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

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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 Ca^{2+} 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 (Ca^{2+}) into the presynaptic terminal (Ghosh and Greenberg, 1995). Because of this role of Ca^{2+} in neurotransmitter release, many neuronal functions are dependent on dynamics of Ca^{2+} signaling. Resting levels of intracellular free Ca^{2+} ($[Ca^{2+}]_i$) in neurons are maintained at very low levels, but can be increased by influx of extracellular Ca^{2+} through voltage-, receptor-, or store-operated channels on the plasma membrane or by release from intracellular Ca^{2+} stores, predominantly the ryanodine receptor and inositol trisphosphate (IP_3) receptor dependent endoplasmic reticulum (ER). Most Ca^{2+} signals are delivered as brief transients with spatial and temporal properties. The frequency of the repetitive transients and the $[Ca^{2+}]_i$ obtained encode information to control cellular processes. Also the localization of these events at specific regions of the cell (Ca^{2+} 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 $[Ca^{2+}]_i$ at the Ca^{2+} microdomain level is critical for proper neuronal activity, because insufficient levels of $[Ca^{2+}]$ can lead to impaired functioning whereas excessive cytosolic $[Ca^{2+}]$ levels can cause overstimulation and ultimately cell death (Berridge et al., 1998).

One way to maintain appropriate intracellular $[Ca^{2+}]$ is repolarization of the membrane potential by initiating K^+ efflux from the cell. Increased K^+ permeability in response to elevated cytosolic $[Ca^{2+}]$ 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 Ca^{2+}-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 $^{42}K^+$ efflux (Den Hertog, 1981) and in differentiating neuroblastoma cells using voltage-clamp electrophysiology (Hugues et al., 1982). Voltage-insensitive Ca^{2+}-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 Ca^{2+}-activated K^+ channels can be identified. The International Union of Pharmacology has put the Ca^{2+}-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 Ca^{2+}-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 Ca^{2+}-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 Ca^{2+}.

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 ($IC_{50} \sim 70$ pM) followed by $K_{Ca}2.3$ channels ($IC_{50} \sim 0.63$–6 nM) and the human isoform of $K_{Ca}2.1$ channels ($IC_{50} \sim 1$–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 Ca^{2+} 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 Ca^{2+} sensitivity. In the open state, dephosphorylation of CaM by protein phosphatase 2A increases the Ca^{2+} sensitivity of the channel (Allen et al., 2007). Therefore, Ca^{2+} sensitivity is dependent on the intracellular Ca^{2+} 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 leiurotoxin 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 charybdotoxin 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

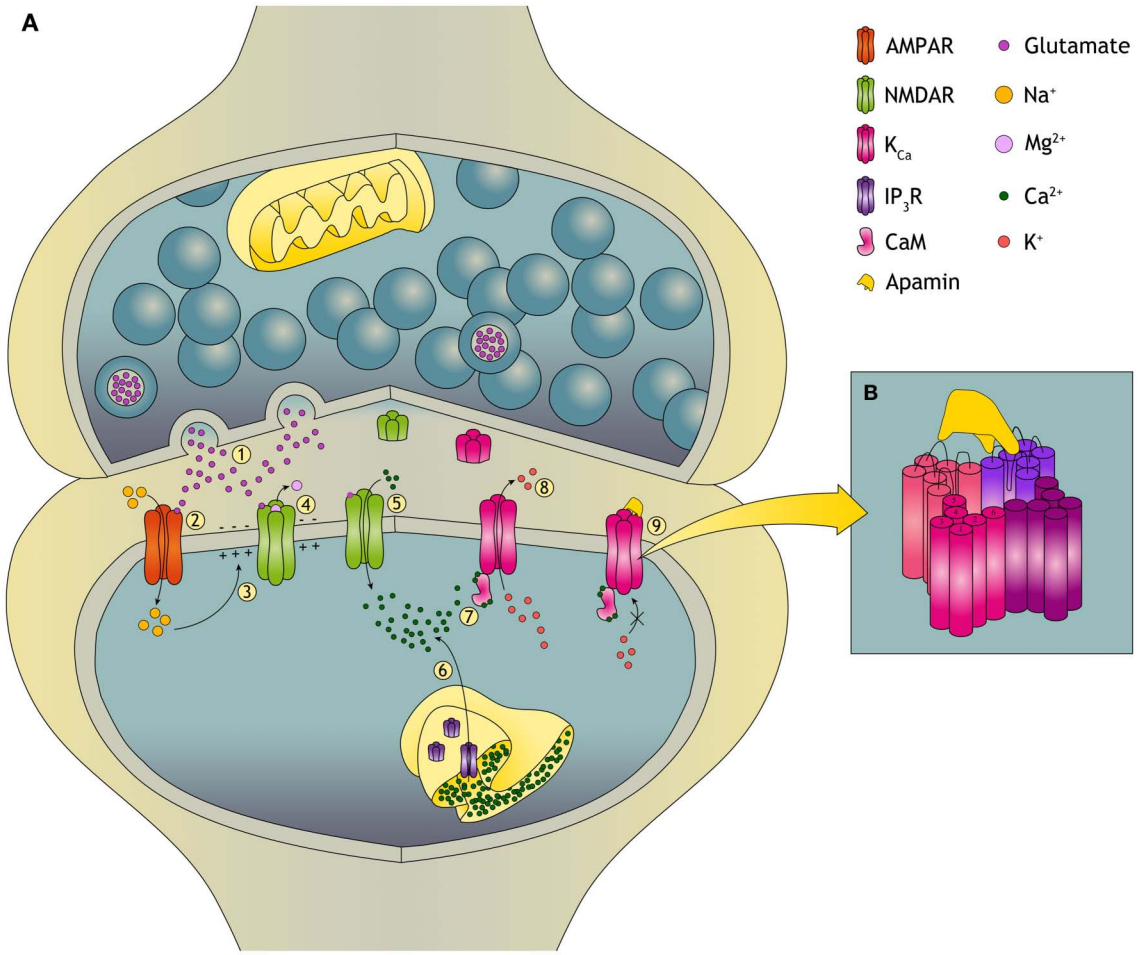

FIGURE 1 | Plasticity in the glutamatergic synapse and the role of K_{Ca} channels. (A) (1) During synaptic transmission, glutamate is released from the presynaptic neuron and acts on the two primary excitatory glutamate receptors: AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors and 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 Mg^{2+} block. (3) Influx of Na^+ causes depolarization of the postsynaptic neuron. (4) The depolarization relieves the Mg^{2+} block of the NMDAR and an excitatory postsynaptic potential (EPSP) is induced. (5) This allows, next to Na^+, for Ca^{2+} influx into the dendritic spine. Changes in the dendritic spine Ca^{2+} concentration can initiate synaptic plasticity. The dynamics of changes in $[Ca^{2+}]$ upon tetanic stimulation determines whether the synapse will undergo long-term potentiation (LTP) or long-term depression (LTD). (6) Ca^{2+} can also be released from the ER, predominantly dependent on ryanodine receptors and inositol trisphosphate receptors (IP_3R). (7) When intracellular levels of Ca^{2+} increase, K_{Ca} channels are activated through calmodulin (CaM). Ca^{2+} 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 Mg^{2+} block of the NMDARs which reduces Ca^{2+} 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,

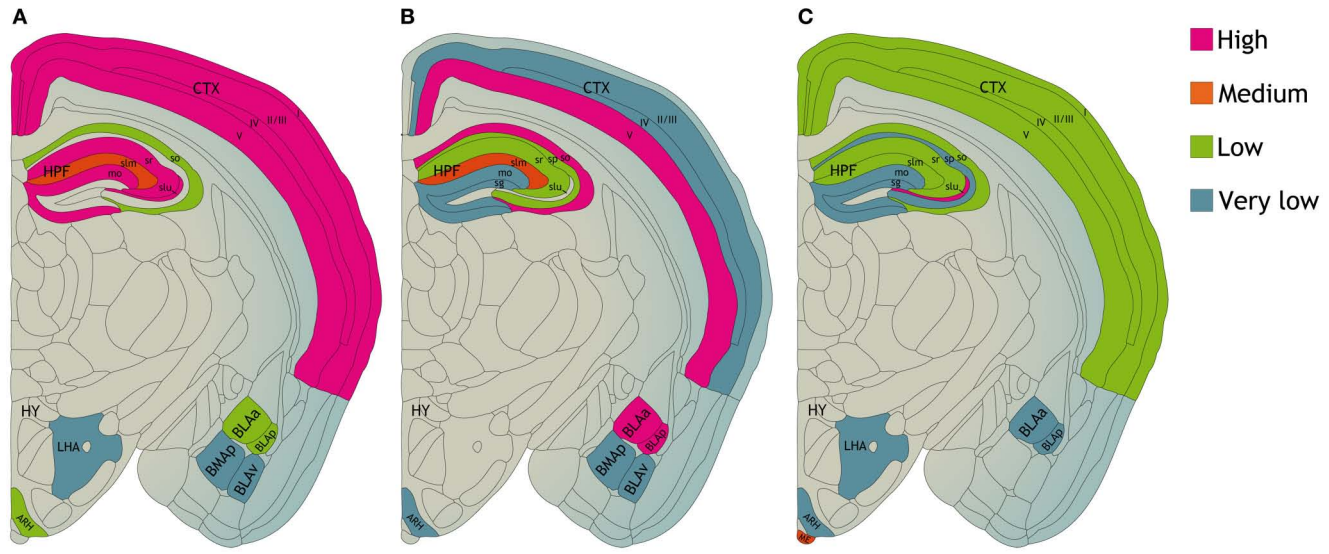

FIGURE 2 | Distribution of (A) $K_{Ca}2.1$, (B) $K_{Ca}2.2$, and (C) $K_{Ca}2.3$ proteins in various compartments of the mouse central nervous system. CTX, neocortex. HPF, hippocampal formation CA1–CA3 region; so, stratum oriens; sp, stratum pyramidale; sr, stratum radiatum; slm, stratum lacunosum moleculare; slu, stratum lucidum. Dentate gyrus; mo, molecular layer; sg, granule cell layer. HY, hypothalamus; LHA, lateral hypothalamic area; ARH, arcuate hypothalamic nucleus; ME, median eminence. BLAa, basolateral amygdalar nucleus, anterior part; BLAp, basolateral amygdalar nucleus, posterior part; BLAv, basolateral amygdalar nucleus, ventral part; BMAp, basomedial amygdalar nucleus, posterior part based on data from Sailer et al. (2004).

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; Félétou 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 (Félétou 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 cardiovasculature, $K_{Ca}3.1$, $K_{Ca}2.2$, 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 Ca^{2+} (Debanne et al., 2004; Yamin, 2009; Malenka and Malinow, 2011). In hippocampal CA1 pyramidal neurons, changes in dendritic spine Ca^{2+} 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), Ca^{2+} 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 Mg^{2+} block of the NMDARs which reduces Ca^{2+} influx (Allen et al., 2011b). By regulating Ca^{2+} 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 Ca^{2+} 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; Borght 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 (Mulholland 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 Ca^{2+}. 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 Ca^{2+} 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 Ca^{2+} levels may slowly increase, affecting critical Ca^{2+} signaling throughout cells and affecting cellular activity (Toescu et al., 2004; Shetty et al., 2011). Indeed, in neurons from aged rats, elevated levels of $[Ca^{2+}]_i$ can lead to a prolonged Ca^{2+}-dependent K^+-mediated AHP, resulting in deleterious effects on neurons (Landfield and Pitler, 1984; Norris et al., 1998). Also an immediate abnormal increase in $[Ca^{2+}]_i$ and exacerbated activation of glutamate receptor-coupled Ca^{2+} channels, like NMDA receptors, are established hallmarks of neuronal cell death in acute and chronic neurological diseases (Dolga et al., 2011). Neurons modulate Ca^{2+} signals by regulating the influx into the cell from the extracellular environment or by its release from internal sources such as the ER via IP_3 receptors and ryanodine receptors in the ER membrane (LaFerla, 2002; Stutzmann, 2005). The regulation of the $[Ca^{2+}]_i$ is critical, because insufficient levels of $[Ca^{2+}]$ can lead to impaired functioning whereas excessive cytosolic $[Ca^{2+}]$ levels can cause overstimulation and even cell death (Berridge et al., 1998). Several factors can trigger increases in $[Ca^{2+}]_i$ in neurons, like exposure to glutamate, which activates NMDA receptors (Randall and Thayer, 1992; Dolga et al., 2011). In physiological conditions, glutamate receptor-coupled Ca^{2+} channels are responsible for the primary depolarization in glutamate-mediated neurotransmission and changes in dendritic spine Ca^{2+} 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 $[Ca^{2+}]$, functional alterations in K_{Ca} channels can play a significant role in the regulation of Ca^{2+} 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 Ca^{2+} 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 $[Ca^{2+}]_i$ deregulation, an effect that

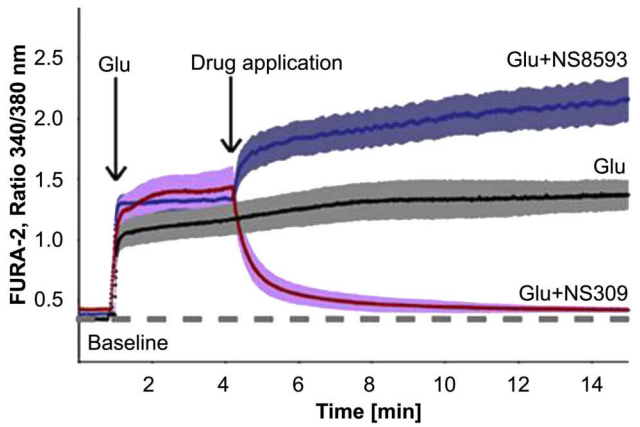

FIGURE 3 | Effect of a negative modulator (NS8593) and an positive modulator (NS309) of K_{Ca} channel activity on the glutamate (Glu)-induced intracellular Ca^{2+} concentrations of primary cortical neurons, seen as changes in fluorescence intensities of the Ca^{2+}-sensitive dye FURA-2. Single neurons 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 Ca^{2+} signaling, which seems to be central to the pathogenesis of AD (LaFerla, 2002; Santos et al., 2009). However, some forms of Ca^{2+} 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 Ca^{2+} signaling through interaction with NMDA receptors, reducing lethal amounts of Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 glutaminergic synapse plasticity	Reduction withdrawal hyperexcitability	1-EBIO, apamin	Mulholland 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}	*In vivo* 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	$K_{Ca}2.2$	TNFα mediated neuroprotection; upregulation $K_{Ca}2.2$	Reduction glutamate-induced neuronal death	Apamin, CyPPA, NS309, siRNA	Dolga 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	Dolga 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 Aβ42 inhibited PFC network via AHP; high dose promoted excitability	Modulation neuronal network excitability		Wang et al. (2009)

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