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What are the roles of the many different types of potassium channel expressed in cerebellar granule cells?

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Potassium (K) channels have a key role in the regulation of neuronal excitability. Over a hundred different subunits encoding distinct K channel subtypes have been identified so far. A major challenge is to relate these many different channel subunits to the functional K currents observed in native neurons. In this review, we have concentrated on cerebellar granule neurons (CGNs). We have considered each of the three principal super families of K channels in turn, namely, the six transmembrane domain, voltage-gated super family, the two transmembrane domain, inward-rectifier super family and the four transmembrane domain, leak channel super family. For each super family, we have identified the subunits that are expressed in CGNs and related the properties of these expressed channel subunits to the functional currents seen in electrophysiological recordings from these neurons. In some cases, there are strong molecular candidates for proteins underlying observed currents. In other cases the correlation is less clear. We show that at least 26 potassium channel α subunits are moderately or strongly expressed in CGNs. Nevertheless, a good empirical model of CGN function has been obtained with just six distinct K conductances. The transient K_A current in CGNs, seems due to expression of $K_V4.2$ channels or $K_V4.2/4.3$ heteromers, while the K_{Ca} current is due to expression of large-conductance slo channels. The G-protein activated K_{IR} current is probably due to heteromeric expression of $K_{IR}3.1$ and $K_{IR}3.2$. Perhaps $K_{IR}2.2$ subunits underlie the K_{IR} current when it is constitutively active. The leak conductance can be attributed to TASK-1 and or TASK-3 channels. With less certainty, the $I_{K\text{-}slow}$ current may be due to expression of one or more members of the KCNQ or EAG family. Lastly, the delayed-rectifier K_V current has as many as six different potential contributors from the extensive K_V family of α subunits. Since many of these subunits are highly regulated by neurotransmitters, physiological regulators and, often, auxiliary subunits, the resulting electrical properties of CGNs may be highly dynamic and subject to constant fine-tuning.

Keywords:
Potassium channels, cerebellar granule cells/neurons, K_v, K_{ir}, two pore domain K channels, weaver mice

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Introduction

Potassium (K) channels play an important role in a number of different aspects of the electrical responses of the nervous system. K channel activity determines neuronal action potential frequency, shapes the neuronal action potential waveform and controls the strength of synaptic contacts between neurons.[1] Furthermore, K channels have a role in setting (or contributing to) the neuronal resting membrane potential and in regulating the excitability of individual neurons. Since the first molecular cloning of K channel components in the late 1980s, well over a hundred different proteins—subunits of distinct types of K channels—have been identified and this number is still growing.[2] There are a number of good reviews that discuss particular aspects of K channels such as their structure, distribution and functional properties.[2–14]

A major focus of our work concerns the physiological role of K channels in the CNS. We concentrate, largely on the cerebellum. However, even simply to describe the localization and function of K channels in the cerebellum is a daunting task. In their authoritative 1999 review, Coetzee et al.[2] described the tissue expression of 35 different principal (α) K channel subunits in the cerebellum. Since then, the number has grown to well over 40. In this review, then, we will concentrate primarily on cerebellar granule neurons (CGNs). We will describe the K currents seen, physiologically in native granule cells and correlate these data with information available from localization and distribution studies of the many K channel subunits expressed in these cells. By combining this information and building as complete

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a picture as possible of the channels and currents present in CGNs, we hope to provide a description of how multiple functioning K channels act together to regulate the excitability of these important neurons. While interesting in their own right, CGNs are often considered to be model CNS neurons, perhaps because of their abundance and comparative ease of isolation and identification. So, in addition, the information provided should give some idea of the level of complexity of K channels in other neurons in the CNS.

Cerebellar granule cells

Granule cells of the cerebellum are small glutamatergic interneurons that are by far the most numerous cell type in the brain. It is estimated that they number somewhere between 10^{10} and 10^{11}.[15] CGNs receive inputs from mossy fibers or from the axons of brush cells.[16] Granule cell axonal projections form the parallel fibers of the cerebellum and terminate on the dendrites of Purkinje neurons. It has been estimated that a single Purkinje neuron can receive inputs from 80,000 CGNs. Golgi cells, stellate cells and basket cells also receive inputs from granule cell parallel fibers.

Because of their abundance and their many interactions with other cell types in the cerebellum, CGNs play an important transduction role in cerebellar function. This is exemplified in the *weaver* mutation in mice (probably a mutation of an inward-rectifier K channel, K_{IR} 3.2; see below) where most CGNs fail to differentiate and then die, causing severe disruption of the cerebellar network and severe motor dysfunction.[17,18] In normal, mature, CGNs, firing is most often fast and repetitive,[19] but theta-frequency spike bursting can also be observed, which may play an important role in determining synchronization, rhythmicity and learning in the cerebellum.[20] Both the complement and the activity of granule cell potassium channels will profoundly determine the firing properties of these cells.

Potassium channel superfamilies

From the sequences of known potassium channel α subunits, it is clear that three major superfamilies of K channels can be delineated (Figure 1). They are the six transmembrane domain channels which are voltage- and/or calcium-gated; the two transmembrane domain inward-rectifiers and the four transmembrane, two-pore domain leak potassium channels.

The six transmembrane domain super family is made up of a number of different families, such as the voltage-gated K_V family of channels ($K_V1.x$ – $K_V9.x$) which are thought to underlie voltage-gated delayed-rectifier and A-type K channels. KCNQ and EAG channels are also in this super family. These are low-threshold voltage-gated currents which are G-protein regulated and which often have a non-inactivating component open near the resting membrane potential of the cell. Functionally, in neurons, these channels underlie currents such as the M current. Finally in this super family are the slo and SK families of K channel which underlie functionally observed calcium-activated K currents. The two transmembrane domain super family of inward-rectifier K channels (K_{IR} 1.x – 7.x) underlie strong inward-rectifier currents, inward-rectifier currents activated by G-protein coupled receptors and, together with sulphonylurea receptors, ATP-sensitive K channels. The more recently described four transmembrane, two-pore domain K channels (such as TWIK-1, TASK-1 and TREK-1) are thought to underlie leak currents open at all potentials and are expressed heterologously throughout the CNS.

Six transmembrane domain K channels

Functional studies of voltage-gated K currents

In functional studies, the voltage-gated K current of mature CGNs is usually divided, quite straightforwardly, into two components: a transient component (or A-type current) which activates then inactivates rapidly

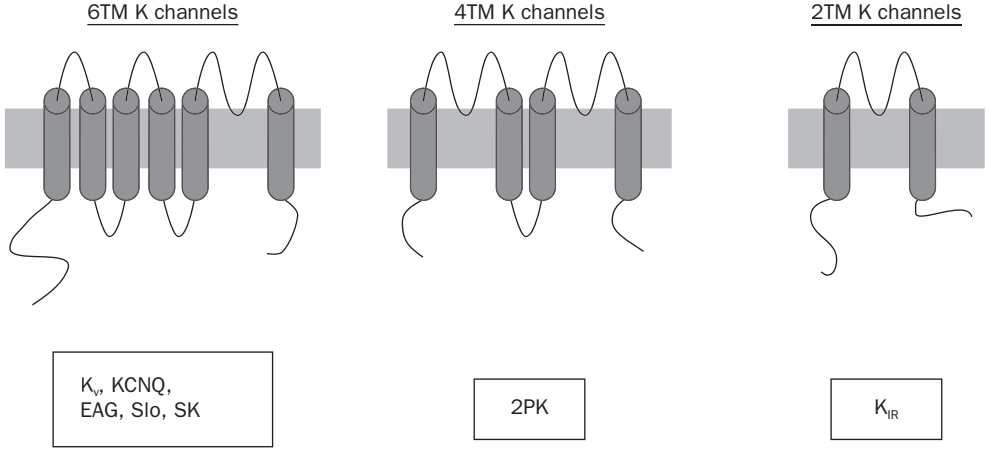

Figure 1
Potassium channel superfamilies.

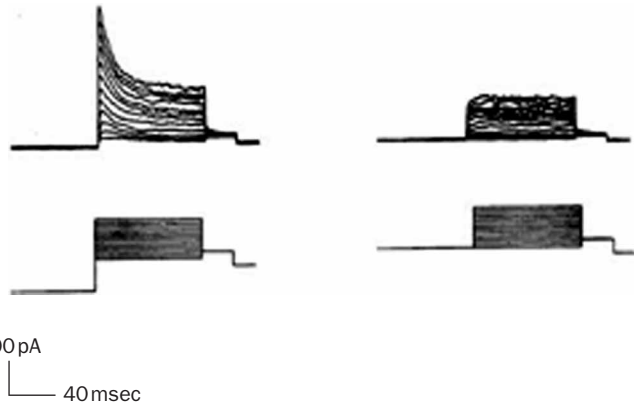

Figure 2
K_V and K_A currents in rat cerebellar granule cells. Currents were evoked by progressive 10 mV depolarizing steps for 85 ms from a holding potential of –70 mV following a 250 ms prepulse to either –140 mV (left hand side) or –50 mV (right hand side). The currents on the left-hand side following a hyperpolarizing prepulse have both a transient and a sustained component while those on the right-hand side following a depolarizing prepulse have only a sustained component.

following depolarization and a sustained current (or delayed-rectifier) which shows little inactivation over the time course of a normal depolarizing voltage step (see Figure 2).

These two components of voltage-gated outward current have been well characterized by a number of different groups since their first description in the late 1980s, using whole-cell voltage clamp recording methods from both CGNs in tissue culture and acutely isolated cells in cerebellar slices.[21–29]

The sustained current activates with a time constant of about 10 ms at test potentials more depolarized than around −50 mV and shows no inactivation over a period of at least 150 ms.[23,26] It is moderately susceptible to block by tetraethylammonium ions (TEA), being blocked by around 60% by 5 mM TEA,[27] 82% by 10 mM TEA[30] and completely blocked by 20 mM TEA.[23,26] The sustained current, in some instances, can be further separated into a calcium-independent component and a calcium-dependent component[23] (also see below).

Removal of inactivation of the transient current, I_A, by use of a hyperpolarizing prepulse, followed by step depolarizations to potentials positive to −60 mV, reveals a current that peaks in 1–2 ms then inactivates with a time constant of around 10 ms.[23] This current is comparatively insensitive to TEA. 4-Aminopyridine (4-AP, 1–5 mM) reduces both the transient and sustained component of current[23,27] consistent with its lack of selectivity between most members of the K_V family.[2,10]

K_V channel distribution

In a simple world, CGNs would express two K_V channel subunits, one with the characteristics of the sustained component of current and the other with the characteristics of the transient current. Unfortunately, the true picture is considerably more complicated. α-subunits from each of the four major classes of K_V channels (K_V1.x – K_V4.x) are strongly expressed in CGNs (Table 1).

K_V1 channels

CGNs have been shown to have strong immunoreactivity for K_V1.1, 1.3, 1.5 & 1.6 channels.[31] In the absence of accessory subunits, all four of these clones give functional currents that resemble delayed-rectifer type, slow-inactivating currents. Chung et al.[31] also found low immunoreactivity for K_V1.2 and no staining for K_V1.4. These results correlate reasonably well with earlier labeling studies (see Table 1 and refs 32–35), however earlier studies have found no labeling for K_V1.6 in CGNs.[32,36,37] In a separate study, good K_V1.1 staining was seen in cell bodies of adult granule cells, however expressed channel numbers were seen to decline in aged rats.[38] This study, again, found much weaker labeling for K_V1.2 in granule cell bodies and that this didn't change with age. It is of interest that in other regions of the cerebellum, notably basket cell termini there is strong expression of K_V1.2 channel subunits.[39,40] This suggests a role of these subunits in the regulation of transmitter release, functioning either as homomers or even heteromers with other K_V1 subunits.

The K_V1 family is often associated with regulatory β subunits which alter their functional properties from those expected of homomer channels. For example, K_Vβ3.1 is highly expressed in cerebellum and converts K_V1.5 from a non-inactivating delayed-rectifier type current to an inactivating current.[41] Similarly K_V1.1 and K_Vβ1 are expressed in CGNs.[35,42] Again K_Vβ1 is known to convert K_V1.1 from a non-inactivating to an inactivating current if the two subunits are co-expressed.[43] It is worth noting however that CGNs express both K_Vβ1 and K_Vβ2 at comparatively low levels compared with other regions of the brain.[44] The labelling for K_Vβ1 is much less intense than that seen in Purkinje cells.[45]

Mutations in K_V1.1 channels give rise to episodic ataxia (or familial periodic cerebellar ataxia, a dominantly inherited human cerebellar disease) and to myokymia syndrome. These are associated with non-functional or malfunctioning K_V1.1 channels[46,47] perhaps because of the normal role of this subunit in regulating granule cell excitability. K_V1.1 subunits are often expressed at synaptic terminals and dendrites and such a distribution is also seen in CGNs. A reduction in K_V1.1 channel activity will lead, therefore, to a prolongation of action potential duration.

K_V2 channels

K_V2.1 and K_V2.2 channels have distinct non-overlapping distributions in the mammalian brain. Both channels, when expressed as homomers, give rise to

Table 1
Expression of K_V channel α subunits in cerebellar granule cells

Channel	Synonym	Species	Age	RNA/protein	Level	References
$K_V1.1$	RCK1	rat mouse	P7/ adult	RNA/protein	moderate/ abundant	31, 32, 34, 35, 38, 39 (but see 37)
$K_V1.2$	RCK5	rat mouse	young/ adult	RNA/protein	low	31, 32, 33, 34, 38, 39, 145
$K_V1.3$	RCK3	rat	adult	RNA/protein	moderate	31, 32, 34
$K_V1.4$	RCK4	rat	adult	RNA/protein	none	31, 32
$K_V1.5$	RCK7	rat	adult	RNA/protein	moderate	31, 32
$K_V1.6$	RCK2	rat	adult	RNA/protein	none	32, 36, 37 (but see 31)
$K_V2.1$	DRK1	rat	adult	RNA	low	32, 36, 48
$K_V2.2$	CDRK	rat	adult	RNA	abundant	48
$K_V3.1$	Raw2	rat mouse	adult	RNA/protein	abundant	32, 36, 50, 51, 55
$K_V3.2$	Raw1	rat	adult	RNA	low	32
$K_V3.3$		mouse	adult	RNA	none	50, 144
$K_V3.4$	Raw3	rat	adult	RNA/protein	low	32, 34
$K_V4.1$		rat	adult	RNA	none	57
$K_V4.2$		rat mouse	P3–P10/ adult	RNA	highly abundant	32, 53, 56, 57
$K_V4.3$		rat	adult	RNA	abundant	56, 57
$K_V5.1$	IK8	rat	adult	RNA	none	36, 37
$K_V6.1$	K13	rat	adult	RNA	moderate/ abundant	36, 37
$K_V8.1$		rat hamster	adult	RNA	abundant	60, 61
$K_V9.1$		mouse	adult	RNA	abundant	63 (see also 64)
$K_V9.2$		mouse	adult	RNA	abundant	63
$K_V9.3$		mouse	adult	RNA	in brain	64

Note: see text for information on KCNQ, EAG, slo and SK channel α-subunit expression in CGNs.

delayed-rectifier currents with slow inactivation and moderate sensitivity to block by TEA. $K_V2.2$ expression is high in CGNs[48] while low levels of $K_V2.1$ are seen.[32,36,48] Expression levels of $K_V2.2$ can be enhanced up to six-fold by $mK_V\beta4$ with no change in channel properties. $mK_V\beta4$ is also expressed in CGNs.[49] Interestingly $K_V5.1$, 6.1, 6.2, 8.1, 9.1, 9.2, & 9.3 give no functional currents in expression systems but can form heteromers with $K_V2.x$ channels changing their properties[2] (see below).

K_V3 channels

$K_V3.1$ channels are expressed in the somata of CGNs, along the entire length of their axons (the parallel fibers) and in presynaptic boutons, however there is low or no expression in dendrites and glomeruli.[32,36,50–53] In cerebellar slices, application of TEA at a concentration that preferentially blocks $K_V3.1$ channels resulted in parallel fiber action potential broadening and an increase in excitatory post-synaptic currents at granule cell–Purkinje cell synapses.[54] Expression of the $K_V3.3b$ channel is highly enriched in the brain, particularly in the cerebellum, where its expression is confined to Purkinje cells and deep cerebellar nuclei with little expression in CGNs. There are also detectable levels of $K_V3.2$ and 3.4 found in CGNs.[32,34] Expressed K_V3 channels have extremely rapid kinetics of activation and deactivation and a high threshold of activation (more positive than –20 mV). The deactivation of K_V3 channels is at least ten-fold faster than all K_V1 channels. As a result, K_V3 channels are thought to underlie the fast after-hyperpolarization required for high frequency firing. They are highly sensitive to block by TEA.[10]

$K_V3.1$ and $K_V3.3$ knock-out animals exist, which on their own show little phenotype.[55] However, severe ataxia is seen when both channels are mutated in the same animals. This is thought to result from a combination of a lack of $K_V3.1$ in CGNs and a lack of $K_V3.3$ in Purkinje cells.[55] Surprisingly, there is no gross alteration in cerebellar morphology associated with the double mutant.

K_V4 channels

CGNs express $K_V4.2$ and 4.3 but not $K_V4.1$ channels.[32,36,53,56,57] Both $K_V4.2$ and 4.3 give rise to transient A-type potassium conductances in expression systems. A number of studies have suggested that K_V4 subunits are the major component of transient I_A currents in the mammalian CNS.[56,57] K_V4 channels can be regulated by a family of K channel interacting proteins (KChIPs[58]). These act to increase total K_V4 current, accelerate recovery from inactivation and moderately slow inactivation. They are calcium-binding proteins some of which (KChIP1 and KChIP3) are predominantly expressed in neurons. Another member of this family KChIP4a, acts to remove inactivation of K_V4 currents.[59] Both KChIP1 and KChIP4a are expressed in CGNs[59] and can act in combination to modify K_V4 channel properties.

K_V5-9 subunits

There are several K_V subunits ($K_V5.1$, 6.1, 6.2, 8.1, 9.1, 9.2 and 9.3) that do not form functional channels when expressed on their own but do seem to form heteromers with $K_V2.x$ channels giving them different functional properties from homomeric $K_V2.x$ channels.[2]

In CGNs, the more important of these subunits seem to be $K_V8.1$, $K_V9.1$ and $K_V9.2$. $K_V8.1$ is known to be present in the granule cell layer of the cerebellum.[60,61] At high levels of expression it abolishes the function of other K_V channels ($K_V2.1$, 2.2 and 3.4) via association with these subunits through its N terminal domain. At lower levels it modifies the activity of $K_V2.1$ and 2.2. The major effect of the co-expression of $K_V8.1$ with $K_V2.2$ in COS cells concerns the inactivation process. The voltage-dependence of $K_V2.2$ is shifted toward negative potentials, and its rate of inactivation is considerably slowed down. Clearly then, any $K_V2.2/K_V8.1$ heteromers present in CGNs would have kinetic properties different from $K_V2.2$ homomers.[62]

There are also high levels of $K_V9.1$ and 9.2 expression in cerebellar granule cells.[63] $K_V9.1$ and 9.2 cause minimal changes in inactivation of $K_V2.2$ channels but reduce the current amplitude and shift the voltage-dependence of inactivation of the channel to more negative values. $K_V9.3$ channels are expressed in the CNS, but their expression levels and functional importance in CGNs is not known.[64]

$K_V5.1$, $K_V6.1$ and $K_V6.2$ are known to regulate $K_V2.1$ functional properties.[63,65] However, $K_V5.1$ is not expressed in the cerebellum to any degree.[36,37] $K_V6.1$ is highly expressed in CGNs[36,37] but the presence or absence of $K_V6.2$ and the functional importance of $K_V6.1$ remains to be established.

Correlation of functional currents and expressed K_V subunits

Considering homomers of the primary subunits alone, a plausible case can be made for seven different voltage-gated K_V channels (1.1, 1.3, 1.5, 2.2, 3.1, 4.2 and 4.3) as being major contributors to the whole-cell voltage-gated K current in CGNs. If heteromers can be formed, or if regulatory subunits have a prominent role, the situation is even more complicated. How can we reconcile these data with the two primary components of current, transient and sustained, observed in functional studies from CGNs?

The best correlative evidence currently available concerns the transient component of current. Shibata et al.[35] have constructed dominant negative cDNA for the $K_V4.2$ subunit. When this is expressed in CGNs it results in a large reduction in A current in these cells. This provides strong evidence that the native A current is carried through $K_V4.2$ channels, however an interaction with $K_V4.3$ channels cannot be ruled out. The functional properties of $K_V4.2$ channels in expression systems are broadly similar (but not identical) to those seen of native A currents in the CGNs.[26,35] Such differences may be accounted for by the multiple regulatory actions of KChIPs on K_V4 channels in CGNs.[59] Nevertheless, either $K_V4.3$ homomeric channels or heteromers of $K_V4.2$ and 4.3 channels may contribute to the A current. $K_V1.4$ subunits which give A currents in expression systems, are not expressed in CGNs, however co-expression of $K_V1.1$[35] with $K_V\beta1$[42] could give rise to a functional A current in CGNs as could co-expression of $K_V\beta3.1$ with $K_V1.5$ (see above). Any of these possibilities could explain the residual 25% of transient current seen in CGNs treated with dominant negative $K_V4.2$.[35]

The delayed-rectifier component is much more difficult to assign to a particular K_V subunit. Since loss of either $K_V1.1$ or 3.1 in CGNs can lead to the generation of episodic ataxia, this would suggest that both these subunits may be functionally important. The whole-cell granule cell sustained current, however, is much less sensitive to block by TEA (60% at 5 mM) when compared with $K_V1.1$ and K_V3 channels which have, respectively, IC_{50}s for block of 0.5 and around 0.2 mM. By contrast, $K_V1.3$ and 1.5 are rather too insensitive to TEA block to be candidates for the sustained current. This leaves $K_V1.6$ and $K_V2.2$, which have IC_{50}s of around 2–7 mM and 8 mM respectively for TEA block.[2,10] This criterion, taken together with the distribution studies (Table 1 and above), would suggest that $K_V2.2$ is the most likely candidate to underlie the sustained voltage-gated current in CGNs since there is some doubt as to whether $K_V1.6$ is expressed.

Of course the whole-cell sustained current in CGNs may easily comprise of more than one expressed α subunit. Furthermore, the existence of splice variants and the potential formation of heteromers between different α subunits or between α and β subunits adds complexity. All K_V channels have consensus sequence sites for serine/threonine phosphorylation, while at least some can be phosphorylated on tyrosine residues (see for example refs 66, 67). These phosphorylation events

can markedly alter channel properties (see ref. 10), which would make identification even more difficult. Finally, it is likely that different K_V channels are expressed in different regions of CGNs. For example, K_V1.1 and 3.1 expression may be predominantly localized to presynaptic terminals and parallel fibers.

EAG and KCNQ channels

The EAG and KCNQ family of K channels encode voltage-gated potassium channels that are open close to the resting membrane potential of neurons.[2,12,13] Both EAG currents and KCNQ currents can be inhibited following the activation of certain G-protein coupled receptors such as muscarinic acetylcholine receptors.

EAG family

The different members of the EAG family of K channels have quite distinct kinetic and pharmacological properties when studied in expression systems.[12] They can be divided into three subfamilies (eag 1–2; elk 1–3 (eag-like) and erg 1–3 (eag-related)) on the basis of their distinct structural and functional properties. One noticeable feature, however, is that all eight known members of the EAG family give a large component of non-inactivating current near the membrane potential.[68] Interestingly, like K_V channels, they may form heteromers within subfamilies.

In situ hybridization studies in CGNs reveals very high levels of eag1, but no detectable eag2; moderate levels of erg1 but no erg2 or erg3; and moderate to high levels of elk2, but no elk1 or elk3.[68,69] Interestingly then, there is no overlap of expression of members of the same EAG subfamily in CGNs, therefore there is probably no heteromer formation between different EAG channel subunits.

In general, roles for EAG potassium channels in the mammalian CNS remain to be found.[68] However Hoshi et al.[70] have suggested that the non-inactivating current, IK_{SO}, seen in CGNs (ref. 71 and below) may be due to co-expression of eag1 with a novel auxiliary subunit KCR1 (see also refs 72, 73).

KCNQ family

KCNQ channels in neurons are also thought to encode for non-inactivating voltage-gated currents with a low threshold for activation. For example, KCNQ2/KCNQ3 heteromers have been suggested to underlie M currents in a number of different neurons.[13,74] Each of these KCNQ subunits when expressed alone results in much less M-like current than when the two are co-expressed.[74] Saganich et al.[68] showed very high levels of KCNQ2 expression, yet no or very little KCNQ3 expression in CGNs (see also ref. 75). In many neurons expression of KCNQ2 and KCNQ3 overlaps, so it is surprising that this does not seem to occur in CGNs. There is little expression of KCNQ1 channels in the brain,[2] while little or no KCNQ4 or KCNQ5 expression is detected in CGNs.[76–78] So KCNQ2 is the only detectable KCNQ subunit identified so far in CGNs.

A recent study has shown that CGNs in cerebellar slices possess a novel slow K conductance, which in many respects resembles the M current seen in other neurons (see Figure 3). This current was resistant to 4-AP (4 mM) and TEA (20 mM) but reduced by external Ba^{2+} or internal Cs^+ ions.[20] It is possible that this current results from the expression of KCNQ2 and/or one or more of the EAG family of subunits expressed in CGNs.

Ca-activated K channels

Ca-activated K channels can be divided into three broad groups. The large conductance maxi-K channels (or BK channels) corresponding to the slo family of K channels subunits; the small-conductance or SK channels (corresponding to SK1-3) and the intermediate conductance K channels which probably correspond to SK4 (also referred to as $IK_{Ca}1$) channels.

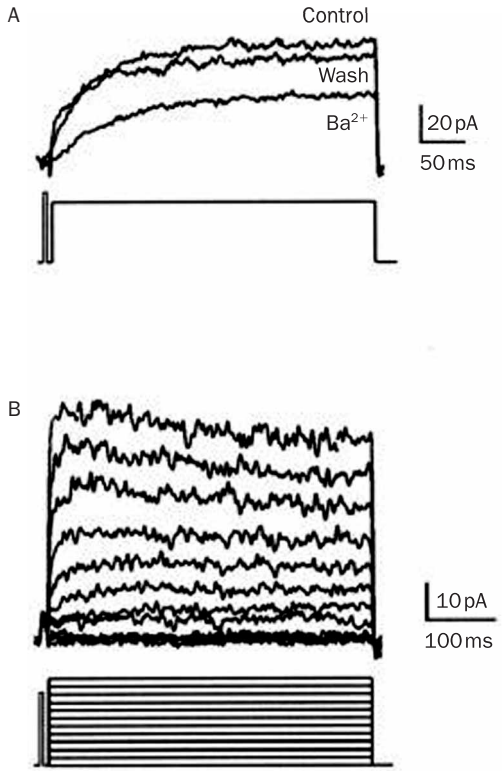

Figure 3
A slow outward K current ($I_{K\text{-slow}}$) in cerebellar granule cells. (A) $I_{K\text{-slow}}$ was generated by a step from –80 mV to +30 mV in the presence of 20 mM TEA and 4 mM 4-AP. It was reversibly inhibited by Ba^{2+} (1 mM). (B) Activation of $I_{K\text{-slow}}$ by a series of 1 sec, 10 mV depolarizing steps from –80 mV. Adapted from D'Angelo et al. (2001), ref. 20, with permission. Copyright 2001, the Society for Neuroscience.

BK/slo channels

Functional studies in CGNs have shown the presence of a Ca-activated K conductance. Originally this was seen in single-channel recordings where a large conductance channel was observed with a single channel conductance of 110–185pS.[79] This would suggest that the channel is a member of the BK class of Ca-activated K channels. BK channels in CGNs are activated following metabotropic glutamate receptor activation[79] via ryanodine receptors coupled to L-type Ca channels.[80] A corresponding calcium-dependent whole-cell K current has been observed in granule cells in cerebellar slices[26] and it is believed that BK channels participate in granule cell repolarization following an action potential.[20] BK channels may also stabilize repetitive firing by enhancing fast after hyperpolarizing potential and Na channel de-inactivation.[20]

It is generally envisaged that such BK channels result from expression of a member of the slo family of K channel subunits.[81,82] However expression levels of slo are rather low in CGNs when compared with other regions of the brain, including cerebellar Purkinje cells.[83–85]

SK channels

There are only moderate levels of SK2 expression in CGNs, while no SK1 or SK3 could be detected by *in situ* hybridization.[86] SK4 (or $IK_{Ca}1$) channels are thought to be predominantly expressed in non-excitable tissue.[87] Furthermore, there is no effect of apamin on whole-cell K currents in CGNs, which suggests that SK channels may not have a major functional role in these cells.[20]

Two Transmembrane Domain K channels

Inward-rectifier currents in granule cells

A G-protein activated inwardly-rectifying K current is evident from studies in cultured CGNs from mouse.[88–92] The current is activated by GTP-γ-S, baclofen, somatostatin and trans-APCD and blocked by Ba^{2+}, Cs^{+} and treatment with *pertussis* toxin. A study in mouse CGNs *in situ* showed that the inward-rectifier current changed its properties through the time-course of cell development[93] (see Figure 4). The majority of cells in the internal granule cell layer, 10–15 days after birth, displayed only a G-protein activated inwardly-rectifying current similar to that seen in the cultured cells. However, a constitutively active inward current was observed in the remainder of cells. CGNs at a more advanced developmental stage, 20–21 days after birth, displayed, for the most part, this latter current. Both currents share similar pharmacological properties, but they exhibit different biophysical characteristics. The G-protein activated current displays mostly fast activation with no inactivation. The fast activation appears almost voltage-independent and instantaneous, similar to observations in cultured CGNs.[88,89] Meanwhile, the constitutively active current has slower activation and a steeper voltage-dependence. Note, also, that there is no evidence for any I_h—like current in cerebellar granule cells.[20]

Distribution and localization of K_{IR} subunits

In terms of the G-protein activated $K_{IR}3$ channels, a variety of different methods have revealed the presence of $K_{IR}3.1$, 3.2 and 3.3 subunits and lower levels of $K_{IR}3.4$ subunits in CGNs of both rat and mouse[94–100] (see Table 2). Co-immunoprecipitation studies show direct physical association of $K_{IR}3.1$ and $K_{IR}3.2$ in COS cells[101] and mouse brain tissue[95] suggesting that they exist and function as heteromers.

There are high levels of the strong inward-rectifier $K_{IR}2.2$ in CGNs but no detectable levels of $K_{IR}2.3$ or 2.4 subunits[96,102,103] (see Table 2). It is not clear from the literature whether $K_{IR}2.1$ subunits are present in CGNs.[96,102] For ATP-sensitive K channels, *in situ* hybridization also reveals weak mRNA signal for $K_{IR}6.2$ (but no detectable $K_{IR}6.1$) and low levels of its associated subunit SUR1 in CGNs.[104,105]

A number of K_{IR} channel subunits ($K_{IR}1.1$, 4.1, 4.2 and 7.1) are not expressed in CNS neurons.[97] Furthermore, $K_{IR}5.1$, although expressed in the CNS, cannot function as a homomeric channel, as it seems to only form functional heteromers with $K_{IR}4.1$ or 4.2.[106]

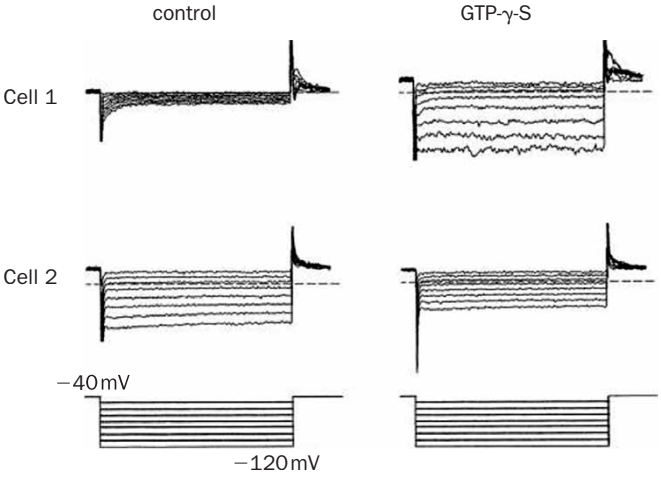

Figure 4
K_{IR} currents in mouse cerebellar granule cells. Recordings were performed with patch pipettes containing GTP-γ-S. Traces were taken at the beginning (control) and 6 min (GTP-γ-S) after the beginning of the recordings. The voltage-clamp protocol is illustrated at the bottom. Cell 1 was recorded at P12 and is an immature postmigratory neuron. It has no constitutively active current but has an inward-rectifier current activated by GTP-γ-S. Cell 2 was recorded at P22 and is a mature postmigratory neuron. It has a constitutively active inward-rectifier current which is not enhanced further by GTP-γ-S. Adapted from Rossi et al. (1998), ref. 93, with permission. Copyright 1998, the Society for Neuroscience.

Table 2.
Expression of K_{IR} channel α subunits in cerebellar granule cells

Channel	Synonym	Species	Age	RNA/protein	Level	References
$K_{IR}1.1$	ROMK	rat		RNA	not in brain	97
$K_{IR}2.1$	IRK1	rat mouse	adult	RNA/protein	low	96, 99 (but see 102)
$K_{IR}2.2$	IRK2	rat mouse	P21-adult	RNA	abundant	96, 102
$K_{IR}2.3$	IRK3	rat mouse	E13-adult	RNA	none	96, 102
$K_{IR}2.4$	IRK4	rat	adult	RNA	none	103
$K_{IR}3.1$	GIRK1	rat mouse	E15-adult	RNA/protein	moderate	95, 96, 97, 99 (but see 146)
$K_{IR}3.2$	GIRK2	rat mouse	E13-adult	RNA/protein	abundant	94, 95, 96, 97, 98 100, 146
$K_{IR}3.3$	GIRK3	rat mouse	E15-adult	RNA	abundant	96, 97, 146
$K_{IR}3.4$	GIRK4	rat	adult	RNA/protein	none	96, 100
$K_{IR}4.1$	BIR10	rat		RNA	not in brain	97
$K_{IR}4.2$		rat		RNA	not in brain	97
$K_{IR}5.1$	BIR9	rat		RNA	low in brain	97 (see 106)
$K_{IR}6.1$	uKATP-1	rat	adult	RNA/protein	none	105
$K_{IR}6.2$	BIR IKATP	rat mouse	adult	RNA	low	104
$K_{IR}7.1$		rat		RNA	not in brain	97

Functional properties of K_{IR} subunits

$K_{IR}3.2$ homomultimers in *Xenopus* oocytes display G-protein activated, K selective currents which are enhanced by carbachol, acetylcholine and Gβγ[88,101,107] $K_{IR}3.1$ homomers in *Xenopus* oocytes produce similar currents but with slower activation kinetics.[107] Currents elicited by the presence of both $K_{IR}3.1$ and $K_{IR}3.2$ are also enhanced by G-protein coupled receptor activation.[101] They exhibit slow kinetics, attributed to the presence of $K_{IR}3.1$.[107] Similar currents are obtained by engineered $K_{IR}3.1/K_{IR}3.2$ dimers.[107] It is thought likely that, *in vivo*, these channels form as heteromers.

Correlation of the channel subtypes present with functional properties

The activation of the inwardly-rectifying currents by GTP-γ-S and various $GABA_B$ and muscarinic agonists in CGNs, identify it as composed of $K_{IR}3.x$ channels. The slower activation in response to hyperpolarization suggests the presence of the $K_{IR}3.1$ subunit. Considered together with the distribution and localization studies and the *weaver* mutation below, it is most likely that the dominant inward-rectifier K current in CGNs is due to the expression of $K_{IR}3.1$ and $K_{IR}3.2$ heteromers. There may also be a contribution of $K_{IR}3.3$ subunits. The developmental change from G-protein activated to constitutive, as well as from generally fast to slower activation kinetics in CGNs *in situ* is not understood. It may be that $K_{IR}2.2$ channels underlie the constitutively active current, since CGNs express this subunit in abundance (Table 2). At present, no information is available on developmental expression of $K_{IR}2.2$.

The *weaver* mutation

The *weaver* mutation of mouse (*wv*) arose spontaneously in C7BL/6 mice over 30 years ago and was identified by, and named after, its instability of gait. Homozygous (*wv*/*wv*) mice exhibit mild locomotor hyperactivity, male sterility, and severe ataxia within two weeks of birth. The cerebellum is smaller in size with the loss of CGNs occurring within one week of birth. Rakic & Sidman[17] observed that *wv* granule cell precursors are normal at birth, but display defects through differentiation. They fail to extend neurites or migrate along glial fibres to form bipolar processes.

The *wv* gene was mapped to mouse chromosome 16, a region associated with Down's Syndrome in humans,[108] and sequencing revealed a missense mutation in a region coding for $K_{IR}3.2$.[18] The mutation, G156S (nucleotide G935A), resides in the 'H5' or 'p' region that is highly conserved amongst K channels and structurally forms the selectivity filter of the channel.[109] The gene is autosomal recessive,[107] and heterozygous mice (*wv*/+) show milder abnormalities than homozy-

gous ones. However, it should be noted that $K_{IR}3.2$ knock-out mice (−/−), whilst still more susceptible to induced seizures than wild-type (WT), remain morphologically similar to WT and exhibit milder cerebellar abnormalities than *wv*. This would suggest that the *wv* phenotype may not simply be due to the loss of functional $K_{IR}3.2$ channels.

wv$K_{IR}3.2$ channels expressed in cell lines display altered currents to WT$K_{IR}3.2$ (see Figure 5). The cells themselves, whether CHO cells or *Xenopus* oocytes, show decreased survival.[101] The currents become constitutively active and non-selective for K^+.[88,101,107] Differing results have emerged from studies on cultured CGNs. Some studies observe a basal, non-selective current that depolarizes the cell's resting potential,[88,107] analogous to the constitutively active current observed in *wv*$K_{IR}3.2$-containing channels in oocytes. This current can be blocked by the cation channel blockers MK-801 and QX-314, which are also able to enhance cell viability and neurite outgrowth.[88] However, other studies reveal a profound reduction in G-protein activated currents[107] or no inwardly-rectifying currents with or without G-protein activation.[91,92] Slices of *wv* mouse cerebellum display altered architecture with no discernible internal granule cell layer. In slices, pre-migratory *wv*CGNs do not exhibit any G-protein activated inward-rectifier currents. Putative CGNs that have escaped degeneration express a constitutively active inwardly-rectifying current with reduced selectivity to K that is blocked by QX-314. The kinetics are slower, compatible with *wv*$K_{IR}3.1$ homomultimers. However there is no net increase in leakage current.[93]

With such a variety of results and no explanation for the differences, no clear hypothesis of mechanism emerges. However, the dominant effect is of a depolarized granule cell resting potential, whether this occurs by a gain of basal Na conductance or a loss of agonist-activated K conductance. This could lead to cell death or failure to drive cell differentiation and motility via the activation of voltage-gated Ca^{2+} channels and NMDA receptors. Alternatively *wv*$K_{IR}3.2$ may act less directly, altering the expression of other genes or the mutation in $K_{IR}3.2$ may be merely closely associated with the *wv* gene and be a coincidental finding.[92]

Four transmembrane domain/two-pore domain K channels

Leak currents in granule cells

CGNs possess a non-inactivating outward potassium current that is active at all membrane potentials. This current, termed IK_{SO} (for standing-outward current), which has a major role in regulating the excitability of these cells, is openly rectifying and is inhibited by the activation of muscarinic acetylcholine receptors[71,110,111] (see Figure 6). IK_{SO} is insensitive to the classical K channel blockers tetraethylammonium and 4-aminopyridine, but can be blocked by Ba^{2+}, small extracellular acidification[112] and the endocannabinoid, anandamide.[113] It is enhanced by the volatile anaesthetic agent halothane.[113] Inhibition of this current by muscarinic receptor activation or extracellular acidification increases granule cell excitability[71,112] (see Figure 7). CGNs have also been shown to possess a background K channel that can be activated by arachidonic acid and other polyunsaturated fatty acids.[114] Activation of this current by arachidonic acid reduces granule cell excitability.[114]

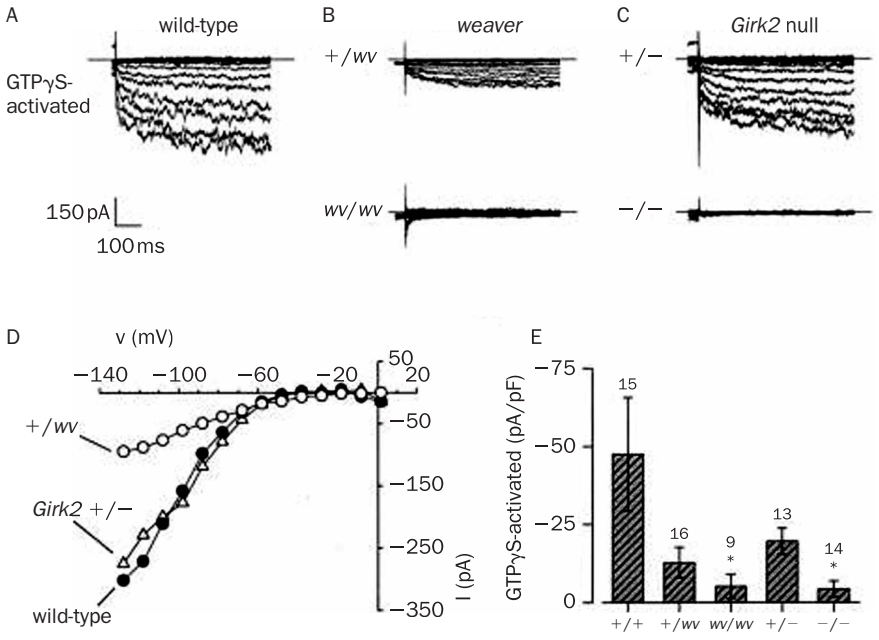

Figure 5
Reduction of K_{IR} currents in mouse cerebellar granule cells from *weaver* mice. Examples of GTP-γ-S-activated currents recorded from wild-type (A), *weaver* (B), and Girk2 null (C) mutant mice are shown. GTP-γ-S-activated currents are markedly reduced in granule cells isolated from *weaver* and Girk2 null mutant mice. Currents were elicited by voltage steps from 130 to +10 mV from a holding potential of 0 mV. The GTP-γ-S-activated current was obtained by subtracting the current recorded at the beginning of the whole-cell recording from the current recorded after GTP-γ-S activation. (D) Current-voltage plots show the strong rectification for +/+, +/−, and +/*wv* granule cells. (E) Bar graph shows the mean amplitude of the GTP-γ-S-activated currents divided by the cell capacitance for +/+, +/*wv*, *wv*/*wv*, +/−, and −/− granule cells. Adapted from Slesinger et al. (1997), ref. 90, with permission. Copyright 1997, the National Academy of Sciences (USA).

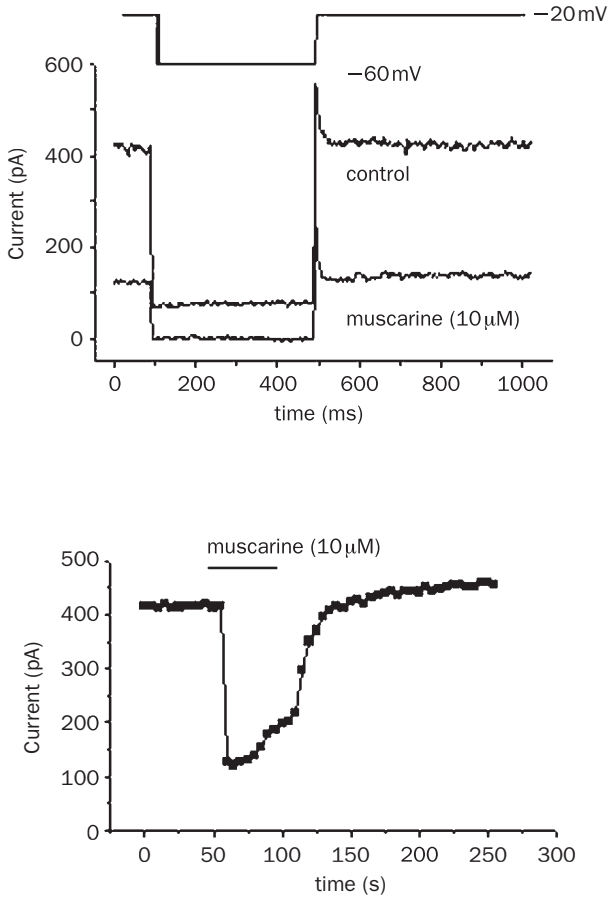

Figure 6
Muscarinic ACh receptor activation inhibits IK_{SO}. Granule cells were held at –20 mV and stepped to –60 mV for 400 ms. This protocol was repeated once every 5 seconds. The upper panel shows currents recorded in the absence and presence of muscarine (10 μM). The time course for muscarinic inhibition of IK_{SO} is shown in the lower panel. IK_{SO} was measured at -20 mV after the CGNs had been at this potential for 4.6 seconds. Adapted from Boyd & Mathie (2002), ref. 110.

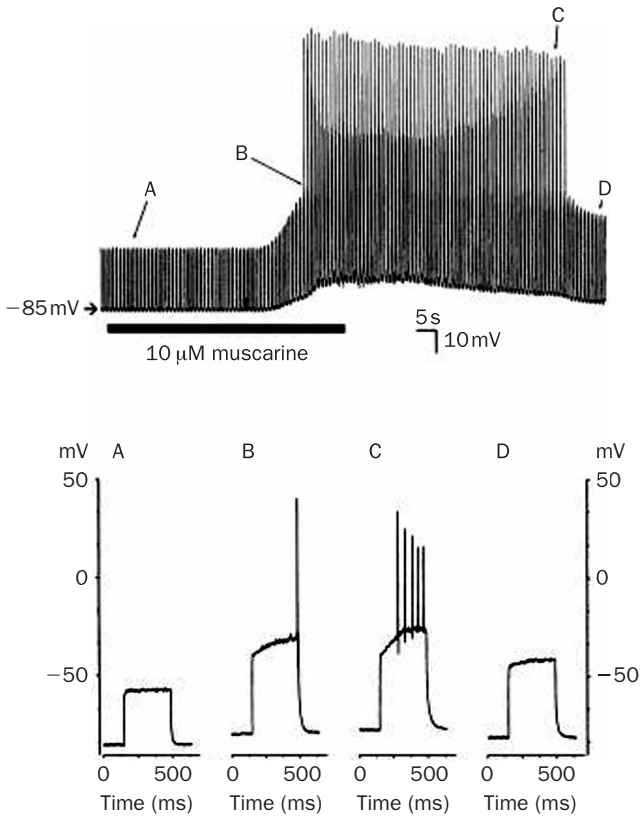

Figure 7
IK_{SO} blockade increases granule cell excitability. In current clamp recording, injection of 100 pA of current depolarized the cerebellar granule cell but did not evoke action-potential firing (A). Application of 10 μM muscarine blocked IK_{SO} and increased granule cell excitability such that the same amount of current injection now depolarized the cell sufficiently to evoke action-potential firing (B, C). Adapted from Watkins & Mathie (1996), ref. 71.

Two pore domain potassium channels and localization in CGNs

Recently a group of K selective pore-forming subunits with four transmembrane domains and two pore domains per subunit have been discovered. Named two pore domain potassium (2PK) channels, due to this unique feature, it is these channels that are thought to underlie the "leak" potassium currents that have been recorded in CGNs. To date, 14 members of the mammalian 2PK family have been described.[14,115,116] These subunits are thought to form together as dimers to provide the four P domains required to produce a functional channel.[14] They can be grouped, loosely, into a number of different classes on the basis of structural and functional properties. TWIK-1 (*t*andem of P domains in a *w*eak-*i*nward-rectifier *K* channel) was the first to be cloned[117] and all subsequent channels have been named in relation to this one. A separate nomenclature refers to this channel as KCNK-1.[14]

TWIK-1 and TWIK-2[118,119] as their names suggest, are thought to be weak inward-rectifier K channels but there is some doubt about whether they can form functional channels independently of auxiliary subunits (e.g. ref. 14). A number of 2PK channels have been shown to be sensitive to small acidifications of the external solution and have been termed *T*WIK-related *a*cid-*s*ensitive *K* channels (TASK). TASK-1, 3 & 5 have rather different structural and functional characterstics to TASK-2 and TASK-4.[120–129] Closely related to TASK-2 are the *T*WIK-related *al*kaline pH activated *K* channels (TALK-1 and TALK-2) with TALK-2 being identical to TASK-4.[130] In addition, *T*WIK *re*lated *K* channels (TREK-1 and TREK-2) and the *T*WIK-*r*elated *a*rachidonic *a*cid sensitive *K* channel (TRAAK) are potentiated by arachidonic acid, volatile anaesthetics, heat and mechanical stress.[116,131–133] *T*andem pore domain *h*alothane *i*nhibited *K* channels (THIK-1 and THIK-2) have been cloned[134] and a background current in mouse cerebellar Purkinje cells with many properties in common with this family of 2PK channels has recently been described.[135] Finally, a 2PK clone, KCNK-7 does

not form functional channels when heterologously expressed alone or in combination.[136] THIK-2 and TASK-5 have also proved to be non-functional so far.

No fewer than seven of these subunits have been found in CGNs (see Table 3). High levels of TASK-1, TASK-3, TREK-2, TWIK-1[128,137–139] and THIK-2[134] were found, whilst lower, but measurable levels of TREK-1, TRAAK[137,140,141] were also seen. The TREK-2 isoform in CGNs has very recently been shown to be TREK-2c.[141] In addition, TWIK-2 and KCNK-7 subunits are expressed in the cerebellum.[119,138]

The molecular identity of leak currents in CGNs

All of the functional properties of IK_{SO} correlate well with those of the 2PK channel TASK-1. Both IK_{SO} currents and currents through TASK-1 channels in expression systems are open rectifiers which are insensitive to TEA and 4-AP, blocked by Ba^{2+}, muscarinic receptor activation, anandamide and external acidification, enhanced by halothane and not enhanced by arachidonic acid. This has led to the suggestion that TASK-1 channels underlie IK_{SO}.[112,113,139] However, it is extremely difficult to distinguish the functional properties of TASK-1 channels from those of the more recently cloned TASK-3 channels at the whole-cell level, so it is possible either that TASK-3 currents contribute to IK_{SO}[142] or that heterodimers could be formed between TASK-1 and TASK-3.[143] Similarly, the arachidonic acid enhanced current in CGNs has been attributed to TREK-1 channels[114] but recent expression studies might suggest a more likely correlate is the TREK-2c channel which is highly expressed in CGNs.[141]

Conclusion

A surprisingly large number of K channels are expressed in CGNs (and, it seems likely, every other neuron in the brain too). More precisely, there is evidence for strong or moderate expression levels of at least 26 K channel α subunits: $K_V1.1$, $K_V1.3$, $K_V1.5$, $K_V2.2$, $K_V3.1$, $K_V4.2$, $K_V4.3$, $K_V6.1$, $K_V8.1$, $K_V9.1$, $K_V9.2$, eag1, erg1, elk2, KCNQ2, slo, SK2, $K_{IR}2.2$, $K_{IR}3.1$, $K_{IR}3.2$, $K_{IR}3.3$, TASK-1, TASK-3, TREK-2c, THIK-2 and TWIK-1. Furthermore, there is evidence for detectable levels of expression of a number of other α subunits while several regulatory β subunits are also expressed. It is not at all clear why CGNs need so many different K channels.

If we consider granule cells from a functional perspective, D'Angelo et al.[20] have shown that it is quite possible to obtain a good empirical model of CGN function through the use of only five distinct K conductances, a leak conductance, three Na conductances and a Ca conductance. The five K conductances are a delayed rectifier conductance (K_V), a transient A-type conductance (K_A), a Ca-activated conductance (K_{Ca}) an inward-rectifier conductance (K_{IR}) and a slowly activating conduc-

Table 3
Expression of 2PK channel subunits in cerebellar granule cells

Channel	Synonym	Species	Age	RNA/protein	Level	References
TASK-1	KCNK-3	rat human	P7/ adult	RNA/protein	moderate/ abundant	112, 128, 137 139, 147, 148
TASK-2	KCNK-5	human	adult	RNA	none in cerebellum	138 (but see 149)
TASK-3	KCNK-9 KT3.2	rat	adult	RNA	abundant	127, 128, 137 139
TASK-4	KCNK-17 TALK-2	human	adult	RNA	not in brain	130
TASK-5	KT3.3	rat	adult	RNA	none	128
TALK-1	KCNK-16	human	adult		not in brain	130
TREK-1	KCNK-2	rat human	adult	RNA	low	137, 140, 141
TREK-2	KCNK-10	rat	adult	RNA	abundant	137, 141
TRAAK	KCNK-4	rat	adult	RNA	low	137
TWIK-1	KCNK-1	rat	adult	RNA	abundant	137, 139
TWIK-2	KCNK-6	human	adult	RNA	low in cerebellum	119, 138
KCNK-7		human	adult	RNA	abundant in cerebellum	138
THIK-1	KCNK-13	rat	adult	RNA	none	134
THIK-2	KCNK-12	rat	adult	RNA	abundant	134

tance (K_{slow}). There is also a requirement for a leak conductance (I_{leak}). In fast repetitive firing mode, K_V and K_{Ca} account for most of the active K current during the spike and fast AHP. K_A, K_{IR} and K_{slow} are active during the interspike interval, K_A acting to delay spike activation. Bursting behaviour is revealed when K_{Ca} is reduced (such as by TEA) or by G-protein coupled receptor action.

As we have shown above, in some cases, it is possible to make a good correlation between a functional current and an expressed channel. The transient K_A current for example, seems to be predominantly due to $K_V4.2$ channels or $K_V4.2/4.3$ heteromers, while the K_{Ca} current is likely due to expression of large-conductance slo channels. Similarly the G-protein activated K_{IR} current is probably due to heteromeric expression of $K_{IR}3.1$ and $K_{IR}3.2$, while the constitutively active component of K_{IR} may be due to $K_{IR}2.2$ expression. The leak conductance can be attributed to TASK-1 and/or TASK-3 channels. With less certainty, the K_{slow} current identified by D'Angelo et al.[20] may result from the expression of KCNQ2 and/or one or more of the EAG family of channels, however a possible small contribution of KCNQ3 or KCNQ5 channels cannot be ignored. The delayed-rectifier, K_V current is least well accounted for with five or more possible K_V subunits as potential contributors.

Measuring the whole-cell CGN current may well be important in determining granule cell excitability, but at the level of individual dendrites or release sites, CGNs may tailor the complement of K channel subunits present to suit particular roles. For example, the biophysical properties of $K_V1.1$ and $K_V3.1$ channels may be best suited to regulating transmitter release from granule cell terminals,[2] while TASK-1/TASK-3 channels on the soma may fundamentally control granule cell excitability. The function of all these K channels can be regulated by co-expression of regulatory subunits (e.g. $K_V2.2$ with $K_V8.1$ or $K_V1.1$ with $K_V\beta1$), by the action of neurotransmitters such as acetylcholine (e.g. $K_{IR}3.1/3.2$, TASK-1/TASK-3, eag1) or by other physiological regulators. Therefore the complement of functioning K channels determining the electrical properties of granule cells at any given moment may be highly dynamic and subject to constant fine-tuning.

Acknowledgements

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