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Functions of SK channels in central neurons

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Summary

1. SK channels are small conductance calcium-activated potassium channels that are widely expressed in neurons. The traditional view of the functional role of SK channels is in mediating one component of the afterhyperpolarisation that follows action potentials. Calcium influx *via* voltage-gated calcium channels active during action potentials opens SK channels and the resultant hyperpolarisation lowers the firing frequency of action potentials in many neurons.

2. Recent advances have shown that in addition to controlling action potential firing frequency, SK channels are also important in regulating dendritic excitability, synaptic transmission and synaptic plasticity.

3. In accordance with their role in modulating synaptic plasticity, SK channels are also important in regulating several learning and memory tasks, and may also play a role in a number of neurological disorders.

4. The present review will discuss recent findings on the role of SK channels in central neurons.

Introduction

SK channels are calcium-activated potassium channels that have been termed as such due to their relatively small single channel conductance of approximately 10 pS.[1,2] Three types of SK channels have been cloned from mammalian systems: SK1, SK2, and SK3, encoded for by KCNN1, KCNN2 and KCNN3, respectively[3] (Figure 1). Each of these genes has splice variants. 20 SK1 splice variants have been detected in mouse brains.[4] Two isoforms of SK2 protein have been described in the mouse brain, a short isoform and a long isoform with an extended N terminus.[5] SK3 is reported to have two splice variants in human brain, with the truncated SK3 channel protein behaving as a dominant negative to SK channels.[6] However, other than the truncated form of SK3, the functional roles and locations of the other SK channel splice variants are unknown.

SK channels are insensitive to changes in membrane potential but are activated by rises in cytosolic calcium with a half maximal activation in the 300–800 nM range.[1,7] These channels are structurally similar to voltage-dependent potassium channels with six putative transmembrane spanning regions and cytoplasmic carboxy and amino terminals (Figure 1a), and are thought to assemble as tetramers.[8] Their primary structure shows approximately 60% sequence homology with each other but SK channels only share significant homology with voltage-gated potassium channels in the pore region[3] (Figure 1b). SK channels lack an obvious calcium-binding domain and their calcium sensitivity is conferred by calmodulin, which is constitutively bound to the C terminus of the channel and causes channel opening upon binding of calcium.[9-11]

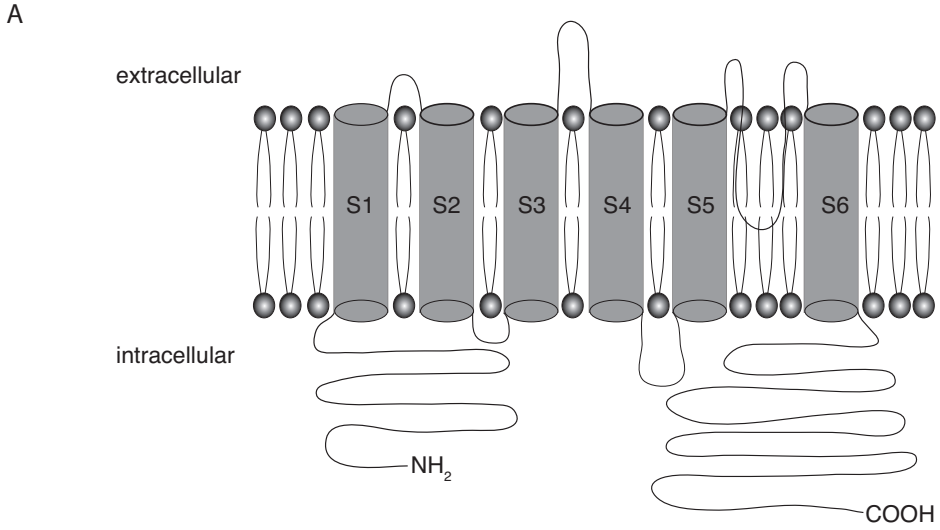
In situ hybridisation[3,12,13] and immunohistochemistry[14,15] have shown that SK channels are widely expressed throughout the central nervous system. SK1 and SK2 subunits are expressed at their highest density in the hippocampus and cortex, whereas SK3 subunits are expressed at their highest levels in regions such as the hypothalamus, thalamus and midbrain. When expressed as homomultimers,[3] SK channel subunits form ion channels that have functional characteristics typical of apamin-sensitive currents in neurons. Thus, they respond rapidly to calcium and are voltage-independent.[16] While SK channels can assemble as heteromultimers in expression systems,[17,18] immunoprecipitation studies suggest that native channels are homomultimers.[15,19,20]

Several types of calcium-activated potassium channels are known to be present in neurons[21] and SK channels were initially distinguished by their potent block by the bee venom apamin.[1,22,23] The measured IC_{50} of SK channels for apamin is 63 pM for SK2,[3] 2 nM for SK3,[24] and between 3.3 nM and 12 nM for SK1 channels[25,26] (Table 1). SK channels are also blocked by the scorpion toxin scyllatoxin,[27-29] tubocurarine, quaternary salts of bicuculline,[30,31] dequalinium, UCL1848 and a large set of related bis-quinolinium cyclophanes[25,32-34] (See Table 1 for IC_{50} values). Recently SK2 channels have been found to be selectively blocked by the scorpion toxin tamapin[35] and by Lei-Dab[36] (Table 1). Conversely SK channel-mediated currents can be enhanced by 1-ethyl-2-benzimidazolinone (EBIO), which enhances their calcium sensitivity and open probability[37,40] and by NS309[41] (Table 2).

Modulation of SK channels

Many ion channels contain consensus phosphorylation sites for protein kinases and phosphorylation of some of these has been found to modulate function or trafficking of channels. To date there have been few demonstrations of modulation of SK channels. Despite containing several potential phosphorylation sites for protein kinase A and protein kinase C, biophysical evidence for modulation of SK channels by these kinases has been lacking. Interestingly, SK2 channels have been shown to co-assemble with casein

A



B

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1   - - - - - - - - - - - - - - - - M P G P R A A C S - - - - - - - - E - - - - - - - - - - - - - - - - - P - - - - - - - - N - KCNN1
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64  V A K S E P A R P S P G S P R G Q P Q D Q D D D E D D E E D E A G R Q R A S G - - - - - - - - - - - - - - - - - - - - KCNN1
68  V S K P E H N N S N N L A L Y G T G G G - G S T G G G G G G G G S G H G S S S - - - - - - - - - - - - - - - - - - - - KCNN2
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106 - - - G T K - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - KCNN2
181 S G G V M K P L S R L S A S R R N L I E A E T E G Q P L Q L F S P S N P P E I V I S S R E D N H A H Q T L L H H P N A T KCNN3

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509 T L E T K L E T L I G S I H A L P G L I S Q T I R Q Q Q R D F I E A Q M E S Y D K H V T Y N A E R S R S S S R R R S S KCNN2
658 S L E S K L E H L T A S F N S L P L L I A D T L R Q Q Q Q Q L S A I I E A R G V S V A V G T T H T P I S D S P I G V S KCNN3

554 P V A P S D C G                                                                                                 KCNN1
569 S T A P P T S S E S S                                                                                         KCNN2
718 S T S F P T P Y T S S S S C                                                                                   KCNN3
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Figure 1. SK channel structure. ***A:*** *Schematic diagram of the structure of one SK channel subunit. The calmodulin-binding domain resides in the C terminus.* ***B:*** *Alignment of human amino acid sequences of SK1-3 (shown KCNN1-3 on right). The homologous regions are outlined in boxes. Sequence accession numbers were Q5KR10 for KCNN1, Q0VFZ4 for KCNN2 and Q5VT74 for KCNN3 (NCBI).*

Table 1. Pharmacology of SK channel blockers. *IC_{50} values are shown for each SK channel subunit.*

	SK1	SK2	SK3
Apamin	3.3-12 nM[25,26]	63 pM[3]	2 nM[24]
Tubocurarine	24-350 µM[3,24,25,26]	2-17 µM[3,24,26]	210 µM[45]
Bicuculline methiodide	1-16 µM[26,44]	1-25 µM[26,44]	7 µM[46]
Scyllatoxin	80-330 nM[26,36]	0.3 nM[26]	1-8 nM[36,47]
Dequalinium	400-500 nM[25,26]	100-400 nM[26,48]	30 µM[45]
UCL1848	1 nM[25]	0.1 nM[18,47]	2 nM[47]
Tamapin	42 nM[35]	0.02 nM[35]	1.7 nM[35]
Lei-dab7	6 µM[36]	24 nM[36]	2.5 µM[36]

Table 2. Pharmacology of SK channel enhancers. *EC_{50} values are shown for each SK channel subunit.*

	SK1	SK2	SK3
1-EBIO	Not tested	400-600 µM[38,41]	Not tested
NS309	Not tested	0.62 µM[41]	Not tested

kinase 2, activation of which phosphorylates calmodulin, reducing the calcium sensitivity of SK channels.[42] More recently, direct phosphorylation of the C terminus of SK channels by protein kinase A has been demonstrated.[43] When expressed in COS cells, phosphorylation of SK2 channels by protein kinase A led to a reduction in their surface expression, suggesting that like other voltage-dependent potassium channels, SK channels may be regulated by trafficking.[6,49-51]

Role of SK channels in neuronal function

The role of SK channels in controlling neuronal excitability through regulation of action potential discharge has been reviewed extensively elsewhere.[21,52,53] Thus the present review will give an overview of this role but will focus more on the recent discoveries showing a role for SK channels in modulating dendritic excitability, synaptic transmission and plasticity and learning and memory.

Regulation of firing patterns

In neurons, trains of action potentials are followed by an afterhyperpolarisation (AHP) that can last several seconds. This AHP typically has three components; the fast AHP, the medium AHP and the slow AHP. These are primarily mediated by calcium-activated potassium channels. They are activated following calcium influx through voltage-gated calcium channels, which open during the action potential.[54-58] The fast AHP, which activates rapidly and typically lasts 1-10 ms, is mediated by BK-type calcium-activated potassium channels as well as some voltage-gated potassium conductances, and is responsible for action potential repolarisation.[21,40] The medium AHP, which also activates rapidly has a decay time constant of approximately 100 ms, is predominately mediated by SK channels[59-63] (Figure 2a, b), although in hippocampal CA1 neurons the M current and BK channels have also been shown to contribute to the medium AHP.[56,64,65] The time course of the medium AHP is dependent on the amount of calcium influx and the kinetics of the calcium transient.[14,58,66-69] The slow AHP, which has a slower rise time than the medium AHP, can last several seconds[21] (Figure 2a, b). This current is largely responsible for generating spike frequency adaptation,[21,70] but the channels underlying the slow AHP are still unknown. Initially SK1 channels were speculated to underlie the slow AHP due to their insensitivity to apamin in some expression systems.[21] However, in addition to other inconsistencies that have been previously discussed,[21] the finding that the slow AHP is still present following knockout of all known SK channels[71,72] is in strong agreement with the suggestion that SK channels cannot underlie the slow AHP in most neurons. Despite these findings, however, SK channels have been shown to mediate a slow AHP in gonadotrophin-releasing neurons in the hypothalamus.[73]

The functional role of the apamin-sensitive current has been proposed to control action potential discharge frequency. This has been shown to be the case in hippocampal neurons,[12,38,74,75] midbrain dopaminergic neurons,[19,76-78] dorsal vagal neurons,[20,62] sympathetic neurons,[60] nucleus reticularis thalamic neurons,[79] inferior olive neurons,[80] spinal and hypoglossal motoneurons,[67,81] mitral cells in the olfactory bulb[82] and cortical neurons.[63] In lateral amygdala neurons, however, despite the presence of a prominent medium AHP, apamin-sensitive channels do not significantly regulate the firing frequency of neurons (Figure 2c), unless SK channel activation is enhanced either pharmacologically with EBIO or by increasing calcium influx by slowing action potential repolarisation.[40]

Regulation of dendritic excitability

As discussed above, activation of SK channels by calcium influx during action potentials modulates the frequency of action potential discharge in most neurons. While the location of the channels that underlie this effect is not known, it is generally presumed to be somatic, near the initiation site for action potentials. However, it is now clear that apamin-sensitive channels are also present in the dendritic tree where they can be activated by calcium rises

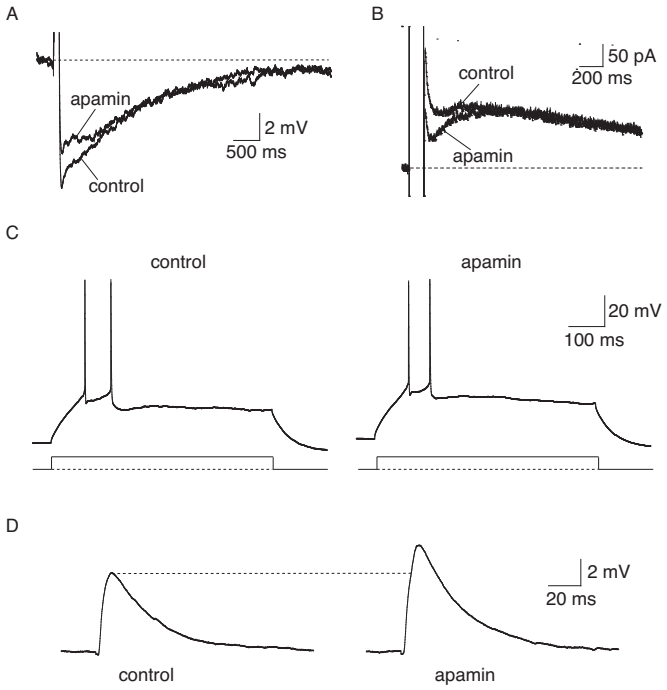

Figure 2. Physiological roles of SK channels in neurons, illustrated using the selective blocker apamin. A: *An AHP evoked by current injection. The medium AHP is selectively blocked by apamin, leaving the slow AHP intact.* ***B:*** *The current underlying the AHP is evoked by a voltage step from a holding potential of -50 mV. The current underlying the medium AHP, I_{AHP}, is blocked by apamin.* ***C:*** *Apamin has no significant effect on action potential firing frequency in a pyramidal neuron in the lateral amygdala. Action potential firing was evoked by a current injection, shown below the traces.* ***D:*** *In lateral amygdala neurons, SK channels shunt excitatory synaptic transmission, demonstrated by an enhancement of the EPSP by apamin.*

from sources other than voltage-gated calcium channels. For example, in dopamininergic[83] and cortical pyramidal neurons,[84,85] calcium released from intracellular stores activates an apamin-sensitive conductance and a resultant hyperpolarising potential. In CA1 hippocampal neurons, exogenous application of NMDA to dendrites generates a plateau potential that is terminated by activation of SK channels.[86] In Lamprey spinal motoneurons, SK channels can also be activated following dendritic activation of NMDA receptors, where they also act to terminate the resulting dendritic plateau potential.[87] In these neurons dendritic SK channels also contribute to an afterhyperpolarisation, which shunts excitatory inputs if triggered during the afterhyperpolarisation. However this shunt requires action potential-mediated activation of SK channels since blockade of SK channels alone has no effect on single EPSPs or trains of EPSPs.[88] Finally, dendritic SK channels can also be activated following NMDA receptor activation in mitral cells in the olfactory bulb, where they regulate dendritic excitability.[82]

Regulation of synaptic transmission and plasticity

A role for SK channels in synaptic transmission was first shown in dopaminergic neurons in the ventral tegmental area and the substantia nigra, where SK channels were shown to contribute to an inhibitory postsynaptic potential. Activation of SK channels followed release of calcium from intracellular stores, triggered by glutamate acting at metabotropic glutamate receptors.[83] Subsequent to this, SK channels were also shown to mediate an inhibitory postsynaptic conductance in auditory outer hair cells following activation by calcium influx through calcium-permeable nicotinic acetylcholine receptors.[89] More recently SK channels have been shown to shunt fast excitatory synaptic transmission in lateral amygdala and hippocampal pyramidal neurons[90,91] (Figure 2d). In these neurons, calcium influx through NMDA receptors during basal synaptic transmission activates SK channels, which are co-localised in the spines of hippocampal and amygdala pyramidal neurons.[90] The resultant hyperpolarisation shunts the EPSP and enhances magnesium block of NMDA receptors. Application of apamin reverses this effect, increasing the NMDA receptor-mediated calcium transient in the spine head.[91]

In lateral amygdala pyramidal neurons, shunting of excitatory synaptic transmission by SK channels reduces the amount of depolarisation during repetitive stimulation of cortical afferents, and thus reduces the extent of long-term potentiation at these synapses.[90] Similarly in the hippocampus, blockade of SK channels enhanced long-term potentiation following low frequency tetanic stimulation of Schaffer collaterals[75] and lowered the threshold for long-term potentiation in CA1 pyramidal neurons.[92-94] These effects were attributed to depression of the medium AHP and the consequent increase in action potential discharge. However it has since become clear that these effects are most likely due to the SK channel-mediated shunt on excitatory synaptic transmission rather than the relatively minor regulation of firing frequency.[91] In agreement with a role of SK channels in limiting long-term potentiation, over-expression of SK2 channels in the hippocampus reduced long-term potentiation in CA1 neurons.[95]

Regulation of learning and memory

Blockade of SK channels with apamin has been shown to facilitate learning in a number of behavioural paradigms.[96] Since SK channels are now known to modulate both basal excitatory synaptic transmission and plasticity, this result is consistent with the view that the cellular substrate for learning and memory is synaptic plasticity.[97-99] All but three studies[100-102] have found that the effects of apamin are on the acquisition but not consolidation of the learning task. Blockade of SK channels by systemic administration of apamin in rats enhanced learning in an object recognition task.[103] Furthermore apamin reversed a spatial navigation deficit induced by medial septum and hippocampus lesions in mice in the Morris water maze spatial memory task[104,105] and improved the performance of intact mice in this task.[96,75] In

accordance with these studies, apamin also induced expression of the immediate early genes c-fos and c-jun in the hippocampus, genes that are thought to be the initial markers for memory formation.[106] Conversely, overexpression of SK2 channels led to an impairment in the performance of rats in the Morris water maze, contextual fear conditioning and amygdala-dependent cued fear conditioning.[95] In addition, apamin also enhanced learning in an appetite-motivated bar pressing response in mice[101,100] and in an olfactory discrimination learning task following intracerebroventricular application of apamin.[102] Finally, elevations in SK3 expression have also been shown to underlie an age-related deficit in hippocampal-mediated learning tasks.[107] Together, these results show that SK channels play a key role in negatively regulating learning and memory formation in the mammalian brain.

Role in neurological disorders

As described above, SK channels play a role in learning and memory. Thus modulators of SK channels that improve performance in learning tasks could be useful therapeutic agents to treat memory disorders and cognitive dysfunction. However at present agents that block SK channels, such as apamin, have a narrow therapeutic window. Thus new agents are required that offer less risk for therapeutic treatment.[108] In fact, high doses of apamin can evoke epileptic-like activity, and agents that enhance the activity of SK channels, such as EBIO or NS309, may be useful for the treatment of epilepsy. Similarly, potentiators of SK channels could also be useful to treat emotional disorders such as phobias and depression, since enhancing SK channel activity could raise the threshold for fear conditioning,[95] and apamin improves performance in the forced swimming test, which is a measure of antidepressant activity.[96] Interestingly, several antidepressants, including Prozac, have a high affinity for SK channels (for review see Stocker *et al.*[109]).

As noted above, SK channels are present in midbrain dopaminergic neurons where they control firing patterns. Burst firing in these neurons causes the release of dopamine, which is depleted in Parkinson's disease. SK channel blockade causes burst firing in these neurons,[78] suggesting that treatment of midbrain dopaminergic neurons with SK channel blockers may alleviate some of the symptoms of Parkinson's disease.[108] Finally, SK3 channels have also been implicated in schizophrenia. The gene for SK3 channels (hSKCa3 or KCNN3) contains a sequence of trinucleotide CAG repeats that has been associated with schizophrenia and bipolar illness, suggestive of a link between SK channel function and these disorders.[110-113] In addition, in one schizophrenic patient a mutated version of the SK3 channel was found to behave as a dominant-negative to SK3, suggesting that reduction of SK3 function may be associated with schizophrenia.[6,114]

Conclusions and future directions

Although SK channels play an important role in setting action potential discharge frequency in many neuronal cell types, recent findings indicate that in limbic regions, such as the amygdala and the hippocampus, the predominant role of SK channels is more likely to be in regulating dendritic excitability, excitatory synaptic transmission and synaptic plasticity. To date the stoichiometry of SK subunits underlying the medium AHP has not been resolved in many neurons,[109] with the exception of CA1 hippocampal neurons, where SK2 homomultimers mediate the medium AHP[15,71,95] and in midbrain dopaminergic neurons and dorsal vagal neurons, which express SK3 homomultimers.[19,20] The finding that SK2 overexpression impairs learning in cued fear conditioning suggests that, as in CA1 hippocampal neurons, SK2 may also be the subunit located synaptically in the lateral amygdala.[95] However it is possible that in neurons where SK channels control both synaptic transmission and action potential firing frequency, SK channels underlying these functions may have differing subunit compositions, in addition to being activated by calcium from different sources. Further immunocytochemical studies are required to resolve these issues, along with development of more selective SK channel subunit blockers.[108]

Many neuronal processes are associated with rises in cytosolic calcium. The exquisite sensitivity of SK channels to rises in intracellular calcium and the resultant hyperpolarisation has a multitude of effects, from terminating dendritic plateau potentials, shunting excitatory postsynaptic potentials and limiting synaptic plasticity. This myriad of actions endows a neuron with the ability to self regulate its activity and to curb excessive excitability. It is now clear that SK channels in neurons are critical in regulating both incoming information, through modulation of synaptic transmission, and outgoing information, through setting action potential discharge patterns. Thus SK channels provide an elegant mechanism of intrinsic feedback control. Understanding whether and how these channels are modulated will open up a new level of complexity in terms of regulation of neuronal excitability, synaptic plasticity and the computational abilities of neuronal circuits.

Acknowledgements

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