Clinical and Experimental Pharmacology and Physiology (2007) **34**, 1077–1083 doi: 10.1111/j.1440-1681.2007.04725.x

Proceedings of the Australian Physiological Society Symposium: Development and Physiological Adaptations of Neuronal Circuits and Synapses-I

FUNCTIONS OF SK CHANNELS IN CENTRAL NEURONS

ES Louise Faber and Pankaj Sah

Queensland Brain Institute, University of Queensland, St Lucia, Queensland, Australia

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 after-hyperpolarization that follows action potentials. Calcium influx via voltage-gated calcium channels active during action potentials opens SK channels and the resultant hyperpolarization 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 discusses recent findings on the role of SK channels in central neurons.

Key words: after-hyperpolarization, apamin, calcium activated potassium channels, synaptic plasticity, synaptic transmission.

INTRODUCTION

The SK channels are calcium-activated potassium channels that have been termed as such owing 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] (Fig. 1). Each of these genes has splice variants. Twenty SK1 splice variants have been detected in mouse brain.[4] Two isoforms of SK2 protein have been described in the mouse brain: (i) a short isoform; and (ii) a long isoform with an extended N terminus.[5] The SK3 protein 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 nmol/L 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 (Fig. 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] (Fig. 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 hybridization[3,12,13] and immunohistochemistry[14,15] have shown that SK channels are widely expressed throughout the central nervous system. The 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 insensitive.[16] Although 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 pmol/L for SK2,[3] 2 nmol/L for SK3[24] and between 3.3 and 12 nmol/L for SK1 channels[25,26] (Table 1). The SK channels are also blocked by the scorpion toxin scyllatoxin,[27–29] tubocurarine, quaternary salts of bicuculline,[30,31] dequalinium, UCL 1848 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,[37,38] and by NS309[39] (Table 2).

Correspondence: Louise Faber, Queensland Brain Institute, University of Queensland, St Lucia, Qld 4072, Australia. Email: l.faber@uq.edu.au

Presented at the AuPS Symposium Development and Physiological Adaptations of Neuronal Circuits and Synapses-I, September 2006. The papers in these proceedings were peer reviewed under the supervision of the AuPS Editor. The papers are being published with the permission of AuPS and were initially published on the AuPS website http://www.aups.org.au

Received 26 January 2007; revision 10 April 2007; accepted 25 April 2007.

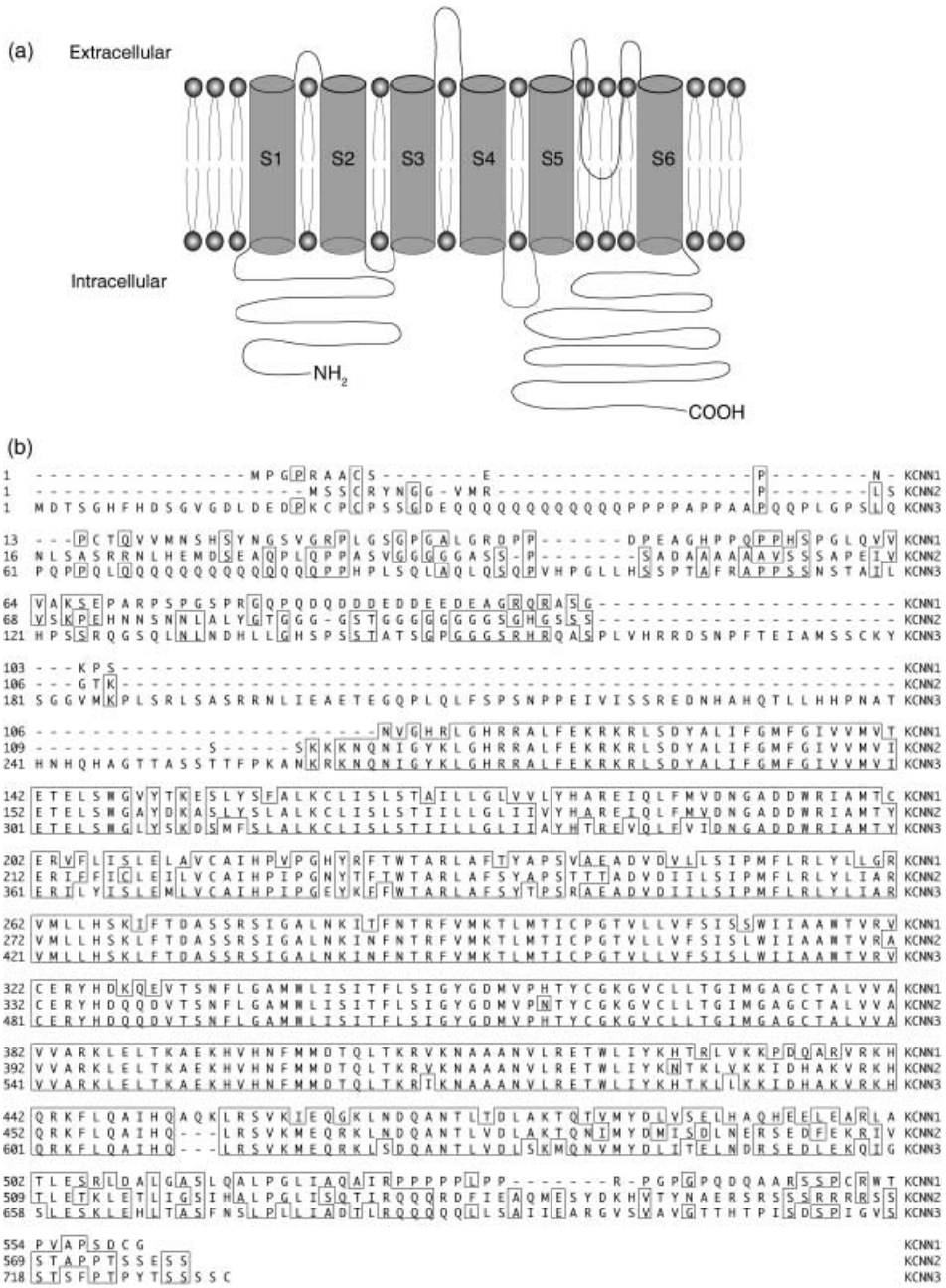

Fig. 1 SK channel structure. (a) Schematic diagram of the structure of one SK channel subunit. The calmodulin-binding domain resides in the C-terminus. (b) Alignment of human amino acid sequences of SK1-3 (shown *KCNN1–3* on right). The homologous regions are outlined in boxes. Sequence accession numbers were Q5KR10 for *KCNN1*, Q0VFZ4 for *KCNN2* and Q5VT74 for *KCNN3* (National Center for Biotechnology Information (NCBI); http://www.ncbi.nlm.nih.gov/).

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 (PK) A and PKC, biophysical evidence for modulation of SK channels by these kinases has been lacking. Interestingly, SK2 channels have been shown to coassemble with casein kinase 2, activation of which phosphorylates calmodulin, reducing the calcium sensitivity of SK channels.[40] More recently, direct phosphorylation of the C-terminus of SK channels by PKA has been demonstrated.[41] When expressed in COS cells, phosphorylation of SK2 channels by PKA led to a reduction in their surface expression, suggesting that, like voltage-dependent potassium channels, SK channels may be regulated by trafficking.[6,42–44]

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.[21,45,46] 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.

Table 1 Pharmacology of SK channel blockers, showing IC_{50} values for each SK channel subunit

	SK1	SK2	SK3
Apamin	3.3–12 nmol/L[25,26]	63 pmol/L[3]	2 nmol/L[24]
Tubocurarine	24–350 μmol/L[3,24–26]	2–17 μmol/L[3,24,26]	210 μmol/L[109]
Bicuculline methiodide	1–16 μmol/L[26,110]	1–25 μmol/L[26,110]	7 μmol/L[111]
Scyllatoxin	80–330 nmol/L[26,36]	0.3 nmol/L[26]	1–8 nmol/L[36,112]
Dequalinium	400–500 nmol/L[25,26]	100–400 nmol/L[26,113]	30 μmol/L[109]
UCL1848	1 nmol/L[25]	0.1 nmol/L[18,112]	2 nmol/L[112]
Tamapin	42 nmol/L[35]	0.02 nmol/L[35]	1.7 nmol/L[35]
Lei-dab7	6 μmol/L[36]	24 nmol/L[36]	2.5 μmol/L[36]

Table 2 Pharmacology of SK channel enhancers showing EC_{50} values for each SK channel subunit

	SK1	SK2	SK3
EBIO	Not tested	400–600 μmol/L[6,39]	Not tested
NS309	Not tested	0.62 μmol/L[39]	Not tested

Regulation of firing patterns

In neurons, trains of action potentials are followed by an after-hyperpolarization (AHP) that can last several seconds. This AHP typically has three components: (i) the fast AHP; (ii) the medium AHP; and (iii) 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.[47–51] The fast AHP, which activates rapidly and typically lasts 1–10 msec, is mediated by BK-type calcium-activated potassium channels, as well as some voltage-gated potassium conductances, and is responsible for action potential repolarization.[21,38] The medium AHP, which also activates rapidly, has a decay time constant of approximately 100 msec and is predominately mediated by SK channels[52–56] (Fig. 2a,b), although in hippocampal CA1 neurons the M current and BK channels have also been shown to contribute to the medium AHP.[49,57,58] The time-course of the medium AHP is dependent on the amount of calcium influx and the kinetics of the calcium transient.[14,51,59–62] The slow AHP, which has a slower rise time than the medium AHP, can last several seconds[21] (Fig. 2a,b). This current is largely responsible for generating spike frequency adaptation,[21,63] but the channels underlying the slow AHP are still unknown. Initially, SK1 channels were speculated to underlie the slow AHP owing to their insensitivity to apamin in some expression systems.[21] However, in addition to other inconsistencies that have been discussed previously,[21] the finding that the slow AHP is still present following knockout of all known SK channels[64,65] is in strong agreement with the suggestion that SK channels cannot underlie the slow AHP in most neurons. However, despite these findings SK channels have been shown to mediate a slow AHP in gonadotrophin-releasing neurons in the hypothalamus.[66]

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,[12,67–69] midbrain dopaminergic neurons,[19,70–72] dorsal vagal neurons,[20,55] sympathetic neurons,[53] nucleus reticularis thalamic neurons,[73] inferior olive neurons,[74] spinal and hypoglossal motoneurons,[60,75] mitral cells in the olfactory bulb[76] and cortical neurons.[56] However, in lateral amygdala neurons, despite the presence of a prominent medium AHP, apamin-sensitive channels do not significantly regulate the firing frequency of neurons (Fig. 2c), unless SK channel activation is enhanced either pharmacologically with EBIO or by increasing calcium influx by slowing action potential repolarization.[38]

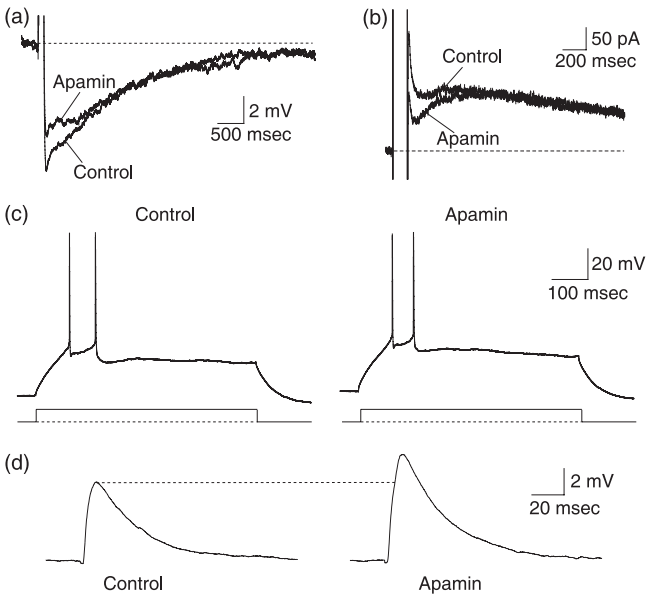

Fig. 2 Physiological roles of SK channels in neurons, illustrated using the selective blocker apamin. (a) An after-hyperpolarization (AHP) evoked by current injection. The medium AHP is selectively blocked by apamin, leaving the slow AHP intact. (b) The current underlying the AHP is evoked by a voltage 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 excitatory post-synaptic potential (EPSP) by apamin.

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. Although 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 from sources other than voltage-gated calcium channels. For example, in dopamininergic[77] and cortical pyramidal neurons,[78,79] calcium released from intracellular stores activates an apamin-sensitive conductance and a resultant hyperpolarising potential. In CA1 hippocampal neurons, exogenous application of *N*-methyl-D-aspartate (NMDA) to dendrites generates a plateau potential that is terminated by activation of SK channels.[80] 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.[81] In these neurons, dendritic SK channels also contribute to an AHP, which shunts excitatory inputs if triggered during the AHP. However, this shunt requires action potential-mediated activation of SK channels because blockade of SK channels alone has no effect on single excitatory post-synaptic potentials (EPSPs) or trains of EPSPs.[82] Finally, dendritic SK channels can also be activated following NMDA receptor activation in mitral cells in the olfactory bulb, where they regulate dendritic excitability.[76]

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 post-synaptic potential. Activation of SK channels followed release of calcium from intracellular stores, triggered by glutamate acting at metabotropic glutamate receptors.[77] Subsequent to this, SK channels were also shown to mediate an inhibitory post-synaptic conductance in auditory outer hair cells following activation by calcium influx through calcium-permeable nicotinic acetylcholine receptors.[83] More recently, SK channels have been shown to shunt fast excitatory synaptic transmission in lateral amygdala and hippocampal pyramidal neurons[84,85] (Fig. 2d). In these neurons, calcium influx through NMDA receptors during basal synaptic transmission activates SK channels, which are colocalized in the spines of hippocampal and amygdala pyramidal neurons.[84,85] The resultant hyperpolarization shunts the EPSP and enhances the magnesium block of NMDA receptors. Application of apamin reverses this effect, increasing the NMDA receptor-mediated calcium transient in the spine head.[85]

In lateral amygdala pyramidal neurons, shunting of excitatory synaptic transmission by SK channels reduces the amount of depolarization during repetitive stimulation of cortical afferents and, thus, reduces the extent of long-term potentiation (LTP) at these synapses.[84] Similarly, in the hippocampus, blockade of SK channels enhanced LTP following low-frequency tetanic stimulation of Schaffer collaterals[69] and lowered the threshold for LTP in CA1 pyramidal neurons.[86–88] 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.[85] In agreement with a role for SK channels in limiting LTP, overexpression of SK2 channels in the hippocampus reduced LTP in CA1 neurons.[89]

Regulation of learning and memory

Blockade of SK channels with apamin has been shown to facilitate learning in a number of behavioural paradigms.[90] Because 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.[91–93] All but three studies[94–96] 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.[97] Furthermore apamin reversed a spatial navigation deficit induced by medial septum and hippocampus lesions in mice in the Morris water maze spatial memory task[98,99] and improved the performance of control mice in this task.[69,90] 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.[100] 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.[89] In addition, apamin also enhanced learning in an appetite-motivated bar-pressing response in mice[94,95] and in an olfactory discrimination learning task following intracerebroventricular application of apamin.[96] Finally, elevations in SK3 expression have been shown to underlie an age-related deficit in hippocampal-mediated learning tasks.[101] 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.[102] 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 be useful to treat emotional disorders, such as phobias and depression, because enhancing SK channel activity could raise the threshold for fear conditioning,[89] and apamin improves performance in the forced swimming test, which is a measure of antidepressant activity.[90] Interestingly, several antidepressants, including fluoxetine, have a high affinity for SK channels (for a review, see Stocker *et al.*[103]).

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. Blockade of SK channels causes burst firing in these neurons,[72] suggesting that treatment of midbrain dopaminergic neurons with SK channel blockers may alleviate some of the symptoms of Parkinson's disease.[102] 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.[104–107] 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.[6,108]

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 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,[103] with the exception of CA1 hippocampal neurons, where SK2 homomultimers mediate the medium AHP,[15,64,89] 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.[89] 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.[102]

Many neuronal processes are associated with rises in cytosolic calcium. The exquisite sensitivity of SK channels to rises in intracellular calcium and the resultant hyperpolarization has a multitude of effects, from terminating dendritic plateau potentials, shunting excitatory post-synaptic 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.

ACKNOWLEDGEMENT

The authors' work reported herein was supported by the National Health and Medical Research Council of Australia.

REFERENCES

1. Blatz AL, Magleby KL. Single apamin-blocked Ca^{2+}-activated K^+ channels of small conductance in cultured rat skeletal muscle. *Nature* 1986; **323**: 718–20.
2. Hirschberg B, Maylie J, Adelman JP, Marrion NV. Gating properties of single SK channels in hippocampal CA1 pyramidal neurons. *Biophys. J*. 1999; **77**: 1905–13.
3. Kohler M, Hischberg B, Bond CT *et al*. Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* 1996; **273**: 1709–14.
4. Shmukler BE, Bond CT, Wilhelm S *et al*. Structure and complex transcription pattern of the mouse SK1 K (Ca) channel gene, KCNN1. *Biochem. Biophys. Acta* 2001; **1518**: 36–46.
5. Strassmaier T, Bond CT, Sailer CA, Knaus HG, Maylie J, Adelman JP. A novel isoform of SK2 assembles with other SK subunits in mouse brain. *J. Biol. Chem*. 2005; **280**: 21 231–6.
6. Tomita H, Shakkottai VG, Gutman GA *et al*. Novel truncated isoform of SK3 potassium channel is a potent dominant-negative regulator of SK currents: Implications in schizophrenia. *Mol. Psychiatry* 2003; **8**: 524–35.
7. Park Y-B. Ion selectivity and gating of small conductance Ca^{2+}-activated K^+ channels in cultured rat adrenal chromaffin cells. *J. Physiol*. 1994; **481**: 555–70.
8. Vegara C, Latorre R, Marrion NV, Adelman JP. Calcium-activated potassium channels. *Curr. Opin. Neurobiol*. 1998; **8**: 321–9.
9. Xia X-M, Falker B, Rivard A *et al*. Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature* 1998; **395**: 503–7.
10. Keen JE, Khawaled R, Farrens DL *et al*. Domains responsible for constitutive and Ca^{2+}-dependent interactions between calmodulin and small conductance Ca^{2+}-activated potassium channels. *J. Neurosci*. 1999; **19**: 8830–8.
11. Schumacher MA, Rivard AF, Bachinger HP, Adelman JP. Structure of the gating domain of a Ca^{2+}-activated K^+ channel complexed with Ca^{2+}/calmodulin. *Nature* 2001; **410**: 1120–4.
12. Stocker M, Krause M, Pedarzani P. An apamin-sensitive Ca^{2+}-activated K^+ current in hippocampal pyramidal neurons. *Proc. Natl Acad. Sci. USA* 1999; **96**: 4662–7.
13. Stocker M, Pedarzani P. Differential distributions of three Ca^{2+}-activated K^+ channel subunits, SK1, SK2 and SK3 in the adult rat central nervous system. *Mol. Cell. Neurosci*. 2000; **15**: 476–93.
14. Bowden SE, Fletcher S, Loane DJ, Marrion NV. Somatic co-localization of rat SK1 and D class (Ca(v)1.2) L-type calcium channels in rat CA1 hippocampal pyramidal neurons. *J. Neurosci*. 2001; **21** (RC1**75**): 1–6.
15. Sailer CA, Hu H, Kaufmann WA *et al*. Regional differences in distribution and functional expression of small-conductance Ca^{2+}-activated K^+ channels in rat brain. *J. Neurosci*. 2002; **22**: 9698–707.
16. Hirschberg B, Maylie J, Adelman JP, Marrion NV. Gating of recombinant small-conductance Ca^{2+}-activated K^+ channels by calcium. *J. Gen. Physiol*. 1998; **111**: 565–81.
17. Monaghan AS, Benton DC, Bahia PK *et al*. The SK3 subunit of small conductance Ca^{2+}-activated K^+ channels interacts with both SK1 and SK2 subunits in a heterologous expression system. *J. Biol. Chem*. 2004; **279**: 1003–9.
18. Benton DC, Monaghan AS, Hosseini R, Bahia PK, Haylett DG, Moss GW. Small conductance Ca^{2+}-activated K^+ channels formed by the expression of rat SK1 and SK2 genes in HEK 293 cells. *J. Physiol*. 2003; **553**: 13–19.
19. Wolfart J, Neuhoff H, Franz O, Roeper J. Differential expression of the small-conductance, calcium-activated potassium channel SK3 is critical for pacemaker control in dopaminergic midbrain neurons. *J. Neurosci*. 2001; **21**: 3443–56.
20. Pedarzani P, Kulik A, Muller M, Ballanyi K, Stocker M. Molecular determinants of Ca^{2+}-dependent K^+ channel function in rat dorsal vagal neurones. *J. Physiol*. 2000; **527**: 283–90.
21. Sah P, Faber ESL. Channels underlying neuronal calcium-activated potassium currents. *Prog. Neurobiol*. 2002; **66**: 345–53.
22. Burgess GM, Claret M, Jenkinson DH. Effects of quinine and apamin on the calcium-dependent potassium permeability of mammalian hepatocytes and red cells. *J. Physiol*. 1981; **317**: 67–90.
23. Romey G, Hugues M, Schmid-Antomarchi H, Lazdunski M. Apamin. A specific toxin to study a class of Ca^{2+}-dependent K^+ channels. *J. Physiol*. 1984; **79**: 259–64.
24. Ishii TM, Maylie J, Adelman JP. Determinants of apamin and d-tubocurarine block in SK potassium channels. *J. Biol. Chem*. 1997; **272**: 23 195–200.
25. Shah M, Haylett DG. The pharmacology of hSK1 Ca^{2+}-activated K^+ channels expressed in mammalian cell lines. *Br. J. Pharmacol*. 2000; **129**: 627–30.
26. Strobaek D, Jorgensen TD, Christophersen P, Ahring PK, Olesen S-P. Pharmacological characterization of small-conductance Ca^{2+}-activated

K^+ channels stably expressed in HEK 293 cells. *Br. J. Pharmacol*. 2000; **129**: 991–9.
27. Castle NA, Strong PN. Identification of two toxins from scorpion (*Leiurus quinquestriatus*) venom which block distinct classes of calcium-activated potassium channel. *FEBS Lett*. 1986; **209**: 117–21.
28. Chicchi GG, Gimenez-Gallego G, Ber E, Garcia ML, Winquist R, Cascieri MA. Purification and characterization of a unique, potent inhibitor of apamin binding from *Leiurus quinquestriatus hebraeus* venom. *J. Biol. Chem*. 1988; **263**: 10 192–7.
29. Auguste P, Hugues M, Grave B *et al*. Leiurotoxin I (scyllatoxin), a peptide ligand for Ca^{2+}-activated K^+ channels. Chemical synthesis, radiolabeling, and receptor characterization. *J. Biol. Chem*. 1990; **265**: 4753–9.
30. Johnson SW, Seutin V. Bicuculline methiodide potentiates NMDA-dependent burst firing in rat dopamine neurons by blocking apamin-sensitive Ca^{2+}-activated K^+ currents. *Neurosci. Lett*. 1997; **231**: 13–16.
31. Seutin V, Johnson SW. Recent advances in the pharmacology of quaternary salts of bicuculline. *Trends Pharmacol. Sci*. 1999; **20**: 268–70.
32. Campos Rosa J, Galanakis D, Piergentili A *et al*. Synthesis, molecular modeling, and pharmacological testing of bis-quinolinium cyclophanes: Potent, non-peptidic blockers of the apamin-sensitive Ca^{2+}-activated K^+ channel. *J. Med. Chem*. 2000; **43**: 420–31.
33. Chen J-Q, Galanakis D, Ganellin CR, Dunn PM, Jenkinson DH. bis-Quinolinium cyclophanes: 8,14-Diaza-1,7(1,4)-diquinolinacyclotetradecaphane (UCL 1848), a highly potent and selective, nonpeptidic blocker of the apamin-sensitive Ca^{2+}-activated K^+ channel. *J. Med. Chem*. 2000; **43**: 3478–81.
34. Dunn PM. Dequalinium, a selective blocker of the slow afterhyperpolarization in rat sympathetic neurones in culture. *Eur. J. Pharmacol*. 1994; **252**: 189–94.
35. Pedarzani P, D'Hoedt D, Doorty KB *et al*. Tamapin, a venom peptide from the Indian red scorpion (*Mesobuthus tamulus*) that targets small conductance Ca^{2+}-activated K^+ channels and afterhyperpolarization currents in central neurons. *J. Biol. Chem*. 2002; **277**: 46 101–9.
36. Shakkottai VG, Regaya I, Wulff H *et al*. Design and characterization of a highly selective peptide inhibitor of the small conductance calcium-activated K^+ channel, SKCa2. *J. Biol. Chem*. 2001; **276**: 43 145–51.
37. Olesen SP, Munch E, Moldt P, Drejer J. Selective activation of Ca^{2+}-dependent K^+ channels by novel benzimidazolone. *Eur. J. Pharmacol*. 1994; **251**: 53–9.
38. Faber ESL, Sah P. Physiological role of calcium-activated potassium currents in the rat lateral amygdala. *J. Neurosci*. 2002; **22**: 1618–28.
39. Pedarzani P, McCutcheon JE, Rogge G *et al*. Specific enhancement of SK channel activity selectively potentiates the afterhyperpolarizing current I_{AHP} and modulates the firing properties of hippocampal pyramidal neurons. *J. Biol. Chem*. 2005; **280**: 41 404–11.
40. Bildl W, Strassmaier T, Thurm H *et al*. Protein kinase CK2 is co-assembled with small conductance Ca^{2+}-activated K^+ channels and regulates channel gating. *Neuron* 2004; **43**: 847–58.
41. Ren Y, Barnwell LF, Alexander JC *et al*. Regulation of surface localization of the small conductance Ca^{2+}-activated potassium channel, SK2, through direct phosphorylation by cAMP-dependent protein kinase. *J. Biol. Chem*. 2006; **281**: 11 769–79.
42. Heusser K, Schwappach B. Trafficking of potassium channels. *Curr. Opin. Neurobiol*. 2005; **15**: 364–9.
43. Licata L, Haase W, Eckhardt-Strelau L, Parcej DN. Over-expression of a mammalian small conductance calcium-activated K^+ channel in Pichia pastoris: Effects of trafficking signals and subunit fusions. *Protein Expr. Purif*. 2006; **47**: 171–8.
44. Misonou H, Trimmer JS. Determinants of voltage-gated potassium channel surface expression and localization in mammalian neurons. *Crit. Rev. Biochem. Mol. Biol*. 2004; **39**: 125–45.
45. Faber ESL, Sah P. Calcium-activated potassium channels: Multiple contributions to neuronal function. *Neuroscientist* 2003; **9**: 181–94.
46. Bond CT, Maylie J, Adelman JP. SK channels in excitability, pacemaking and synaptic integration. *Curr. Opin. Neurobiol*. 2005; **15**: 305–11.
47. Lancaster B, Nicoll RA. Properties of two calcium-activated hyperpolarizations in rat hippocampal neurones. *J. Physiol*. 1987; **389**: 187–204.
48. Storm JF. Action potential repolarization and a fast after-hyperpolarization in rat hippocampal pyramidal cells. *J. Physiol*. 1987; **385**: 733–59.
49. Storm JF. Potassium currents in hippocampal pyramidal cells. *Prog. Brain Res*. 1990; **83**: 161–87.
50. Sah P. Ca^{2+}-activated K^+ currents in neurones. Types, physiological roles and modulation. *Trends Neurosci*. 1996; **19**: 150–4.
51. Marrion NV, Tavalin SJ. Selective activation of Ca^{2+}-activated K^+ channels by co-localised Ca^{2+} channels in hippocampal neurons. *Nature* 1998; **395**: 900–5.
52. Adams PR, Constanti A, Brown DA, Clark RB. Intracellular Ca^{2+} activates a fast voltage-sensitive K^+ current in vertebrate sensory neurones. *Nature* 1982; **296**: 746–9.
53. Pennefather P, Lancaster B, Adams PR, Nicoll RA. Two distinct Ca^{2+}-dependent K^+ currents in bullfrog sympathetic ganglionic cells. *Proc. Natl Acad. Sci. USA* 1985; **82**: 3040–4.
54. Sah P, McLachlan EM. Ca^{2+}-activated K^+ currents underlying the afterhyperpolarization in guinea pig vagal neurons: A role for Ca^{2+}-activated Ca^{2+} release. *Neuron* 1991; **7**: 257–64.
55. Sah P, McLachlan EM. Potassium currents contributing to action potential repolarization and the afterhyperpolarization in rat vagal motoneurons. *J. Neurophysiol*. 1992; **68**: 1834–41.
56. Schwindt PC, Spain WJ, Foehring RC, Stafstrom CE, Chubb MC, Crill WE. Multiple potassium conductances and their functions in neurons from cat sensorimotor cortex *in vitro*. *J. Neurophysiol*. 1988; **59**: 424–49.
57. Storm JF. An after-hyperpolarization of medium duration in rat hippocampal pyramidal cells. *J. Physiol*. 1989; **409**: 171–90.
58. Williamson A, Alger BE. Characterization of an early afterhyperpolarization after a brief train of action potentials in rat hippocampal neurons *in vitro*. *J. Neurophysiol*. 1990; **63**: 72–81.
59. Sah P. Different calcium channels are coupled to potassium channels with distinct physiological roles in vagal neurons. *Proc. R. Soc. Lond*. 1995; **260**: 105–11.
60. Viana F, Bayliss DA, Berger AJ. Multiple potassium conductances and their role in action potential repolarization and repetitive firing behavior of neonatal rat hypoglossal motoneurons. *J. Neurophysiol*. 1993; **69**: 2150–63.
61. Davies PJ, Ireland DR, McLachlan EM. Sources of Ca^{2+} for different Ca^{2+}-activated K^+ conductances in neurones of the rat superior cervical ganglion. *J. Physiol*. 1996; **495**: 353–66.
62. Tanabe M, Gahwiler BH, Gerber U. L-type Ca^{2+} channels mediate the slow Ca^{2+}-dependent afterhyperpolarisation current in rat CA3 pyramidal cells *in vitro*. *J. Neurophysiol*. 1998; **80**: 2268–73.
63. Faber ESL, Sah P. Independent roles of calcium and voltage-dependent potassium currents in controlling spike frequency adaptation in lateral amygdala pyramidal neurons. *Eur. J. Neurosci*. 2005; **22**: 1627–35.
64. Bond CT, Herson PS, Strassmaier T *et al*. Small conductance Ca^{2+}-activated K^+ channel knock-out mice reveal the identity of calcium-dependent afterhyperpolarization currents. *J. Neurosci*. 2004; **24**: 5301–6.
65. Villalobos C, Shakkottai VG, Chandy KG, Michelhaugh SK, Andrade R. SK_{Ca} channels mediate the medium but not the slow calcium-activated afterhyperpolarization in cortical neurons. *J. Neurosci*. 2004; **24**: 3537–42.
66. Kato M, Tanaka N, Usui S, Sakuma Y. The SK channel blocker apamin inhibits slow afterhyperpolarization currents in rat gonadotropin-releasing hormone neurones. *J. Physiol*. 2006; **574**: 431–42.
67. Pedarzani P, Mosbacher J, Rivard A *et al*. Control of electrical activity in central neurons by modulating the gating of small conductance Ca^{2+}-activated K^+ channels. *J. Biol. Chem*. 2001; **276**: 9762–9.
68. Osmanovic SS, Shefner SA, Brodie MS. Functional significance of the apamin-sensitive conductance in rat locus coeruleus neurons. *Brain Res*. 1990; **530**: 283–9.
69. Stackman RW, Hammond RS, Linardatos E *et al*. Small conductance Ca^{2+}-activated K^+ channels modulate synaptic plasticity and memory encoding. *J. Neurosci*. 2002; **22**: 10 163–71.

70. Seutin V, Johnson SW, North RA. Apamin increases NMDA-induced burst-firing of rat mesencephalic dopamine neurons. *Brain Res*. 1993; **630**: 341–4.
71. Shepard PD, Bunney BS. Repetitive firing properties of putative dopamine-containing neurons *in vitro*: Regulation by an apamin-sensitive Ca^{2+}-activated K^+ conductance. *Exp. Brain Res*. 1991; **86**: 141–50.
72. Waroux O, Massotte L, Alleva L *et al*. SK channels control the firing pattern of midbrain dopaminergic neurons *in vivo*. *Eur. J. Neurosci*. 2005; **22**: 3111–21.
73. Bal T, McCormick DA. Mechanisms of oscillatory activity in guinea-pig nucleus reticularis thalami *in vitro*: A mammalian pacemaker. *J. Physiol*. 1993; **468**: 669–91.
74. Bal T, McCormick DA. Synchronized oscillations in the inferior olive are controlled by the hyperpolarization-activated cation current I(h). *J. Neurophysiol*. 1997; **77**: 3145–56.
75. Zhang L, Krnjevic K. Apamin depresses selectively the after-hyperpolarization of cat spinal motoneurons. *Neurosci. Lett*. 1987; **74**: 58–62.
76. Maher BJ, Westbrook GL. SK channel regulation of dendritic excitability and dendrodendritic inhibition in the olfactory bulb. *J. Neurophysiol*. 2005; **94**: 3743–50.
77. Fiorillo CD, Williams JT. Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons. *Nature* 1998; **394**: 78–82.
78. Yamada S, Takechi H, Kanchiku I, Kita T, Kato N. Small-conductance Ca^{2+}-dependent K^+ channels are the target of spike-induced Ca^{2+} release in a feedback regulation of pyramidal cell excitability. *J. Neurophysiol*. 2004; **91**: 2322–9.
79. Gulledge AT, Stuart GJ. Cholinergic inhibition of neocortical pyramidal neurons. *J. Neurosci*. 2005; **25**: 10 308–20.
80. Cai X, Liang CW, Muralidharan S, Kao JP, Tang CM, Thompson SM. Unique roles of SK and Kv4.2 potassium channels in dendritic integration. *Neuron* 2004; **44**: 351–64.
81. Grillner S, Wallen P, Hill R, Cangiano L, El Manira A. Ion channels of importance for the locomotor pattern generation in the lamprey brainstem-spinal cord. *J. Physiol*. 2001; **533**: 23–30.
82. Cangiano L, Wallen P, Grillner S. Role of apamin-sensitive K_{Ca} channels for reticulospinal synaptic transmission to motoneuron and for the afterhyperpolarization. *J. Neurophysiol*. 2002; **88**: 289–99.
83. Oliver D, Klocker N, Schuck J, Baukrowitz T, Ruppersberg JP, Fakler B. Gating of Ca^{2+}-activated K^+ channels controls fast inhibitory synaptic transmission at auditory outer hair cells. *Neuron* 2000; **26**: 595–601.
84. Faber ESL, Delaney AJ, Sah P. SK channels regulate excitatory synaptic transmission and plasticity in the lateral amygdala. *Nat. Neurosci*. 2005; **8**: 635–41.
85. Ngo-Anh TJ, Bloodgood BL, Lin M, Sabatini BL, Maylie J, Adelman JP. SK channels and NMDA receptors form a Ca^{2+}-mediated feedback loop in dendritic spines. *Nat. Neurosci*. 2005; **8**: 642–9.
86. Norris CM, Halpain S, Foster TC. Reversal of age-related alterations in synaptic plasticity by blockade of L-type Ca^{2+} channels. *J. Neurosci*. 1998; **18**: 3171–9.
87. Behnisch T, Reymann KG. Inhibition of apamin-sensitive calcium dependent potassium channels facilitates the induction of long-term potentiation in the CA1 region of rat hippocampus *in vitro. Neurosci. Lett*. 1998; **253**: 91–4.
88. Kramar EA, Lin B, Lin CY, Arai AC, Gall CM, Lynch G. A novel mechanism for the facilitation of theta-induced long-term potentiation by brain-derived neurotrophic factor. *J. Neurosci*. 2004; **24**: 5151–61.
89. Hammond RS, Bond CT, Strassmaier T *et al*. Small-conductance Ca^{2+}-activated K^+ channel type 2 (SK2) modulates hippocampal learning, memory, and synaptic plasticity. *J. Neurosci*. 2006; **26**: 1844–53.
90. van der Staay FJ, Fanelli RJ, Blokland A, Schmidt BH. Behavioral effects of apamin, a selective inhibitor of the SK_{Ca}-channel, in mice and rats. *Neurosci. Biobehav. Rev*. 1999; **23**: 1087–110.
91. Moser EI, Krobert KA, Moser MB, Morris RG. Impaired spatial learning after saturation of long-term potentiation. *Science* 1998; **281**: 2038–42.
92. Pastalkova E, Serrano P, Pinkhasova D, Wallace E, Fenton AA, Sacktor TC. Storage of spatial information by the maintenance mechanism of LTP. *Science* 2006; **313**: 1141–4.
93. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. *Science* 2006; **313**: 1093–7.
94. Messier C, Mourre C, Bontempi B, Sif J, Lazdunski M, Destrade C. Effect of apamin, a toxin that inhibits Ca^{2+}-dependent K^+ channels, on learning and memory processes. *Brain Res*. 1991; **551**: 322–6.
95. Belcadi-Abbassi W, Destrade C. Post-test apamin injection suppresses a Kamin-like effect following a learning session in mice. *Neuroreport* 1995; **6**: 1293–6.
96. Fournier C, Kourrich S, Soumireu-Mourat B, Mourre C. Apamin improves reference memory but not procedural memory in rats by blocking small conductance Ca^{2+}-activated K^+ channels in an olfactory discrimination task. *Behav. Brain Res*. 2001; **121**: 81–93.
97. Deschaux O, Bizot JC, Goyffon M. Apamin improves learning in an object recognition task in rats. *Neurosci. Lett*. 1997; **222**: 159–62.
98. Ikonen S, Schmidt B, Riekkinen Jr P. Apamin improves spatial navigation in medial septal-lesioned mice. *Eur. J. Pharmacol*. 1998; **347**: 13–21.
99. Ikonen S, Riekkinen Jr P. Effects of apamin on memory processing of hippocampal-lesioned mice. *Eur. J. Pharmacol*. 1999; **382**: 151–6.
100. Heurteaux C, Messier C, Destrade C, Lazdunski M. Memory processing and apamin induce immediate early gene expression in mouse brain. *Brain Res. Mol. Brain Res*. 1993; **18**: 17–22.
101. Blank T, Nijholt I, Kye MJ, Radulovic J, Spiess J. Small-conductance, Ca^{2+}-activated K^+ channel SK3 generates age-related memory and LTP deficits. *Nat. Neurosci*. 2003; **6**: 911–12.
102. Liegeois JF, Mercier F, Graulich A, Graulich-Lorge F, Scuvee-Moreau J, Seutin V. Modulation of small conductance calcium-activated potassium (SK) channels: A new challenge in medicinal chemistry. *Curr. Med. Chem*. 2003; **10**: 625–47.
103. Stocker M, Hirzel K, D'Hoedt D, Pedarzani P. Matching molecules to function: Neuronal Ca^{2+}-activated K^+ channels and afterhyperpolarizations. *Toxicon* 2004; **43**: 933–49.
104. Gargus JJ, Fantino E, Gutman GA. A piece in the puzzle: An ion channel candidate gene for schizophrenia. *Mol. Med. Today* 1998; **4**: 518–24.
105. Chandy KG, Fantino E, Wittekindt O *et al*. Isolation of a novel potassium channel gene hSKCa3 containing a polymorphic CAG repeat: A candidate for schizophrenia and bipolar disorder? *Mol. Psychiatry* 1998; **3**: 32–7.
106. Dror V, Shamir E, Ghanshani S *et al*. hKCa3/KCNN3 potassium channel gene: Association of longer CAG repeats with schizophrenia in Israeli Ashkenazi Jews, expression in human tissues and localization to chromosome 1q21. *Mol. Psychiatry* 1999; **4**: 254–60.
107. Ritsner M, Modai I, Ziv H *et al*. An association of CAG repeats at the KCNN3 locus with symptom dimensions of schizophrenia. *Biol. Psychiatry* 2002; **51**: 788–94.
108. Miller MJ, Rauer H, Tomita H *et al*. Nuclear localization and dominant-negative suppression by a mutant SKCa3 N-terminal channel fragment identified in a patient with schizophrenia. *J. Biol. Chem*. 2001; **276**: 27 753–6.
109. Terstappen GC, Pula G, Carignani C, Chen MX, Roncarati R. Pharmacological characterisation of the human small conductance calcium-activated potassium channel hSK3 reveals sensitivity to tricyclic antidepressants and antipsychotic phenothiazines. *Neuropharmacology*. 2001; **40**: 772–83.
110. Khawaled R, Bruening-Wright A, Adelman JP, Maylie J. Bicuculline block of small-conductance calcium-activated potassium channels. *Pflügers Arch*. 1999; **438**: 314–21.
111. Grunnet M, Jespersen T, Angelo K *et al*. Pharmacological modulation of SK3 channels. *Neuropharmacology* 2001; **40**: 879–87.
112. Hosseini R, Benton DCH, Dunn PM, Jenkinson DH, Moss GWJ. SK3 is an important component of K^+ channels mediating the afterhyperpolarization in cultured rat SCG neurones. *J. Physiol*. 2001; **535**: 323–34.
113. Dreixler JC, Bian J, Cao Y, Roberts MT, Roizen JD, Houamed KM. Block of rat brain recombinant SK channels by tricyclic antidepressants and related compounds. *Eur. J. Pharmacol*. 2000; **401**: 1–7.