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POTASSIUM CHANNELS IN NERVOUS TISSUE

JEFFREY K. ARONSON

MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, U.K.

Abstract—There is a multiplicity of potassium channels in nervous tissue. These have been characterized on the basis of their electrophysiological actions but more information is required on their structures and on the functions of the different subtypes of channel in different parts of the nervous system. We currently also lack drugs which are specific in opening or closing individual subtypes of channel. However, when more is known about the structure and function of these channels and when more specific modulators of their activity are available, it is likely that the use of such compounds may be of great value in the treatment of a variety of conditions affecting the nervous system, including epilepsy, the damage due to cerebral anoxia, neurodegenerative disorders and demyelinating disorders.

The propagation of an impulse along a nerve fibre is initiated by depolarization, a change in the resting potential of the cell from negative to positive. This is followed by repolarization, a return to a resting negative potential, in preparation for the next depolarization. There may also be hyperpolarization, a return to a potential slightly lower than the resting negative potential. Since the observation of Hodgkin and Huxley [1] it has been known that potassium currents are responsible for the repolarization of the action potential in neurones. However, it is only recently that specific types of potassium channel associated with potassium currents have been identified in nervous and other tissues and their enormous diversity demonstrated.

For the most part these channels permit the efflux of potassium from within the cell. They therefore lead to the outward flux of positive charge, and this either tends to oppose depolarization or causes repolarization or hyperpolarization. Unusually, there are some potassium channels which operate in the opposite direction.

CLASSIFICATION OF POTASSIUM CHANNELS

There is no satisfactory classification of potassium channels. Satisfactory pharmacological classification is obviated by a dearth of compounds which act specifically at individual subtypes of potassium channel, although there is no shortage of compounds which act with greater or lesser specificity at a variety of channels. The best current classification is therefore based on the electrophysiological characterization of the properties of potassium channels. The classification I shall present here is based on classifications which have been presented elsewhere, notably by Rudy [2] and by Halliwell [3].

In this classification there are five different types of potssium channel: voltage-activated; calcium-activated; ligand-activated; ATP-activated and others (sodium-activated; volume-activated and a flux which is characterized currently as "leak").

The symbols I shall use to designate these channels are those of Halliwell [3]. In these symbols the letter "I" refers to current and the subscripts have a variety of disparate origins. For example, the subscript "K(V)" in the symbol used to designate the delayed rectifier current, $I_{K(V)}$, stands for potassium (voltage-activated); in contrast, the "A" in the symbol for the fast, transient current designated I_A stands for Aplysia, the organism in which it was first identified.

Voltage-activated potassium channels

Voltage-activated potassium currents in nervous tissue are of at least five different types.

The delayed rectifier current ($I_{K(V)}$). This current is activated by depolarization, albeit with some delay (in the order of hundreds of milliseconds). It acts to repolarize the cell and therefore influences the duration of the action potential. It may also affect the duration of the refractory period.

The fast transient potassium current (I_A). This current activates in response to depolarization, but much more rapidly than the delayed rectifier does (in under 20 msec in most species). As this current is inactivated very rapidly during depolarization it operates mainly at around the negative voltages present in resting cells; it may therefore function to control the rate at which neurons depolarize. It may also be responsible for the transient hyperpolarization which sometimes occurs after repolarization.

The fast slowly-inactivating current (I_D). This is a current which is also activated rapidly (within milliseconds) but which takes much longer to inactivate. It functions to delay the onset of the action potential.

The M current (I_M). This current is so called because it was first identified in muscarinic neurones. It is activated slowly (over about 200 msec) but is not inactivated and may provide a background of current opposing depolarization.

The inward rectifier currents (also known as anomalous rectifiers) ($I_{f.i.r.}$ and I_Q). There are at least two different types of inward rectifier channel. These mediate inward potassium currents rather than outward currents, as the others do. They are activated by hyperpolarization at voltages around the resting potential of most cells and they may be involved in maintaining the plateau of the action potential and in controlling the duration of hyperpolarization after repolarization.

Calcium-activated currents

The calcium-activated currents have been classified into three types. These are the so-called high-conductance, medium-conductance and low-conductance currents, also known as BK (big K), IK (intermediate K) and SK (small K) (symbolically $I_{K(Ca)f}$, $I_{K(Ca)m}$ and $I_{K(Ca)s}$, respectively, where f, m, and s stand for fast, medium and slow). These potassium currents are responsible for the repolarization of the cell and may also contribute to the after hyperpolarizations which occur when repolarization is complete.

Ligand-activated currents

The ligand-activated potassium currents are those which respond to a wide variety of neurotransmitter ligands, including noradrenaline (at α_2 receptors), acetylcholine (at M_2 receptors), dopamine (at D_2 receptors), 5-hydroxytryptamine (at 5-HT_{1a} receptors), opiates (at μ receptors) and GABA (at $GABA_B$ receptors). These channels may be activated either by a direct interaction of subunits of the receptors with the channel or via a second messenger (for reviews see Refs 4 and 5). It is currently believed that second messenger activity linked to these potassium channels is mediated via the action of a G-protein (either G_i or G_o). However, there is also evidence that activation of these channels may be mediated via stimulation of the arachidonic acid cascade by a phospholipase which may in turn act directly on the channel via a protein kinase or through some action on a G-protein.

ATP-activated potassium currents

These have been identified in pancreatic β cells, and the presence of sulphonylurea binding sites in the brain suggests that such channels may exist there too, since the sulphonylureas bind to the ATP-activated channels in the pancreas and inhibit their action. However there is also evidence that there may be sulphonylurea binding sites in the brain which are not linked to ATP. It is not clear what the functions of these channels are in neuronal tissue.

Other types of potassium channel

Other types of potassium channel in nervous tissue have not been well characterized. Channels which are thought to be sodium-activated have been identified on the basis of inhibition by tetrodotoxin and volume-activated channels have also been observed. A residual leak may prove to consist of other as yet unidentified types of potassium channel.

Although this classification is of help in distinguishing varieties of potassium channels, it is unsatisfactory for several reasons. Firstly, it describes the electrophysiological phenomena of the potassium channels without describing their functions. Secondly, it gives no insight into the roles of the different channels in different parts of the nervous system. For example, 5-HT decreases potassium conductance in myenteric neurones but increases it in the hippocampus (see Ref. 6). Thirdly, there is much overlap among the different subsections of the classification. For example, the calcium-activated potassium currents have been classified as such simply because they are inhibited by calcium antagonists; however, the large conductance calcium-activated channels, for example, are also voltage-activated. Similarly, the ligand-activated channels have been classified as such because of their responses to neurotransmitter ligands; however, the M current, which is sensitive to the actions of muscarinic agonists, is not so classified, being regarded as a voltage-activated current.

It is likely that when the structures of these channels are better understood a more useful classification will emerge. However, any useful classification will have to be linked to the functions of the channels in different parts of the nervous system, about which little is currently understood.

INHIBITORS OF POTASSIUM CHANNELS

The voltage-activated channels are inhibited by either tetraethylamonium (TEA*) or 4-aminopyridine. TEA affects predominantly the delayed rectifier current, the M current and the inward rectifier current, while 4-aminopyridine affects predominantly the fast transient and fast slowly-inactivating currents. However, there are other substances which are effective in inhibiting these currents. For example, tetrahydroacridine inhibits the fast transient current and barium and caesium are effective on several of the voltage-activated currents. Certain toxins which are derived from mambas (dendrotoxin from the *Dendroaspis angusticeps* and toxin I from the *Dendroaspis polylepis*) inhibit the delayed rectifier and fast transient currents (see Ref. 7). However, the actions of these toxins on fast transient currents in different species and different neurones within the same species show that there must be further subtypes of this type of current, at least based on pharmacological differences.

The calcium-activated potassium currents are inhibitable by calcium antagonists but some are also inhibitable by TEA, by quinine (which also inhibits some of the voltage-activated currents) and by toxins such as charybdotoxin, from the venom of the scorpion *Leiurus quinquestriatus*, and apamin, from the venom of the honey bee *Apis mellifera*.

The ligand-activated potassium currents, because of their action through G-proteins, are inhibitable by analogues of GDP and GTP; they are also inhibitable by tetrahydroacridine and the toxin derived from the bacterium *Bordetella pertussis*.

The ATP-activated channels are in general inhibited by the sulphonylureas, such as glibenclamide [8], although, as mentioned above, there may be sulphonylurea binding sites in the brain which are not related to ATP-activated channels [9].

In addition to the toxins mentioned above there are other toxins which inhibit different potassium channels. For example, noxiustoxin from the venom of a scorpion, *Centruroides noxius*, inhibits the delayed rectifier current and the large-conductance

* Abbreviation: TEA, tetraethylammonium.

calcium-activated currents. Capsaicin, the constituent which makes peppers taste hot, inhibits fast-activating potassium currents. Bungarotoxin from the snake *Bungarus multicinctus* inhibits a voltage-activated current which is also sensitive to dendrotoxin.

DIVERSITY OF POTASSIUM CHANNELS

There is enormous diversity among potassium channels, the sources of which have been studied mainly in *Drosophila*. From these studies, several of the mechanisms which contribute to this diversity have been identified. These include mechanisms at the genomic, molecular and post-translational levels.

At the genomic level, diversity can result from multiplicity of the genes which code for potassium channel proteins and from alternative splicing of those genes [10]. At the molecular level, diversity might result from differences in subunits of different types of potassium channel [11]. At the post-translational level, there may be differences in the ways in which different subunits are assembled in the cell membrane and differences in their post-translational glycosylation and phosphorylation [12] which may also contribute to diversity. For example, there is evidence that the DMB binding protein (so called because it binds dendrotoxin, mast cell degranulating peptide and bungarotoxin) is subject to modulation by an endogenous kinase [13].

Finally, it is not known whether there are endogenous modulators of potassium channel activity, in addition to the neurotransmitters and the relevant G-proteins, which might contribute to differences in potassium channel activities in different tissues.

Increased understanding of the factors which contribute to the diversity of potassium channels will almost certainly enrich our understanding of their functions.

DRUGS WHICH MODULATE POTASSIUM CHANNELS

Most of the work on drugs which affects the activity of potassium channels has been carried out in relation to the effects of potassium channel openers on smooth muscle. This has been related mostly to cardiovascular diseases but also to other abnormalities of smooth muscle, including bladder muscle and bronchial smooth muscle. Thus, drugs such as cromakalim, nicorandil and pinacidil, which were developed as potassium channel openers, act on smooth muscle and have been studied in relation to their effects in angina pectoris or in hypertension. Furthermore, it has been discovered that drugs which have been in use for some years, such as minoxidil and diazoxide, also seem to open potassium channels in vascular smooth muscles. Similarly, some drugs which are known to be effective anti-arrhythmic agents, such as acecainide and clofilium, have also been discovered to be potassium channel blockers, and this may be the mechanism whereby they exhibit their Class III anti-arrhythmic activity.

Although much less work has been done on the effects of these drugs in the nervous system, some of them have been shown to have effects on potassium channels there. For example, cromakalin alters the excitability of neurones in guinea-pig hippocampus [14]. In addition to the effect of the sulphonylureas on ATP-activated channels in the brain, as mentioned above, there is recent evidence that the well-established antiepileptic drug, carbamazepine, can increase potassium currents in rat cortical neurones [15].

POTENTIAL THERAPEUTIC APPLICATIONS OF POTASSIUM CHANNEL MODULATORS IN THE NERVOUS SYSTEM

The number of potential therapeutic applications for drugs which act on potassium channels in the nervous system is embarrassingly large. However, there are definitely some conditions under which they promise to be useful including epilepsy, cerebral anoxia, and neurodegenerative and demyelinating disorders. Other areas which have been proposed include those of appetite and memory.

Epilepsy

Since the opening of potassium channels tends to stabilize the membrane potential at around its resting value, drugs which open potassium channels in nervous tissue might prevent the spontaneous and spasmodic discharge which is the feature of epileptic seizures. The evidence that cromakalim may do this in brain slices is quoted above, and the interesting possibility that established antiepileptic drugs, such as carbamazepine, may act through effects on potassium channels (also mentioned above) is worthy of further investigation. In addition to this *in vitro* evidence, there is also *in vivo* evidence that cromakalim may modify seizures in epileptic animals [16].

Cerebral anoxia

There has been much interest in recent years in the roles of peptide neurotransmitters, in particular glutamate, in the damage to neurones which occurs after cerebral anoxia. During anoxia depolarization of presynaptic fibres causes release of glutamate which causes neuronal damage by a postsynaptic effect. At the same time the intracellular concentrations of ATP fall thus activating ATP-activated potassium channels which tends to oppose the release of glutamate; glutamate release can also be enhanced by sulphonylureas. All this suggests that potassium channel openers might be of value in limiting the actions of glutamate after stroke and therefore perhaps in reducing cerebral anoxic damage. Indeed, it has been shown that diazoxide can reduce the depolarization of damaged fibres in these circumstances (see Ref. 17).

Neurodegenerative disorders

Analogous to the possible role of potassium channels in modulating the damage caused by cerebral anoxia, it is possible that the damage which occurs in the neurones of patients with Parkinson's disease or Alzheimer's disease might also be affected by potassium channel openers. This is supported by the observation that the opening of ATP-sensitive

potassium channels in the substantia nigra can counteract the effects of cyanide in those neurones [18].

Demyelinating disorders

The disposition of potassium channels in myelinated nerve fibres is unusual in that they are to be found not only in the unmyelinated nodes of Ranvier but also in the myelinated sections of the nerves [19]. In demyelinating disorders these potassium channels will be unmasked, and it is therefore reasonable to suppose that inhibition of their activity might be of value in the treatment of the effects of such disorders. The results of a clinical trial of the effects of 4-aminopyridine in patients with multiple sclerosis are encouraging in this respect [20].

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