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Small conductance Ca^{2+}-activated K^+ channels in the plasma membrane, mitochondria and the ER: Pharmacology and implications in neuronal diseases

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ABSTRACT

Ca^{2+}-activated K^+ (K_{Ca}) channels regulate after-hyperpolarization in many types of neurons in the central and peripheral nervous system. Small conductance Ca^{2+}-activated K^+ ($K_{Ca}2$/SK) channels, a subfamily of K_{Ca} channels, are widely expressed in the nervous system, and in the cardiovascular system. Voltage-independent SK channels are activated by alterations in intracellular Ca^{2+} ($[Ca^{2+}]_i$) which facilitates the opening of these channels through binding of Ca^{2+} to calmodulin that is constitutively bound to the SK2 C-terminus. In neurons, SK channels regulate synaptic plasticity and $[Ca^{2+}]_i$ homeostasis, and a number of recent studies elaborated on the emerging neuroprotective potential of SK channel activation in conditions of excitotoxicity and cerebral ischemia, as well as endoplasmic reticulum (ER) stress and oxidative cell death. Recently, SK channels were discovered in the inner mitochondrial membrane and in the membrane of the endoplasmic reticulum which sheds new light on the underlying molecular mechanisms and pathways involved in SK channel-mediated protective effects. In this review, we will discuss the protective properties of pharmacological SK channel modulation with particular emphasis on intracellularly located SK channels as potential therapeutic targets in paradigms of neuronal dysfunction.
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Contents

1. Introduction

Regulation of cellular ion homeostasis is an important physiological process to maintain the integrity of the plasma membrane and of intracellular organelles. Ion homeostasis is mainly

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determined by balanced concentrations of intracellular sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}). While Na^+ and K^+ are more involved in maintaining the membrane potential, Ca^{2+} is also a secondary messenger regulating intracellular signaling (De Stefani et al., 2012; Endo, 2006). In the past decades, numerous proteins have been identified to coordinate intracellular ion homeostasis. These are ion exchangers such as the Na^+/Ca^{2+} exchanger (NCX) (Iwamoto et al., 1996), the H^+/Ca^{2+} exchanger (HCX) (Crompton et al., 1977) or the H^+/K^+ exchanger (KHE) (Froschauer et al., 2005; Gursahani and Schaefer, 2004), voltage-gated Ca^{2+} channels (VGCC) (Bloodgood and Sabatini, 2007), ATP-dependent potassium channels (K_{ATP}) (Paucek et al., 1992) or the mitochondrial Ca^{2+} uniporter (MCU) (Pan et al., 2013; Csordas et al., 2013). The regulation of Ca^{2+} flux across membranes, and Ca^{2+}-dependent activation of downstream signaling targets are key physiological processes with particular importance for neuronal function. In the past decades, numerous studies exploited the activity and function of Ca^{2+}-activated K^+ (K_{Ca}) channels which belong to a large family of K^+ channel proteins. K_{Ca} channels control neuronal excitability and regulate synaptic plasticity, and their dysfunction was associated with ageing and diseases of the brain such as psychiatric disorders, neurodegenerative diseases or cerebral ischemia (Kuiper et al., 2012; Grube et al., 2011; Gargus, 2006).

In this review, we discuss the emerging roles of a subfamily of these K^+ channels, namely the small conductance Ca^{2+}-activated K^+ ($K_{Ca}2$/SK) channels, as a target in neurodegenerative diseases. In particular, we will delineate the function of SK channels at different intracellular localizations such as the inner mitochondrial membrane and the endoplasmic reticulum (ER), and highlight their importance for the regulation of intracellular calcium ($[Ca^{2+}]_i$) homeostasis and neuronal cell viability.

1.1. Ca^{2+}-activated K^+ (K_{Ca}) channels

Ca^{2+}-activated K^+ (K_{Ca}) channels were first described in nervous tissues (Meech, 1978) where they mediate after-hyperpolarization of the membrane. They are subdivided into three major families based on their molecular and pharmacological features: large conductance ($K_{Ca}1.1$/BK_{Ca}/BK), intermediate conductance ($K_{Ca}3.1$/SK4/IK_{Ca}/IK) and small conductance ($K_{Ca}2.1$–2.3/SK_{Ca}/SK) K_{Ca} channels. BK channels are activated by millimolar concentrations of Ca^{2+} and by voltage changes, which is unique for this subfamily of K_{Ca} channels (Wei and Salkoff, 1994; Schreiber and Salkoff, 1997). In conditions of low Ca^{2+}, BK channels open upon depolarization of the membrane, while at normal Ca^{2+} concentrations BK channels can open at a physiological membrane potential (DiChiara and Reinhart, 1995; McManus and Magleby, 1991; Cui et al., 1997). They are expressed in smooth muscle cells and in neurons of the central nervous system (Sausbier et al., 2006; Shao et al., 1999). IK and SK channels are structurally very similar, and in contrast to BK channels, they are voltage-independent and are activated at submicromolar (0.5 μM) Ca^{2+} concentrations (Dutta et al., 2009; Bychkov et al., 2002; Burnham et al., 2002). IK and SK channel activation is mediated by Ca^{2+} binding to calmodulin which is constitutively bound to the C-terminal tail of the channel proteins (Xia et al., 1998; Fanger et al., 1999). IK channels are widely expressed in different cell types including mast cells, astrocytes, thrombocytes, T lymphocytes, smooth muscles of the urinary bladder and the placenta, endothelial cells of lung vessels, crypts of the colon and pancreatic duct cells (Yang et al., 2011; Mahaut-Smith, 1995; Logsdon et al., 1997; Grissmer et al., 1993; Afeli et al., 2012; Lin et al., 2015; Duffy et al., 2015; Brereton et al., 2013; Lomax et al., 1996; Hayashi et al., 2012; Longden et al., 2011). SK channels are predominantly expressed in microglia, mast cells and neurons, in cardiac myocytes, and also occur in endothelial cells of coronary arteries (Burnham et al., 2002; Dolga and Culmsee, 2012; Eder, 1998; Li et al., 2009; Schlichter et al., 2010).

The activity of K_{Ca} channels plays an essential role in shaping oscillations of $[Ca^{2+}]_i$. A plethora of pharmacological modulators is available which elicit different binding specificities for the K_{Ca} channel subfamilies (see Table 1). For example, many substances were developed with high specificity for BK channels, such as NS1619 (EC_{50} 3 μM), NS15904 (EC_{50} 11 μM) or NS11021 (EC_{50} 400 nM) (Nausch et al., 2014; Bentzen et al., 2007; Layne et al., 2010), and the fluoro-oxindole BMS204352 (EC_{50} 300–400 nM) (Cheney et al., 2001). Due to the great similarities between IK and SK channels, there are currently no specific activators available that only target IK channels. However, a number of substances have been developed with large differences in their selectivity towards the K_{Ca} channel subtype. NS309, 1-EBIO and SKA-31 activate both IK and SK channel subtypes, although they are more specific for IK channels (EC_{50}: NS309 10 nM, 1-EBIO 74 μM and SKA-31 0.11–0.26 μM) compared to SK channels (EC_{50}: NS309 30 nM, 1-EBIO 700 μM and SKA-31 0.4–3 μM) (Pedarzani et al., 2001; Jensen et al., 1998; Sankaranarayanan et al., 2009). SKA-111 and SKA-121 seem to show the highest selectivity for the IK channel subtype (EC_{50}: SKA-111 111 nM and SKA-121 109 nM) compared to SK channels (EC_{50}: SKA-111 13.7 μM and SKA-121 4.4 μM) (Coleman et al., 2014).

The generation of SK channel subtype-specific positive modulators is an emerging field, as there are many rather non-specific compounds (see Table 2). For the selective activation of the SK1 channel isoform, GW542573X (EC_{50} 8.2 μM) and (−)CM-TPMF (EC_{50} 24 nM) were developed (Hougaard et al., 2009, 2012). Both substances show a 20× higher selectivity for SK1 channels compared to SK2/3 channels. So far, only CyPPA (EC_{50} 5.6–14 μM) and its derivative NS13001 (EC_{50} 0.14–1.9 μM) are known to specifically activate SK2 and SK3 channels while they do not activate SK1. Both compounds exerted neuroprotective properties in a mouse model of spinocerebellar ataxia type 2 (Hougaard et al., 2007; Kasumu et al., 2012). These studies also revealed a higher specificity of CyPPA (SK3-EC_{50} 5.6 μM compared to SK2-EC_{50} 14.4 μM), and of NS13001 (SK3-EC_{50} 0.14 μM compared to SK2-EC_{50} 1.9 μM) for the activation of the SK3 channel isoform (see Table 1).

Concerning K_{Ca} channel inhibitory compounds, the available substances seem to be more specific. Tetraethylammonium is the only pharmacological substance inhibiting only BK channel activity with an IC_{50} of 500 nM (Kang et al., 1996). For IK channel inhibition, TRAM-34, clotrimazole and rac-16 can be used, of which rac-16 (IC_{50} 8 nM) is more potent than TRAM-34 (IC_{50} 20–25 nM) or clotrimazole (IC_{50} 390 nM) (Logsdon et al., 1997; Wulff et al., 2000; Urbahns et al., 2005). For SK1 channel inhibition (−)B-TPMF is effective (IC_{50} 31 nM) in inhibiting this channel subtype (Hougaard et al., 2012). In addition, ICAGEN also preferentially inhibits SK1 channels with an IC_{50} of 4 nM compared to SK2 (IC_{50} 110 nM) or SK3 channels (IC_{50} 59 nM) (Gentles et al., 2008). In contrast, the membrane-permeable substance UCL1684 (IC_{50} 0.364 nM), which is able to bind to intracellular domains of the membrane-bound SK channels (Rosa et al., 1998) as well as dequalinium chloride (IC_{50} 162 nM) are 3–4x more potent in inhibiting SK2/3 channels compared to SK1 channels (Zhang et al., 2005; Hosseini et al., 2001). In contrast, NS8593 shows similar potencies for all SK channel subtypes (IC_{50} 100 nM) (Strøbæk et al., 2006; Jenkins et al., 2011). Recently, a few more studies were published presenting new subtype-specific inhibitors, one of which was Ohmline (IC_{50} 300 nM) showing a greater potency for SK3 channel inhibition compared to SK1, and negligible effects on SK2 channel isoforms (Girault et al., 2011). Based on the structure of Ohmline, new analogues were developed which also inhibited SK3 channels, yet did not block SK2 channels (Berthe et al., 2016) (Table 2).

Table 1
Synthetic modulators of K_{Ca} channels.

Substance	Effect	Chemical name	K_{Ca} channel	K_D value or IC/ EC_{50}	Reference
NS1619	Activator	1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one	BK channels	EC_{50} 3 μM	(Olesen et al., 1994)
NS19504	Activator	5-[(4-Bromophenyl)methyl]-2-thiazolamine	BK channels	EC_{50} 11 μM	(Nausch et al, 2014)
NS11021	Activator	1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]-thiourea	BK channels	EC_{50} 400 nM	(Bentzen et al, 2007) (Layne et al., 2010)
BMS204352	Activator	(3S)-(+)-(5-Chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one	BK channels	EC_{50} 300 −400 nM	(Cheney et al, 2001; Gribkoff et al., 2001)
SKA-111	Activator	5-methylnaphtho [1,2-d]thiazol-2-amine	IK channels	EC_{50} 111 nM	(Coleman et al, 2014)
SKA-121	Activator	5-methylnaphtho [2,1-d]oxazol-2-amine	IK channels	EC_{50} 109 nM	(Coleman et al, 2014)
NS13001	Activator	4-Chlorophenyl)[2-(3,5-dimethylpyrazol-1-yl)-9-methyl-9H-purin-6-yl]amine	SK channels	EC_{50} 0.14 −1.9 μM	(Kasumu et al, 2012)
CyPPA	Activator	Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine	SK channels	EC_{50} 5.6−14 μM	(Hougaard et al, 2007)
NS309	Activator	6,7-dichloro-1H-indole-2,3-dione 3-oxime	SK channels IK channels	EC_{50} 30 nM EC_{50} 10 nM	(Pedarzani et al, 2005; Strøbæk et al., 2004)
1-EBIO	Activator	1-Ethylbenzimidazolinone	SK channels IK channels	EC_{50} 700 μM EC_{50} 74 μM	(Pedarzani et al, 2001) (Jensen et al, 1998)
SKA-31	Activator	Naphtho [1,2-d]thiazol-2-ylamine	SK channels IK channels	EC_{50} 0.4−3 μM EC_{50} 115 −260 nM	(Sankaranarayanan et al, 2009)
TEA	Inhibitor	Tetraethylammonium	BK channels	IC_{50} 500 nM	(Kang et al., 1996)
TRAM-34	Inhibitor	1-[(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole	IK channels	IC_{50} 20−25 nM	(Wulff et al, 2000)
Clotrimazole	Inhibitor		IK channels	IC_{50} 390 nM	(Logsdon et al., 1997)
Rac-16	Inhibitor	N-methyl amino-substituted cyclohexadiene	IK channels	IC_{50} 8 nM	(Urbahns et al, 2005)
NS8593	Inhibitor	N-[(1R)-1,2,3,4-Tetrahydro-1-naphthalenyl]-1H-benzimidazol-2-amine hydrochloride	SK channels	IC_{50} 104 nM	(Jenkins et al, 2011; Strøbæk et al, 2006)
UCL1684	Inhibitor	6,10-diaza-3 (1,3)8, (1,4)-dibenzena-1,5 (1,4)-diquinolinacy clodecaphane	SK channels	IC_{50} 0.36 −0.76 nM	(Strøbaek et al., 2000)
ICAGEN	Inhibitor	N-(pyridin-2-yl)-4-(pyridin-2-yl) thiazol-2-amine	SK channels	IC_{50} 4−11 nM	(Gentles et al, 2008)
Ohmline	Inhibitor	(1-O- hexadecyl-2-O-methyl-sn-glycero-3-lactose)	SK channels	IC_{50} 4−11 nM	(Girault et al, 2011)

Table 2
SK channel modulators.

Effect	Substance	Selectivity			Effect	Substance	Selectivity		
		SK1	SK2	SK3			SK1	SK2	SK3
Activation	GW542373X	+++	+	+	Inhibition	ICAGEN	+++	+	++
	(−)CM-TPMF	+++	+	+		(−)B-TPMF	+++		
	Lei-Dab[7]	−	+++	−		UCL1684	+	+++	+++
	CyPPA	−	++	+++		Dequalinium	+	+++	+++
	NS13001	−	++	+++		Tamapin	+	+++	++
	1-EBIO	+	+	+		Scyllatoxin	++	+++	+++
	NS309	+	+	+		Apamin	+	+++	+++
	SKA-31	+	+	+		Ohmline	+	−	+++
						NS8593	+	+	+

In addition to synthetic pharmacological modulators, substances of natural origin have been identified to alter K_{Ca} channel activity (Table 3), some of which are derived from toxins of different scorpion species; iberiotoxin (IC_{50} 0.36−0.76 nM) potently blocks BK channels and charybdotoxin (IC_{50} 3 nM) inhibits BK and IK channels. Notably, tamapin (IC_{50} 0.024 nM) and scyllatoxin (IC_{50} 0.29−80 nM) specifically block SK channels (Grissmer et al., 1993; Layne et al., 2010; Hanselmann and Grissmer, 1996; Strøbaek et al., 2000; Pedarzani et al., 2002). The antiseptic compound dequalinium chloride (IC_{50} 0.16−0.44 nM) and the bee venom toxin apamin (IC_{50} 0.83−3.3 nM), are also highly selective blockers for SK channels (Hanselmann and Grissmer, 1996; Strøbaek et al., 2000; Weatherall et al., 2011). Apamin which binds to the extracellular loop of SK channels facing the extracellular space, is more selective for SK2 channels (IC_{50} 0.083 nM) compared to SK1 channels (IC_{50} 3.3 nM) which is similar to scyllatoxin (SK2-IC_{50} 0.29 nM compared

Table 3
Natural modulators of K_{Ca} channels.

Substance	Effect	Origin	K_{Ca} channels	K_D value or IC_{50}	Reference
Iberiotoxin	Inhibitor	Scorpion toxin	BK channels	IC_{50} 0.36 −0.76 nM	(Layne et al., 2010)
Charybdotoxin	Inhibitor	Scorpion toxin	BK channels IK channels	IC_{50} 3 nM	Grissmer et al., 1993; Hanselmann and Grissmer, 1996)
Scyllatoxin	Inhibitor	Scorpion toxin	SK channels	IC_{50} 0.29 −80 nM	(Hanselmann and Grissmer, 1996; Strøbaek et al., 2000)
Tamapin	Inhibitor	Scorpion toxin	SK channels	IC_{50} 0.024 nM	(Pedarzani et al, 2002)
Dequalinium chloride	Inhibitor	Antiseptic compund	SK channels	IC_{50} 0.16 −0.44 nM	(Strøbaek et al., 2000)
Apamin	Inhibitor	Bee venom toxin	SK channels	IC_{50} 0.83 −3.3 nM	(Hanselmann and Grissmer, 1996; Strøbaek et al., 2000)
Lei-Dab^7	Activator	Based on scorpion leiurotoxin I with di-aminobutanoic acid (Dab)	SK channels	IC_{50} 34.5 nM	(Mpari et al., 2008)

to SK1-IC_{50} 80 nM) (Strøbaek et al., 2000). In line, also tamapin shows SK2 channel selectivity with an IC_{50} of 0.024 nM compared to SK3 (IC_{50} 1.7 nM) or SK1 (IC_{50} 42 nM) channels (Pedarzani et al., 2002). One peptide derivative of the scorpion toxin leiurotoxin, Lei-Dab^7, was identified as a potent activator of SK2 channel subtypes with an IC_{50} of 34.5 nM (Shakkottai et al., 2001; Mpari et al., 2008; Aidi-Knani et al., 2015) (Table 2).

The identification and development of SK channel specific modulators (both positive and negative) allowed for analyzing the functional impact of these channels on neuronal excitability, neuronal dysfunction and neuro-inflammatory responses *in vitro* and *in vivo*. How SK channels expressed at the plasma membrane, in mitochondria and the ER are involved in neuronal cell function and in different paradigms of neurodegeneration will be discussed in detail in the following parts of the review.

1.2. Small conductance Ca^{2+}-activated K^+ ($K_{Ca}2/SK$) channels

The three isoforms of SK channels (K_{Ca}2.1-3/SK1-3) are distinguished based on their expression profile and responsiveness to defined pharmacological modulators. In humans, the expression of SK1 (K_{Ca}2.1) channels is mainly restricted to the brain while SK2 (K_{Ca}2.2) channels are found in several organs including brain and heart. SK2 channels are also found in smooth muscle of the urinary bladder, the kidneys and in bile duct cells of the liver. SK3 (K_{Ca}2.3) channels are widely expressed in the body with particular enriched expression levels in brain cells, skeletal muscle and vascular smooth muscle cells of different organs (Thorneloe et al., 2008; Sorensen et al., 2011; Feranchak et al., 2004; Chen et al., 2004; Favero et al., 2008; Klemm and Lang, 2002).

SK channels are highly abundant in the brain, and they have been involved in $[Ca^{2+}]_i$-dependent processes such as synaptic plasticity, cell metabolism and cell survival. In mice, decreasing SK channel activity by apamin determined synaptic strength and initiated long-term potentiation (LTP), while an increase in SK channel activity reduced synaptic strength and promoted long-term depression (LTD) (Stackman et al., 2002; Ngo-Anh et al., 2005). SK channels are found in the postsynaptic membrane of glutamatergic neurons in close proximity to N-methyl-D-aspartate receptors (NMDAR) and VGCC (Ngo-Anh et al., 2005; Allen et al., 2011; Griffith et al., 2016), where they are activated by NMDAR-mediated Ca^{2+} influx that leads to a rise in $[Ca^{2+}]_i$ in response to action potential generation at the incoming synapse. Opening of SK channels induces K^+ efflux which alters the membrane potential and reduces the excitatory postsynaptic potential (Faber, 2010). Further, K^+ efflux and SK channel-mediated reduction of $[Ca^{2+}]_i$ create a local current that re-establishes NMDA receptor blockade by Mg^{2+}, thereby preventing re-excitation of the neurons (Ngo-Anh et al., 2005). In addition to modulating neuronal excitability, SK channels are involved in regulating the late repolarization phase during cardiac action potentials in human and mouse heart cells (Xu et al., 2003), and in regulating blood flow, (micro) vascular relaxation and contraction in endothelial cells (Edwards et al., 2010; Zhou et al., 2010). Further, SK channels play a role in maintaining the blood-brain-barrier, as SK channel currents were increased by ATP-induced $[Ca^{2+}]_i$ rises, and subsequent hyperpolarization augmented the proliferation of brain capillary endothelial cells (Yamazaki et al., 2006).

1.3. Regulation of SK channel activity and localization

SK channel activity is regulated by binding of Ca^{2+} to calmodulin in the calmodulin-binding domain (CaMBD). In this domain, calmodulin is constitutively bound to the C-terminal tail of SK channels (SK2-CTD) and is regulated by phosphorylation and dephosphorylation (Wissmann et al., 2002). SK channel isoforms (SK1-3) share common features in their homology and in their mechanisms of gating, yet, most studies on the regulation of channel gating were performed on the SK2 channel isoform. The cytoplasmic termini of SK2 channels interact with the catalytic and regulatory subunits of casein kinase 2 (CK2) which facilitates the phosphorylation of SK2-bound calmodulin at Thr80. Thereby, the Ca^{2+} affinity of calmodulin is decreased and SK channels are deactivated. Further, the SK2-CTD, CK2 and calmodulin assemble into a large multiprotein complex with protein phosphatase 2A (PP2A) which is suggested to create a dynamic environment for phosphorylation and dephosphorylation events to regulate SK channel function. PP2A can dephosphorylate Thr80, thereby increasing the Ca^{2+} affinity of calmodulin and activating SK channel function (Bildl et al., 2004; Allen et al., 2007). PP2A and CK2 alter the phosphorylation state of the same threonine residue suggesting further protein interactions within this large complex at the SK2-CTD which contribute to the regulation of SK channel function in neurons (Hériché et al., 1997). For instance, enhanced CK2 activity increased calmodulin phosphorylation and thereby reduced SK channel function in hypothalamic neurons (Pachuau et al., 2014).

On the other hand, membrane SK channel localization is regulated through phosphorylation by cAMP-dependent protein kinase (PKA) at Ser136 in the N-terminal domain and Ser568-570 in the C-terminal domain (Ren et al., 2006). PKA activity increased the

accumulation of SK channels into nanoclusters in somatodendritic spines of hippocampal neurons, and strongly restricted their expression to the soma, thus reducing SK channel function at the plasma membrane (Abiraman et al., 2016). Transient $GABA_B$ receptor stimulation in dopaminergic (DA) neurons in the substantia nigra caused irregular spiking which was evoked by reduced PKA activity and concomitant increasing surface SK channel expression in these neurons (Estep et al., 2016). In line with these observations, isoprenaline-mediated β-adrenergic stimulation of rat pyramidal neurons in the lateral amygdala activated PKA and induced SK channel internalization at the level of excitatory synapses (Faber et al., 2008).

Many proteins were identified to play a role in SK channel expression, trafficking and internalization into endosomes, such as the F-actin crosslinking protein α-actinin (Lu et al., 2009) and the scaffold protein filamin A (Rafizadeh et al., 2014). Co-expression of SK2 channels and α-actinin or filamin A enhanced the expression of SK channels at the plasma membrane of HEK293 cells, and this was mediated by recycling from endosomes (Zhang et al., 2016). Blocking endosome recycling with primaquine (van Weert et al., 2000) reduced membrane SK channel expression, while inhibition of endocytosis by the dynamin inhibitor dynasore (Kirchhausen et al., 2008) had no effect on the membrane expression. Furthermore, the Rab GTPases Rab4 and Rab11 were involved in anterograde trafficking of SK channels further supporting the concept that the expression of SK channels at the plasma membrane is regulated through recycling from endosomes.

1.4. The role of SK channels in neuronal disease pathology

Due to the broad expression pattern of SK channels in the brain and the importance of these channels in maintaining homeostasis of Ca^{2+} and K^+ fluxes within and across neuronal cells, SK channels are highly promising targets for the therapy of diseases affecting the brain.

The contribution to synaptic plasticity links SK channel function to disorders affecting learning and memory such as Alzheimer's disease, and to psychiatric disorders such as schizophrenia (Grube et al., 2011; Gargus, 2006; Imbrici et al., 2013; Jacobsen et al., 2009; Tomita et al., 2003). Further, it was hypothesized that $[Ca^{2+}]_i$ levels are slowly, but steadily, elevated with increasing age thereby contributing to pathological $[Ca^{2+}]_i$ signaling in neurons (Toescu et al., 2004; Shetty et al., 2011; Norris et al., 1998). The decreased ability of aged hippocampal neurons to undergo after-hyperpolarization (Disterhoft et al., 1996) suggests on the one hand that SK channel expression might decrease with age and on the other hand that activation of remaining SK channels might compensate for age-related cellular defects that are associated with dysfunctional $[Ca^{2+}]_i$ handling and/or excitability. This concept is supported by our study showing that SK channel activation by NS309 prevented channel degradation, excitotoxicity-induced $[Ca^{2+}]_i$ deregulation and prevented cell death of cultured primary cortical neurons (Dolga et al., 2011). In agreement with this idea, SK2 channels were shown to be internalized in a model of ischemia, an effect that was reversed upon by administration of 1-EBIO (Allen et al., 2011).

In the past years, a large number of studies demonstrated the neuroprotective potential of SK channels in different *in vitro* and *in vivo* models of cell death. Notably, after the discovery of intracellularly expressed SK channels in the ER and in mitochondria, recent studies now focus more on the impact of these intracellularly located SK channels in paradigms of oxidative stress and cell death (Richter et al., 2015a; Dolga et al., 2013; Kuum et al., 2012; Drion et al., 2012). In the following part, we will discuss the current knowledge on SK channel expression in different neuronal cell types which are known to be involved in neurodegenerative diseases, and we will highlight findings that link the neuroprotective effect of SK channel activation to the function of intracellularly expressed SK channels (see Fig. 1).

1.5. SK channels at the plasma membrane

In the central nervous system of the mouse, the SK channel subtypes are differentially expressed as shown by Sailer and colleagues (Sailer et al., 2004). The SK1 isoform is highly expressed in the cortex (layers I-IV), in the hippocampus (stratum lucidum, stratum radiatum, dentate gyrus, subiculum), midbrain (superior colliculus, interpeduncular nucleus), cerebellum (molecular and Purkinje cell layer) and in the spinal cord, while SK2 is predominantly expressed in the ganglionic layer of the cortex, the hippocampus (stratum oriens, subiculum), in the anterior and posterior basolateral nuclei of the amygdala, the medial habenula, the area postrema and in the inferior olivary complex. The SK3 isoform is found in the olfactory bulbs, the hilus of the dentate gyrus, the stratum lucidum, the stratiopallidal system, in most parts of the thalamus and in the locus coeruleus. In all these cell types, SK channels are abundant in the plasma membrane where they contribute to ion homeostasis, both by inducing K^+ efflux into the extracellular space and by regulating $[Ca^{2+}]_i$ homeostasis. The expression of SK channels in the brain is of special importance, as neuronal loss in the aforementioned brain regions is associated with different diseases.

In mouse hippocampal CA1 pyramidal neurons, SK channels shape the after-hyperpolarizing current and modulate spike amplitude and duration (Pedarzani et al., 2005; Bond et al., 2010; Chen et al., 2014). Activation of these K_{Ca} channels prevented neuronal damage by blocking NMDAR-mediated excitotoxicity *in vitro*. For instance, in cultured primary cortical neurons glutamate stimulation induced cell death by deregulating $[Ca^{2+}]_i$ calcium homeostasis (Dolga et al., 2011). Enhanced $[Ca^{2+}]_i$ accumulation by glutamate led to suppression of SK channel expression at the plasma membrane which was prevented by pharmacological SK channel activation. In this study, we identified a substantial role for SK channel activity in neuroprotection against excitotoxicity, and SK channel-mediated regulation of $[Ca^{2+}]_i$ homeostasis as an underlying molecular mechanism of protection. Our results from the neuronal cell cultures *in vitro* were transferred to an *in vivo* model of middle cerebral artery occlusion where intraperitoneal application of the positive SK channel modulator NS309 prior to the insult significantly reduced the infarct size. Furthermore, neuroprotective effects of SK channel activation were confirmed in a model of cerebral ischemia following cardiac arrest and cardiopulmonary resuscitation. In this model of global cerebral ischemia, CA1 pyramidal neurons were damaged and this resulted in a reduction of LTP and cognitive impairments (Orfila et al., 2014). Post-insult (30min) SK channel activation by 1-EBIO restored LTP by a mechanism involving post-synaptic signaling, likely by regulation of $[Ca^{2+}]_i$ handling. In line with these findings, two post-insult injections of 1-EBIO (30min and 6 h) reduced neuronal cell death and improved the associated cognitive defects in the same model system (Allen et al., 2011). Further, enhanced SK2 channel expression after viral SK2 plasmid delivery to the dentate gyrus in rats also alleviated kainate-induced lesions in the CA3 region *in vivo*, reduced the excitability of granule cells in hippocampal slices *in vitro*, yet was accompanied by a post-training memory deficit in SK2 channel transduced animals (Lee et al., 2003).

In addition to paradigms of acute brain injury such as cerebral ischemia, there is also increasing evidence for a therapeutic potential of SK channel modulators in neurodegenerative diseases such as Parkinson's disease (PD). PD progression is characterized by

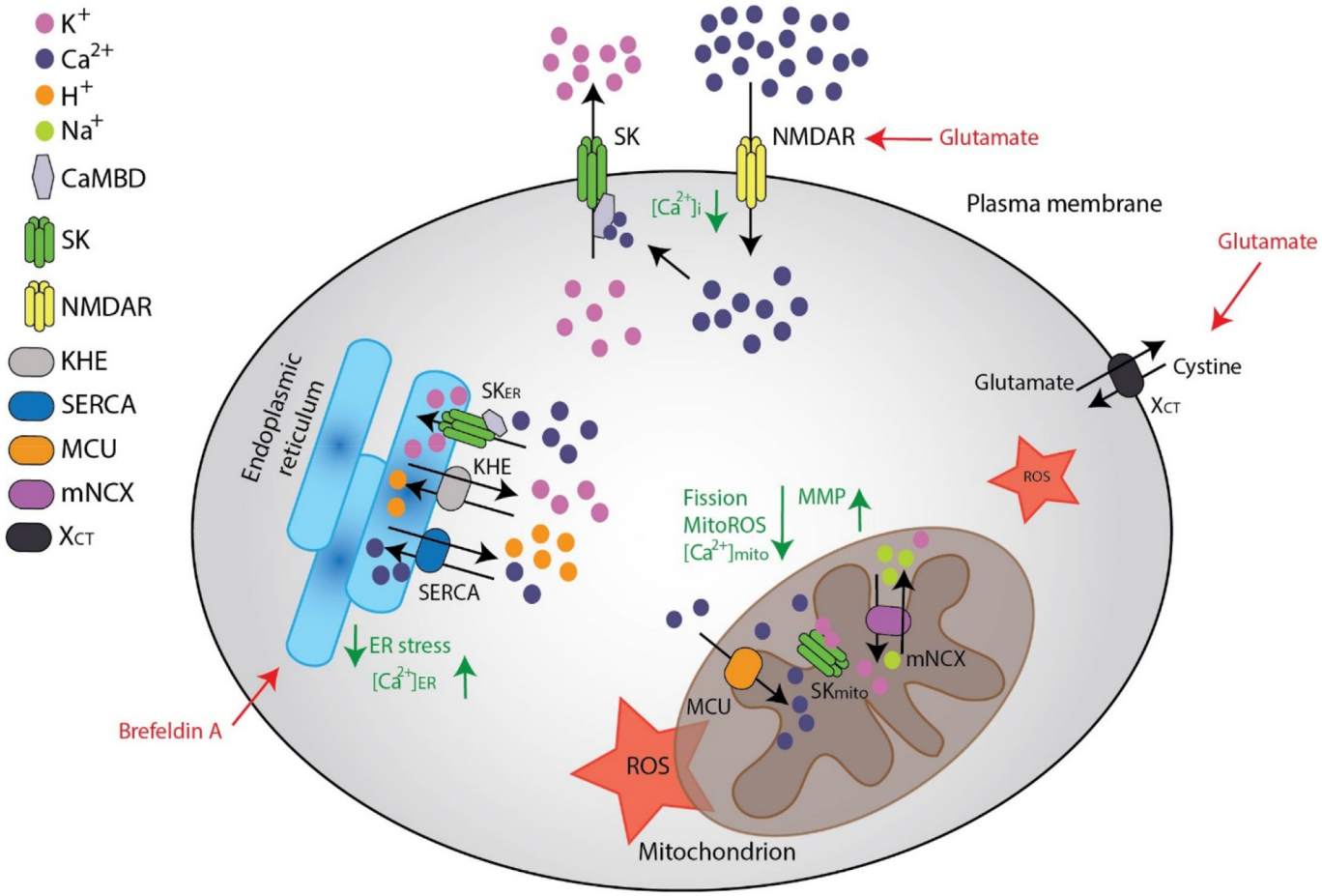

Fig. 1. SK channel function at the plasma membrane and in membranes of the endoplasmic reticulum and the mitochondria. SK channels are expressed in the plasma membrane, in the endoplasmic reticulum (ER) and in the inner mitochondrial membrane. In the plasma membrane of neurons, they are in close proximity to N-methyl-D-aspartate receptors (NMDAR) and are activated through NMDAR-dependent Ca^{2+} influx. SK channel opening induces K^+ efflux and leads to hyperpolarization of the membrane, thereby controlling the activation of NMDA receptors in physiological paradigms of long-term potentiation (LTP) in learning and memory formation, and in pathological paradigms of glutamate-induced excitotoxicity. In response to excitotoxic activation of NMDAR by glutamate, SK channel activation prevents cell death by attenuating excessive Ca^{2+} influx (Dolga et al, 2011). In the ER membrane, ER-SK (depicted as SK_{ER}) channels, the K^+/H^+ exchanger (KHE) and the sarco-/endoplasmic reticulum Ca^{2+} ATPase (SERCA) coordinate ER Ca^{2+} release and retention to maintain ER Ca^{2+} homeostasis (Richter et al., 2015). At this intracellular site, ER-SK channel-mediated K^+ flux establishes the driving force for KHE to transport protons into the ER lumen which in turn drives SERCA-mediated ER-Ca^{2+} uptake. ER-SK channel activation preserves $[Ca^{2+}]_{ER}$ levels and cell viability in conditions of brefeldin A-induced ER stress. In the mitochondria, mitoSK (depicted as SK_{mito}) channels reside in the inner mitochondrial membrane. Together with the mitochondrial Ca^{2+} uniporter (MCU) and the mitochondrial Na^+/Ca^{2+} exchanger (mNCX), mitoSK channels contribute to balancing mitochondrial Ca^{2+} uptake and efflux. In response to oxidative glutamate toxicity through inhibition of the glutamate-cystine antiporter (X_{CT}), mitoSK channel activation restores the mitochondrial membrane potential, prevents mitochondrial fission, and attenuates the formation of mitochondrial reactive oxygen species (ROS) as well as $[Ca^{2+}]_{mito}$ overload (Honrath et al, 2017).

the loss of DA neurons in the substantia nigra pars compacta which coordinate movement and working memory, and SK channels regulate the Ca^{2+}-dependent pacemaker activity of these cells (Tomita et al., 2003; Kang and Kitai, 1993; Wolfart et al., 2001; Benitez et al., 2011). Our work revealed a protective role for SK channels in human postmitotic DA neurons challenged with the mitochondrial complex I inhibitor rotenone (Dolga et al., 2014). In this study, SK channel activation by NS309 preserved the cellular network and cell survival against rotenone toxicity *in vitro* suggesting that SK channel activation may be beneficial in diseases involving the degeneration of DA neurons. In line with our observations, CyPPA application dose-dependently suppressed the depolarization-induced dopamine release from DA neurons in midbrain slices, and prevented the hyperactive phenotype induced by methylphenidate, a blocker of dopamine/norepinephrine reuptake, *in vivo* (Herrik et al., 2012). In the so called *frissonant* mutant mice a deletion in the 5′UTR of *Kcnn2* leads to loss of SK2 channel expression, and these animals show constant rapid tremor along with deficits in locomotor activity due to altered neuronal firing (Szatanik et al., 2008), thereby presenting a link to the motor dysfunction in PD patients. SK channel-mediated regulation of neuronal excitability was also linked to the development of schizophrenia. For instance, reduced expression of *Disrupted in Schizophrenia 1* (DISC-1) altered cAMP signaling and lead to upregulation of NMDAR-mediated Ca^{2+} influx and SK channel-mediated hyperpolarization in cortical slices obtained from adult rats (Elhassar et al., 2014).

In addition, recent studies have examined the role of SK channels in serotonergic neurons in model systems of mood disorders such as depression. In animals exposed to chronic social isolation, Sargin and colleagues identified a reduced activity of serotonin-producing neurons which was accompanied by increased SK3 channel protein expression, and *in vivo* SK channel inhibition normalized the depressive-like behavior (Sargin et al., 2016). In the same study, also inhibition of VGCC suppressed the pathological phenotype supporting the concept that restoring $[Ca^{2+}]_i$ signaling is essential to attenuate the progression of affective disorders. Furthermore, using the SK2/3 channel inhibitor apamin and the

SK2 isoform-specific inhibitor Lei-Dab[7], the authors showed that serotonergic neurons in socially isolated animals were insensitive to SK2 channel inhibition while the responsiveness to apamin (affecting also SK3 channels) was unchanged. This study not only links SK channel activity and $[Ca^{2+}]_i$ signaling to the regulation of serotonergic neurons, yet also gives first insights into a distinct function of the SK3 channel isoform in these cells and their potential as a target for the therapy of affective disorders.

In a model of spinocerebellar ataxia type 2 (SCA2), oral administration of the SK2/3 channel-specific activator NS13001 restored the pacemaker activity of Purkinje cells in cerebellar slices obtained from transgenic SCA2 mice, and improved motor performance of these animals (Kasumu et al., 2012). Likewise, computational modeling of deep cerebellar nuclei revealed an increase in the firing rate upon SK channel blockage which is suggested to contribute to the development of cerebellar ataxia (Abbasi et al., 2016). In agreement, SK channel activation by CyPPA and NS309 reduced Purkinje cell spiking activity *in vivo* in aged rats (22–28 months) compared to young adult rats (3–6 months) (Karelina et al., 2016) indicating that SK channel activation not only reduced cerebellar defects in pathological conditions, yet also compensated for the age-related impairment of cerebellar function. Similarly, endothelial dysfunction of mesenteric arteries in >24 months old rats was associated with impaired SK channel function together with decreased nitric oxide supplementation further indicating a protective role of SK channel activity in ageing (Zhou et al., 2010).

1.6. Mitochondrial SK (mitoSK) channels

In addition to the well-investigated functional expression at the plasma membrane, SK channels were also identified in the inner mitochondrial membrane of neuronal cells and guinea pig cardiomyocytes where they play a crucial role for cellular homeostasis and survival. In murine immortalized hippocampal HT22 cells, we identified SK channels in the inner mitochondrial membrane (mitoSK) by immunostaining using SK2-specific antibodies and immunoblotting of mitochondria-enriched fractions obtained from subcellular fractionation, and we confirmed their functional expression using patch-clamp recordings of isolated mitoplasts (Dolga et al., 2013). In HT22 cells, cell death is triggered by high extracellular glutamate concentrations which induces oxidative stress, mitochondrial dysfunction and NMDAR-independent cell death (Murphy et al., 1989; Kroemer et al., 2007; Tobaben et al., 2011). We observed that mitoSK channel activation in HT22 cells blocked major hallmarks of mitochondrial damage in response to glutamate treatment and prevented cell death (Honrath et al., 2017). Interestingly, SK channel activation or overexpression of a mitochondria-targeted SK2 channel plasmid enhanced mitochondrial resilience against oxidative glutamate toxicity by reducing mitochondrial respiration and by attenuating mitochondrial Ca^{2+} ($[Ca^{2+}]_m$) overload. Similar results were obtained in another study in neuronal HT22 cells challenged with H_2O_2 (Richter et al., 2015b). Here, cell death triggered by exogenous H_2O_2 also induced mitochondrial damage, and SK channel activation by CyPPA provided protection. In these conditions of oxidative stress, CyPPA dose-dependently decreased mitochondrial respiration while it increased glycolysis, thus inducing an adaptive metabolic switch in the cells.

Notably, our study in human postmitotic DA neurons exposed to rotenone not only showed that SK channel activation rescued from loss of the dendritic network and cell death, yet also restored cellular ATP levels, thus mitochondrial function (Dolga et al., 2014). In these cells, SK2 and SK3 channel isoforms were identified both, at the plasma membrane and in the inner mitochondrial membrane. This study shows that there is a potential crosstalk between SK channels at the plasma membrane and those in the inner mitochondrial membrane, likely through the regulation of $[Ca^{2+}]_i$ handling. On the one hand, this suggests that inhibiting SK channels at the plasma membrane will also affect mitoSK channels and might therefore change mitochondrial function. However, on the other hand SK channel activators will also activate mitoSK channels and may provide further protection at the level of the mitochondria which might not have been considered so far.

Functional expression of mitoSK channels was also reported in guinea pig hearts (Stowe et al., 2013). Their activation by 1-EBIO prior to initiation of ischemia-reperfusion injury (IRI) significantly reduced the infarct size, maintained mitochondrial function and attenuated the formation of reactive oxygen species (ROS). Further, a study in neutrophils revealed an effect of SK channel modulation on mitochondrial integrity. Upon exposure of pathogens, neutrophils elicit an immune response that induces an oxidative burst and the release of neutrophil extracellular traps (NET), also termed NETosis (Fuchs et al., 2007). SK channel activation by 1-EBIO lead to partial mitochondrial ROS formation under basal conditions which induced NETosis in neutrophils (Douda et al., 2015) suggesting that the SK channel-mediated effect on mitochondrial function is a component of the immune response against invading pathogens. SK channels were also identified in cultured primary microglial cells, and their activation by CyPPA decreased the inflammatory response (cytokine and nitric oxide release) elicited by lipopolysaccharide stimulation (Dolgaet al, 2013). Future studies are warranted to further elucidate functional SK channel expression also in microglia and to evaluate their potential impact on the pro- and anti-inflammatory effects in paradigms of neuronal disease.

Not only mitoSK channels have been identified and are involved in protective mechanisms, yet also mitoIK and mitoBK channels were identified in human colon cancer cells (De Marchi et al., 2009) and rat or guinea pig cardiomyocytes (Behmenburg et al., 2015; Sato et al., 2005), indicating that protection by mitochondrial isoforms could be a class effect of this K_{Ca} channels family, and that mitoSK channel modulation serves as a potential target for neurodegenerative diseases or cardiac injuries where mitochondrial demise contributes to disease progression.

1.7. Endoplasmic reticulum-bound SK (ER-SK) channels

In the ER, different ion channels are involved in balancing ion flow between the cytoplasm and the ER lumen, and Ca^{2+} storage in the ER depends on the counter-transport of protons (Levy et al., 1990; Yu et al., 1993). Kuum and colleagues showed that SK channels present in the ER membrane (ER-SK), along with the K^+/H^+ exchanger (KHE) control transmembrane proton flux to allow ER-$[Ca^{2+}]$ uptake and retention. This was the first study identifying SK channel expression in the ER membrane of rat cortical neurons and cardiac fibers using immunofluorescence analysis, and in ER fractions isolated from brain tissues (Kuum et al., 2012).

In neuronal HT22 cells transfected with GFP-tagged SK2 channel plasmids, SK2 channels partially co-localized with the ER as shown by immunofluorescence. Furthermore, the SK2 channel protein was detectable in an ER-microsome enriched fraction after subcellular fractionation of these cells (Richter et al., 2015a). In this study, HT22 cells were challenged with toxic concentrations of brefeldin A, a substance that inhibits protein trafficking in the ER endomembrane system and subsequently leads to accumulation of unfolded proteins in the ER lumen (Klausner et al., 1992). In this model system, ER-SK channel activation by CyPPA successfully protected against brefeldin A-induced cell death. Notably, we confirmed a substantial regulatory function of ER-SK channels in ER-$[Ca^{2+}]$ homeostasis in conditions of ER stress as CyPPA-

mediated ER-SK channel activation attenuated thapsigargin-induced ER-[Ca^{2+}] release. Furthermore, a study on spatial working memory in rats described an interplay between inositol-1,4,5-triphosphate receptor-mediated ER-[Ca^{2+}] release in conditions of stress and subsequent activation of SK channels to induce hyperpolarization of neurons in the prefrontal cortex (Brennan et al., 2008). Similarly, in porcine coronary arteries, endothelial dysfunction induced by homocysteine was mediated through ER stress which led to suppression of IK/SK channel currents and reduced expression of SK channels at the plasma membrane (Wang et al., 2015). This study also suggests a role for ER stress in failing vascular relaxation and contraction, and in addition associates ER stress with a change in SK channel protein expression. Taken together, ER-SK channel function can therefore be linked to regulation of ER-[Ca^{2+}] homeostasis.

Interestingly, the ER forms a dynamic interface with mitochondria to facilitate Ca^{2+} transfer from ER-resident channels to the mitochondrial matrix. Tightening ER-mitochondrial coupling enhances Ca^{2+} transfer and promotes cell death (Egnatchik et al., 2014; Rapizzi et al., 2002). SK channels were identified in membranes of the ER and in mitochondria, however, the effect of SK channel modulation in this subcellular compartment of ER-mitochondrial connections has not been investigated so far. We suggest that regulation of $[Ca^{2+}]_i$ homeostasis in neuronal cells depends on both, SK channel activities at the plasma membrane and at the subcellular levels of mitochondria and the ER, including regulation of ER-mitochondrial interfaces. Future studies should elucidate how SK channels are regulated in the ER and in mitochondria, and how plasma membrane-SK channels and subcellular SK channels in these organelles orchestrate their activities to modulate $[Ca^{2+}]_i$, neuronal function and survival.

1.8. Concluding remarks

The therapeutic potential of pharmacological SK channel modulators in the treatment of diseases affecting the nervous system, the cardiovascular system and the immune system is supported by a large number of studies investigating the molecular mechanisms and identifying new implications for SK channel function in physiological and pathological pathways.

Especially studies in neurons related to dysfunctional Ca^{2+} signaling revealed an essential role for SK channels in cell physiology and ion homeostasis, and pointed towards the therapeutic application of SK channel modulating compounds in brain disorders. Most intriguingly, a new role for SK channels has been unraveled in conditions where mitochondrial demise and ER dysfunction are critical. In these cell death paradigms, SK channel activation mediated neural protection by maintaining mitochondrial integrity and by restoring ER Ca^{2+} homeostasis in concert with other ER ion channels. In many neuronal cells, SK channels are expressed at the plasma membrane as well as in the inner mitochondrial membrane. Thus, pharmacological modulation of SK channels, which was originally intended to alter synaptic plasticity, also affects $[Ca^{2+}]_{mito}$ and $[Ca^{2+}]_{ER}$ homeostasis, and in consequence the function of mitochondria and the ER. These new findings need to be taken into account in future studies. Furthermore, Ca^{2+} transfer facilitated by ER-mitochondrial coupling is an important aspect for cell death signaling in neurons and in non-neuronal cells. The involvement of SK channels in $[Ca^{2+}]_i$ signaling between these organelles and the implication of ER-mitochondrial contact formation in different cell death paradigms is an emerging field of research which may provide novel targets for therapeutic intervention.

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