Calcium-Activated Potassium Channels: Multiple Contributions to Neuronal Function

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Calcium-activated potassium channels are a large family of potassium channels that are found throughout the central nervous system and in many other cell types. These channels are activated by rises in cytosolic calcium largely in response to calcium influx via voltage-gated calcium channels that open during action potentials. Activation of these potassium channels is involved in the control of a number of physiological processes from the firing properties of neurons to the control of transmitter release. These channels form the target for modulation for a range of neurotransmitters and have been implicated in the pathogenesis of neurological and psychiatric disorders. Here the authors summarize the varieties of calcium-activated potassium channels present in central neurons and their defining molecular and biophysical properties. NEUROSCIENTIST 9(3):181–194, 2003. DOI: 10.1177/1073858403252673

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Calcium influx into cells has a variety of consequences that includes activation of second messenger systems, initiation of 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 that are gated by a rise in intracellular calcium. These channels have a number of physiological roles ranging from secretion to the control of neuronal firing properties. In recent years, the functional roles of calcium-activated potassium channels have begun to be elucidated. In this review, we will discuss the molecular and physiological properties of calcium-activated potassium channels and the functions that have been attributed to these channels, including their role in memory and learning, aging and disease.

Types of Calcium-Activated Potassium Channel

Three broad families of calcium-activated potassium channels have been identified, which can be separated on biophysical and pharmacological grounds. These have been called BK, SK, and IK channels (Sah 1996;Vegara and others 1998).

BK Channels

BK channels, also known as large conductance or maxiK channels (Marty 1981), were the first calcium-activated potassium channels to be identified. They were also the first type to be cloned from *Drosophila*, as the product of the *slowpoke* gene (Adelman and others 1992; Atkinson and others 1992). Subsequently, BK channels have been identified in a number of other species. These channels are highly potassium selective, have large single-channel conductances of 200 to 400 pS, and require both calcium and membrane depolarization for their activation (Marty 1981; McManus 1991). The calcium dependence of these channels is steeply dependent on the membrane potential (Cui and others 1997), the Kd for calcium being in the micromolar range at resting membrane potentials (~–60 mV) but in the nanomolar range at depolarized potentials (+20 to +40 mV) (Latorre and others 1989). Interestingly, these channels can open in the absence of calcium, and it appears that the effects of calcium and membrane potential are independent processes, both of which enhance the open probability (Horrigan and Aldrich 2002). Although the voltage dependence of these channels is relatively weak when compared with purely voltage-dependent potassium channels, their voltage dependence allows these channels to operate as coincidence detectors and is of central importance to their physiological function.

BK channels open rapidly when calcium is raised on the cytosolic face and close rapidly upon removal of calcium. 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 and others 1990). Recently, the

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mycotoxins paxilline and penitrem A have also been shown to block BK channels (Knaus, McManus, and others 1994; Sanchez and McManus 1996; Strobaek and others 2000) (Fig. 2). Of these agents, iberiotoxin and paxilline are selective for BK channels whereas the other agents also block a number of other potassium channels. Some BK channels can also be specifically activated by dehydrosoyasaponin-1 (DHS-1), a compound isolated from a Ghanese medicinal herb (McManus and others 1993).

As with many other ion channels, two distinct subunits, named α and β, have been associated with BK channels. The primary sequence of the pore-forming α subunit shares significant homology with the pore regions of other members of the potassium channel family (Jan and Jan 1997). In agreement, the crystal structure of a homologous bacterial BK channel suggests that the ion-selective pores of BK channels share many properties with other potassium selective channels (Wei and others 1994; Meera and others 1997; Jiang and others 2002). However, unlike other voltage-dependent potassium channels, hydropathy analysis suggests that the α subunit has seven membrane-spanning domains (Fig. 1). In addition, an extra four hydrophobic segments, S7–S10, have been identified in the cytoplasmic carboxy terminal domain (Wei and others 1994; Meera and others 1997). The functions of these extra regions are not currently understood. Although BK channels are clearly activated by rises in cytoplasmic calcium, no defined calcium-binding domain has been identified. A series of negatively charged residues near the intracellular C-terminus referred to as the "calcium bowl" have been suggested to contain the calcium-binding site (Wei and others 1994; Schreiber and Salkoff 1997; Jiang and others 2002). However, removal of the C-terminus of BK channels does not disrupt calcium activation of BK channels, indicating that the calcium binds to a region outside of the calcium bowl (Piskorowski and Aldrich 2002). The exact location of the calcium-binding site on these channels still needs resolution.

Unlike other members of the potassium channel family, the pore-forming α subunit of BK channels is coded for by a singe gene—*slowpoke* (Adelman and others 1992). Diversity in the physiological properties of these channels is generated by alternative splicing of the *slowpoke* RNA (Atkinson and others 1992), by phosphorylation of the α subunit (Toro and Stefani 1991; Reinhart and Levitan 1995; Sansom and others 1997), and by heteromeric assembly with the modulatory β subunit (Garcia-Calvo and others 1994; Meera and others 1997). The β subunit is composed of two putative transmembrane domains with a large extracellular loop (Fig. 1). Whereas only one α subunit has been identified, three β subunits, β1, β2/3, and β4, have been cloned so far (Dworetzky and others 1994; Knaus, Folander, and others 1994; Tseng-Crank and others 1996; Brenner and others 2000; Meera and others 2000). The native channel is thought to comprise either an α subunit alone as a tetramer (Shen and others 1994) or coassemble in combination with one to three β subunits (Adelman and others 1992; Garcia-Calvo and others 1994; McManus and others 1995). The exact subunit composition of these channels in vivo, however, has not yet been determined.

Coassembly of the α subunit with β subunits significantly modifies the pharmacology, voltage dependence, and kinetics of the assembled channel. Expression of the β subunit can shift the voltage dependence of activation to more negative membrane potentials and increases the calcium sensitivity (McManus and others 1995; Dworetsky and others 1996; Nimigean and Magleby 1999; Wallner and others 1999). Channels containing the α subunit in isolation or in combination with the β1 or β4 subunits produce sustained currents that do not inactivate (Wallner and others 1999; Meera and others 2000). In contrast, coexpression of the α subunit with β2/3 subunits gives rise to channels that show rapid inactivation, thought to be mediated by blockade of the channel by the N terminus cytoplasmic "ball" (Wallner and others 1999; Xia and others 1999; Brenner and others 2000). Moreover, compared to when the α subunit is expressed alone, coexpression of the β2/3 subunits with the α subunit lowers the channel's sensitivity to charybdotoxin and DHS-1 (Ding and others 1998; Wallner and others 1999; Xia and others 1999). Furthermore, recent electrophysiological studies have shown that coexpression of α subunits with the neuronal β4 subunit confers insensitivity to iberiotoxin and charybdotoxin (Meera and others 2000) and slows the activation time of the channel.

The diversity in BK channel properties produced by posttranslational modification has clear physiological effects. 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 and others 1997; Rosenblatt and others 1997). Furthermore, the splice variants of BK channels, and thus their electrophysiological properties, are also controlled by hormonal status in adrenal chromaffin cells, indicating that the physiological properties of these channels are not fixed but can change with different physiological conditions (Xie and McCobb 1998; Lovell and McCobb 2001).

SK Channels

Three types of SK channels have been cloned: SK1, SK2, and SK3 (Kohler and others 1996). SK channels have a single-channel conductance of 2-20 pS and are 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 (Romey and others 1984; Blatz and Magleby 1986) (Fig. 3), tubocurarine, and quaternary salts of bicuculline (Johnson and Seutin 1997; Seutin and Johnson 1999). A new series of compounds that block SK channels include dequalinium

and a large set of related bis-quinolinium cyclophanes (Dunn 1994; Campos Rosa and others 2000; Chen and others 2000). Furthermore, 1-ethyl-2-benzimidazolinone (EBIO) has been found to activate SK channels by altering their calcium sensitivity and open probability (Olesen and others 1994; Syme and others 2000; Pedarzani and others 2001) (Fig. 3). The activity of SK channels following action potentials leads to more long-lasting currents than those mediated by BK channels, owing to their higher affinity for calcium at hyperpolarized membrane potentials.

SK channels are widely expressed throughout the central nervous system but are also found in the periphery (Kohler and others 1996; Stocker and Pedarzani 2000; Sailer and others 2002). 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 SK channels only share homology with voltage-gated potassium channels in the pore region of the channel (Kohler and others 1996). Owing to 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 and others 1998 #1556). However, direct evidence for this is lacking. Like BK channels, SK channels also do not have a clear calcium-binding domain. Instead, they are covalently linked to the calcium-binding protein calmodulin, and binding of calcium to calmodulin leads to a conformational change in the channel, which causes its opening (Xia and others 1998; Keen and others 1999; Schumacher and others 2001).

When expressed as homomultimers (Kohler and others 1996), SK channel subunits form ion channels that have functional characteristics typical of SK channels described in neurons, skeletal muscle (Romey and others 1984; Romey and Lazdunski 1984; Blatz and Magleby 1987), lymphocytes (Grissmer and others 1993), and adrenal chromaffin cells (Artalejo and others 1993; Park 1994). Thus, they respond rapidly to calcium applied to their cytoplasmic face and are voltage independent (Hirschberg and others 1998). Pharmacologically, SK2 and SK3 channels are very sensitive to blockade by apamin with IC_{50}s in the pM range (Kohler and others 1996; Ishii, Maylie, and others 1997). In contrast, homomeric hSK1 channels initially expressed in *Xenopus* oocytes were described as being apamin insensitive (Kohler and others 1996). However, when expressed in mammalian cell lines, they are blocked by apamin, suggesting that the sensitivity of these channels to apamin is partly dependent on the expression system used (Shah and Haylett 2000; Strobaek and others 2000). Interestingly, the SK1 gene has eight exons and undergoes extensive alternate splicing with over 30 predicted transcripts (Shmukler and others 2001). Of these, at least 20 transcripts have been detected in the brain (Shmukler and others 2001). Although the different predicted proteins have yet to be detected, these findings suggest that there is a much larger diversity of SK channels than previously suspected.

IK Channels

The third type of calcium-activated potassium channel has an intermediate single-channel conductance (20–100 pS) (Ishii, Silvia, and others 1997; Joiner and others 1997; Logsdon and others 1997). These channels have therefore been called intermediate conductance or IK channels and have only been identified in a few nonneuronal cell types, in particular epithelial and red blood cells (Gardos 1958; Ishii, Silvia, and others 1997). IK channels have been poorly studied largely owing 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, Silvia, and others 1997; Joiner and others 1997; Logsdon and others 1997). Thus, these channels are clearly separable from both BK and SK channels. Macroscopic currents due to activation of IK channels have not been identified in central neurons; however, they have been suggested to underlie a slow afterhyperpolarization in myenteric neurons (Vogalis and others 2002).

Physiological Roles

In many neurons, action potentials are followed by an afterhyperpolarization (AHP) that may last up to several seconds. Immediately following the action potential, there is a fast hyperpolarizing potential, the fast AHP, which typically lasts 1-10 ms and is due to the activation of voltage-gated potassium currents and/or a fast calcium-activated potassium current (Fig. 2). Following the fast AHP, there may be a prolonged hyperpolarization lasting between several hundred milliseconds and several seconds. In all cases, the slow component of the AHP results from activation of calcium-activated potassium conductances secondary to calcium entry during the action potential (Lancaster and Adams 1986; Storm 1987, 1990), typically through voltage-gated calcium channels (Lancaster and Adams 1986; Sah 1996; Marrion and Tavalin 1998). In some cell types, calcium release from intracellular stores also contributes to activation of the AHP (Sah and McLachlan 1991; Osmanovic and Schefner 1993; Yoshizaki and others 1995; Tanabe and others 1998). The slower calcium-activated potassium currents can be separated into two distinct components that are distinguishable on kinetic and pharmacological grounds, the medium AHP and the slow AHP (Sah 1996) (Fig. 2). The slower component of the AHP has two functions: it limits the firing frequency of the neuron and is responsible for generating the phenomenon of spike frequency adaptation. In some neurons, both the medium and the slow AHP are apparent, whereas in others only one or the other is present. It is now

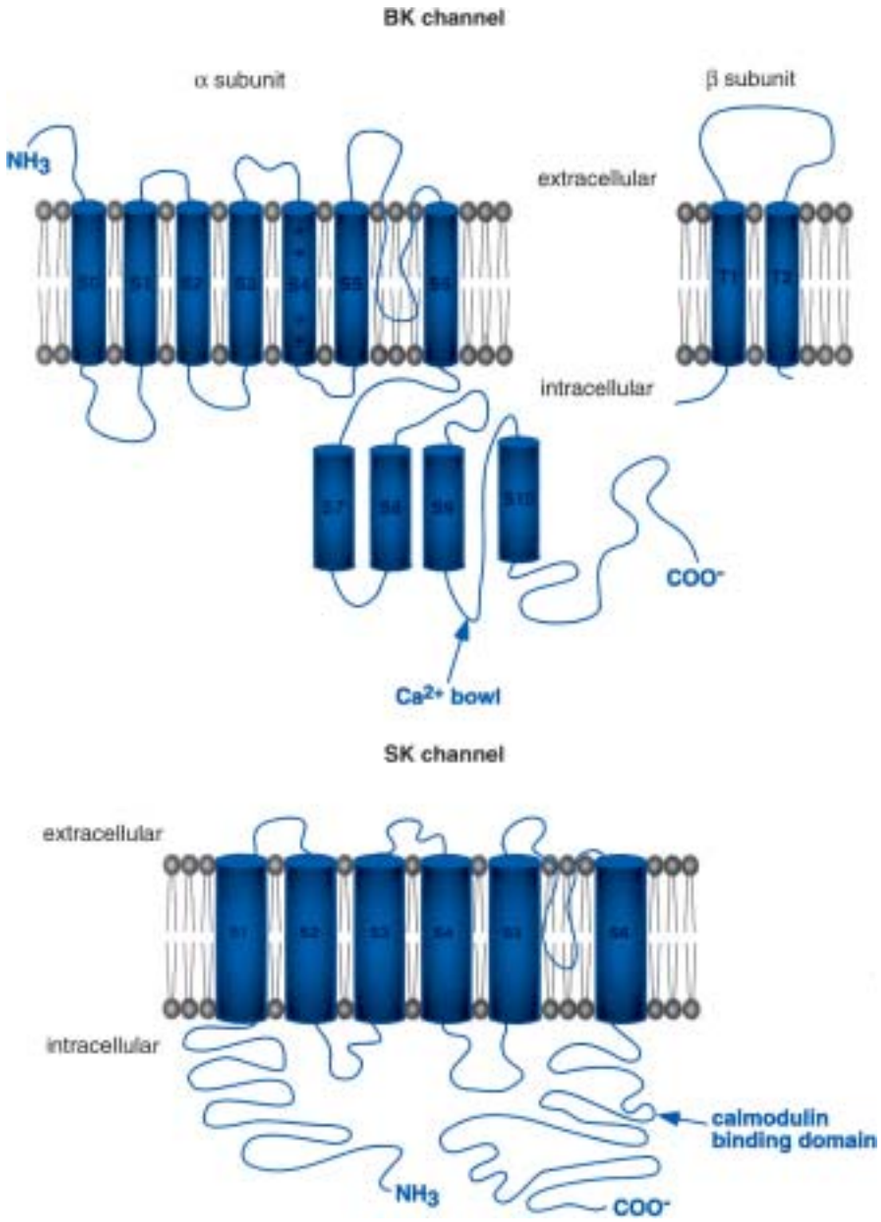

Fig. 1. Proposed structure of large conductance (BK) channels and small conductance (SK) calcium-activated potassium channels. BK channels are formed from alpha and beta subunits in a heteromeric complex. The alpha subunit, a single gene product, has six transmembrane domains (S1-S6). S4 contains positively charged residues that form the proposed voltage sensor. An additional four hydrophobic domains have been identified in the extended C-terminal of the alpha subunit. Beta subunits have two transmembrane domains. SK channels are encoded by four genes SK1 to SK3 that assemble as tetramers to form a calcium-activated potassium channel. SK channels have six transmembrane domains (S1-S6) and a P domain between S5 and S6, which forms the pore region. Both the N terminus and the C terminus are cytoplasmic. The C-terminus contains a site for covalent linkage to calmodulin that binds calcium ions and is the calcium sensor for activation of these channels.

clear that different calcium-activated potassium channels contribute to the three phases of the AHP.

Fast AHP

In many neurons, the fast AHP is mediated by the macroscopic current generated by activation of a calcium-activated potassium current, I_C (Adams and others 1982; Pennefather and others 1985). I_C is blocked by low concentrations of TEA, iberiotoxin, and paxilline, indicating that the underlying channels are BK-type channels (Adams and others 1982; Lancaster and Nicoll 1987; Shao and others 1999). Due to their voltage dependence (Adams and others 1982), BK channels activate rapidly during the upstroke of the action potential and then close rapidly following return of the membrane potential to negative values (Cui and others 1997), accounting for the rapid time course of the fast AHP. BK-type channels are modulated by protein kinase A (PKA)—both the probability of channel opening and the calcium and voltage sensitivity of the channel are modulated by phosphorylation. Levitan and collaborators have shown that the channel itself is the final target of phosphorylation by a closely associated protein kinase (Levitan 1994). Surprisingly, some types of BK-channel are up-regulated by PKA whereas other types are down-regulated. However, modulation of I_C has not been reported, and the functional effects of BK channel modulation in mammalian neurons, if any, are not known.

Consistent with its role in spike repolarization, blockade of I_C by TEA or paxilline slows action potential repolarization and reduces the fast AHP (Adams and others

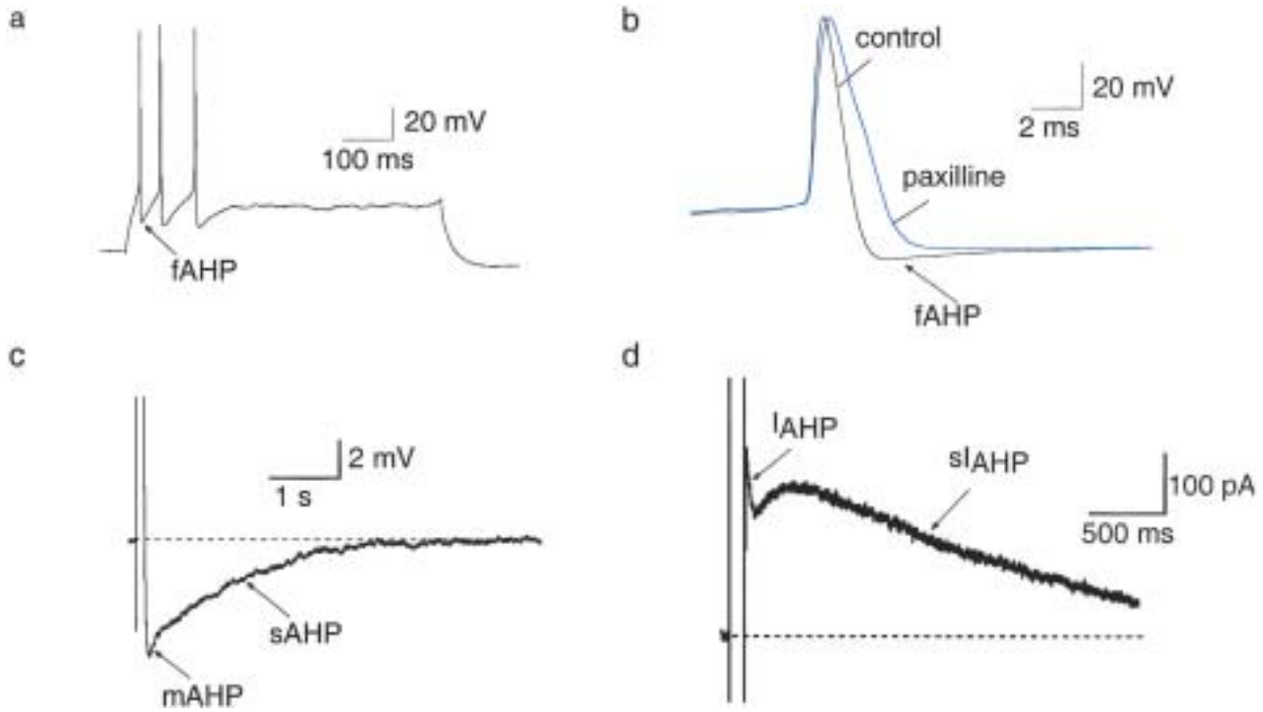

Fig. 2. Action potentials are followed by fast and slow afterhyperpolarizations (AHP). *a*, A prolonged (600 ms) depolarizing current injection evokes a train of action potentials that cease firing after three to four spikes, a phenomenon known as spike frequency adaptation. The fast AHP (fAHP) immediately follows single-action potentials (*b*) and lasts up to tens of milliseconds. The fAHP results from the activity of several potassium channels that contribute to action potential repolarization. BK channels are activated during action potentials and contribute to the repolarization phase of the spike. Blockade of BK channels by paxilline broadens the action potential. The medium AHP (mAHP) is mediated by activation of the I_{AHP} current (*d*) and lasts tens to hundreds of milliseconds. The slow AHP (sAHP) is mediated by activation of sI_{AHP} and lasts several seconds. The slow AHP has a slow time to peak as compared to the medium AHP (*d*).

1982; Lancaster and Nicoll 1987; Storm 1987; Sah 1992) (Fig. 2). However, in other cell types, such as amygdala pyramidal neurons, I_C is active during spike repolarization but does not contribute to the fast AHP (Faber and Sah 2002). As discussed above, some BK channels show marked inactivation. This inactivation of I_C has been shown to contribute to spike broadening during repetitive firing in hippocampal pyramidal neurons (Shao and others 1999). Such broadening is likely to have consequences on transmitter release at axon terminals. Accordingly, BK channels have been shown to be located presynaptically on glutamatergic terminals in the hippocampus where they can control transmitter release under some conditions (Hu and others 2001; Gu and Storm 2002). Moreover, in olfactory bulb granule neurons, a coupling of BK channels with NMDA receptors has recently been demonstrated (Isaacson and Murphy 2001). This co-localization is thought to occur extrasynaptically because the BK channels can only be activated by tetanic stimulation. These latter studies suggest a role for BK channels in acting as a brake in times of excessive calcium influx.

Medium AHP

SK channels mediate the medium AHP and the underlying current, I_{AHP} (Sah 1996). The medium AHP is voltage insensitive, is unaffected by BK channel blockers, but is blocked by apamin, indicating that it is due to the activation of SK-type channels (Pennefather and others 1985; Schwindt and others 1988; Sah and McLachlan 1991, 1992) (Figs. 2 and 3). I_{AHP} has a fast time to peak and decays with a time course dependent on the amount of calcium influx; as calcium load increases, peak amplitude increases and the current decay is slowed owing to saturation of local calcium buffers (Cassell and McLachlan 1987; Goh and Pennefather 1987; Sah 1992). Loading cells with low concentrations of the calcium chelator EGTA accelerates its decay (Sah 1992). These properties are due to the close anatomical proximity of N- or L-type voltage-gated calcium channels to SK channels (Viana and others 1993; Sah 1995a; Davies and others 1996; Marrion and Tavalin 1998; Bowden and others 2001). I_{AHP} was originally recorded from bullfrog sympathetic neurons (Pennefather and others 1985). A similar current has been termed gK_{Ca} in mammalian autonomic neurons (Cassell and McLachlan 1987; Sah and McLachlan 1991) and m-I_{AHP} in cortical neurons (Schwindt and others 1988).

Expression of SK1, SK2, and SK3 subunits as homo- or heteromultimers forms channels with properties similar to those of I_{AHP}. Thus, they are activated by rises in cytosolic calcium, are voltage independent and insensitive to low concentrations of TEA, and are blocked by

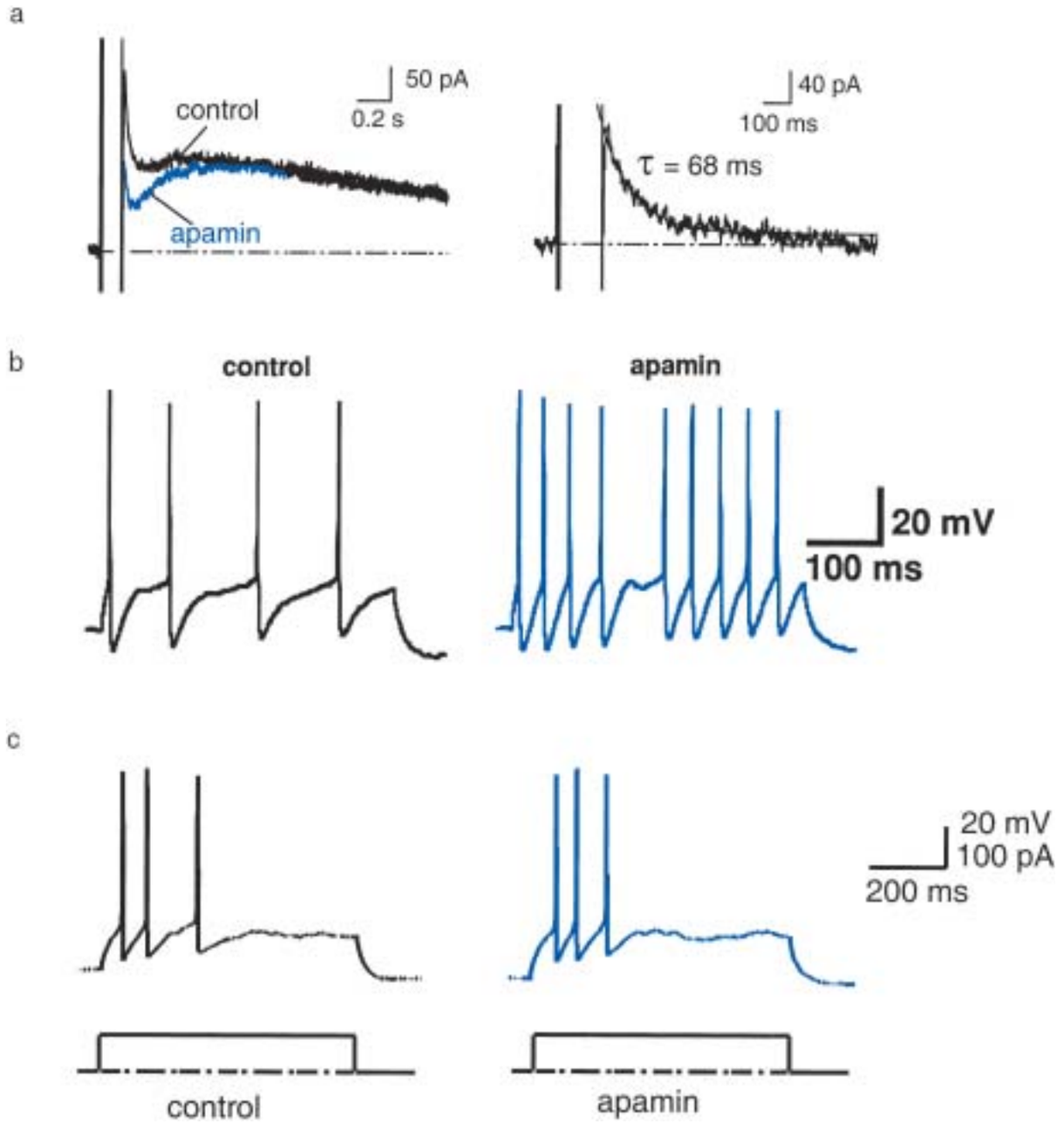

Fig. 3. Role of the apamin-sensitive medium AHP. *a*, Under voltage clamp, the currents underlying the medium and slow AHP are activated by a 100 ms depolarizing voltage step to 0 mV from a holding potential of –50 mV. The fast-activating I_{AHP} current is blocked by apamin (100 nM), whereas the sI_{AHP} is not. Digital subtraction of the traces before and after apamin reveal I_{AHP}, which has rapid inactivation kinetics (trace on *right*). *b*, In cells that express only I_{AHP}, activation of this current is a major contributor to the firing frequency of these cells. Recording from a neuron in the dorsal motor nucleus of the vagus. *c*, In other neurons (pyramidal neuron in the lateral amygdala), the sI_{AHP} dominates spike-frequency adaptation and the apamin-sensitive current (shown in *a*) has only minor effects.

apamin (see below). The distribution of SK channel subunits closely mirrors the distribution of I_{AHP} type currents (Stocker and Pedarzani 2000; Sailer and others 2002) (see below). Within the central nervous system, these channels appear to largely assemble as homomultimers (Sailer and others 2002). 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 (Pedarzani and others 2000), midbrain dopaminergic neurons (Wolfart and others 2001), and superior cervical ganglion neurons (Hosseini and others 2001).

In contrast to the fast AHP, the medium AHP does not contribute to action potential repolarization (Lancaster and Nicoll 1987; Storm 1990; Sah 1996) (Fig. 2). Cells that only express I_{AHP} fire tonically, and activation of I_{AHP} simply slows the maximal firing frequency (Engel and

others 1999) (Fig. 3). In contrast, in cells that express both the medium and slow AHP (see below), the medium AHP only controls the early interspike firing frequency (Stocker and others 1999; Pedarzani and others 2001; Stackman and others 2002). However, in amygdalar pyramidal neurons, although this current is also present, it does not appear to have any functional role in repetitive firing (Faber and Sah 2002) (Fig. 3). Recently, SK channels have been demonstrated to play a role in synaptic plasticity because blockade of SK channels with apamin shifted the threshold for induction of long-term potentiation and long-term depression in hippocampal neurons (see below) (Stackman and others 2002). Thus, the physiological role of this current in different cells needs to be independently evaluated.

Slow AHP

The current that underlies the slow AHP was first described in neurons of the myenteric plexus (Hirst and others 1985). Although in some neurons the slow AHP has been described following a single action potential (Hirst and others 1985; Sah and McLachlan 1991), it is more commonly seen following a train (4–10) of spikes (Lancaster and Nicoll 1987; Schwindt and others 1988; Faber and Sah 2002). Following calcium influx, this current has a time to peak of hundreds of milliseconds then decays to baseline with a time constant of 1–2 seconds at 30°C (Figs. 2 and 4). To distinguish it from I_{AHP}, this current has been designated sI_{AHP} (Sah 1996). As with I_{AHP}, sI_{AHP} requires a rise in cytosolic calcium for activation and is voltage insensitive. sI_{AHP} is not blocked by apamin or TEA. However, sI_{AHP} is modulated by a range of neurotransmitters, all of which block the current (Nicoll 1988) (Fig. 4). For the monoamines, the mechanism of this modulation is either by activation of protein kinase A (Pedarzani and Storm 1993; Torres and others 1996) or by inhibition of calcium-induced calcium release (Torres and others 1996). The second messenger pathways utilized by the other transmitters are as yet unknown, but acetylcholine has been suggested to act through activation of calcium calmodulin kinase II (Muller and others 1992; Pedarzani and Storm 1996). As with many other channels, the target for modulation appears to be the channel-opening probability, with both noradrenaline and acetylcholine lowering the probability for channel opening (Sah and Isaacson 1995).

The identity of the channels that underlie the sI_{AHP} remains a mystery. Direct recordings of these channels have not been successful; however, noise analysis indicates that their unitary conductance is in the range compatible with SK channels (Sah 1995b; Sah and Isaacson 1995; Valiante and others 1997). As SK2 and SK3 are both apamin sensitive, it seems unlikely that these subunits expressed alone could form sI_{AHP}. SK1 was initially reported to be apamin insensitive, and it has been suggested that these channels could underlie sI_{AHP} (Marrion and Tavalin 1998; Bowden and others 2001). However, this proposal has been challenged by others (Sah and Faber 2002).

Physiologically, the slow AHP is responsible for spike frequency adaptation in a number of neuronal cell types (Fig. 3). The presence of the slow AHP leads to a progressive slowing of the discharge frequency and eventual cessation of action potentials (Madison and Nicoll 1982; Sah 1996; Faber and Sah 2002). Modulation of the slow AHP by neurotransmitters (Nicoll 1988) dramatically changes the repetitive discharge properties of neurons that express sI_{AHP} (Fig. 4). Thus, the presence of sI_{AHP} allows for a greater level of control over the firing properties of neurons.

In the hippocampus, the slow AHP is also activated in response to synaptic activation of AMPA or NMDA receptors, and is capable of reducing the postsynaptic response to tetanic input (Sah and Bekkers 1996; Lancaster and others 2001). Furthermore, in lateral amygdala neurons, a slow calcium-activated potassium conductance has been shown to contribute to the inhibitory postsynaptic potential (IPSP) (Lang and Paré 1997; Danober and Pape 1998). In these studies, the AHP could be synaptically evoked by subthreshold stimuli. This suggests that the calcium influx through AMPA and NMDA receptors during the excitatory postsynaptic potential (EPSP) is sufficient to activate the channels and implies that the channels may be coupled to these receptors and located in dendritic spines in order to be activated by such elevations in intracellular calcium. Furthermore, in midbrain dopaminergic neurons, activation of metabotropic glutamate receptors has also been shown to activate apamin-sensitive SK channels by releasing calcium from intracellular stores (Fiorillo and Williams 1998). Thus, synaptic stimulation can activate SK channels by a variety of mechanisms.

Distribution of SK Channels

The distribution of SK channels has been mapped using both in situ hybridization (Kohler and others 1996; Stocker and others 1999; Stocker and Pedarzani 2000) and immunohistochemistry using antibodies against each of the three subunits (Bowden and others 2001; Sailer and others 2002). These studies show that the three SK channel subunits have restricted distributions. SK1 and SK2 subunits are expressed at highest density in the hippocampus and cortex, whereas SK3 subunits are expressed at highest levels in regions such as the hypothalamus, thalamus, and midbrain (Stocker and Pedarzani 2000). Within the hippocampal formation, there are also differences in expression levels between area CA1, CA3, and dentate gyrus (Sailer and others 2002). These distinct distributions largely match the presence of the apamin-sensitive I_{AHP} in these regions (Sailer and others 2002). Interestingly, all three subunits are also found expressed in the neuropil throughout the cortex and hippocampus (Sailer and others 2002), indicating that as for BK channels (Hu and others 2001), SK channels may also play a role in the control of synaptic transmission. In CA1 hippocampal pyramidal neurons, sI_{AHP} channels have been suggested to be located in the proximal apical (Sah and Bekkers 1996; Lancaster and

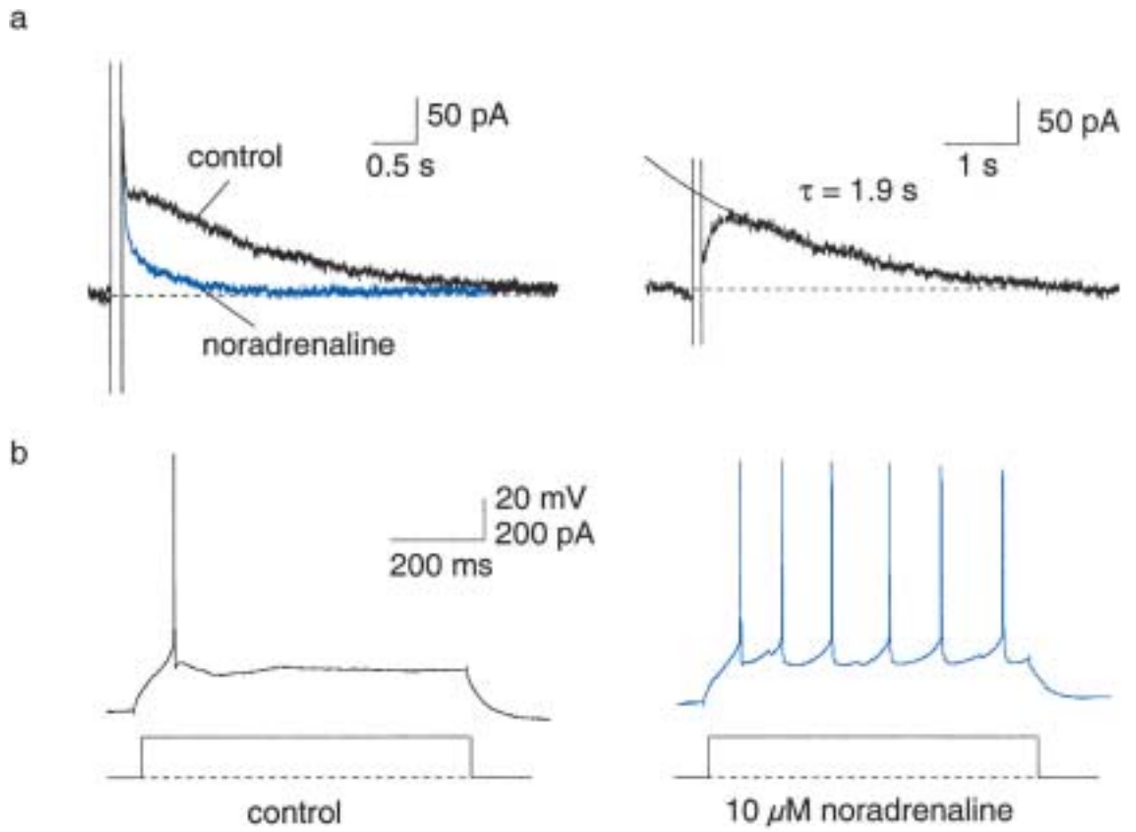

Fig. 4. Role of the slow apamin-insensitive AHP. *a*, Under voltage clamp, the currents underlying the medium and slow AHP are activated by a 100 ms depolarizing voltage step to 0 mV from a holding potential of –50 mV. Application of noradrenaline (10 μM) blocks sI_{AHP} leaving I_{AHP}. Digital subtraction of traces before and after application of noradrenaline reveals the kinetics of sI_{AHP}. This current has a slow rising phase and a slow decay. Physiologically, activation of the slow AHP contributes to spike-frequency adaptation (*b*).

others 2001) or basal (Bekkers 2000) dendrites where they play a role in the integration of synaptic inputs (see below).

Functional Roles

Learning and Memory

Due to its role in regulating both subthreshold and suprathreshold neuronal excitability, the AHP, and in particular the slow AHP, have been hypothesized to play a role in controlling the level of excitability of neurons and thus synaptic plasticity. As neuronal activity plays a key role in the processing of information within the central nervous system, it is perhaps not surprising that a number of recent studies have suggested that changes in both the medium and the slow AHP may be involved in aspects of learning and memory.

Medium AHP

Blockade of SK channels with apamin has been shown to facilitate learning in a number of behavioral paradigms (van der Staay and others 1999). Almost all of the studies have focused on hippocampus-dependent learning paradigms, have administered apamin interperitoneally, and have found that the effects of apamin are on the acquisition of the learning task but not consolidation. Only two studies found an effect of apamin on the consolidation of learning (Messier and others 1991; Belcadi-Abbassi and Destrade 1995). Blockade of SK channels by systemic administration of apamin in rats enhanced learning in an object recognition task (Deschaux and others 1997). Furthermore, apamin reversed a spatial navigation deficit induced by medial septum and hippocampus lesions in mice in the Morris water maze spatial memory task (Ikonen and others 1998; Ikonen and Riekkinen 1999) and improved the performance of intact mice in this task (van der Staay and others 1999). In accordance with these studies, apamin also induced the expression of immediate early genes c-fos and c-jun in the hippocampus, which are thought to be the initial markers for memory formation (Heurteaux and others 1993). In addition to these hippocampal-dependent tasks, apamin also enhanced learning in an appetitively motivated bar-pressing response in mice (Messier and others 1991; Belcadi-Abbassi and Destrade 1995). Furthermore, Fournier and others (2001) applied apamin intracerebroventricularly in an olfactory discrimination learning task and found that

apamin enhanced learning but not consolidation of this task. Finally, an enhancement of the medium AHP recorded in hippocampal neurons was observed following eye blink conditioning in rabbits (de Jonge and others 1990).

In keeping with the view that the cellular substrate for learning and memory is synaptic plasticity (Moser and others 1998), SK channels have been demonstrated to facilitate the induction of plasticity in hippocampal neurons (Behnisch and Reymann 1998; Norris and others 1998; Stackman and others 2002). This effect of apamin was correlated with an increased rate of learning in the presence in hippocampal-dependent spatial (Morris water maze) and nonspatial (object recognition) memory tasks (Stackman and others 2002). As with previous findings, in these experiments, apamin accelerated the rate of learning but had no effect on long-term retention of the memory.

Slow AHP

A number of studies have shown a reduction in the slow AHP in CA1 and CA3 hippocampal neurons in rabbits and rats in response to eye blink conditioning and Morris water maze tasks (Coulter and others 1989; de Jonge and others 1990; Moyer and others 1996; Thompson and others 1996; Oh and others 1999; Oh and others 2001). Both the duration and the amplitude of the slow AHP in hippocampal neurons is reduced following both hippocampus-dependent and -independent conditioning (Disterhoft and others 1986; Disterhoft and others 1988; Coulter and others 1989; Disterhoft and others 1996; Thompson and others 1996). This depression of the slow AHP is concurrent with a reduction in spike frequency adaptation (Coulter and others 1989; Moyer and others 1996; Thompson and others 1996). Similar reductions in the AHP were seen in the rat piriform cortex following conditioning using an olfactory discrimination task (Saar and others 1998). These studies suggest that reductions in the slow AHP are a general mechanism used to increase excitability during learning. As with the proposed role of the medium AHP in the induction but not consolidation of learning, changes in the slow AHP were transient and associated with the onset of learning but not the long-term retrieval (Moyer and others 1996; Thompson and others 1996; Saar and others 1998). This lends further support to the hypothesis that memories are learned in the hippocampus but stored elsewhere, possibly in the cortex (Moyer and others 1996; Thompson and others 1996).

In addition to the above studies, in vitro studies support the notion that the amplitude of the slow AHP is inversely related to the ability to learn, or for synapses to undergo plasticity. Thus, the dendritically located slow AHP in hippocampal CA1 pyramidal neurons is able to shunt synaptic potentials, thereby raising the threshold for synaptic plasticity (Sah and Bekkers 1996). Furthermore, there is a direct correlation between the degree of slow AHP suppression and the extent of induction of plasticity recorded in hippocampal neurons (Cohen and others 1999).

Aging

During aging, the threshold for synaptic plasticity is increased (Deupree and others 1993; Moore and others 1993; Disterhoft and others 1996; Rosenzweig and others 1997) and the performance of aged animals and humans in learning is impaired (Thompson and others 1996; Knuttinen and others 2001; Moyer and others 2000). Impairments in trace eye blink conditioning and the Morris water maze, both of which are hippocampus dependent, have been observed in aged rabbits, rats, and humans (Deyo and others 1989; Gallagher and others 1993; Rapp and Gallagher 1996; Thompson and others 1996; Knuttinen and others 2001; Wu and others 2002). Conversely, an enhancement of the slow AHP recorded in hippocampal neurons with age has been demonstrated (for review, see Pitler and Landfield 1990; Moyer and Disterhoft 1994; Campbell and others 1996; Disterhoft and others 1996; Thibault and Landfield 1996; Power and others 2002; Wu and others 2002). Furthermore, the slow AHP is reduced during learning in aged animals (Landfield and Pitler 1984; Moyer and others 2000). The enlarged slow AHP has been attributed, at least in part, to an increased influx of calcium through L-type voltage-gated calcium channels, allowing a greater activation of the underlying calcium-activated potassium channels (Landfield and Pitler 1984; Moyer and others 1992; Campbell and others 1996; Thibault and Landfield 1996; Norris and others 1998; Power and others 2002). Because the slow AHP is modulated by a number of neurotransmitters (see above), it has been proposed that alterations in these neurotransmitter systems may also underlie the changes in the slow AHP (Wu and others 2002). In accordance with this, drugs that depress the slow AHP, such as calcium channel blockers or cholinergic agonists, have been shown to be effective in improving learning in aged animals (Deyo and others 1989; Moyer and others 1992; Kronforst-Collins and others 1997; Oh and others 1999; Weiss and others 2000).

The consequence of the enhanced slow AHP is a decrease in excitability, with neurons from aged animals showing greater spike frequency adaptation compared with those from young animals (Moyer and others 1992; Oh and others 1999; Moyer and others 2000). These findings, correlated with the role of the slow AHP in learning (see above), suggest that the reduction in excitability of hippocampal neurons caused by the enhancement of the slow AHP is partly responsible for the reduction in age-related learning deficits. Enhancement of the medium AHP also appears to contribute to a reduced ability of hippocampal neurons from aged animals to undergo synaptic plasticity (Norris and others 1998), albeit to a lesser extent than the slow AHP (Power and others 2002; Wu and others 2002). Such deficiencies in learning and memory with aging may contribute to the symptoms of neurodegenerative diseases such as Alzheimer's disease (see below).

Disease

Recent reports have suggested that the medium and slow AHP may be important in Alzheimer's disease. An autoradiographic study showed that apamin binding sites are reduced in the hippocampus of brains from patients with Alzheimer's disease (Ikeda and others 1991). In addition, galantamine, an acetylcholinesterase inhibitor, has been shown to alleviate cognitive deficits in Alzheimer's disease patients, and a proposed mechanism of action is at least partly through inhibition of the slow AHP by an enhanced activation of muscarinic acetylcholine receptors (Wilkinson and Murray 2001; Wu and others 2002).

The slow AHP has been proposed to reduce excitability to prevent the onset of epilepsy in CA1 hippocampal neurons (Martin and others 2001). In this model, during the onset of the ictal state, enhancement of glutamate release by spontaneous EPSPs activates metabotropic glutamate receptors to depress the slow AHP. As the slow AHP plays a key role in neuronal excitability, its depression leads to increased excitability. Similarly, a synaptically evoked calcium-activated potassium conductance has been suggested to play a role in preventing the onset of epileptiform discharges in the amygdala (Danober and Pape 1998), a site of generation of temporal lobe epilepsy. Thus, calcium influx that occurs during strong excitation activates the slow AHP, which may act as a brake on the system to prevent overexcitation and the generation of epileptic-like activity (Danober and Pape 1998). This is in accordance with an in vivo study showing a reduced AHP during an epileptic state (Matsumoto and Ajmone-Marsan 1964). However, when measured directly in the rat piriform cortex, kindling did not cause any change in the AHP (Saar and others 1998). Thus, the precise contribution of the AHP to the prevention of epilepsy remains to be clarified.

A variety of mendelian genetic diseases are now known to be due to mutations in ion channels (Ashcroft 2000). The presence of polyglutamine repeat expansions is a newly recognized mechanism of disease that has been linked to a number of rare, late onset neurological diseases such as Huntington's disease and fragile X syndrome (Ashley and Warren 1995). Recently, a small conductance calcium-activated potassium channel gene (hSKCa3 or KCNN3), which codes for a channel with properties identical to SK channels, has been identified that has CAG repeats in its coding region (Chandy and others 1998). In genetic screens, the presence of trinucleotide repeats has been shown to be associated with schizophrenia and bipolar illness, suggestive of a possible link between SK channel function and these disorders (Gargus and others 1998; Dror and others 1999; Ritsner and others 2002).

Conclusions

Calcium-activated potassium channels form a diverse family of potassium channels that play important roles in the control of neuronal excitability and transmitter release. Some of these channels are the target for modulation of a number of transmitters. Of these channels, much is understood of the molecular structure and biophysical properties of one family of these channels, the BK channels. In contrast, the study of small conductance, SK channels is just beginning to reach a similar stage. In particular, little is known of the nature of the channels that underlie the macroscopic calcium-activated potassium currents. Mutations of these channels may underlie some neurological and psychiatric diseases. With the mapping of the human genome nearing completion, our understanding of these channels and their involvement in disease will no doubt improve in the future.

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