated with glutamate (20 μM) and then treated with NS309 (50 μM), NS8593 (50 μM; obtained with permission from Dolga et al., 2011).

correlates with the time window of the progressive decline of K_{Ca}2.2 channel expression levels upon glutamate damage. These data were substantiated in *in vivo* stroke studies of middle cerebral artery occlusion and focal ischemia, which cause significant cell loss and reduced K_{Ca}2.2 channel activity due to the internalization of synaptic K_{Ca}2.2 channels (Allen et al., 2011b). In both studies, pharmacological activation of K_{Ca}2 channels with either NS309 or 1-EBIO reduced neuronal death and ischemic brain damage, and restored K_{Ca}2.2 channel expression and activity. Thus, the activation of K_{Ca}2.2 channels could be used as potential therapeutic strategy for the treatment of acute and chronic neurodegenerative disorders (Allen et al., 2011b; Dolga et al., 2011).

ALZHEIMER'S DISEASE

In Alzheimer's disease (AD) certain parts of the brain like the hippocampus are especially vulnerable to pathogenic mechanisms. Early degenerative symptoms include significant deficits in the performance of hippocampal-dependent cognitive abilities such as spatial learning and memory (Yamin, 2009). AD has many hallmarks including neuroinflammation and accumulation of β-amyloid (Aβ) plaques and tau pathology (Maezawa et al., 2011). Recent experimental evidence suggests that Aβ oligomers disturb the NMDA receptor-dependent LTP induction in the hippocampal CA1 and DG regions both *in vivo* and *in vitro* (Stutzmann, 2005; Yamin, 2009). The disturbance by Aβ and inflammation can lead to a destabilization of Ca²⁺ signaling, which seems to be central to the pathogenesis of AD (LaFerla, 2002; Santos et al., 2009). However, some forms of Ca²⁺ dysregulation may represent compensatory mechanisms to modulate neuronal excitability and slow AD pathology in the early stages of the disease (Supnet and Bezprozvanny, 2010). K_{Ca}2 channels can provide a negative feedback on Ca²⁺ signaling through interaction with NMDA

receptors, reducing lethal amounts of Ca²⁺ influx (Allen et al., 2011b).

Recently, K_{Ca}3.1 channels have been found to play a role in AD. K_{Ca}3.1 channels are present in microglia, which are activated by aggregated forms of Aβ. Aβ oligomers induce a unique pattern of microglia activation that requires the activity of K_{Ca}3.1 channels (Maezawa et al., 2011). Suppression of K_{Ca}3.1 might be useful for reducing microglia activity in stroke, traumatic brain injury, MS, and Alzheimer's disease (Chen et al., 2011). In brain tissue, cerebrospinal fluid and plasma in AD and in other central nervous system disorders, the inflammatory cytokine tumor necrosis factor-α (TNF-α) is found to be increased. An increase in TNF-α increases the expression of K_{Ca}2.2 channels in cortical neurons (Murthy et al., 2008). TNF-α has been implicated as contributing to both neuroprotection and neurodegeneration, depending on the tissue and experimental paradigm and the increase in K_{Ca}2 channels makes neurons more resistant to excitotoxic cell death. In an *in vitro* model of glutamate-induced cell death of primary cortical neurons, TNF-α was shown to have neuroprotective properties. By blocking K_{Ca}2 channels with apamin, the neuroprotective effect of TNF-α against glutamate-induced excitotoxicity was blocked (Dolga et al., 2008). In addition to this results, in cortical tissue from AD patients a significantly higher expression level of a short, inactive form of K_{Ca}2.2 mRNA has been found which impairs the negative feedback of K_{Ca}2.2 channels on Ca²⁺ signaling and probably also had a negative effect on the neuroprotective effect of TNF-α (Murthy et al., 2008). Also in mice with K_{Ca}2.2-S-containing channels, the channels were excluded from the PSD and EPSPs or LTP were not increased by adding apamin (Allen et al., 2011a). In contrast to this result, in mice with partial hippocampal-lesions, mimicking the pathophysiological hallmark also observed in AD, blocking K_{Ca}2 channels by apamin could alleviate the impairment in spatial reference memory and working memory (Ikonen and Riekkinen, 1999). Due to these findings, apamin has been proposed as a therapeutic agent in AD treatment (Romero-Curiel et al., 2011). It is of interest to determine whether K_{Ca}2.2 channel protein expression increases with age and whether blocking K_{Ca}2.2 channels can limit age-related memory impairment (Stackman et al., 2008).

CONCLUSION

Three decades of research on K_{Ca} channels has revealed a broad range of processes in which these channels are critically involved. The apamin-sensitive K_{Ca}2 channels contribute to the AHP and are crucial regulators of neuronal excitability. Several compounds affecting these channels have been synthesized and tested in models for neurological diseases *in vitro* as well as *in vivo*. Some of these features are summarized in **Table 1**. In the nearer future, treatment of neurodegenerative diseases caused by neuronal hyperexcitability, progressive disturbance of Ca²⁺ homeostasis and excitotoxic neuronal death might benefit from enhancers of K_{Ca}2 channel activity, whereas, although less clear, deficiencies in learning and memory might benefit from inhibition of these channels.

Table 1 | The role of K_{Ca} channels as studied in various model systems.

Pathology	Specie	Channel involved	Effect on model organism	Role K _{Ca} activation	Enhancer/inhibitor used	Reference
Sensory nerve injury	Human	hK _{Ca} 2.1 hK _{Ca} 3.1	Decreased immunoreactivity after injury			Boettger et al. (2002)
Multiple sclerosis	Human		Reduction cervical cord atrophy	Neuroprotection	Riluzole	Killestein et al. (2005)
Chronic alcohol consumption	Rat/mouse	K _{Ca} 2	Downregulation K _{Ca} 2, adaptation glutamergic synapse plasticity	Reduction withdrawal hyperexcitability	1-EBIO, apamin	Muholland et al. (2011)
Chronic alcohol consumption	Rat	K _{Ca}	Reduction in alcohol seeking after abstinence	Inhibition of firing of core nucleus accumbens neurons	1-EBIO, apamin, chlorzoxazone	Hopf et al. (2010, 2011b)
Cannabinoid tolerance	Mouse	K _{Ca}	<i>In vivo</i> modulation of K _{Ca} on LTD	Rescue cannabinoid-induced striatal plasticity and behavioral control	Apamin, NS309	Nazzaro et al. (2012)
Obesity/endothelial dysfunction	Rat	K _{Ca} 2 K _{Ca} 3.1	Vasodilation mediated by K _{Ca} 3.1 increased, by K _{Ca} 2 decreased, restored by enhancers	Contribution to EDHF vasodilation	1-EBIO, apamin, CyPPA, TRAM-34	Haddock et al. (2011)
Diabetes/endothelial dysfunction	Rat	K _{Ca} 2 K _{Ca} 3.1	Restoration of relaxation	Contribution to EDHF vasodilation	Apamin, NS309, TRAM-34	Brøndum et al. (2010)
Atrial fibrillation	Rat, rabbit, guinea-pig	K _{Ca}	Antiarrhythmic properties channel inhibitors		ICA, NS8593, UCL1684	Diness et al. (2010)
Aging and atrial fibrillation	Rat	K _{Ca}	Channel inhibition decreased atrial fibrillation duration; no aging effect	Role in atrial repolarization	NS8593, UCL1684	Diness et al. (2011)
Aging GnRH releasing neurons	Mouse	K _{Ca}	Age-related contribution of K _{Ca} to depolarizing after potential		Apamin	Wang et al. (2009)
Age associated learning	Mouse	K _{Ca} 2.3	Reduced LTP and hippocampal learning	Reduction synaptic plasticity	Overexpression	Blank et al. (2003)
Age associated learning	Rat	K _{Ca}	Prolonged AHP in hippocampal neurons aged rats	Modulation neuronal network excitability		Landfield and Pitler (1984)
Cerebellar ataxia	Mouse	K _{Ca} 2.3	Loss of the apamin-sensitive AHP; increased spontaneous firing	Reduction neuronal hyperexcitability	Apamin, expression	Shakkottai et al. (2004)
Cerebral ischemia	Mouse	K _{Ca}	CA1 neuronal death; cognition; internalization synaptic K _{Ca} 2	Neuroprotection	1-EBIO, apamin	Allen et al. (2011b)
Cerebral ischemia/excitotoxicity	Mouse	K _{Ca} 2.2	TNF α mediated neuroprotection; upregulation K _{Ca} 2.2	Reduction glutamate-induced neuronal death	Apamin, CyPPA, NS309, siRNA	Dolja et al. (2008)
Cerebral ischemia/excitotoxicity	Mouse	K _{Ca} 2.2	Neuronal excitotoxicity; downregulation K _{Ca} 2.2	Reduction glutamate-induced intracellular Ca ²⁺ level	Apamin, NS309, NS8593	Dolja et al. (2011)
Alzheimer's disease	Rat	K _{Ca}	hAPP expression inhibits neuronal network excitability	Modulation neuronal network excitability	Apamin	Santos et al. (2009)
Alzheimer's disease	Rat	K _{Ca}	Low dose A β 42 inhibited PFC network via AHP; high dose promoted excitability	Modulation neuronal network excitability		Wang et al. (2009)

REFERENCES

- Adelman, J. P., Maylie, J., and Sah, P. (2012). Small-conductance Ca(2+)-activated K(+) channels: form and function. *Annu. Rev. Physiol.* 74, 245–269.
- Allen, D., Bond, C. T., Lujan, R., Ballesteros-Merino, C., Lin, M. T., Wang, K., Klett, N., Watanabe, M., Shigemoto, R., Stackman, R. W. Jr., Maylie, J., and Adelman, J. P. (2011a). The SK2-long isoform directs synaptic localization and function of SK2-containing channels. *Nat. Neurosci.* 14, 744–749.
- Allen, D., Nakayama, S., Kuroiwa, M., Nakano, T., Palmateer, J., Kosaka, Y., Ballesteros, C., Watanabe, M., Bond, C. T., Lujan, R., Maylie, J., Adelman, J. P., and Herson, P. S. (2011b). SK2 channels are neuroprotective for ischemia-induced neuronal cell death. *J. Cereb. Blood Flow Metab.* 31, 2302–2312.
- Allen, D., Fakler, B., Maylie, J., and Adelman, J. P. (2007). Organization and regulation of small conductance Ca²⁺ activated K⁺ channel multi-protein complexes. *J. Neurosci.* 27, 2369–2376.
- Baker, K. D., Edwards, T. M., and Rickard, N. S. (2011). Blocking SK channels impairs long-term memory formation in young chicks. *Behav. Brain Res.* 216, 458–462.
- Banks, B. E., Brown, C., Burgess, G. M., Burnstock, G., Claret, M., Cocks, T. M., and Jenkinson, D. H. (1979). Apamin blocks certain neurotransmitter-induced increases in potassium permeability. *Nature* 282, 415–417.
- Behnisch, T., and Reymann, K. G. (1998). Inhibition of apamin-sensitive calcium dependent potassium channels facilitate the induction of long-term potentiation in the CA1 region of rat hippocampus in vitro. *Neurosci. Lett.* 253, 91–94.
- Benton, D. C., Monaghan, A. S., Hosseini, R., Bahia, P. K., Haylett, D. G., and Moss, G. W. (2003). Small conductance Ca²⁺ activated K⁺ channels formed by the expression of rat SK1 and SK2 genes in HEK 293 cells. *J. Physiol.* 553, 13–19.
- Berridge, M. J. (2006). Calcium microdomains: organization and function. *Cell Calcium* 40, 405–412.
- Berridge, M. J., Bootman, M. D., and Lipp, P. (1998). Calcium – a life and death signal. *Nature* 395, 645–648.
- Blank, T., Nijholt, I., Kye, M. J., Radulovic, J., and Spiess, J. (2003). Small-conductance, Ca²⁺ activated K⁺ channel SK3 generates age-related memory and LTP deficits. *Nat. Neurosci.* 6, 911–912.
- Blatz, A. L., and Magleby, K. L. (1986). Single apamin-blocked Ca-activated K⁺ channels of small conductance in cultured rat skeletal muscle. *Nature* 323, 718–720.
- Bliss, T., and Collingridge, G. (1993). A synaptic model of memory-long-term potentiation in the hippocampus. *Nature* 361, 31–39.
- Boettger, M. K., Till, S., Chen, M. X., Anand, U., Otto, W. R., Plumpton, C., Trezise, D. J., Tate, S. N., Bountra, C., Coward, K., Birch, R., and Anand, P. (2002). Calcium-activated potassium channel SK1- and IK1-like immunoreactivity in injured human sensory neurones and its regulation by neurotrophic factors. *Brain* 125, 252–263.
- Bond, C. T., Herson, P. S., Strassmaier, T., Hammond, R., Stackman, R., Maylie, J., and Adelman, J. P. (2004). Small conductance Ca²⁺ activated K⁺ channel knock-out mice reveal the identity of calcium-dependent after hyperpolarization currents. *J. Neurosci.* 24, 5301–5306.
- Borghot van der, K., Wallinga, A. E., Luiten, P. G. M., Eggen, B. J. L., and Zee van der, E. A. (2005). Morris water maze learning in two rat strains increases the expression of the polysialylated form of the neural cell adhesion molecule in the dentate gyrus but has no effect on hippocampal neurogenesis. *Behav. Neurosci.* 119, 926–932.
- Brøndum, E., Kold-Petersen, H., Simonsen, U., and Aalkjaer, C. (2010). NS309 restores EDHF-type relaxation in mesenteric small arteries from type 2 diabetic ZDF rats. *Br. J. Pharmacol.* 159, 154–165.
- Brugnara, C., Gee, B., Armsby, C. C., Kurth, S., Sakamoto, M., Rifai, N., Alper, S. L., and Platt, O. S. (1996). Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J. Clin. Invest.* 97, 1227–1234.
- Cao, Y.-J., Dreixler, J. C., Couey, J. J., and Houamed, K. M. (2002). Modulation of recombinant and native neuronal SK channels by the neuroprotective drug riluzole. *Eur. J. Pharmacol.* 449, 47–54.
- Chandy, K. G., Wulff, H., Beeton, C., Pennington, M., Gutman, G. A., and Cahalan, M. D. (2004). K⁺ channels as targets for specific immunomodulation. *Trends Pharmacol. Sci.* 25, 280–289.
- Chen, M. X., Gorman, S. A., Benson, B., Singh, K., Hieble, J. P., Michel, M. C., Tate, S. N., and Trezise, D. J. (2004). Small and intermediate conductance Ca(2+)-activated K⁺ channels confer distinctive patterns of distribution in human tissues and differential cellular localisation in the colon and corpus cavernosum. *Naunyn Schmiedeberg's Arch. Pharmacol.* 369, 602–615.
- Chen, Y.-J., Raman, G., Bodendiek, S., O'Donnell, M. E., and Wulff, H. (2011). The KCa3.1 blocker TRAM-34 reduces infarction and neurological deficit in a rat model of ischemia/reperfusion stroke. *J. Cereb. Blood Flow Metab.* 31, 2363–2374.
- Cipolla, M. J., Smith, J., Kohlmeyer, M. M., and Godfrey, J. A. (2009). SKCa and IKCa channels, myogenic tone, and vasodilator responses in middle cerebral arteries and parenchymal arterioles: effect of ischemia and reperfusion. *Stroke* 40, 1451–1457.
- Dalsgaard, T., Kroigaard, C., Bek, T., and Simonsen, U. (2009). Role of calcium-activated potassium channels with small conductance in bradykinin-induced vasodilation of porcine retinal arterioles. *Invest. Ophthalmol. Vis. Sci.* 50, 3819–3825.
- Dalsgaard, T., Kroigaard, C., Misfeldt, M., Bek, T., and Simonsen, U. (2010). Openers of small conductance calcium-activated potassium channels selectively enhance NO-mediated bradykinin vasodilation in porcine retinal arterioles. *Br. J. Pharmacol.* 160, 1496–1508.
- Damkjaer, M., Nielsen, G., Bodendiek, S., Staehr, M., Gramsbergen, J.-B., de Wit, C., Jensen, B. L., Simonsen, U., Bie, P., Wulff, H., and Köhler, R. (2012). Pharmacological activation of KCa3.1/KCa2.3 channels produces endothelial hyperpolarisation and lowers blood pressure in conscious dogs. *Br. J. Pharmacol.* 165, 223–234.
- Debanne, D., Daoudal, G., Sourdet, V., and Russier, M. (2004). Brain plasticity and ion channels. *J. Physiol.* 97, 403–414.
- Den Hertog, A. (1981). Calcium and the alpha-action of catecholamines on guinea-pig taenia caeci. *J. Physiol.* 316, 109–125.
- Den Hertog, A. (1982). Calcium and the action of adrenaline, adenosine triphosphate and carbachol on guinea-pig taenia caeci. *J. Physiol.* 325, 423–439.
- Deschaux, O., and Bizot, J. C. (1997). Effect of apamin, a selective blocker of Ca²⁺ activated K⁺-channel, on habituation and passive avoidance responses in rats. *Neurosci. Lett.* 227, 57–60.
- Deschaux, O., Bizot, J. C., and Goyffon, M. (1997). Apamin improves learning in an object recognition task in rats. *Neurosci. Lett.* 222, 159–162.
- D'Hoedt, D., Hirzel, K., Pedarzani, P., and Stocker, M. (2004). Domain analysis of the calcium-activated potassium channel SK1 from rat brain. Functional expression and toxin sensitivity. *J. Biol. Chem.* 279, 12088–12092.
- Diness, J. G., Skibsbjerg, L., Jespersen, T., Bartels, E. D., Sørensen, U. S., Hansen, R. S., and Grunnet, M. (2011). Effects on atrial fibrillation in aged hypertensive rats by Ca(2+)-activated K(+) channel inhibition. *Hypertension* 57, 1129–1135.
- Diness, J. G., Sørensen, U. S., Nissen, J. D., Al-Shahib, B., Jespersen, T., Grunnet, M., and Hansen, R. S. (2010). Inhibition of small-conductance Ca²⁺ activated K⁺ channels terminates and protects against atrial fibrillation. *Circ. Arrhythm. Electrophysiol.* 3, 380–390.
- Ding, H., Hashem, M., Wiehler, W. B., Lau, W., Martin, J., Reid, J., and Triggle, C. (2005). Endothelial dysfunction in the streptozotocin-induced diabetic apoE-deficient mouse. *Br. J. Pharmacol.* 146, 1110–1118.
- Dolga, A. M., Granic, I., Blank, T., Knaus, H. G., Spiess, J., Luiten, P. G., Eisel, U. L., and Nijholt, I. M. (2008). TNF-alpha mediates neuroprotection against glutamate-induced excitotoxicity via NF-kappaB-dependent up-regulation of K2.2 channels. *J. Neurochem.* 107, 1158–1167.
- Dolga, A. M., Terpolilli, N., Kepura, F., Nijholt, I. M., Knaus, H. G., D'Orsi, B., Prehn, J. H., Eisel, U. L., Plant, T., Plesnila, N., and Culmsee, C. (2011). KCa2 channels activation prevents [Ca²⁺]_i deregulation and reduces neuronal death following glutamate toxicity and cerebral ischemia. *Cell Death Dis.* 2, e147.
- Edwards, G., Félétou, M., and Weston, A. H. (2010). Endothelium-derived hyperpolarizing factors and associated pathways: a synopsis. *Pflugers Arch.* 459, 863–879.
- Eichler, I., Wibawa, J., Grgic, I., Knorr, A., Brakemeier, S., Pries, A. R., Hoyer, J., and Köhler, R. (2003). Selective blockade of endothelial Ca²⁺-activated small- and intermediate-conductance K⁺-channels suppresses EDHF-mediated vasodilation. *Br. J. Pharmacol.* 138, 594–601.

- El-Hassar, L., Hagenston, A. M., Bertetto, D. L., and Yeckel, M. (2011). mGluRs regulate hippocampal CA1 pyramidal neuron excitability via Ca²⁺ wave-dependent activation of SK and TRPC channels. *J. Physiol.* 589, 3211–3229.
- Faber, E. S. (2009). Functions and modulation of neuronal SK channels. *Cell Biochem. Biophys.* 55, 127–139.
- Faber, E. S. L., Delaney, A. J., and Sah, P. (2005). SK channels regulate excitatory synaptic transmission and plasticity in the lateral amygdala. *Nat. Neurosci.* 8, 635–641.
- Faber, E. S. L., and Sah, P. (2007). Functions of SK channels in central neurons. *Clin. Exp. Pharmacol. Physiol.* 34, 1077–1083.
- Fanger, C. M., Rauer, H., Neben, A. L., Miller, M. J., Wulff, H., Rosa, J. C., Gallin, C. R., Chandy, K. G., and Cahalan, M. D. (2001). Calcium-activated potassium channels sustain calcium signaling in T lymphocytes. Selective blockers and manipulated channel expression levels. *J. Biol. Chem.* 276, 12249–12256.
- Faraci, F. M., Lynch, C., and Lamping, K. G. (2004). Responses of cerebral arterioles to ADP: eNOS-dependent and eNOS-independent mechanisms. *Am. J. Physiol. Heart Circ. Physiol.* 287, H2871–H2876.
- Féltou, M., and Vanhoutte, P. M. (2007). Endothelium-dependent hyperpolarizations: past beliefs and present facts. *Ann. Med.* 39, 495–516.
- Féltou, M., and Vanhoutte, P. M. (2009). EDHF: an update. *Clin. Sci.* 117, 139–155.
- Feng, J., Liu, Y., Clements, R. T., Sodha, N. R., Khabbaz, K. R., Senthilnathan, V., Nishimura, K. K., Alper, S. L., and Sellke, F. W. (2008). Calcium-activated potassium channels contribute to human coronary microvascular dysfunction after cardioplegic arrest. *Circulation* 118, S46–S51.
- Fujita, A., Takeuchi, T., Saitoh, N., Hanai, J., and Hata, F. (2001). Expression of Ca(2+)-activated K(+) channels, SK3, in the interstitial cells of Cajal in the gastrointestinal tract. *Am. J. Physiol. Cell Physiol.* 281, C1727–C1733.
- Gardos, G. (1958). The function of calcium in the potassium permeability of human erythrocytes. *Biochim. Biophys. Acta* 30, 653–654.
- Geinisman, Y., Berry, R. W., Disterhoft, J. F., Power, J. M., and Van der Zee, E. A. (2001). Associative learning elicits the formation of multiple-synapse boutons. *J. Neurosci.* 21, 5568–5573.
- Geurts, J. J. G., Wolswijk, G., Bö, L., van der Valk, P., Polman, C. H., Troost, D., and Aronica, E. (2003). Altered expression patterns of group I and II metabotropic glutamate receptors in multiple sclerosis. *Brain* 126, 1755–1766.
- Ghanshani, S., Wulff, H., Miller, M. J., Rohm, H., Neben, A., Gutman, G. A., Cahalan, M. D., and Chandy, K. G. (2000). Up-regulation of the IKCa1 potassium channel during T-cell activation. Molecular mechanism and functional consequences. *J. Biol. Chem.* 275, 37137–37149.
- Ghosh, A., and Greenberg, M. E. (1995). Calcium signaling in neurons: molecular mechanisms and cellular consequences. *Science* 268, 239–247.
- Grgic, I., Eichler, I., Heinau, P., Si, H., Brakemeier, S., Hoyer, J., and Köhler, R. (2005). Selective blockade of the intermediate-conductance Ca²⁺ activated K⁺ channel suppresses proliferation of microvascular and macrovascular endothelial cells and angiogenesis in vivo. *Arterioscler. Thromb. Vasc. Biol.* 25, 704–709.
- Gschwend, S., Henning, R. H., de Zeeuw, D., and Buikema, H. (2003). Coronary myogenic constriction antagonizes EDHF-mediated dilation: role of K_{Ca} channels. *Hypertension* 41, 912–918.
- Habermann, E. (1984). Apamin. *Pharmacol. Ther.* 25, 255–270.
- Haddock, R. E., Grayson, T. H., Morris, M. J., Howitt, L., Chadha, P. S., and Sandow, S. L. (2011). Diet-induced obesity impairs endothelium-derived hyperpolarization via altered potassium channel signaling mechanisms. *PLoS ONE* 6, e16423. doi:10.1371/journal.pone.0016423
- Hammond, R. S., Bond, C. T., Strassmaier, T., Ngo-Anh, T. J., Adelman, J. P., Maylie, J., and Stackman, R. W. (2006). Small-conductance Ca²⁺ activated K⁺ channel type 2 (SK2) modulates hippocampal learning, memory, and synaptic plasticity. *J. Neurosci.* 26, 1844–1853.
- Hannah, R. M., Dunn, K. M., Bonev, A. D., and Nelson, M. T. (2011). Endothelial SK(Ca) and IK(Ca) channels regulate brain parenchymal arteriolar diameter and cortical cerebral blood flow. *J. Cereb. Blood Flow Metab.* 31, 1175–1186.
- Havekes, R., Nijholt, I. M., Luiten, P. G. M., and Van der Zee, E. A. (2006). Differential involvement of hippocampal calcineurin during learning and reversal learning in a Y-maze task. *Learn. Mem.* 13, 753–759.
- Hilgers, R. H., Janssen, G. M., Fazzi, G. E., and De Mey, J. G. (2010). Twenty-four-hour exposure to altered blood flow modifies endothelial Ca²⁺ activated K⁺ channels in rat mesenteric arteries. *J. Pharmacol. Exp. Ther.* 333, 210–217.
- Hopf, F. W., Bowers, M. S., Chang, S. J., Chen, B. T., Martin, M., Seif, T., Cho, S. L., Tye, K., and Bonci, A. (2010). Reduced nucleus accumbens SK channel activity enhances alcohol seeking during abstinence. *Neuron* 65, 682–694.
- Hopf, F. W., Seif, T., and Bonci, A. (2011a). The SK channel as a novel target for treating alcohol use disorders. *Channels (Austin)* 5, 289–292.
- Hopf, F. W., Simms, J. A., Chang, S. J., Seif, T., Bartlett, S. E., and Bonci, A. (2011b). Chlorzoxazone, an SK-type potassium channel activator used in humans, reduces excessive alcohol intake in rats. *Biol. Psychiatry* 69, 618–624.
- Hosseini, R., Benton, D. C., Dunn, P. M., Jenkinson, D. H., and Moss, G. W. (2001). SK3 is an important component of K(+) channels mediating the afterhyperpolarization in cultured rat SCG neurones. *J. Physiol.* 535, 323–334.
- Hougaard, C., Eriksen, B. L., Jørgensen, S., Johansen, T. H., Dyhring, T., Madsen, L. S., Strøbaek, D., and Christophersen, P. (2007). Selective positive modulation of the SK3 and SK2 subtypes of small conductance Ca²⁺ activated K⁺ channels. *Br. J. Pharmacol.* 151, 655–665.
- Hugues, M., Romey, G., Duval, D., Vincent, J. P., and Lazdunski, M. (1982). Apamin as a selective blocker of the calcium-dependent potassium channel in neuroblastoma cells: voltage-clamp and biochemical characterization of the toxin receptor. *Proc. Natl. Acad. Sci. U.S.A.* 79, 1308–1312.
- Ikonen, S., and Riekkinen, P. (1999). Effects of apamin on memory processing of hippocampal-lesioned mice. *Eur. J. Pharmacol.* 382, 151–156.
- Ishii, T. M., Silvia, C., Hirschberg, B., Bond, C. T., Adelman, J. P., and Maylie, J. (1997). A human intermediate conductance calcium-activated potassium channel. *Proc. Natl. Acad. Sci. U.S.A.* 94, 11651–11656.
- Jacobsen, J. P., Redrobe, J. P., Hansen, H. H., Petersen, S., Bond, C. T., Adelman, J. P., Mikkelsen, J. D., and Mirza, N. R. (2009). Selective cognitive deficits and reduced hippocampal brain-derived neurotrophic factor mRNA expression in small-conductance calcium-activated K⁺ channel deficient mice. *Neuroscience* 163, 73–81.
- Jensen, B. S., Odum, N., Jørgensen, N. K., Christophersen, P., and Olesen, S. P. (1999). Inhibition of T cell proliferation by selective block of Ca(2+)-activated K(+) channels. *Proc. Natl. Acad. Sci. U.S.A.* 96, 10917–10921.
- Jensen, B. S., Strøbaek, D., Christophersen, P., Jørgensen, T. D., Hansen, C., Silhtaroglu, A., Olesen, S. P., Ahring, P. K., Physiol, A. J., and Liver, G. (1998). Characterization of the cloned human intermediate-conductance Ca²⁺-activated K⁺ channel. *Am. J. Physiol. Cell Physiol.* 275, C848–C856.
- Joiner, W. J. (1997). hSK4, a member of a novel subfamily of calcium-activated potassium channels. *Proc. Natl. Acad. Sci. U.S.A.* 94, 11013–11018.
- Kaushal, V., Koeberle, P. D., Wang, Y., and Schlichter, L. C. (2007). The Ca²⁺ activated K⁺ channel KCNN4/KCa3.1 contributes to microglia activation and nitric oxide-dependent neurodegeneration. *J. Neurosci.* 27, 234–244.
- Khanna, R., Roy, L., Zhu, X., and Schlichter, L. C. (2001). K⁺ channels and the microglial respiratory burst. *Am. J. Physiol. Cell Physiol.* 280, C796–C806.
- Killestein, J., Kalkers, N. F., and Polman, C. H. (2005). Glutamate inhibition in MS: the neuroprotective properties of riluzole. *J. Neurol. Sci.* 233, 113–115.
- Köhler, M., Hirschberg, B., Bond, C. T., Kinzie, J. M., Marrion, N. V., Maylie, J., and Adelman, J. P. (1996). Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* 273, 1709–1714.
- Köhler, R., Wulff, H., Eichler, I., Kneifel, M., Neumann, D., Knorr, A., Grgic, I., Kämpfe, D., Si, H., Wibawa, J., Real, R., Borner, K., Brakemeier, S., Orzechowski, H. D., Reusch, H. P., Paul, M., Chandy, K. G., and Hoyer, J. (2003). Blockade of the intermediate-conductance calcium-activated potassium channel as a new therapeutic strategy for restenosis. *Circulation* 108, 1119–1125.
- LaFerla, F. M. (2002). Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. *Nat. Rev. Neurosci.* 3, 862–872.
- Lamy, C., Goodchild, S. J., Weatherall, K. L., Jane, D. E., Liegeois, J. F., Seutin, V., and Marrion, N. V. (2010). Allosteric block of K_{Ca}2 channels by apamin. *J. Biol. Chem.* 285, 27067–27077.

- Landfield, P., and Pitler, T. (1984). Prolonged Ca²⁺ dependent after-hyperpolarizations in hippocampal neurons of aged rats. *Science* 226, 1089–1092.
- Lappin, S. C., Dale, T. J., Brown, J. T., Trezise, D. J., and Davies, C. H. (2005). Activation of SK channels inhibits epileptiform bursting in hippocampal CA3 neurons. *Brain Res.* 1065, 37–46.
- Leuranguer, V., Gluais, P., Vanhoutte, P. M., Verbeuren, T. J., and Féléto, M. (2008). Openers of calcium-activated potassium channels and endothelium-dependent hyperpolarizations in the guinea pig carotid artery. *Naunyn Schmiedebergs Arch. Pharmacol.* 377, 101–109.
- Lin, M. T., Luján, R., Watanabe, M., Adelman, J. P., and Maylie, J. (2008). SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nat. Neurosci.* 11, 170–177.
- Longden, T., Dunn, K., Draheim, H., Nelson, M., Weston, A., and Edwards, G. (2011). Intermediate-conductance calcium-activated potassium channels participate in neurovascular coupling. *Br. J. Pharmacol.* 164, 922–933.
- Maas, A. J., Den, H. A., Ras, R., and Van den Akker, J. (1980). The action of apamin on guinea-pig taenia caeci. *Eur. J. Pharmacol.* 67, 265–274.
- Maas, A. J., and Den Hertog, A. (1979). The effect of apamin on the smooth muscle cells of the guinea-pig taenia coli. *Eur. J. Pharmacol.* 58, 151–156.
- Maezawa, I., Zimin, P. I., Wulff, H., and Jin, L. W. (2011). Amyloid-beta protein oligomer at low nanomolar concentrations activates microglia and induces microglial neurotoxicity. *J. Biol. Chem.* 286, 3693–3706.
- Malenka, R., and Malinow, R. (2011). Recollection of lost memories. *Nature* 469, 44–45.
- Marrelli, S. P., Eckmann, M. S., and Hunte, M. S. (2003). Role of endothelial intermediate conductance K_{Ca} channels in cerebral EDHF-mediated dilations. *Am. J. Physiol. Heart Circ. Physiol.* 285, H1590–H1599.
- Matsumoto, T., Ishida, K., Taguchi, K., Kobayashi, T., and Kamata, K. (2010). Losartan normalizes endothelium-derived hyperpolarizing factor-mediated relaxation by activating Ca²⁺ activated K⁺ channels in mesenteric artery from type 2 diabetic GK rat. *J. Pharmacol. Sci.* 112, 299–309.
- McNeish, A. J., Dora, K. A., and Garland, C. J. (2005). Possible role for K⁺ in endothelium-derived hyperpolarizing factor-linked dilatation in rat middle cerebral artery. *Stroke* 36, 1526–1532.
- McNeish, A. J., Sandow, S. L., Neylon, C. B., Chen, M. X., Dora, K. A., and Garland, C. J. (2006). Evidence for involvement of both IKCa and SKCa channels in hyperpolarizing responses of the rat middle cerebral artery. *Stroke* 37, 1277–1282.
- Messier, C., Mourre, C., Bontempi, B., Sif, J., Lazdunski, M., and Destraide, C. (1991). Effect of apamin, a toxin that inhibits Ca(2+)-dependent K⁺ channels, on learning and memory processes. *Brain Res.* 551, 322–326.
- Mongan, L. C., Hill, M. J., Chen, M. X., Tate, S. N., Collins, S. D., Buckley, L., and Grubb, B. D. (2005). The distribution of small and intermediate conductance calcium-activated potassium channels in the rat sensory nervous system. *Neuroscience* 131, 161–175.
- Morgado-Bernal, I. (2011). Learning and memory consolidation: linking molecular and behavioral data. *Neuroscience* 176, 12–19.
- Morikawa, K., Matoba, T., Kubota, H., Hatanaka, M., Fujiki, T., Takahashi, S., Takeshita, A., and Shimokawa, H. (2005). Influence of diabetes mellitus, hypercholesterolemia, and their combination on EDHF-mediated responses in mice. *J. Cardiovasc. Pharmacol.* 45, 485–490.
- Mpari, B., Sreng, L., Manrique, C., and Mourre, C. (2010). K_{Ca}2 channels transiently downregulated during spatial learning and memory in rats. *Hippocampus* 20, 352–363.
- Mulholland, P. J., Becker, H. C., Woodward, J. J., and Chandler, L. J. (2011). Small conductance calcium-activated potassium type 2 channels regulate alcohol-associated plasticity of glutamatergic synapses. *Biol. Psychiatry* 69, 625–632.
- Murthy, S. R., Teodorescu, G., Nijholt, I. M., Dolga, A. M., Grissmer, S., Spiess, J., and Blank, T. (2008). Identification and characterization of a novel, shorter isoform of the small conductance Ca²⁺-activated K⁺ channel SK2. *J. Neurochem.* 106, 2312–2321.
- Nazzaro, C., Greco, B., Cerovic, M., Baxter, P., Rubino, T., Trusel, M., Parolaro, D., Tkatch, T., Benfenati, F., Pedarzani, P., and Tonini, R. (2012). SK channel modulation rescues striatal plasticity and control over habit in cannabinoid tolerance. *Nat. Neurosci.* 15, 284–293.
- Ngo-Anh, T. J., Bloodgood, B. L., Lin, M., Sabatini, B. L., Maylie, J., and Adelman, J. P. (2005). SK channels and NMDA receptors form a Ca²⁺ mediated feedback loop in dendritic spines. *Nat. Neurosci.* 8, 642–649.
- Nolting, A., Ferraro, T., D'Hoedt, D., and Stocker, M. (2007). An amino acid outside the pore region influences apamin sensitivity in small conductance Ca²⁺ activated K⁺ channels. *J. Biol. Chem.* 282, 3478–3486.
- Norris, C. M., Halpain, S., and Foster, T. C. (1998). Reversal of age-related alterations in synaptic plasticity by blockade of L-type Ca²⁺ channels. *J. Neurosci.* 18, 3171–3179.
- O'Donnell, C., Nolan, M. F., and van Rossum, M. C. W. (2011). Dendritic spine dynamics regulate the long-term stability of synaptic plasticity. *J. Neurosci.* 31, 16142–16156.
- Pedarzani, P., and Stocker, M. (2008). Molecular and cellular basis of small – and intermediate-conductance, calcium-activated potassium channel function in the brain. *Cell. Mol. Life Sci.* 65, 3196–3217.
- Randall, R. D., and Thayer, S. A. (1992). Glutamate-induced calcium transient triggers delayed calcium overload and neurotoxicity in rat hippocampal neurons. *J. Neurosci.* 12, 1882–1895.
- Ren, Y., Barnwell, L. F., Alexander, J. C., Lubin, F. D., Adelman, J. P., Pfaffinger, P. J., Schrader, L. A., and Anderson, A. E. (2006). Regulation of surface localization of the small conductance Ca²⁺ activated potassium channel, Sk2, through direct phosphorylation by cAMP-dependent protein kinase. *J. Biol. Chem.* 281, 11769–11779.
- Rimini, R., Rimland, J. M., and Terstappen, G. C. (2000). Quantitative expression analysis of the small conductance calcium-activated potassium channels, SK1, SK2 and SK3, in human brain. *Mol. Brain Res.* 85, 218–220.
- Ro, S., Hatton, W. J., Koh, S. D., and Horowitz, B. (2001). Molecular properties of small-conductance Ca²⁺ activated K⁺ channels expressed in murine colonic smooth muscle. *Am. J. Physiol. Gastrointest. Liver Physiol.* 281, G964–G973.
- Romero-Curiel, A., López-Carpinteyro, D., Gamboa, C., De la Cruz, F., Zamudio, S., and Flores, G. (2011). Apamin induces plastic changes in hippocampal neurons in senile Sprague-Dawley rats. *Synapse* 65, 1062–1072.
- Sailer, C. A., Hu, H., Kaufmann, W. A., Trieb, M., Schwarzer, C., Storm, J. F., and Knaus, H.-G. (2002). Regional differences in distribution and functional expression of small-conductance Ca²⁺ activated K⁺ channels in rat brain. *J. Neurosci.* 22, 9698–9707.
- Sailer, C. A., Kaufmann, W. A., Marksteiner, J., and Knaus, H. G. (2004). Comparative immunohistochemical distribution of three small-conductance Ca²⁺ activated potassium channel subunits, SK1, SK2, and SK3 in mouse brain. *Mol. Cell. Neurosci.* 26, 458–469.
- Sankaranarayanan, A., Raman, G., Busch, C., Schultz, T., Zimin, P. I., Hoyer, J., Kohler, R., and Wulff, H. (2009). Naphtho[1,2-d]thiazol-2-ylamine (SKA-31), a new activator of K_{Ca}2 and K_{Ca}3.1 potassium channels, potentiates the endothelium-derived hyperpolarizing factor response and lowers blood pressure. *Mol. Pharmacol.* 75, 281–295.
- Santos, S. F., Pierrot, N., Morel, N., Gailly, P., Sindic, C., and Octave, J.-N. (2009). Expression of human amyloid precursor protein in rat cortical neurons inhibits calcium oscillations. *J. Neurosci.* 29, 4708–4718.
- Schilling, T., Repp, H., Richter, H., Koschinski, A., Heinemann, U., Dreyer, F., and Eder, C. (2002). Lysophospholipids induce membrane hyperpolarization in microglia by activation of IKCa1 Ca(2+)-dependent K(+) channels. *Neuroscience* 109, 827–835.
- Schumacher, M. A., Rivard, A. F., Bächinger, H. P., and Adelman, J. P. (2001). Structure of the gating domain of a Ca²⁺ activated K⁺ channel complexed with Ca²⁺/calmodulin. *Nature* 410, 1120–1124.
- Shah, M., and Haylett, D. G. (2000). The pharmacology of hSK1 Ca²⁺-activated K⁺ channels expressed in mammalian cell lines SPECIAL REPORT. *Br. J. Pharmacol.* 129, 627–630.
- Shakkottai, V. G., Chou, C. H., Oddo, S., Sailer, C. A., Knaus, H. G., Gutman, G. A., Barish, M. E., LaFerla, F. M., and Chandy, K. G. (2004). Enhanced neuronal excitability in the absence of neurodegeneration induces cerebellar ataxia. *J. Clin. Invest.* 113, 582–590.
- Shetty, P. K., Galeffi, F., and Turner, D. A. (2011). Age-induced alterations in hippocampal function and metabolism. *Aging Dis.* 2, 196–218.
- Shuba, M., and Vladimirova, I. (1980). Effect of apamin on the electrical responses of smooth muscle to adenosine 5'-triphosphate and to non-adrenergic, non-cholinergic nerve stimulation. *Neuroscience* 5, 853–859.

- Stackman, R. W., Bond, C. T., and Adelman, J. P. (2008). Contextual memory deficits observed in mice overexpressing small conductance Ca²⁺ activated K⁺ type 2 (KCa2.2, SK2) channels are caused by an encoding deficit. *Learn. Mem.* 15, 208–213.
- Stackman, R. W., Hammond, R. S., Linardatos, E., Gerlach, A., Maylie, J., Adelman, J. P., and Tzounopoulos, T. (2002). Small conductance Ca²⁺ activated K⁺ channels modulate synaptic plasticity and memory encoding. *J. Neurosci.* 22, 10163–10171.
- Stocker, M., and Pedarzani, P. (2000). Differential distribution of three Ca(2+)-activated K(+) channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol. Cell. Neurosci.* 15, 476–493.
- Strassmaier, T., Bond, C. T., Sailer, C. A., Knaus, H. G., Maylie, J., and Adelman, J. P. (2005). A novel isoform of SK2 assembles with other SK subunits in mouse brain. *J. Biol. Chem.* 280, 21231–21236.
- Strobaek, D., Jorgensen, T. D., Christophersen, P., Ahring, P. K., and Olesen, S. P. (2000). Pharmacological characterization of small-conductance Ca(2+)-activated K(+) channels stably expressed in HEK 293 cells. *Br. J. Pharmacol.* 129, 991–999.
- Strobaek, D., Teuber, L., Jorgensen, T. D., Ahring, P. K., Kjaer, K., Hansen, R. S., Olesen, S. P., Christophersen, P., and Skaaning-Jensen, B. (2004). Activation of human IK and SK Ca2+-activated K⁺ channels by NS309 (6,7-dichloro-1H-indole-2,3-dione 3-oxime). *Biochim. Biophys. Acta* 1665, 1–5.
- Stutzmann, G. E. (2005). Calcium dysregulation, IP3 signaling, and Alzheimer's disease. *Neuroscientist* 11, 110–115.
- Supnet, C., and Bezprozvanny, I. (2010). The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium* 47, 183–189.
- Tacconi, S., Carletti, R., Bunnemann, B., Plumpton, C., Pich, E. M., and Terstappen, G. C. (2001). Distribution of the messenger RNA for the small conductance calcium-activated potassium channel SK3 in the adult rat brain and correlation with immunoreactivity. *Neuroscience* 102, 209–215.
- Taylor, S., and Weston, A. (1988). Endothelium-derived hyperpolarizing factor: a new endogenous inhibitor from the vascular endothelium. *Trends Pharmacol. Sci.* 9, 272–274.
- Toescu, E. C., Verkhatsky, A., and Landfield, P. W. (2004). Ca2+ regulation and gene expression in normal brain aging. *Trends Neurosci.* 27, 614–620.
- Vandorpe, D. H., Shmukler, B. E., Jiang, L., Lim, B., Maylie, J., Adelman, J. P., de Franceschi, L., Cappellini, M. D., Brugnara, C., and Alper, S. L. (1998). cDNA cloning and functional characterization of the mouse Ca²⁺-gated K⁺ channel, mIK1. Roles in regulatory volume decrease and erythroid differentiation. *J. Biol. Chem.* 273, 21542–21553.
- Vick, K. A., Guidi, M., and Stackman, R. W. Jr. (2010). In vivo pharmacological manipulation of small conductance Ca(2+)-activated K(+) channels influences motor behavior, object memory and fear conditioning. *Neuropharmacology* 58, 650–659.
- Visan, V., Sabatier, J.-M., and Grissmer, S. (2004). Block of maurotoxin and charybdotoxin on human intermediate-conductance calcium-activated potassium channels (hIKCa1). *Toxicon* 43, 973–980.
- Wang, W., Zhang, K., Yan, S., Li, A., Hu, X., Zhang, L., and Liu, C. (2011). Enhancement of apamin-sensitive medium after hyperpolarization current by anandamide and its role in excitability control in cultured hippocampal neurons. *Neuropharmacology* 60, 901–909.
- Wang, Y., Zhang, G., Zhou, H., Barakat, A., and Querfurth, H. (2009). Opposite effects of low and high doses of Abeta42 on electrical network and neuronal excitability in the rat prefrontal cortex. *PLoS ONE* 4, e8366. doi:10.1371/journal.pone.0008366
- Weatherall, K. L., Goodchild, S. J., Jane, D. E., and Marrion, N. V. (2010). Small conductance calcium-activated potassium channels: from structure to function. *Prog. Neurobiol.* 91, 242–255.
- Weatherall, K. L., Seutin, V., Liégeois, J.-F., and Marrion, N. V. (2011). Crucial role of a shared extracellular loop in apamin sensitivity and maintenance of pore shape of small-conductance calcium-activated potassium (SK) channels. *Proc. Natl. Acad. Sci. U.S.A.* 108, 18494–18499.
- Wei, A. D., Gutman, G. A., Aldrich, R., Chandy, K. G., Grissmer, S., and Wulff, H. (2005). International union of pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. *Pharmacol. Rev.* 57, 463–472.
- Weston, A., Richards, G., Burnham, M., Feletou, M., Vanhoutte, P., and Edwards, G. (2002). K+-induced hyperpolarization in rat mesenteric artery: identification, localization and role of Na⁺/K⁺-ATPases. *Br. J. Pharmacol.* 136, 918–926.
- Wulff, H., and Zhorov, B. S. (2008). K⁺ channel modulators for the treatment of neurological disorders and autoimmune diseases. *Chem. Rev.* 108, 1744–1773.
- Xia, X. M., Fakler, B., Rivard, A., Wayman, G., Johnson-Pais, T., Keen, J. E., Ishii, T., Hirschberg, B., Bond, C. T., Lutsenko, S., Maylie, J., and Adelman, J. P. (1998). Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature* 395, 503–507.
- Yamazaki, D., Aoyama, M., Ohya, S., Muraki, K., Asai, K., and Imaizumi, Y. (2006). Novel functions of small conductance Ca²⁺ activated K⁺ channel in enhanced cell proliferation by ATP in brain endothelial cells. *J. Biol. Chem.* 281, 38430–38439.
- Yamin, G. (2009). NMDA receptor-dependent signaling pathways that underlie amyloid beta-protein disruption of LTP in the hippocampus. *J. Neurosci. Res.* 87, 1729–1736.
- Zhou, E., Qing, D., and Li, J. (2010). Age-associated endothelial dysfunction in rat mesenteric arteries: roles of calcium-activated K⁺ channels (KCa). *Physiol. Res.* 59, 499–508.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 09 March 2012; paper pending published: 11 April 2012; accepted: 19 May 2012; published online: 11 June 2012.

Citation: Kuiper EFE, Nelemans A, Luiten P, Nijholt I, Dolga A and Eisel U (2012) K_{Ca}2 and K_{Ca}3 channels in learning and memory processes, and neurodegeneration. *Front. Pharmacol.* 3:107. doi: 10.3389/fphar.2012.00107

This article was submitted to *Frontiers in Neuropharmacology*, a specialty of *Frontiers in Pharmacology*.

Copyright © 2012 Kuiper, Nelemans, Luiten, Nijholt, Dolga and Eisel. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.