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Review

Molecular and cellular basis of small- and intermediate-conductance, calcium-activated potassium channel function in the brain

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Abstract. Small conductance calcium-activated potassium (SK or $K_{Ca}2$) channels link intracellular calcium transients to membrane potential changes. SK channel subtypes present different pharmacology and distribution in the nervous system. The selective blocker apamin, SK enhancers and mice lacking specific SK channel subunits have revealed multifaceted functions of these channels in neurons, glia and cerebral blood vessels. SK channels regulate neuronal firing by contributing to the afterhyperpolarization following action potentials and mediating I_{AHP}, and partake in a calcium-mediated feedback loop with NMDA receptors, controlling the threshold for induction of hippocampal long-term potentiation. The function of distinct SK channel subtypes in different neurons often results from their specific coupling to different calcium sources. The prominent role of SK channels in the modulation of excitability and synaptic function of limbic, dopaminergic and cerebellar neurons hints at their possible involvement in neuronal dysfunction, either as part of the causal mechanism or as potential therapeutic targets.

Keywords. Calcium-activated potassium channel, afterhyperpolarization, I_{AHP}, apamin, long-term potentiation, pacemaking neuron, glial cell, cerebral blood vessel endothelium.

An introduction to small-conductance Ca^{2+}-activated K^+ channels (SK channels)

Molecular physiology of SK channels

Potassium currents purely activated by raises in the intracellular concentration of calcium and insensitive to membrane voltage have been characterized in different types of neurons, where they modulate the firing patterns of action potentials, and thereby play a pivotal role in signal encoding in a concerted action with other ion channels. Ca^{2+}-activated K^+ currents display heterogeneous kinetic and pharmacological properties, due to different types of Ca^{2+}-activated K^+ channels that mediate them (reviewed in [1–7]).

Large-conductance Ca^{2+}-activated K^+ channels (BK or maxi-K channels; $K_{Ca}1.1$) were the first Ca^{2+}-dependent K^+ channels to be identified in single channel recordings [8, 9]. BK channels have a single channel conductance of around 100 pS under physiological conditions, which can reach 250 pS when the extracellular and intracellular potassium concentrations are equal. They are activated by voltage and their open probability is modulated by Ca^{2+}. They are widely expressed in different tissues, including different cell types of the nervous system. A more detailed

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description of BK channels and BK-mediated currents can be found in recent reviews [10–17].

Three members of the small conductance, Ca^{2+}-activated K^+ channel (SK) family, SK1 ($K_{Ca}2.1$), SK2 ($K_{Ca}2.2$) and SK3 ($K_{Ca}2.3$), were cloned in 1996 by Adelman and colleagues [18], shortly followed by the cloning of the intermediate conductance, Ca^{2+}-activated K^+ channel (IK, SK4, $K_{Ca}3.1$) [19–21]. Splice variants have been identified for the three SK channel genes. In the mouse brain, for example, splice variants have been identified that may lead to up to 16 different SK1 polypeptides [22] and two SK2 α-subunits with N termini of different length [23]. Three splice variants have been described for SK3, two of which can be found in the human brain [24, 25]. The biophysical characterization in heterologous expression systems showed the voltage independence of SK and IK channels and a half maximal activation by ~300 nM free calcium [19–21, 26]. Under recording conditions using concentrations of K^+ higher than 100 mM on both sides of the membrane, SK channels display a single channel conductance of ~10 pS [18, 27], whereas the IK channel shows a larger single channel conductance of 33–42 pS [20, 21]. The general topology of SK and IK channels is similar to that of voltage-gated potassium channels of the Shaker superfamily, with six transmembrane spanning regions (S1–S6) and the conducting pore located between S5 and S6 [18–21]. The gating is conferred upon SK and IK channels by Ca^{2+} binding to calmodulin, which is constitutively bound to the carboxy-terminus of each channel subunit [26, 28–30].

Detection of RNA by Northern analysis, *in situ* hybridization or RT-PCR analysis and protein by immunohistochemistry have revealed that SK1, SK2, and SK3 channels are expressed in the central (CNS) and peripheral (PNS) nervous system [18, 31–38], while IK seems not to be present in central neurons, but is expressed in blood and epithelial cells [19–21, 39], and in peripheral sensory, sympathetic and enteric neurons [37, 38, 40–43]. *In situ* hybridization and immunohistochemistry studies on brain tissue from adult rat and mouse have shown further that the SK1, SK2 and SK3 channel subunits have partially overlapping but clearly distinct distribution patterns, with SK1 and SK2 frequently expressed in the same neurons, and SK3 presenting a complementary distribution [32, 34–36]. Moreover, immunohistochemical analysis has suggested that SK3 might be localized in presynaptic terminals at the neuromuscular junction [44] and in hippocampal neuronal cultures [45]. Altogether, these studies suggest that SK channels formed by specific subunits influence neuronal excitability and function in different brain regions and possibly, on a cellular level, in different neuronal compartments.

Pharmacology of SK channels

The bee venom toxin apamin is the prototypical, highly specific blocker of SK channels and SK channel subtypes vary in their sensitivities for apamin. This pharmacological difference has been used, in combination with the above-mentioned expression data, to distinguish the contribution of the various SK channels in different physiological contexts. The human SK1 (hSK1) channels are the least sensitive (IC_{50}: 0.7–12 nM; Table 1), the SK2 channels, independently of the species (human, rat, mouse), are the most sensitive (IC_{50}: 27–140 pM; Table 1), and the SK3 channels present an intermediate sensitivity to apamin (IC_{50}: 0.6–4 nM; Table 1). The rat SK1 channel (rSK1) does not form functional homomultimeric channels in expression systems [46–48]. However, chimeric channel subunits containing the transmembrane domain of rSK1, including the pore region, and at least the intracellular carboxy-terminus of SK2 or hSK1 form functional channels [48]. This rSK1 chimera furthered our understanding on the mechanism by which apamin and potentially other toxins block SK channels, because it showed a 25-fold reduction in apamin sensitivity, despite having an identical primary sequence to hSK1 in the pore region. The reduced apamin sensitivity was surprising because the molecular determinants for toxins blocking K^+ channels are located in the pore region between the transmembrane segments S5 and S6. A further analysis revealed that not only amino acids of the pore region [49], but also a residue located in the extracellular loop between the transmembrane segments S3 and S4 influence the apamin sensitivity of SK channels [50]. We think that this observation might hold the key to the explanation as to why certain toxins (maurotoxin, Pi1, PO1 and Tsκ) potently displace ^{125}I-labeled apamin binding [51–56], but show little or no block of SK channel-mediated currents [57]. Beside apamin, scorpion toxins also specifically target SK channels. These include scyllatoxin (leiurotoxin I), isolated from the scorpion *Leiurus quinquestriatus* [58–60], P05 from *Androctonus mauretanicus* [61], and tamapin from *Mesobuthus tamulus* [62] (Table 1). Moreover, all three SK channel subtypes are also blocked by a number of organic compounds (curare, quaternary salts of bicuculline, dequalinium, *N*-methyl-laudanosine, UCL 1684 and UCL 1848) (Table 1, for reviews see also [2, 7]). IK channels present a distinct pharmacology [19–21], being insensitive to apamin, but blocked by the scorpion toxins charybdotoxin (IC_{50}: 2–28 nM; Table 2) and maurotoxin (IC_{50}: 0.8–1.4 nM; Table 2).

Table 1. Pharmacology of recombinantly expressed SK channels.

Toxins				
Compound	IC_{50}	SK1 ($K_{Ca}2.1$)[a]	SK2 ($K_{Ca}2.2$)	SK3 ($K_{Ca}2.3$)
Apamin	nM	0.70[b] [245], 1.3[d] [246], 2.9[i] [247], 3.2[i] [48, 50], 5.1[k] [247], 7.7[i] [248], 8[c] [249], 12.2[l] [248], >100[m] [18, 49]	0.027 [245], 0.03 [50], 0.063 [18], 0.07[d] [246], 0.083 [247], 0.095 [47], 0.14 [249],	0.63 [70], 1[d] [246], 1.1 [249], 1.4 [33], 2 [49], 3[h] [250], 4 [245], 13.2[e] [77], 19.1 [77],
PO5	nM			25 [57]
Scyllatoxin (Leiurotoxin I)	nM	80 [247], 325 [57]	0.29 [247], 0.3 [251]	1.1 [57], 8.3 [33]
Lei-Dab7[f]	nM	6000 [57]	5.5 [57]	2500 [57]
Tamapin	nM	42 [62]	0.024 [62]	1.7 [62]
Tsκ	nM			198 [57]
Organic blockers/inhibitors				
Compound	IC_{50}	SK1 ($K_{Ca}2.1$)[a]	SK2 ($K_{Ca}2.2$)	SK3 ($K_{Ca}2.3$)
Quaternary Bicuculline salts	μM	1.4 [252], 15.9 [247]	1.1 [252], 25 [247]	6.6 [70]
Dequalinium	μM	0.44 [247], 0.48 [248]	0.16 [247], 0.35 [76]	30[e] [77]
d-Tubocurarine	μM	23.5 [248], 27 [247], 30.8 [50], 76.2 [18], 354 [49]	2.4 [18], 5.4 [49], 17 [247]	210[e] [77]
UCL 1684	nM	0.76 [247]	0.28 [253], 0.36 [247]	5.8 [33], 9.5 [253]
UCL 1848	nM	1.1 [248]	0.11 [47], 0.12 [33],	2.1 [33]
Calyculin A	nM			240[e] [77]
Okadaic acid	nM			506[e] [77]
Amitriptyline	μM		54.8 [76]	39 [70]
Carbamazepine	μM		14.5 [76]	
Chlorpromazine	μM		12.8 [76]	0.6 [70], 33[e] [77]
Cyproheptadine	μM		15.3 [76]	9.2 [70]
Desipramine	μM			29[e][77]
Fluoxetine	μM	9 [e] [78]	7 [e] [78]	17 [78], 20[e] [78]
Fluphenazine	μM			13[e] [77]
Imipramine	μM		21.7 [76]	44[e] [77]
Nortriptyline	μM			20[e] [77]
Promethazine	μM			31[e] [77]
Tacrine	μM		53.7 [76]	
Trifluoperazine	μM		7.6 [76]	48[e] [77]
Methyl-laudanosine	μM	1.2 [254]	0.8 [254]	1.8 [254]
Methyl-noscapine	μM	5.9 [254]	5.6 [254]	3.9 [254]
NS8593[g]	μM	415 [75]	598 [75]	726 [75]
4-Aminopyridine (4-AP)	μM			512 [70]
Tetraethylammonium (TEA)	mM	5.2 [50], 14.1 [255], 14.6 [49]	2.8 [255]	8.7 [255]
Enhancers				
Compound	EC_{50}	SK1 ($K_{Ca}2.1$)[a]	SK2 ($K_{Ca}2.2$)	SK3 ($K_{Ca}2.3$)
1-EBIO	μM	631 [193]	453 [72], 654 [66], 866 [193], 996 [68]	87 [7], 545[h] [250], 789 [193, 250], 1040 [74]
Dichloro-EBIO (DCEBIO)	μM		27 [72]	12 [7], 16 [74], 28 [250], >100[h] [250],
NS309	μM		0.62 [72]	0.12 [7], 0.30 [74], 0.46 [250], 1.20[h] [250],

Table 1 *(Continued)*

Enhancers				
CyPPA	μM	>100 (inactive [74])	14 [74]	5.6 [74]
Riluzole	μM		43 [69]	
Zoxazolamine	μM		696 [68]	
Chlorzoxazone	μM		87 [67], 960 [68]	
GW275919X	μM			170 [250], >100[h] [250]
CCI7950	μM			5[h] [250]

Reported are IC_{50} values obtained from electrophysiological recordings, rubidium flux and functional fluorescence assays. Underlined values have been obtained from the human SK channel clones, all other values from the rat SK channel clones.
[a] Rat SK1 (rSK1) subunits do not seem to form functional homomeric channels [46–48]. However, chimeric channel subunits containing the transmembrane domain of rSK1, including the pore region, and intracellular N and C termini or solely C termini of rat SK2 (rSK2) or human SK1 (hSK1), form channels with an IC_{50} for apamin >100 nM and for d-tubocurarine >50 μM [48].
[b] Second component with IC_{50} of 196 nM.
[c] Up to 39% residual current.
[d] Rubidium flux measurements.
[e] Fluorescence assays.
[f] Lei-Dab7: unnatural amino acid diaminobutanotate replacing methionine in Leiurotoxin at position 7 [57].
[g] NS8593 is not a classical blocker, but an inhibitory gating modulator, the first of its kind, that reduces the apparent affinity of the SK channels for Ca^{2+} [75].
[h] Results obtained by planar array electrophysiology (population patch [250]).
[i] Channels expressed in HEK293 cells.
[k] Channels expressed in CHO cells.
[l] Channels expressed in COS-7 cells.
[m] Channels expressed in *X. laevis* oocytes.

Pharmacological tools for the study of SK and IK channel function comprise, beside blockers, positive modulators/enhancers and negative modulators. The prototypical SK channel enhancer is 1-ethyl-2-benzimidazolinone (1-EBIO), first described as acting on native IK channels in colonic epithelial cells [63], and subsequently shown to enhance the activity of recombinant IK channels in transfected cell lines [64, 65]. By increasing the apparent Ca^{2+} sensitivity of SK channels, 1-EBIO enhances their activity by almost one order of magnitude [66]. Structurally related compounds, such as the muscle relaxants chlorzoxazone and zoxazolamine, similarly enhance the activity of IK and SK2 channels [67, 68]. The neuroprotective drug riluzole (2-amino-6-trifluoromethoxy benzothiazole), which has some structural resemblance to 1-EBIO, similarly enhances the activity of SK2 [69] and SK3 channels [70]. DCEBIO, a dichlorinated analogue of 1-EBIO, enhances the activity of IK channels with a ~100-fold and SK channels with a ~17-fold higher potency compared to 1-EBIO ([71, 72], and Tables 1 and 2). The most specific and potent positive modulator of IK and SK channels characterized so far is NS309, displaying a potency ~7400-fold (IK channels) and ~730-fold (SK channels) higher than 1-EBIO ([72, 73], and Tables 1 and 2). 1-EBIO, DCEBIO and NS309 all have in common a higher potency on IK compared to SK channels and a relative lack of selectivity for the three SK channel subtypes. A novel positive modulator, CyPPA, has been recently characterized that is more potent than 1-EBIO and DCEBIO, but less potent than NS309 [74]. However, the most remarkable feature of CyPPA is its selectivity. CyPPA does not affect hIK and hSK1 channels but enhances currents mediated by hSK3 (EC_{50} = 5.6 μM) and hSK2 (EC_{50} = 14 μM) channels ([74], and Table 1). While 1-EBIO, DCEBIO, NS309 and CyPPA can be best described as positive gating modulators that increase the apparent Ca^{2+}-sensitivity of SK channels, a recent study has proposed NS8593 to be a negative gating modulator. Negative gating modulation is a novel principle for the selective inhibition of SK channels [75]. NS8593 is chemically different from all known small, organic molecule blockers of SK channels in that it decreases the apparent Ca^{2+} sensitivity of SK channels by shifting their activation curve by calcium to the right, without affecting their maximal activation [75]. The potency of NS8593 is similar for SK1, SK2 and SK3 channels, while IK channels are not affected ([75], Table 1). Finally, SK channels have been shown to be the targets of a number of neuroactive drugs suppressing channel activity and including tricyclic antidepressants, Prozac[®] (fluoxetine hydrochloride) and anti-psychotic phenothiazines, as summarized in Table 1 [70, 76–78]. The availability of this rich collection of pharmacological tools, unprecedented for most other K^+ channels, and the recent generation of genetically modified animal models lacking specific SK and IK subunits [79–82] have fostered a number of studies on the function of SK and IK channels in different tissues and brain regions. A number of excellent reviews have

Table 2. Pharmacology of the cloned IK channel blockers.

Compound	IC_{50}	hIK ($hK_{Ca}3.1$)
Charybdotoxin (CTX)	[nM]	2 [19], 2.5 [21], 3[b] [256], 3.3 [257], 10 [20], 28 [64]
CTX-Glu^{32}	[nM]	33[b] [256]
Maurotoxin	[nM]	0.81 [257], 1.1[a] [246], 1.4 [246]
Margatoxin (MgTX)	[nM]	50 [7], 459 [64], >100 [20]
Orthochirus toxin (OSK1)	[nM]	225 [258]
Stichodactyla toxin (ShK)	[nM]	291 [64], 30[b] [256, 259]
Bunodosoma toxin (BgK)	[nM]	172 [259]
Clotrimazole	[nM]	24.8 [21], 70[b] [256], 70–85 [260], 153 [64], 387 [20],
Econazole	[μM]	2.4 [64], 10 [260], 12[b] [256]
Ketoconazole	[μM]	30[b] [256], 35 [260]
Miconazole	[μM]	0.785 [64]
Nifedipine	[μM]	4[b] [256], 1.5[64]
Nimodipine	[μM]	1[b] [256]
Nitrendipine	[μM]	0.9[b] [256], 0.027 [64]
Verapamil	[μM]	72 [64]
Diltiazem	[μM]	154 [64]
Cetiedil	[μM]	79 [64]
TEA	[mM]	24[b] [256], 30 [20]
Tram-3[c]	[nM]	520 [260]
Tram-34	[nM]	20[b] [256, 261], 310[d] [250]
Tram-39	[nM]	60 [260]
Promethazine	[μM]	9.3[e] [262], 49 [262]
	Enhancers	
Compound	EC_{50}	hIK ($hK_{Ca}3.1$)
1-EBIO	μM	74 [64], 84 [67, 71], 28.4 [66], 67[d] [250], 136 [193, 250]
Dichloro-EBIO (DCEBIO)	μM	0.84 [71], 2 [250], 4[d] [250]
NS309	nM	10 [73], 27 [7], 30 [250], 90[d] [250]
CyPPA	μM	>10 (inactive [74])
Chlorzoxazone	μM	98 [67]
GW275919X	μM	7[d] [250]
CCI7950	μM	0.07 [250]; 0.25[d] [250]

Reported are IC_{50} values obtained from electrophysiological recordings and rubidium flux assays.
[a] Rubidium flux measurements.
[b] amino-terminal GFP-tagged channel was expressed.
[c] TRAM, triarylmethane.
[d] Results obtained by planar array electrophysiology (population patch [250]).
[e] Applied to the in-side of a patch.

recently focused on different aspects of Ca^{2+}-activated K^+ currents and channels [1–7]. In this review we highlight some recent progress in our understanding of the function of SK and IK channels in selected regions and cell types of the brain.

Small-conductance Ca^{2+}-activated K^+ channels in central neurons

SK channel distribution in the limbic system and neocortex

Pyramidal neurons in the neocortex and in the hippocampal formation display high levels of SK1 and SK2 mRNA [32, 83] and protein [35, 36], while neurons in the basolateral amygdala express all three SK channel subunits [32, 36]. The cellular distribution of SK

channel proteins in the neocortex of adult rat and mouse brain shows SK1 immunoreactivity mainly associated with the neuropil, in particular with fibers extending from layer 5 to layer 1 that might represent the apical dendrites of layer 5 pyramidal neurons [35, 36]. SK2 immunolabeling is most prominent in the somata and proximal portion of the dendritic tree of layer 5 pyramidal cells, while SK3 displays only a very weak and diffuse immunoreactivity throughout the neocortex [35, 36]. In the hippocampal formation, SK1 immunolabeling is most pronounced in the neuropil of layers CA1-CA3, in particular in the stratum radiatum and, to a slightly lower extent, stratum oriens and lacunosum moleculare, while the pyramidal neuron somata are devoid of signal. Similarly, while the dentate gyrus granule cells show no immunoreactivity at the cell body layer, the mossy fiber system and molecular layer present intense SK1 staining [35, 36]. SK2 immunolabeling is strongest in the CA1-CA2 stratum radiatum and oriens and moderate in the pyramidal cell body layer. In the CA1 stratum radiatum, SK2 has further been shown to be present in dendritic spines, in close proximity to NMDA receptors by double immunogold labeling [84]. Only low level SK2 immunoreactivity is present in the stratum lucidum and dentate gyrus, while high levels have been reported in scattered interneurons in the stratum oriens and radiatum [35, 36], in agreement with the presence of SK2 mRNA [85]. SK3 labeling is most prominent in the hilus and in the stratum lucidum of CA3. Staining in the mossy fiber system is punctuate, and moderate staining is associated with the stratum lacunosum moleculare, the strata oriens and radiatum and the molecular layer of the dentate gyrus. SK3 immunoreactivity is very weak to almost absent in the granule and pyramidal cells [35, 36]. However, the expression of SK3 has been reported to increase with age in the hippocampal formation and correlate with age-dependent deficits in synaptic plasticity and hippocampus-dependent learning [86]. Finally, in the amygdala the most prominent immunostaining was observed for SK2 in the lateral and basolateral nuclei. There is only limited information on the cellular distribution of the SK2 protein in these regions, pointing at a somato-dendritic pattern [36].

SK channel function in the neocortex

In neocortical layer 3–6 pyramidal neurons, an apamin-sensitive Ca^{2+}-activated K^+ current has been shown to contribute to the generation of the medium duration phase of the afterhyperpolarization (mAHP) that follows single or short bursts of action potentials [87–89]. In these neurons, inhibition of SK channels by apamin leads to a faster steady firing rate and an increased instantaneous firing rate, due to a reduction in the extent of the membrane potential repolarization during the interspike intervals [87, 88]. The SK-mediated mAHP following trains of action potentials results from the activation of voltage-gated Ca^{2+} channels of the P-type in layer 2–3 neurons, generating elevations of $[Ca^{2+}]_i$ that cause the opening of SK channels [90]. Additionally, SK channels, activated through muscarinic type 1 or group I metabotropic glutamate receptors and IP_3 signaling, mediate slow cholinergic and glutamatergic inhibition of layer 2–3 and 5 pyramidal neurons in several cortical areas [91, 92]. Overexpression of SK1 and SK2 subunits, as well as the application of 1-EBIO, lead to a selective enhancement of the apamin-sensitive I_{AHP} [93, 94], while this current is strongly reduced in layer 5 pyramidal neurons from transgenic mice expressing a truncated form of the SK3 subunit that acts in a dominant negative fashion and suppresses the expression of all SK and IK channels [94]. These results, together with the observation that rSK1 α-subunits seem not to form functional homomeric channels, suggest the presence of heteromeric SK1/SK2 channels in neocortical neurons. However, the actual subunit composition of the SK channels shaping the firing pattern and mediating the cholinergic inhibition of layer 5 neocortical neurons has not been elucidated so far.

SK channel function in the limbic system

In hippocampal CA1 pyramidal neurons SK2 seems to be the main SK channel subunit responsible for the generation of the apamin-sensitive afterhyperpolarizing current I_{AHP}, as supported by pharmacological and *in situ* hybridization evidence [83], immunohistochemistry [35] and current measurements in mouse neurons lacking the SK1 or SK2 subunit [81]. Two main functions have been described for the SK channels in hippocampal pyramidal neurons. The first is a contribution to the mAHP following bursts of action potentials. Several groups have observed an apamin sensitive component of the mAHP in CA1 pyramidal neurons [83, 95–99], suggesting that SK channels are activated by the opening of voltage-gated calcium channels triggered by action potentials, mediate part of the mAHP, and thereby influence the firing pattern. However, a different result has been reported in one study, which proposed instead that SK channels, although available for activation, are not activated by action potential bursts in CA1 pyramidal cells, and consequently do not affect the mAHP [100]. The reasons for these contrasting results are as yet not clear. The second function of SK channels in hippocampal pyramidal neurons is a consequence of the functional coupling between these channels and NMDA receptors. Exogenous application of NMDA

or glutamate to hippocampal pyramidal neuron dendrites has been shown to activate SK channels that, in turn, limit the duration of dendritic plateau potentials [101, 102]. In distal dendritic branches voltage-gated Ca^{2+} channels can be activated by local photolysis of caged glutamate, resulting in Ca^{2+} transients whose duration depends on SK channel activity [102]. Beside this action in dendritic segments, SK channels modulate Ca^{2+} signals at the level of single dendritic spines [84, 103, 104]. Blockade of SK channels by apamin enhances the amplitude of subthreshold glutamatergic excitatory postsynaptic potentials, which is mainly due to the potentiation of the NMDA receptor-mediated component, resulting in an increased influx of Ca^{2+} in single dendritic spines [84, 104]. The proposed mechanism in the absence of apamin is that SK channels are activated by Ca^{2+} entering the spine through NMDA receptors. This causes a local hyperpolarization of the membrane potential that helps to restore the Mg^{2+} block of the NMDA receptor channels, thereby limiting the amplitude of synaptic potentials and reducing Ca^{2+} influx through NMDA receptors [104]. Additionally, R-type Ca^{2+} channels are found selectively on dendritic spines of hippocampal pyramidal neurons and also Ca^{2+} influx through R-type Ca^{2+} channels leads also to the activation of SK channels in dendritic spines, resulting in a local dampening of synaptically driven Ca^{2+} transients and somatic potentials [105]. Given the importance of Ca^{2+} transients in dendritic spines for the induction of synaptic plasticity [106, 107], these negative feedback systems, where Ca^{2+} entering the cell activates SK channels, which in turn shut the sources of Ca^{2+} entry, might explain the role of SK channels and the effects of apamin in lowering the threshold for the induction of long-term potentiation (LTP) and facilitating hippocampus-dependent learning and memory processes [108–111].

In the basolateral amygdala, where both SK2 and SK3 subunits are expressed [32], SK channels activated by somatic depolarizations mediate the mAHP, but do not regulate spike frequency adaptation [112]. Instead, a coupling similar to that described in the hippocampus between SK channels and NMDA receptors has been observed at glutamatergic synapses in pyramidal neurons of the lateral amygdala, where Ca^{2+} influx through NMDA receptors activates SK channels and shunts the ensuing synaptic potentials [103]. Through this mechanism, SK channels can act as modulators of synaptic plasticity [103], and might ultimately affect amygdala-dependent memory formation and fear conditioning [113].

SK channel modulation

The central position of the SK channels in the above-described negative feedback systems makes them ideal targets for the neuromodulatory control of intrinsic excitability and synaptic function. However, not much is known about modulation of SK channel activity at the systemic level. At the molecular level, SK channels have been shown to be part of a multiprotein complex comprising casein kinase 2 and protein phosphatase 2A [114, 115]. Casein kinase 2 decreases the sensitivity of SK channels to Ca^{2+} by phosphorylating calmodulin. This results in a reduction of SK channel activity and a faster deactivation of SK-mediated currents [114, 115]. Thus, the phosphorylation state of the SK-CaM-CK2-PP2A complex might determine the amplitude and duration of the afterhyperpolarizing potentials shaping the firing patterns of neurons [114, 115]. However, because casein kinase 2 lacks an on-off switch, it is as yet not clear how its activity might be regulated and coordinated with that of protein phosphatase 2A in a physiological context.

In layer 5 neocortical pyramidal neurons, the activation of type 5 metabotropic glutamate receptors (mGluR5) leads to a long-lasting reduction of the apamin-sensitive I_{AHP} and the mAHP, resulting in the LTP of intrinsic excitability and increased spike timing precision [93]. It will be interesting to see which signal transduction pathways are involved in the modulation of I_{AHP} by mGluR5. Further support that SK channels are modulated in a physiological context results from the application of brain-derived neurotrophic factor (BDNF), which inhibits the SK-mediated AHP, possibly by activating serine/threonine protein kinases phosphorylating SK2 channels [96]. The kinase activated by BDNF is not known, but a candidate is protein kinase A (PKA), which can be transiently activated by BDNF signaling in the hippocampus [116]. This is interesting because PKA regulates the surface expression of SK2 channels heterologously expressed in COS7 cells. Here, PKA activation decreases the number of SK2 channels in the plasma membrane, while PKA inhibition has the opposite effect [117]. Taken together, these findings suggest that BDNF might facilitate the induction of LTP by inhibiting SK-mediated currents possibly through the reduction of SK2 surface expression in CA1 pyramidal neurons [96, 117]. However, to conclusively test this hypothesis the direct effect of BDNF on the I_{AHP} and the signal transduction steps leading from BDNF release to the modulation of SK channel activity need to be scrutinized and studied in detail. As for the effect of PKA phosphorylation on SK channels natively expressed in neurons, a recent study has shown that during LTP induction SK2 channels are internalized

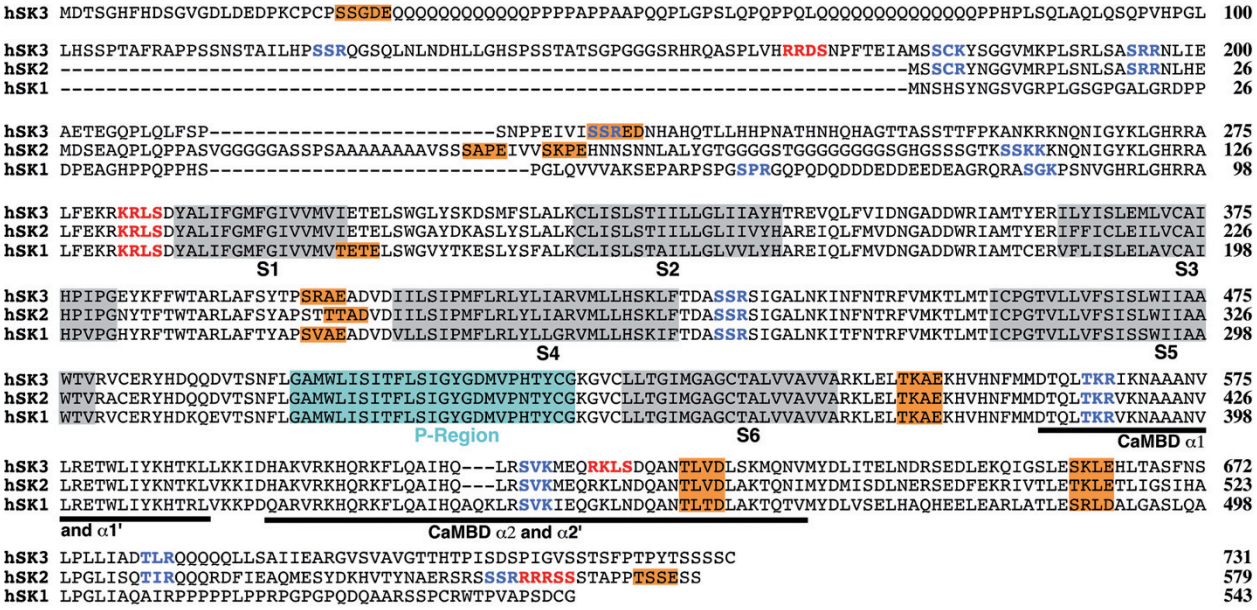

Figure 1. Sequence alignment of the human small conductance Ca^{2+}-activated K^+ channels hSK1, hSK2 and hSK3. The putative transmembrane spanning regions, S1–S6, are boxed in gray. The pore region (P-Region) is boxed in turquoise. The calmodulin-binding domain (CaMBD) is indicated by black bars. Amino acids corresponding to phosphorylation consensus sequences for the cyclic AMP- and cyclic GMP-dependent kinases (PKA and PKG) are displayed in red, for protein kinase C (PKC) in blue; and for casein kinase 2 (CK2) boxed in orange. Only intracellular phosphorylation consensus sequences have been labeled for PKA, PKG and PKC, while both intra- and extracellular ones have been highlighted for CK2 because of its potential action as an endo- and ectokinase [263]. Phosphorylation consensus sites have been mapped using the Prosite database: for PKA/PKG: PS00004: [RK](2)-x-[ST]; for PKC: PS00005: [ST]-x-[RK]; for CK2: PS00006: [ST]-x(2)-[DE].

from the postsynaptic density into CA1 dendritic spines in a PKA-dependent manner [84]. The reduction in the surface expression of SK2 channels in dendritic spines and consequent potentiation of NMDA-mediated currents, together with the increase in AMPA receptor surface expression, would contribute the synaptic strengthening underlying LTP induction in CA1 neurons [84]. Finally, a recent study showed that sigma-1 receptor activation leads to the inhibition of SK channel activity, resulting in a potentiation of NMDA receptor-mediated currents and LTP in CA1 pyramidal neurons [118]. The mechanism underlying the modulation of neuronal SK channels by sigma receptors remains to be elucidated and will be interesting to study. In conclusion, the presence of multiple consensus phosphorylation sites in the sequences of all three SK channel subunits (Fig. 1), together with the emerging evidence summarized above, suggests that SK channels are important targets for neuromodulatory effects in the brain. The neurotransmitters and signal transduction pathways leading to the modulation of neuronal SK channel activity will be the matter of future studies.

SK channel function in spontaneously active and pacemaking neurons

SK channel function in dopaminergic neurons. Dopaminergic midbrain neurons express high levels of SK3 mRNA [32, 34, 119] and protein [120]. The emphasis in the research on the role of SK channels in the dopaminergic system is motivated by the impact that subtle changes in the firing patterns of dopaminergic neurons might have on the spatio-temporal profile of dopamine release in different target areas of the brain, which affect motor control functions, working memory, reward and goal-directed behaviors under normal and pathological conditions [121–125]. When recorded *in vivo*, dopaminergic midbrain neurons display either a single-spike, pacemaking pattern, burst or irregular firing [126–131], while *in vitro* the main firing pattern observed is a low frequency, single-spike pacemaking activity [120, 127, 132–135]. These spontaneous firing patterns observed *in vivo* and *in vitro* result from the concerted activation and complex interaction of a variety of voltage- and ligand-gated ion channels (reviewed by [122, 136]). In particular, in *in vitro* recordings from neurons in the substantia nigra pars compacta, SK3 channels are activated by Ca^{2+} influx through T-type Ca^{2+} channels and generate a hyperpolarization of the membrane potential resulting in the maintenance of precision and stability

of the single-spike pacemaker activity of these neurons [137]. Upon activation, SK3 channels stabilize the spontaneous firing frequency of dopaminergic neurons in the low frequency range: at higher frequency, when Ca^{2+} influx increases, their activation is stronger and leads to slowing down of the firing rate, thereby resulting in a feedback stabilization of the firing frequency [120]. Additionally, SK channels are essential for the maintenance of the temporal precision of the spontaneously occurring action potentials in dopaminergic neurons of the substantia nigra, as revealed by the effect of apamin that reduces spike time precision by blocking SK channels [120]. While some *in vitro* studies have proposed that SK channel inhibition is *per se* sufficient to switch the firing mode of dopaminergic neurons from single spiking to bursting [138–141], others have failed to observe burst firing in response to the application of SK channel blockers alone [120, 142, 143]. However, the suppression of SK channel activity might favor the transition to a burst firing mode [142, 143], whose occurrence is further facilitated by a concomitant inhibition of T-type Ca^{2+} channels [137].

In vivo recordings from the substantia nigra and the lateral ventral tegmental area (VTA) have revealed a robust switch from single-spike firing to burst firing upon local application of SK channel blockers [131, 144]. Distinct effects of SK channel inhibitors have been observed in dopaminergic neurons of the VTA *in vitro* and *in vivo*. In brain slices containing the medial portion of the VTA, a low level of expression of SK3 channels correlating with a smaller I_{AHP} compared to the one observed in the substantia nigra pars compacta, a reduction of spike timing precision and the lack of effect of SK channel blockers on the firing pattern have been observed [120]. The apparent discrepancy between the strong effect of SK channel blockers *in vivo* and their lack of effect *in vitro* on the firing pattern of VTA neurons might be due to the presence of a pronounced gradient in the expression of SK3 channel subunits. An increase in mRNA expression has been observed in dopaminergic neurons when going from the medial to the lateral and from the posterior to the anterior portion of the VTA [119].

The inhibition of SK channels in VTA neurons by apamin results in an increase in firing and excitability that is accompanied by an increase in the intracellular Ca^{2+} concentration leading to the release of endocannabinoids [145]. The endocannabinoids released from the VTA neurons act as retrograde messengers and modulate the release of glutamate and GABA from the presynaptic terminals of afferent fibers innervating the VTA [145]. In this way, SK channels are thought to act as an important component of a feedback system, whereby burst firing of VTA dopaminergic neurons inhibits synaptic inputs and leads to a fine tuning of the firing pattern of these cells, ultimately affecting the timing and amount of dopamine release in areas such as the nucleus accumbens and the prefrontal cortex [145]. In conclusion, SK3 channels, in concert with synaptic signals, render the firing pattern of dopaminergic neurons more precise and control the releases of a retrograde messenger.

SK channel function in the substantia nigra pars reticulata and subthalamic neurons. GABAergic neurons of the substantia nigra pars reticulata (SNR) are a major output system of the basal ganglia. *In situ* hybridization analysis shows a prevalent presence of SK2 transcript in SNR neurons [32]. Interestingly, at the protein level all three SK subunits are detectable in the SNR [36]. This difference is surprising considering the good agreement of mRNA and protein distribution in other parts of the brain. A detailed study looking at the subcellular distribution and localization of SK in the SNR might provide an explanation. SNR neurons fire spontaneous action potentials and their exposure to apamin leads to a reduction of the AHP following each action potential and a switch from a continuous, single spike discharge mode to a bursting firing pattern [146]. Conversely, application of the SK channel enhancer 1-EBIO leads to an increase in AHP duration, a slowing in the frequency and increased regularity of the discharge of SNR GABAergic neurons, and a prolongation of the silent periods between periods of regular discharge [147]. During action potential discharges, SK channels are activated by calcium coming through voltage-gated calcium channels of the T- and N-type in these cells, while release of calcium from intracellular stores does not seem to contribute [146]. However, in juvenile SNR GABAergic neurons, Yanovsky and colleagues [146, 147] observed spontaneously occurring, transient outward currents due to the activation of SK channels by sparks of calcium released from ryanodine-sensitive intracellular stores (outward current pulses, OCPs), similar to those previously observed in midbrain dopaminergic neurons (spontaneous, miniature outward currents, SMOCs, [148, 149]). The function of SMOCs/OCPs is still unclear. Neurons of the subthalamic nucleus modulate the activity of the two main output structures of the basal ganglia: the SNR and the internal pallidal segment. Two subunits leading to the formation of channels highly (SK2) or less sensitive (SK3) to apamin are expressed in subthalamic neurons [32, 36]. The presence of both subunits might be the molecular background for the intermediate apamin sensitivity ($IC_{50} = 246$ pM) of the observed AHP current [150].

In the subthalamic neurons the SK channels, coupled to N-type Ca^{2+} channels, regulate the time precision of the intrinsic single-spike firing [150], a type of activity that might be relevant for the subthalamic control of basal ganglia function *in vivo* [151]. The effect of SK channels on spike timing precision is less prominent at high firing frequencies (>10 Hz), where calcium accumulates and reaches a concentration that is linearly related to the firing frequency [150]. At high firing frequencies, SK channels mainly influence the frequency of the action potentials rather than their timing [150]. Finally, SK channels contribute to the regulation of the duration and intensity of rebound burst activity in subthalamic neurons. Different from the SK regulation of single-spike firing that depends on the coupling to N-type Ca^{2+} channels, the action of SK channels on rebound burst activity is due to coupling to T-type Ca^{2+} channels in subthalamic neurons [150]. This is an interesting example of how the function of SK channels can vary depending on their functional coupling to different Ca^{2+} sources in the same neuron. Although the functional importance of rebound bursts is not completely understood, bursting of subthalamic neurons has been shown to be associated with pathological conditions, such as Parkinson's disease (see *e.g.*, [152]). Because of their regulation of burst termination and intensity, it might be worthy investigating the role of SK channels in pathologies of the basal ganglia system.

SK channel function in the striatum. Cholinergic interneurons, although representing only 1% of all striatal neurons, innervate the whole striatum and acetylcholine released by these neurons is responsible for a host of important modulatory effects on neuronal excitability and synaptic transmission. These interneurons are tonically active and their firing pauses during learning of stimulus-reward associations [153, 154]. In the slice preparation, striatal cholinergic interneurons display two main spontaneous firing modes: single spiking and rhythmic bursting. In the single-spiking pattern, action potentials activate an apamin-sensitive, SK-mediated potassium current, I_{AHP}, underlying an mAHP [155]. The SK-mediated mAHP leads to the activation of a hyperpolarization-activated cation (HCN, I_h) current, which depolarizes the cells enough to trigger the activation of a persistent sodium current driving the membrane potential towards the action potential threshold [155]. Block of the SK channels favors the transition from the single-spiking to the bursting mode [155]. Rhythmic bursting is instead promoted by a slow, apamin-insensitive, calcium-activated potassium current, sI_{AHP}, that mediates a slow AHP (sAHP) lasting several seconds and terminates bursts or prolonged subthreshold depolarizations [154]. As in other brain regions, the channels underlying sI_{AHP} have not yet been identified [3–5]. The calcium-activated potassium channels underlying I_{AHP} and sI_{AHP} are functionally coupled to different calcium sources in striatal cholinergic interneurons. Thus, while the SK channels are mainly coupled to N-type Ca^{2+} channels ($Ca_v2.2$), the sAHP channels are activated by calcium entering through L-type Ca^{2+} channels (Ca_v1) and released from intracellular stores [156]. In cholinergic interneurons, the amplitude of the mAHP, the level of membrane potential depolarization, and the firing rate are modulated by the activity of N-type Ca^{2+} channels through their coupling to SK channels [156]. Thus, inhibition of N-type Ca^{2+} channels leads to a reduction in the SK-mediated mAHP following action potentials and to burst firing. Under these conditions, further inhibition of the L-type Ca^{2+} channels or of the release of Ca^{2+} from intracellular stores reduces the post-burst sAHP, disrupting the burst activity induced by SK current reduction, and favors the single-spiking mode [156]. Thus, the spontaneous activity of striatal cholinergic interneurons and its modulation result from the subtle interplay between I_{AHP} and sI_{AHP}; the balance between these currents and their specific Ca^{2+} sources is important for the maintenance of striatal function and might be perturbed in pathological conditions such as Parkinson's disease.

SK channel function in the cerebellum. In the cerebellum, SK channels are important players in shaping the firing patterns of Purkinje cells, Golgi cells and neurons of the deep cerebellar nuclei (DCN). In Purkinje cells, the only output neurons in the cerebellar cortex, spike-triggered elevations in intracellular Ca^{2+} lead to the activation of SK channels mainly of the SK2 type [157]. When the spontaneous firing activity of Purkinje cells is measured at room temperature, blockade of SK channels favors the transition from single-spiking to the burst firing mode [157]. Additionally, inhibition of SK channels leads to a shortening of burst duration, an increase in burst frequency and in the intraburst frequency of action potentials [157]. Conversely, SK channel activity enhancement by 1-EBIO stabilizes the single-spiking firing mode and increases spike timing precision in these cells [157]. At higher temperatures (33–35°C), SK channels were shown to contribute to the AHP following single spikes and regulate the firing frequency in both the single-spiking and burst firing modes [158, 159]. The activation of SK channels in Purkinje cells is selectively linked to Ca^{2+} influx through P/Q-type Ca^{2+} channels [158, 160], so that small alterations in P/Q-type Ca^{2+} currents can have a strong impact on the firing properties of the Purkinje

cells through their modulation of SK channel activity [161]. Golgi cells are the main inhibitory neurons of the granular layer in the cerebellum. A recent, elegant study demonstrated the intrinsic pacemaking ability of Golgi cells in slices as a low-frequency, rhythmic firing in the absence of synaptic inputs [162]. Golgi cells express high levels of the SK3 subunit [32]. In these neurons the SK3 channels are activated by Ca^{2+} influx triggered by single action potentials and mediate an AHP following each spike [162]. Their inhibition by apamin leads to a remarkable change in the spike timing precision of Golgi cells, without affecting the overall spike frequency [162]. Thus, as in other low frequency pacemaker neurons, SK channels are essential for generating highly precise pacemaking in Golgi cells [162].

Finally, pharmacological and genetic approaches have been taken to elucidate the function of SK channels in neurons of the DCN [82, 163–165]. These neurons are an important site of integration in the cerebellum, since they receive inhibitory inputs from Purkinje cells in the cerebellar cortex and excitatory inputs from mossy and climbing fibers originating from various precerebellar nuclei and the inferior olive. Integration of these inputs results in the firing of DCN neurons, which in turn project to various premotor centers including the thalamus, red nucleus and superior colliculus. DCN neurons are spontaneously active at rest [163, 166]. Most DCN neurons fire in a single-spiking mode [82, 163, 166]: inhibition of SK channels by apamin leads to a reduction in the post-spike AHP and an increase in the tonic firing frequency [82, 163]. At para-physiological temperatures, SK channel inhibition further favors a transition to a burst-firing mode [163, 165], as observed also in Purkinje cells [157]. Additionally, in DCN neurons SK channels regulate the amplitude and duration of the so-called rebound depolarization, which follows a transient period of hyperpolarization of the membrane potential and is mediated by several current components including T-type Ca^{2+} current and I_h [163]. Apamin increases the frequency of the action potentials overriding the rebound depolarization and leads to a prolongation of its duration, frequently resulting in the generation of plateau potentials in DCN neurons [163]. The SK channels responsible for these effects are most likely formed by SK1 and SK2 subunits, while no [32, 82] or only weak [36] SK3 expression was detected in the DCN. The impact of SK channels on the function of DCN neurons has been further corroborated by experiments performed on transgenic mice expressing a dominant negative variant of the SK3 subunit (SK3–1B, [24]) that suppresses the expression of all SK channel subtypes. In transgenic mouse lines, SK3–1B was only detected in DCN neurons within the cerebellum and consequently suppressed all SK-mediated currents in these neurons. The observed enhancement of spontaneous firing frequencies was similar to those observed after application of apamin [82]. Interestingly, the behavioral correlate of this enhanced excitability and spontaneous firing of DCN neurons is a form of ataxia that develops in spite of an intact cerebellar cortical circuitry [82].

Small- and intermediate-conductance Ca^{2+}-activated K^+ channels in glial cells and cerebral blood vessels

Although the molecular and functional properties of SK channels have been most extensively characterized in neurons, there is emerging evidence for the expression and function of these channels in glial cells. In particular, SK3 channel expression has been shown by light and electron microscopy in astrocytes of the supraoptic nucleus and, at lower expression levels, of the substantia nigra pars compacta in adult rat and mouse brain [167], and in olfactory ensheathing glial cells [168]. However, the function of SK channels in astrocytes is still unknown. Ca^{2+} signaling plays a pivotal role in astrocyte function [169], and SK channels might help to maintain long-lasting hyperpolarizations at moderate $[Ca^{2+}]_i$ or play a role in the timing and propagation of intercellular Ca^{2+} waves. Additionally, SK channels are potential targets for the action of neurotransmitters (*i.e.*, serotonin, [170]) and peptides (*i.e.*, endothelin, [171]) acting through the mobilization of intracellular Ca^{2+} in cultured striatal and cortical astrocytes. Microglial cells, the macrophage-like cells of the CNS, respond to a variety of CNS insults such as microbial invasion, by changing their morphology, rapidly up-regulating a large number of receptor types and producing a variety of secretory products that are thought to contribute to the defense of and, potentially, damage to the infected brain [172]. Activated microglial cells generate so-called "respiratory bursts", leading to the production of superoxide and other reactive oxygen intermediates that have anti-microbial functions but can at the same time damage by-stander cells and cause neurotoxicity. Cultured microglial cells from rat and mouse brain have been shown to express both SK (SK2, SK3) and IK channels [173, 174]. In particular, IK channels play important roles in the membrane hyperpolarization and migration of microglial cells activated by lysophospholipids [174, 175], and in the microglia activation by lipopolysaccharide and consequent nitric oxide-dependent neurotoxic effects [176]. Both SK (most likely SK2) and IK channels play a significant role in the NADPH-mediated respiratory

burst generated by treating microglia with phorbol esters [173]. These studies suggest that SK and IK channels might be potential therapeutic targets for the prevention of microglia-mediated neurotoxic effects triggered, for example, by inflammatory agents.

Another prominent site of expression of SK and IK channels in the brain is the cerebral vasculature, in which the function of these channels has been investigated. Generally, in blood vessels endothelial cells control the tone of the underlying vascular smooth muscle cells by releasing various relaxing and contracting factors, including nitric oxide (NO) and prostacyclin (PGI2) [177]. Besides NO and PGI2, a third endothelium-dependent vasodilatory process has been described in both cerebral and peripheral circulations, which is dependent on an intact endothelium, extracellular Ca^{2+}, and activation of Ca^{2+}-dependent K^+ channels and leads to a smooth muscle hyperpolarization and subsequent vasodilatation (reviewed in [177–179]). This process was initially thought to involve production of an endothelial factor, which was termed endothelium-derived hyperpolarizing factor (EDHF, [180]). On the basis of experimental evidence, at least three different mechanisms have been proposed to underlie EDHF-dependent relaxation in various arterial beds (reviewed in [177–179]): (i) the Ca^{2+}-dependent synthesis of a cytochrome P450 metabolite, which is essential for the subsequent endothelium-dependent relaxation; (ii) K^+, released from endothelial cells through Ca^{2+}-dependent K^+ channels inducing smooth muscle hyperpolarization by activating inwardly rectifying K^+ channels or the Na^+-K^+-ATPase on vascular smooth muscle cells; and (iii) endothelial cell hyperpolarization, possibly due to the opening of Ca^{2+}-dependent K^+ channels, transmitted to the vascular smooth muscle *via* gap junctions. Although the relative contribution of each of these mechanisms and their possible interplay are still somewhat controversial and might depend on the type of blood vessel and stimulation, a considerable consensus has been reached that the initial step of EDHF-dependent relaxation is the activation of SK (in particular SK3) and IK channels in the endothelium (reviewed in [177–179]), as supported also by findings in genetically modified mice overexpressing or lacking SK3 [181] or lacking IK channels [182]. Thus, in peripheral vessels, it has been shown that EDHF-mediated responses are abolished by the combined inhibition of both SK and IK channels [178] that are expressed exclusively in endothelial cells [181, 183, 184]. The cerebrovascular circulation has, however, distinctive features when compared with peripheral vascular beds. For example, local increases in $[K^+]_o$ due to high neuronal activity can cause local vasodilation, leading to an increase in local blood flow, a process known as active hyperemia in the brain [179]. In the specific case of the EDHF-dependent blood vessel relaxation, in cerebral vessels it has been shown that inhibition of IK channels alone is sufficient to prevent EDHF-dependent relaxation and hyperpolarization [185, 186]. A recent study found that while SK2 and SK3 channels are present only in the endothelium, IK channels are expressed both in endothelial and smooth muscle cells of middle cerebral arteries [187]. While SK channels contribute to EDHF-dependent hyperpolarization only when the NO synthesis pathway is intact, IK channels alone are sufficient to mediate hyperpolarization and consequent relaxation in the presence of inhibitors of the NO pathway in middle cerebral arteries [187]. The reasons for this difference in the contribution of SK and IK channels to EDHF-dependent relaxation in cerebral arteries are still unknown. It is, however, clear that Ca^{2+}-dependent K^+ channels of the SK and IK type are both expressed in cerebral blood vessels and play a significant role in the regulation of local blood flow [185–188].

Small-conductance Ca^{2+}-activated K^+ channels in neuropathology and psychiatric disorders

SK channels and epilepsy

The role of SK channels in the modulation of intrinsic excitability and synaptic strength and plasticity has implications for their possible involvement in neuronal dysfunction, either as part of the causal mechanism or as potential therapeutic targets. Although this line of investigation is still at an early stage, most studies have focused on the role of SK channels in hyperexcitability disorders and in particular in epilepsy models. In genetic studies, only the SK3 channel gene (*KCNN3*) was investigated and no associations were found between length variations of two adjacent polymorphic CAG-repeats in the coding region of the channel and susceptibility to common subtypes of idiopathic generalized epilepsy [189]. However, in various *in vitro* models of epilepsy induced in hippocampal slices or slice cultures, a down-regulation of the SK-mediated I_{AHP} paralleled the emergence of epileptiform activity [190], and SK channel inhibitors were shown to shape the duration and increase epileptiform bursting activity in the CA3 region [190, 191]. Conversely, SK channel enhancers (*i.e.*, 1-EBIO) led to a cessation of spontaneous oscillatory activity in hyperexcitable neuronal networks [66] and epileptiform activity in hippocampal slices [190, 192, 193]. Based on these results, SK channels have been proposed as potential new targets for the treatment of epilepsy. However, a thorough *in vivo* study [194]

including different, commonly used epilepsy models has revealed that 1-EBIO, although effective in increasing seizure threshold and reducing their incidence, displayed significant adverse effects (locomotor impairment in the rotarod test) within the therapeutic dose range. 1-EBIO is the prototypical SK channel enhancer, but several of its features might limit its suitability in *in vivo* situations, in particular its low potency, marginal effect on sI_{AHP} [66], similar affinity for all three SK channel subtypes [193], and high affinity for the peripherally expressed IK channels [64, 66]. More potent SK channel enhancers, with an improved selectivity, such as NS309, modulate neuronal firing patterns solely by enhancing the SK-mediated I_{AHP} [72], and might therefore display reduced side effects *in vivo*. Even more promising are SK channel enhancers displaying selectivity for specific SK channel subtypes, and lack of effect on peripheral IK channels, such as the recently characterized CyPPA [74]. It remains to be shown whether SK channel enhancers with a finely tuned selectivity profile might indeed provide new tools for the treatment of epilepsy with a good therapeutic index.

SK channels and ataxia

Episodic ataxia type 2 is a rare form of inherited ataxia characterized by attacks of incoordination, vertigo and strong migraines. This condition is linked to mutations and partial loss of function of voltage-gated Ca^{2+} channels of the P/Q type [195]. P/Q Ca^{2+} channels are highly expressed in the dendrites and somata of cerebellar Purkinje cells, where they play an important role in setting the regularity and timing of spontaneous action potential firing in concert with SK channels, which are in turn activated by the Ca^{2+} entering through P/Q channels [160]. Reduction in P/Q currents caused by selective P/Q type Ca^{2+} channel blockers or mutations found in particular mouse strains leads to a disruption in the pacemaking precision of Purkinje cells [196, 197]. This can to a large extent be compensated by up-regulating the activity of SK channels with enhancers that increase their Ca^{2+} sensitivity and spike timing precision, such as 1-EBIO, *in vitro* [157, 197]. In an elegant study, Walter and collaborators [197] addressed the question as to whether the disruption of spike timing precision is responsible for the ataxic phenotype of mice harboring mutations in P/Q channels or associated proteins. They locally perfused 1-EBIO in the cerebellum of mutant mice and observed a substantial improvement in their performance in tests of cerebellar-dependent motor coordination, while at the same concentration 1-EBIO did not affect wild-type mice [197]. This impressive result suggests that the regularity and precision of Purkinje cell firing is essential for normal cerebellar function, and even subtle disruptions of this pacemaking activity can lead to ataxia [197, 198]. It also opens the way to include SK channels as potential therapeutic targets for the treatment of episodic ataxia in humans. Additionally, an association has been described between the length of the polyglutamine repeat in the SK3 channel gene and autosomal dominant cerebellar ataxia in a case-control study [199], although no causal links could be established and more studies on different patient samples are needed to corroborate this finding and clarify its meaning.

SK channels and disorders of the dopaminergic system

The mesocorticolimbic dopamine system, including dopaminergic projections from the ventral midbrain to the frontal cortex and the striatum, plays a major role in controlling voluntary movements, motivated behaviors and reward processing. Pathological changes in this pathway are associated with the etiology of Parkinson's disease, schizophrenia, and drug addiction. *In vivo*, dopaminergic neurons either fire in regular or irregular single-spike mode or discharge bursts of action potentials [126–131]. During burst firing, dopamine release is increased phasically in striatal [200] and cortical [201] target areas of dopaminergic neurons, whereas tonic release during single-spike activity controls the background of dopamine levels that, among other functions, regulates the intensity of the phasic burst-firing signal [136, 202]. The cellular mechanisms that control the transition between pacemaker and burst firing in dopaminergic neurons comprise a complex interplay between their intrinsic membrane properties and afferent inputs. In particular, SK channels play a pivotal role in controlling the transition from bursting to single-spike firing mode, as explained in SK channel function in dopaminergic neurons above. Changes in the degree and/or pattern of dopamine signaling have been implicated in the pathophysiology of Parkinson's disease and schizophrenia [121, 203–205]; therefore, it is conceivable that the modulation of SK channel activity, preferably by subtype selective SK3 inhibitors or enhancers, might represent a novel therapeutic strategy for the treatment of these diseases. In the case of Parkinson's disease, for example, two possible strategies can be envisaged: the inhibition of SK3 channels to favor burst firing and consequently an enhanced release of dopamine from the residual dopaminergic neurons that might lead to an alleviation of the symptoms (see also [2]); or the blockade of SK3 channels in an early phase of the disease to slow down the degeneration of dopaminergic neurons, as it has been shown that SK channel inhibition, by increasing excitability and

activity of dopaminergic neurons, facilitates their survival *in vitro* [206].

Trinucleotide polymorphism in SK3 and psychiatric diseases

The SK3 gene *KCNN3* has been regarded as an attractive candidate for bipolar disorder and schizophrenia because of its role in the modulation of neuronal excitability, its expression in selected regions of the brain (*i.e.*, monoaminergic neurons), and the presence of two stretches of CAG repeats that code for polyglutamine residues in the amino-terminal region of the channel, one of which is polymorphic ranging from 4 to 28 repeats [207]. Additionally, *KCNN3* maps to chromosome 1q21 [208], and linkage between schizophrenia and chromosome 1q21–22 has been reported [209], making *KCNN3* a potential positional candidate gene for schizophrenia. Chandy and colleagues [210] originally reported that patients with schizophrenia presented a significant excess of larger alleles compared to a control group in a case-control association study performed on subjects of French-Alsatian and North American origin. Two further case-control studies [211, 212] were subsequently published and supported these findings. A number of studies supporting or opposing the original hypothesis of a genetic link between the *KCNN3* gene and schizophrenia can now be found in the literature. Thus, case-control studies on Serbian [213], Jewish [214, 215] and French-German samples [208] provided data supporting a link between long CAG repeats and large allele sizes and schizophrenia. Conversely, a number of case-control [216–222] and family-based studies [222–230] failed to support the finding of an excess transmission of large alleles to schizophrenic patients, in some cases reporting the opposite trend towards excess transmission of smaller alleles [219, 224, 229]. Finally, a rare frameshift mutation has been identified in one schizophrenic patient [231], leading to the expression of a truncated SK3 channel comprising the amino-terminal region but missing the transmembrane domains. This truncated protein was shown to have a nuclear localization and suppress the expression of SK2-mediated currents in Jurkat cells [232]. However, in spite of an extensive analysis of subjects with schizophrenia or schizophrenia spectrum disorders, no further individuals carrying this frameshift mutation could be identified [231]. In their original study, Chandy and colleagues [210] suggested also a trend, although not significant, towards the transmission of large *KCNN3* allele sizes in bipolar disorder. Subsequent studies failed to support this hypothesis [233–238]. More recently, a meta-analysis based on both case-control and family-based studies on the involvement of *KCNN3* in schizophrenia and bipolar disorders has reached the conclusion that the risks for both disorders "are largely, if not entirely, independent of CAG-repeat length in exon 1 of *KCNN3*" [239].

The same factors that prompted the investigations on the possible genetic links between *KCNN3* and schizophrenia or bipolar disorder (physiological role of SK3 in neurons, expression pattern of SK3 in brain, polymorphic CAG-repeats in the SK3 amino-terminal region and chromosomal localization of the SK3 gene; see above) led also to studies on its possible involvement in anorexia. A series of family-based and case-control studies on different ethnic groups in the Israeli Jewish population have shown that *KCNN3* alleles with longer CAG-repeats are over-represented among anorexic patients, suggesting that *KCNN3* might be a significant contributor to predisposition to anorexia [240–242]. These studies await confirmation from other ethnic backgrounds or family samples.

Finally, two studies have presented contrasting results on the possible genetic link between *KCNN3* polymorphisms in the CAG-repeat regions and migraine. In one study on patients recruited from a German headache clinic, an increased frequency of a rare allele comprising 15 CAG-repeats in the second, highly polymorphic stretch of polyglutamines in SK3 was found in migraine patients [243], whereas in the other study on subjects of Caucasian origin no significant association between *KCNN3* allelic frequencies of migraine and non-migraine patients was found [244].

In conclusion, although there is no unequivocal evidence for a direct involvement of SK channels in the pathogenesis of CNS disorders, the increasing understanding of their functional role at the cellular and network level, together with the development of novel pharmacological tools for the fine modulation of their activity, have led to novel hypotheses on their potential role as therapeutic targets that are worth exploring.

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