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Channels underlying neuronal calcium-activated potassium currents

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Abstract

In many cell types rises in cytosolic calcium, either due to influx from the extracellular space, or by release from an intracellular store activates calcium dependent potassium currents on the plasmalemma. In neurons, these currents are largely activated following calcium influx via voltage gated calcium channels active during the action potentials. Three types of these currents are known: I_c, I_{AHP} and I_{sAHP}. These currents can be distinguished by clear differences in their pharmacology and kinetics. Activation of these potassium currents modulates action potential time course and the repetitive firing properties of neurons. Single channel studies have identified two types of calcium-activated potassium channel which can also be separated on biophysical and pharmacological grounds and have been named BK and SK channels. It is now clear that BK channels underlie I_c whereas SK channels underlie I_{AHP}. The identity of the channels underlying I_{sAHP} are not known. In this review, we discuss the properties of the different types of calcium-activated potassium channels and the relationship between these channels and the macroscopic currents present in neurons.

Contents

1. Introduction

Calcium influx into cells has a variety of consequences including activation of second messenger systems, gene transcription, release of calcium from intracellular stores, and opening of calcium dependent ion channels. Among the best studied of these events is the activation of calcium dependent potassium channels. Initial indications that rises in cytosolic calcium could change plasmalemmal potassium permeability in response to changes in intracellular calcium concentrations were made by Gardos in red blood cells (Gardos, 1958). The first identification of an ionic current activated by a rise in cytosolic calcium was made by Meech and Strumwasser, who described a calcium-activated potassium current in snail neurons (Meech and Strumwasser, 1970). It is now clear that such currents are present in a wide variety of cell types and are mediated by the opening of potassium selective ion channels gated by rises in intracellular calcium. The activity of these channels is involved in a number of physiological processes ranging from secretion to the control of neuronal firing properties. In recent years, the molecular nature of many of these potassium channels has been identified. In this review, we will discuss the molecular and physiological properties of calcium-activated potassium channels involved in the control of neuronal action potential discharge properties.

Abbreviations: TEA, tetraethylammonium; DHS-1, dehydrosoyasaponin-1; fAHP, fast afterhyperpolarisation; mAHP, medium afterhyperpolarisation; sAHP, slow afterhyperpolarisation; DMV, dorsal motor nucleus of the vagus

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2. Neuronal calcium-activated potassium channels

Three broad families of calcium-activated potassium channel have been identified, which can be separated on both biophysical and pharmacological grounds. These have been called BK, SK, and IK channels (Sah, 1996; Vegara et al., 1998). Of the three types, the first described were the large conductance, maxiK or BK channels (Marty, 1981). They were initially described in chromaffin cell membranes (Marty, 1981) and cultured rat skeletal muscle (Pallotta et al., 1981), but, subsequently have been found to be widely distributed. These channels are highly potassium selective and have large single channel conductances of 200–400 pS (in symmetrical potassium) and require both calcium and membrane depolarisation for their activation (Marty, 1981; McManus, 1991). The calcium dependence of these channels is steeply dependent on the membrane potential (Cui et al., 1997). This dependence on both calcium and membrane potential is an important determinant of their role as a feedback mechanism to regulate the activity of voltage dependent calcium channels. Several pharmacological blockers of BK channels are known. These include tetraethylammonium (TEA) in the low micromolar range (Blatz and Magleby, 1987), and the two scorpion derived peptides charybdotoxin and iberiotoxin (Galvez et al., 1990). Recently, the mycotoxins paxilline and penitrem A have also been described to block BK channels (Knaus et al., 1994b; Sanchez and McManus, 1996; Strobaek et al., 2000). Of these agents, iberiotoxin and paxilline are selective for BK channels while the other agents also block a number of other potassium channels. Some BK channels are also specifically activated by dehydrosoyasaponin-1 (DHS-1), a compound isolated from a Ghanese medicinal herb (McManus et al., 1993).

The second type of calcium-activated potassium channel to be identified has a lower single channel conductance of 2–20 pS. Thus, these channels were called SK (small conductance) channels (Blatz and Magleby, 1986; Lang and Ritchie, 1987; Romey and Lazdunski, 1984). SK channels are also activated by rises in cytosolic calcium with half maximal activation in the 400–800 nM range (Blatz and Magleby, 1986; Park, 1994). Unlike BK channels, they are voltage-insensitive and unaffected by low concentrations of TEA, charybdotoxin, or iberiotoxin. However, they are potently blocked by the bee venom apamin (Blatz and Magleby, 1986; Romey et al., 1984), tubocurarine, and quaternary salts of bicuculline (Johnson and Seutin, 1997; Seutin and Johnson, 1999). In addition, a new series of compounds has recently also been described, which are able to inhibit SK channels including dequalinium and a large set of related bis-quinolinium cyclophanes (Campos Rosa et al., 2000; Chen et al., 2000; Dunn, 1994). Furthermore, 1-ethyl-2-benzimidazolinone (EBIO) has been found to activate SK channels by altering their calcium sensitivity and open probability (Olesen et al., 1994; Pedarzani et al., 2001; Syme et al., 2000). As with BK channels, SK channels were also first described in skeletal muscle (Romey and Lazdunski, 1984) but have since been found in many tissues from neurons to smooth muscle (Kohler et al., 1996) where they have been shown to have distinct functional roles.

The third type of calcium-activated potassium channel has an intermediate single channel conductance (20–100 pS) (Ishii et al., 1997b; Joiner et al., 1997; Logsdon et al., 1997). These channels have, therefore, been called intermediate conductance, or IK, channels and have only been identified in a few non-neuronal cell types, in particular epithelial and red blood cells (Gardos, 1958; Ishii et al., 1997b). IK channels have been poorly studied largely due to their sparse distribution. As for SK channels, IK channels are voltage insensitive but gated by rises in cytosolic calcium. Their pharmacological profile has been examined and they have been shown to be sensitive to charybdotoxin, clotrimazole and EBIO but insensitive to apamin and iberiotoxin (Ishii et al., 1997b; Joiner et al., 1997; Logsdon et al., 1997). Thus, these channels are clearly separable from both BK and SK channels. As no clear role for IK channels has been demonstrated in neurons, they will not be discussed further in this review.

3. Molecular identity of calcium-activated potassium channels

3.1. BK channels

BK channels were the first type of calcium-activated potassium channel to be cloned from *Drosophila*, as the product of the *slowpoke* gene (Adelman et al., 1992; Atkinson et al., 1992). Subsequently, BK channels have also been identified in a number of other species. The primary sequence of the pore forming α subunit shares significant homology with similar regions of other members of the potassium channel family (Jan and Jan, 1997). However, unlike other voltage dependent potassium channels, hydropathy analysis suggests that the α subunit has seven membrane spanning domains. In addition, an extra four hydrophobic segments, S7–S10, have been identified in the cytoplasmic carboxy terminal domain (Meera et al., 1997; Wei et al., 1994). While BK channels are clearly activated by rises in cytoplasmic calcium, no clear calcium binding domain has been identified. However, a series of negatively charged amino acids near S10 referred to as the "calcium bowl" has been suggested to contain the calcium binding site (Schreiber and Salkoff, 1997; Wei et al., 1994). Furthermore, unlike other members of the potassium channel family, the pore forming α subunit of BK channels has only been attributed to the *slowpoke* gene (Adelman et al., 1992). Diversity in the physiology of these channels is generated by alternative splicing of the slowpoke RNA (Atkinson et al., 1992), by phosphorylation of the α subunit (Reinhart and Levitan, 1995; Sansom et al., 1997; Toro and Stefani, 1991), and heteromeric assembly with a modulatory β subunit (Garcia-Calvo et al., 1994; Meera et al., 1997) (Fig. 1). The β subunit comprises two

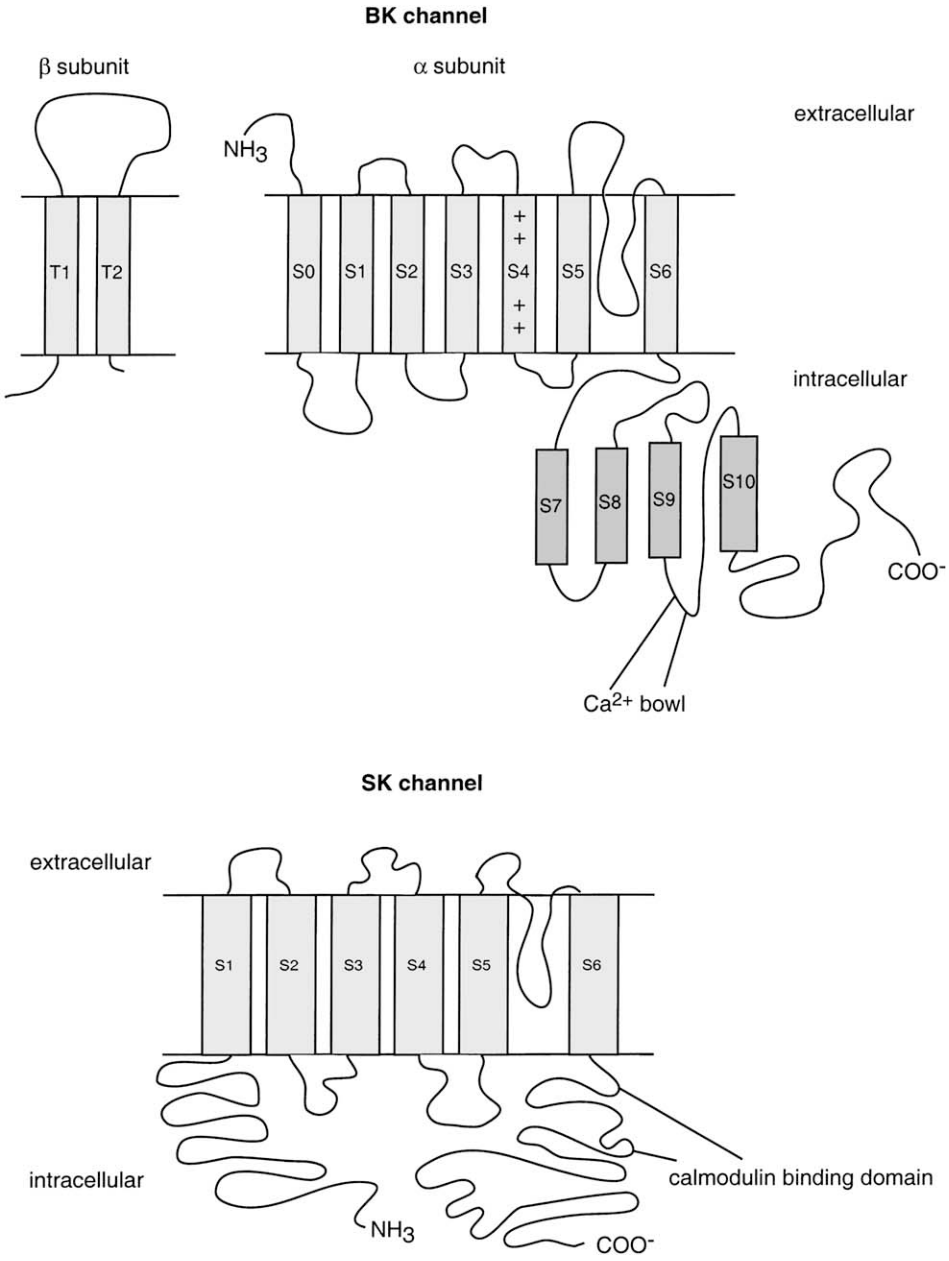

Fig. 1. Molecular structure of BK and SK channels. The proposed membrane topology for BK and SK channels. In BK channels, the α subunit is proposed to have seven transmembrane regions with an extracellular amino terminal domain. As in other voltage sensitive potassium channels, S4 has positively charged residues, which form the voltage sensor, and the region between segments S5 and S6 forms the pore lining domain. In addition, there are an additional four hydrophobic segments that are thought to be cytoplasmic. The region between segments S9 and S10 has putative calcium binding sites and has been called the 'calcium bowl' and is suggested to be involved in calcium activation. The regulatory β subunit, which has only two transmembrane domains, is shown for comparison. SK channels have a topology that is similar to that of other channels in the potassium channel family with six transmembrane domains and a pore lining region between segments S5 and S6. There is no calcium binding domain, but in native SK channels calmodulin is constitutively bound to a region of the cytoplasmic carboxy terminal domain and functions as the calcium sensor.

putative transmembrane domains with a large extracellular loop (Fig. 1). While only one α subunit has been identified, three β subunits, β1, β2/3 and β4 have been cloned so far (Brenner et al., 2000; Dworetzky et al., 1994; Knaus et al., 1994a; Meera et al., 2000; Tseng-Crank et al., 1996). The native channel is thought to comprise either an α subunit alone as a tetramer (Shen et al., 1994) or coassemble in combination with one to three β subunits (Adelman et al., 1992; Garcia-Calvo et al., 1994; McManus et al., 1995).

Co-assembly of the α subunit with the β subunit significantly modifies the pharmacology, voltage dependence, and kinetics of the assembled protein. The presence of β subunits with the α subunit shifts the voltage dependence of activation of these channels to more negative membrane poten-

tials and increases the calcium sensitivity (Dworetsky et al., 1996; McManus et al., 1995; Nimigean and Magleby, 1999; Wallner et al., 1999). Channels containing the α subunit in isolation or in combination with the β1 subunit, which is found in smooth muscle, produce sustained currents that do not inactivate (Wallner et al., 1999). Only the β2/3 subunits (found mainly in the kidney, heart, and brain) in combination with the α subunit give rise to channels that show rapid inactivation. Channel inactivation has been shown to be mediated by a blockade of the channel by the N-terminus cytoplasmic "ball" portion of the protein as targeting the β1 subunit with this β2 subunit N-terminus causes the β1 subunit to produce fast inactivating currents (Brenner et al., 2000; Wallner et al., 1999; Xia et al., 1999). Moreover co-expression of the β2/3 subunit with the α subunit lowers the channel's sensitivity to charybdotoxin and DHS-1 compared to when the α subunit is expressed alone (Ding et al., 1998; Wallner et al., 1999; Xia et al., 1999). Further, recent electrophysiological studies have shown that co-expression of α subunits with the neuronal β4 subunit confers iberiotoxin and charybdotoxin insensitivity (Meera et al., 2000); and slows the activation time of the channel; as with the β1 subunit, channels containing β4 subunits do not inactivate (Meera et al., 2000).

The diversity in BK channel properties produced by post-translational modification has clear physiological actions. Thus, for example, in the avian cochlea, differential splicing of BK channels is thought to confer the altered sensitivity of these channels to calcium and leads to the tonotopic organization of these cells (Navaratnam et al., 1997; Rosenblatt et al., 1997). Interestingly, the splice variants of BK channels, and thus, their electrophysiological properties, have also been shown to be controlled by hormonal status in adrenal chromaffin cells (Lovell and McCobb, 2001; Xie and McCobb, 1998).

3.2. SK channels

SK channels have now also been cloned from mammalian systems. Three members of this family were first described: SK1, SK2, and SK3 (Kohler et al., 1996). SK channels are widely expressed throughout the central nervous system but are also found in the periphery (Kohler et al., 1996). These channels are typical potassium channels with six putative transmembrane spanning regions (Fig. 1). Their primary structure shows approximately 60% sequence homology with each other; but only share homology with voltage gated potassium channels in the pore region of the channel (Kohler et al., 1996). On account of the overall similarity in the transmembrane structure between SK channels and voltage gated potassium channels (six putative transmembrane domains and cytoplasmic carboxy and amino terminals), it has been proposed that SK channels assemble as tetramers (Vegara et al., 1998). However, direct evidence for this is lacking. Like BK channels, SK channels also do not have a calcium binding domain on their intracellular face. Instead, they are covalently linked to the calcium binding protein calmodulin. Binding of calcium to calmodulin leads to a conformational change in the channel which causes its opening (Keen et al., 1999; Schumacher et al., 2001; Xia et al., 1998).

When expressed as homomultimers (Kohler et al., 1996), SK channel subunits form ion channels that have functional characteristics typical of SK channels described in neurons, skeletal muscle (Blatz and Magleby, 1987; Romey et al., 1984; Romey and Lazdunski, 1984), lymphocytes (Grissmer et al., 1993), and adrenal chromaffin cells (Artalejo et al., 1993; Park, 1994). Thus, they respond rapidly to calcium applied to their cytoplasmic face and are voltage independent (Hirschberg et al., 1998). Pharmacologically, SK2 and SK3 channels are very sensitive to blockade by apamin with the measured IC_{50} for SK2 and SK3 being 63 pM (Kohler et al., 1996) and 2 nM (Ishii et al., 1997a), respectively. In contrast, SK1 channels have been described as being apamin insensitive (Kohler et al., 1996). Initial experiments on cloned SK channels were done on homomeric hSK1 channels expressed in *Xenopus oocytes*. However, subsequently, SK1 channels expressed in mammalian HEK and COS cell lines were found to be blocked by apamin with IC_{50} values varying between 3.3 and 12 nM, suggesting that the sensitivity of these channels to apamin is partly dependent on the expression system used (Shah and Haylett, 2000; Strobaek et al., 2000).

4. Neuronal calcium-activated potassium currents

In neurons, action potentials are followed by an afterhyperpolarisation that has three components (Fig. 2). These have been called the fast afterhyperpolarisation (fAHP), the medium AHP (mAHP), and the slow AHP (sAHP). The fAHP is activated immediately during the action potential and lasts several tens of milliseconds. The mAHP is also activated rapidly following the action potential (<5 ms) but decays with a time course of several hundred milliseconds. Finally, the third component of the AHP is the slow AHP, which rises to a peak over several hundred milliseconds; and can last up to 5 s following an action potential. While in some neurons slow AHPs have been described following a single action potential (Hirst et al., 1985; Sah and McLachlan, 1991), it is more commonly seen following a train (4–10) of spikes (Faber et al., 2001; Lancaster and Nicoll, 1987; Schwindt et al., 1988). All three types of AHP are known to be mediated by calcium-activated potassium channels, which are activated in response to calcium influx via voltage dependent calcium channels that open during the action potential (Lancaster and Nicoll, 1987; Storm, 1987, 1990).

The current underlying the fAHP has been named I_c. This current is voltage dependent (Adams et al., 1982) and is blocked by low concentrations of TEA, iberiotoxin, and paxilline indicating that the underlying channels are BK-type channels (Adams et al., 1982; Lancaster and Nicoll, 1987; Shao et al., 1999). The exact identity of these channels, however, has not been determined. In contrast, the mAHP is unaffected by BK channel blockers but is blocked by apamin

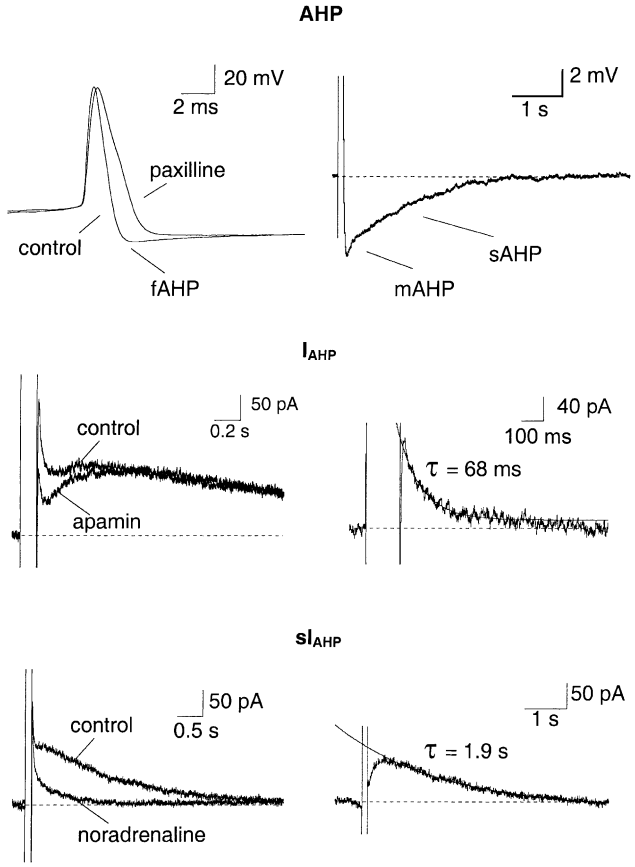

Fig. 2. Three types of calcium-activated potassium currents in central neurons. Current clamp recordings shown in the top traces show the action potential (left trace) and the afterhyperpolarisation (AHP) following an action potential train. The fast AHP immediately follows the action potential and is blocked by the BK channel antagonist paxilline (10 μM). Note the slowing of action potential repolarisation in paxilline showing that these channels also contribute to action potential repolarisation. The AHP (right trace) lasts several seconds and has two components. The medium AHP (mAHP) peaks immediately after the action potential train and lasts several hundred milliseconds. The slow AHP (sAHP) is the slower component and lasts several seconds. The currents generating the AHP are shown in voltage clamp in the lower traces, in response to a 100 ms step from a holding potential of −50 to 0 mV. I_{AHP}, shown in the middle traces peaks immediately after the voltage step and is blocked by the SK channel blocker apamin. I_{AHP} decays with a time constant of 68 ms as shown in the subtracted trace on the right. The slow AHP is unaffected by apamin (middle traces) but is selectively blocked by neurotransmitters such as noradrenaline (lower traces). The I_{sAHP} has a slow time to peak and decays with a time constant of 1–2 s as shown in the subtracted trace on the right.

indicating that it is due to the activation of SK-type channels (Pennefather et al., 1985; Sah and McLachlan, 1991; Sah and McLachlan, 1992; Schwindt et al., 1988). The current that underlies the mAHP has been called I_{AHP} (Adams et al., 1982). It peaks rapidly following calcium influx (<5 ms) and decays with a time constant of 50 to several hundred milliseconds (Pennefather and Goh, 1988; Sah, 1992). It is notable that while activation of BK channels generates the fAHP, these channels also contribute to action potential repolarisation. In contrast, activation of SK channels does not contribute to action potential repolarisation (Lancaster and Nicoll, 1987; Sah, 1996; Storm, 1987, 1990).

As discussed above, three types of SK subunits, SK1, SK2, and SK3, have so far been cloned. These subunits assemble as either homomultimers or heteromultimers and the channels formed have properties very similar to those of I_{AHP}. Thus, they are activated by rises in cytosolic calcium, are voltage independent, insensitive to low concentrations of TEA, but are blocked by apamin. Furthermore, the distribution of SK channel subunits closely mirrors the distribution of I_{AHP} type currents (Stocker et al., 1999; Stocker and Pedarzani, 2000). It is therefore very likely that some combination of SK channels underlies this current, although whether the underlying channel is a homomultimer or a heteromultimer is unknown. The exact subunit composition of I_{AHP} has not been determined in any cell type but is now beginning to be investigated. Thus, recently it has been determined that SK3 channels are the major contributors to the I_{AHP} in neurons of the rat dorsal motor nucleus of the vagus (DMV) (Pedarzani et al., 2000), midbrain dopaminergic neurons (Wolfart et al., 2001), and superior cervical ganglion neurons (Hosseini et al., 2001).

Both BK channels and SK channels are activated by calcium influx via voltage gated calcium channels. Thus different physiological roles of BK and SK channels are likely to be due to a differential colocalisation with voltage activated calcium channels and potassium channels (Marrion and Tavalin, 1998; Sah, 1995).

5. Channels underlying the slow AHP

The current that underlies the slow AHP was first described in neurons in the myenteric plexus (Hirst et al., 1985). Following calcium influx, this current has a time to peak on the order of hundreds of milliseconds, and decays to baseline with a time constant of 1–2 s at 30 °C. To distinguish it from I_{AHP}, this current has been designated I_{sAHP} (Sah, 1996). As with I_{AHP}, this current requires a rise in cytosolic calcium for activation and is voltage insensitive. I_{sAHP} is not blocked by apamin or TEA. However, I_{sAHP} is modulated by a range of neurotransmitters including noradrenaline, serotonin, glutamate, and acetylcholine all of which block the current (Nicoll, 1988).

One question that remains unanswered is, which channels underlie I_{sAHP}? Several possibilities have been suggested. Given that SK2 and SK3 are both apamin sensitive, it seems unlikely that these subunits expressed alone could form I_{sAHP}. SK1 was initially reported to be apamin insensitive, and it has been suggested that these channels could underlie I_{sAHP} (Bowden et al., 2001; Marrion and Tavalin, 1998). However, it seems unlikely that I_{sAHP} is mediated by the cloned SK channels for a number of reasons. (1) Recent studies on the pharmacology of SK1 channels have shown that the apamin sensitivity of these channels is higher than

initially suggested (Shah and Haylett, 2000). Thus, when expressed in mammalian cells, all three cloned SK channels are apamin sensitive whereas I_{sAHP} is not. (2) A new class of compounds has recently been synthesized that selectively block I_{sAHP} in cultured hippocampal neurons but do not affect currents generated by expressed SK channels (Shah et al., 2001). (3) Expression of SK1, SK2 or SK3 channels as homo- or heteromultimers generates currents that activate rapidly following calcium binding (Hirschberg et al., 1998). In contrast, following depolarizing voltage steps, cytosolic calcium rises much faster during action potentials than the rise time of I_{sAHP} (Sah and Clements, 1999). Rapid uncaging of calcium in hippocampal pyramidal neurons initially suggested the channels underlying I_{sAHP} activated rapidly, and it was suggested that the slow time course of activation of this current may be due to diffusion of calcium to a distant site (Lancaster and Zucker, 1994). However, at this time, it was felt that apamin sensitive currents were not present in CA1 pyramidal neurons (Lancaster and Nicoll, 1987) and, therefore, these experiments were not done with apamin sensitive channels blocked. Subsequent experiments have shown that apamin sensitive channels are indeed present in hippocampal pyramidal neurons (Sah and Clements, 1999; Stocker et al., 1999), and rapid uncaging of calcium generates a slowly activating apamin insensitive potassium current while the apamin sensitive current activates rapidly (Sah and Clements, 1999). It has, therefore, been proposed that to account for the slow activation phase of I_{sAHP}, the underlying channels open slowly following binding of calcium (unlike the rapid activation of SK channels) (Sah and Clements, 1999). (4) Finally, I_{sAHP} is well known to be modulated by a number of neurotransmitters, and the site of this modulation is thought to be a direct phosphorylation of the underlying channels. which changes their activation characteristics (Knopfel et al., 1990; Pedarzani and Storm, 1993; Sah and Clements, 1999; Sah and Isaacson, 1995). However, while phosphorylation sites for both PKA and PKC have been found on SK channels, modulation of cloned SK channels has not so far been demonstrated.

These considerations indicate that the cloned SK channels are unlikely to underlie I_{sAHP}. What are the other possibilities? One simple option is that there is an as yet unidentified SK subunit with properties that are similar to those of I_{sAHP}. It is interesting that for SK1, only the properties of expressed human SK1 channels have been studied. Expression of the rat SK1 channel and analysis of its properties have not been done because expression of these genes in cell lines do not appear to assemble as channels. It is, therefore, tempting to speculate that despite their very similar structures, the properties of the rat SK1 channel are somewhat different from those of human SK1 and could underlie the current that underlies the slow AHP.

As described earlier, for BK channels, coassembly of the β subunits with the pore forming α subunit confers novel kinetic and pharmacological properties on the channel. Thus, another possibility is that there are as yet unidentified modulatory subunits that co-assemble with one or more known SK subunits to change the properties of the channels. Finally, it also remains possible that the channels underlying I_{sAHP} are not calcium-activated potassium channels and have, therefore, not been thus far identified. While it is clear that a rise in cytosolic calcium initiates the activation of I_{sAHP} there is no compelling evidence that these channels are in fact gated by calcium. It is conceivable that the rise in cytosolic calcium initiates a second messenger system that ultimately leads to activation of the current underlying I_{sAHP}. The slow activation and inactivation of these currents, coupled with its high temperature sensitivity (Lancaster and Adams, 1986), may be due to the involvement of such a second messenger system.

In conclusion, the known properties of calcium-activated potassium channels are currently undergoing a very large expansion. We now understand in some detail the molecular properties of BK channels and the macroscopic currents that are generated as a result of their activation. Details of the architecture of SK channels are now emerging but there is a paucity of information on the nature of channels mediating currents that underlie the slow afterhyperpolarisation. The recent cloning of the human and mouse genome is bound to lead to a steady increase in this information.

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