Potassium Channels as Targets for Therapeutic Intervention

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(Published 20 September 2005)

Potassium channels constitute a family of proteins with diversified functions. Depending on the specific type of channel and the electrical environment in which it resides, potassium channels can repolarize cells after a depolarization event, modulate the shape of action potentials, determine the frequency of cell firing, and participate in potassium transport in epithelia (*1*, *2*). Consequently, the activity of potassium channels is associated with control of neuronal excitability and neurotransmitter release, heart rate, cardiac and smooth muscle contraction, endocrine secretion, epithelial electrolyte transport, T cell proliferation, apoptosis, and tumor progression. In electrically excitable cells, opening of potassium channels will decrease cell excitability and agents that increase the activity of these proteins should have utility in the treatment of disorders such as epilepsy, pain, hypertension, angina, and stroke. In contrast, inhibitors of potassium channels would promote cell excitability; the consequent increase in neurotransmitter or hormone release could be exploited in the treatment of Alzheimer's disease or type 2 diabetes.

The relevance of potassium channel function is well supported by human genetics. Indeed, a number of inherited diseases, such as cardiac long-QT syndrome, episodic ataxia, benign familial neonatal convulsions, Bartter's syndrome (a disease associated with abnormalities in electrolyte handling), and familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI), are caused by mutations in genes coding for potassium channels or their closely associated regulatory subunits. Under certain circumstances, pharmacological interactions with channels can have major consequences. For instance, the cardiac potassium channel, hERG (human ether-à-go-go related gene), together with the slowly activating delayed-rectifier potassium channel IKs, regulates the duration of the plateau phase of the cardiac action potential (*3*). In certain individuals, susceptibility to the potentially lethal arrhythmia, torsade de pointes, could be correlated with hERG block by various pharmacological agents, including histamine H_1 receptor antagonists, antipsychotics, tricyclic antidepressants, and antibiotics (*4*). Consequently, abolition of any unintentional drug interactions with hERG channels has become an area of high priority in drug development for both pharmaceutical companies and regulatory agencies. Although modulation of potassium channels can lead to undesired physiological consequences in some cases, appropriate intervention at these targets can provide therapeutic benefits. For example, the adenosine 5′-triphosphate (ATP)–dependent potassium channel that is present in pancreatic β cells acts to link glucose metabolism to insulin secretion (*5*). First-line therapy for treatment of type 2 diabetes consists of giving patients sulfonylureas, agents that inhibit this channel and thereby enhance insulin secretion. Although clinical use of sulfonylureas can have adverse effects, such as episodes of hypoglycemia, this class of drug has been available for many years and has been used successfully by many patients. Moreover, despite the presence of similar ion channels in other tissues, such as heart and smooth muscle, clinically appropriate concentrations of sulfonylureas appear to spare these other channels.

The discovery that sulfonylureas could be used to treat diabetes did not occur through the use of a rational, mechanism-based approach, but was the result of observing decreased concentrations of blood glucose in animals given sulfonylureas during evaluation of potential antibiotic agents (*6*). In this genomic era, however, pharmaceutical and biotech concerns would rather identify specific molecular targets relevant to a particular disease state, establish high-capacity in vitro screening systems, including specificity assays, and launch medicinal or combinatorial chemistry campaigns on interesting structural classes of molecules for the identification of promising therapeutic compounds. Proof-of-concept studies in preclinical animal models, and eventually in controlled clinical trials, will most likely require optimization of candidate drugs in terms of their pharmacokinetics, metabolism, and formulation. Thus, the road from the discovery of promising candidates to drug registration can be challenging, and indeed most candidates for drug development fail for any number of unrelated reasons, one of which is lack of clinical efficacy for a defined medical condition. How can we improve the probability of success of clinical trials based on our knowledge of ion channel structure and function? In the rest of this Perspective, we review a number of concepts that are believed to be relevant for the development of new therapies that target potassium channels. There are no simple solutions to many of these issues, but researchers in the field are optimistic that, in the long term, launching of successful drugs that will improve the quality of life of many patients will occur.

Potassium channels constitute a large family of proteins with a common feature: They selectively allow potassium ions to permeate in response to a gating mechanism. The basis for potassium selectivity is well understood, owing to the pioneering work of MacKinnon's laboratory on the high-resolution x-ray structure of bacterial potassium channels (*7*–*10*). There is a common and basic motif present in all potassium channels: four subunits (or two subunits in the case of two pore-domain channels) that associate around a central pore where ion selectivity is mediated (Fig. 1). Different stimuli, such as voltage changes across the plasma membrane, ligand binding, or second messenger interactions, lead to the opening and closing of the ion permeation pathway, and the specific mechanism that controls gating is usually dictated by structural features of the protein. Thus, channels that respond to voltage changes across the membrane typically consist of six transmembrane-spanning domains (S1 through S6). A recent high-resolution structure of one of these mammalian proteins strongly suggests that the S1 to S4 voltage sensor exists as an independent domain from the pore and that it can effect mechanical changes in the pore structure by coupling

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to this entity through the S4 to S5 linker (*11*, *12*). Potassium channels are classified into different families, with common structural features, such as the number of transmembrane-spanning domains, defining these subdivisions.

From the standpoint of drug development, a key question relates to identifying the specific potassium channel(s) that should be targeted because of its presumed role in a particular disease state. Following target identification, drug selectivity will determine the maximal concentration at which any given ion channel modulator can be tested in clinical trials before notable adverse events are observed. Target identification is, however, the major rate-determining step for assuring successful validation of candidate drugs in clinical trials.

In some cases, genetic diseases can help identify which channel is absent or abnormal in a given condition (*3*). Only a small number of potassium channels can be categorized in this way, however, and in many cases the phenotypes are such that they call into question the ability to safely modulate that channel pharmacologically in the general population. For instance, in PHHI, aberrant insulin secretion in children caused by lack of function of the ATP-dependent potassium channel in pancreas can cause hypoglycemia, coma, and brain damage, requiring the removal of all or part of the pancreas (*13*). Nonetheless, pharmacological modulation of the same channel with sulfonylureas is an effective way of treating type 2 diabetes.

For most potassium channels, however, the contribution of these proteins to cell physiology can only be hypothesized through knowledge of their biophysical properties and tissue distribution. However, correlation of biophysical features of native currents with specific gene products can be complicated by factors such as heterotetramerization between members of the same or related channel families or association with auxiliary regulatory subunits, which can substantially alter the properties of the resulting channel complex. In rodents, ablation of genes encoding potassium channels can also provide information about the role of these proteins, although the resulting specific phenotypes must be assessed with some caution in view of putative compensation by other channels, and the fact that these systems are only a model of human physiology. In certain cases, selective ion channel modulators, such as peptides isolated from venom of poisonous organisms, have been successfully used to assess the contribution of particular channels to cell physiology in native and pathophysiological conditions. For instance, recent data based on selective peptide blockers have implicated the voltage-gated potassium channel, Kv1.3, as a therapeutic target for treatment of autoimmune diseases such as multiple sclerosis (MS) (*14*, *15*). It appears that Kv1.3 abundance is specifically increased in myelin-reactive, effector memory T cells in the blood of MS patients, and that Kv1.3 peptide blockers preferentially suppress proliferation of these cells.

Given the above considerations, there are no absolute methods that can be used to identify specific potassium channel(s) for therapeutic drug development; rather, tools have been identified that, if used properly, can help to pinpoint a channel's role in system biology. Once proof of concept has been obtained that a specific potassium channel(s) is a relevant target in a particular pathophysiological context, the next challenge is to identify selective ion channel modulators that act on this target.

Diverse mechanisms contribute to regulation of channel activity (*1*). From gene transcription to cell surface expression of functional potassium channel tetramers, there are numerous ways in which a channel's activity could be modulated. Many of these mechanisms have not been thoroughly explored with ion channels and, because of the generic nature of some of these pathways, it is difficult to envision how they could provide specificity of drug action. For instance, nonspecifically disrupting protein-protein interactions, altering phosphorylation, or modifying cell surface expression through trafficking or gene transcription regulation would be expected to also affect the function of other proteins. Most ion channel drugs now in therapeutic use are channel state–dependent modulators that act directly on the channel. These agents share a high-affinity interaction with specific conformational states encountered during the gating process. For instance, dihydropyridine calcium-entry blockers bind preferentially to the inactivated state of the voltage-gated calcium channel that is present in the vasculature, and thereby spare those calcium channels present in cardiac tissue because during a normal cardiac action-potential cycle, the high-affinity state of the channel for these agents is only present for a very short period of time. Consequently, dihydopyridine calcium-channel blockers relax smooth muscle and are effective antihypertensive agents with minimal effect on cardiac contractility. Most potassium channels exhibit high amino acid homology in the internal pore region where these molecules are thought to bind. However, similar channels could display large differences in sensitivity to a given molecule if, for instance, access of the molecule to its binding site is controlled by gating or if conformations associated with the opening or inactivation processes are more favorable for drug binding in some channels than in others.

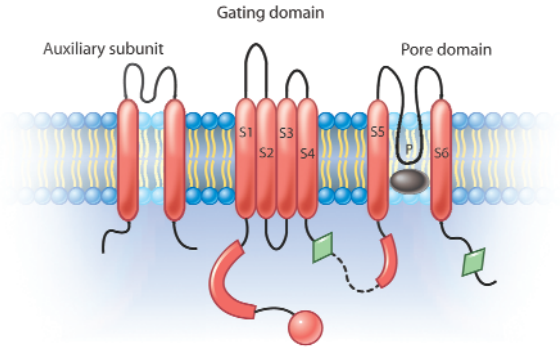

Fig. 1. Most potassium channels are tetrameric structures made up of four subunits consisting of either two transmembrane or six transmembrane domains. (Some potassium channels are dimers of two-pore domain subunits.) The pore domain (S5 and S6) acts as an independent module and determines potassium channel permeability and selectivity. In voltage-gated channels, S1 through S4 regulate channel gating. Auxiliary subunits, which associate with pore-forming subunits through protein-protein interactions, can modify the pharmacological and biophysical properties of the pore-forming subunit. Many mechanisms—from the regulation of their transcription and trafficking to phosphorylation (green diamond) and channel state–dependent pore blockers (black oval)—contribute to regulation of potassium channel function. Selective modulation of potassium channel activity in target tissues is predicted to have therapeutic utility for treating numerous different pathophysiological conditions.

Despite the complexity of ion channel drug development, potassium channels offer a rich source of targets for therapeutic

intervention. Potassium channel modulators could contribute substantially to the treatment of diabetes, hypertension, cardiovascular diseases, urinary incontinence, atrial fibrillation, epilepsy, pain, autoimmunity, cancer, and other diseases. Many of these conditions are poorly treated by current therapies, and although the road to success in the clinic will require overcoming a substantial number of obstacles, it is expected that the large body of information accumulated over the last few years on the structure and function of potassium channels will lead to the development of new therapies that will benefit patients.

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Citation: M. L. Garcia, G. J. Kaczorowski, Potassium channels as targets for therapeutic intervention. *Sci. STKE* **2005**, pe46 (2005).