Ether-a-go-go–Related Gene Potassium Channels: What’s All the Buzz About?

Paul D. Shepard1,2, Carmen C. Canavier3, and Edwin S. Levitan4

Antipsychotic drugs are thought to exert their therapeutic action by antagonizing dopamine receptors but are also known to produce side effects in the heart by inhibiting cardiac ether-a-go-go–related gene (ERG) K+ channels. Recently, it has been discovered that the same channels are present in the brain, including midbrain dopamine neurons. ERG channels are most active after the cessation of intense electrical activity, and blockade of these channels prolongs plateau potentials in bursting dopamine neurons. This change in excitability would be expected to alter dopamine release. Therefore, the therapeutic action of antipsychotic drugs may depend on inhibition of both postsynaptic dopamine receptors and presynaptic ERG K+ channels.

Key words: schizophrenia/bursting/dopamine/antipsychotic drugs/review

Introduction

Efforts to identify the pharmacological basis for the therapeutic actions of antipsychotic drugs have focused primarily on the interaction of these compounds with G-protein–coupled receptors. Early observations that antipsychotics block dopamine receptors in proportion to their clinical potency contributed significantly to formulation of the dopamine hypothesis of schizophrenia.1,2

Subsequent findings showing that many second-generation antipsychotic drugs potently block serotonin receptors gave rise to the notion that these sites are somehow involved in conferring the atypical properties of these drugs.3 In both instances, the existence of a distinct pharmacological action (eg, dopamine or serotonin receptor blockade), shared by a group of compounds with disparate chemical structures, provided important clues as to how these drugs might exert their therapeutic effects in individuals with schizophrenia.

Recent clinical and experimental evidence suggests that members of the phenothiazine, butyrophenone, dibenzepine, and benzamide classes of antipsychotics as well as other structurally heterogeneously neuroleptic drugs share another common pharmacological property—specifically, the ability to block ether-a-go-go–related gene (ERG) potassium channels.4 ERG K+ channels (also referred to as K,11 channels following International Union of Pure and Applied Chemistry nomenclature) belong to a superfamily of voltage-activated K+ channels encoded by 3 distinct gene subfamilies, including ether-a-go-go (eag), ether-a-go-go-like (elk), and ether-a-go-go–related (erg) genes.5 The first member of the family to be identified was discovered in a Drosophila melanogaster mutant and named for the characteristic leg-shaking behavior exhibited when the flies were anesthetized with ether.6 Several years later, a human homolog of eag was identified from low-stringency screening of a human hippocampal cDNA library and subsequently localized to chromosome 7.7 Designated the human eag–related gene, herg (or KCNH2) shares less than 50% sequence homology with other eag genes and is thus considered to represent a distinct subfamily in humans. Erg genes resembling herg have been identified in mice (merg) and rats (terg) and the channels they encode share a common set of functional properties that set them apart from other EAG K+ channels. Accordingly, these genes are referred to simply as erg throughout the remainder of the text.

Biophysical Properties of ERG K+ Channels

ERG K+ channels, like other ion channels, are macromolecular protein complexes that gate the flow of ions, in this case K+, across cell membranes. Functional ERG channels are comprised of 4 alpha subunits, each consisting of a protein comprised of 6 transmembrane-spanning domains (S1–S6). The first 4 domains of each subunit (S1–S4) comprise the voltage sensor which controls channel gating, while S5 and S6 collectively form the pore region of the channel.7 Voltage-dependent changes in the conformation of the protein complex give rise to 3
conductance states: closed (nonconductive), open (conductive), and inactivated (nonconductive) (see figure 1). ERG channels, which are closed at hyperpolarized membrane potentials, open slowly in response to membrane depolarization but inactivate so quickly that very little outward K\(^+\) current flows at the peak of the action potential. As the membrane potential begins to repolarize, the channels rapidly recover from inactivation and must once again enter an open (conductive) state prior to closing. Because the rate of recovery from inactivation greatly exceeds the rate at which the channels deactivate (ie, reenter a close state), a large albeit transient “resurgent” current is generated as the membrane potential repolarizes. Thus, ERG channels act as strong inward rectifiers, preferentially conducting outward currents at relatively hyperpolarized membrane potentials. However, unlike classical inward rectifiers, they must be initially induced to open with depolarization. During repeated spiking or prolonged depolarization, the sum of the fraction of channels in the activated and inactivated states can summate temporally, enhancing the inward rectification effect. These properties ensure that ERG channels are most active at the cessation of intense activity.

**hERG Channels in the Heart**

The discovery and characterization of a K\(^+\) current with the biophysical properties described above preceded identification of the gene that we now know encodes the channel.\(^{10,11}\) Previously designated I\(_{Kr}\), the function of this channel is best understood in the heart where it plays a prominent role in repolarization of cardiac action potentials.\(^{7,12}\) In mammalian heart, native hERG K\(^+\) channels are comprised of 2 erg-1 transcripts (ERG1a and ERG1b) that differ slightly in their amino acid composition and kinetic properties.\(^{13-15}\) The unique gating characteristics of hERG K\(^+\) channels, including their strong inward rectification, limit the amount of outward current occurring during the initial phase of the cardiac action potential which supports the development of the plateau phase and allows adequate time for Ca\(^{2+}\) entry and proper excitation contraction coupling. On the other hand, the ability of the channels to rapidly recover from inactivation, yet deactivate slowly, results in a large outward current that, together with other voltage-dependent K\(^+\) channels, leads to rapid repolarization of the cardiac action potential. The role of hERG K\(^+\) channels in normal cardiac function was revealed in studies showing that missense mutations in herg are responsible for long QT syndrome (LQTS), a cardiac repolarization disorder that predisposes affected individuals to life-threatening ventricular arrhythmias such as torsade de pointes.\(^{16}\) (The QT interval of the electrocardiogram is a measure of cardiac action potential duration and thus depends on hERG channel function.) Inherited LQTS can be caused by nearly 200 different mutations in herg, many of which appear to interfere with the normal trafficking of the channel to the cell membrane.\(^{7,17}\)

**hERG K\(^+\) Channels and Antipsychotic Drugs**

QT prolongation and an increased risk of torsade de pointes are potential side effects of drugs that block hERG K\(^+\) channels. Terfenadine (seldane) and cisapride (propulsid) were both withdrawn from the market because of their propensity to cause fatal arrhythmias particularly when combined with other drugs that decrease cardiac repolarization reserve. A large number of first- and second-generation antipsychotic drugs also potently
Table 1. Comparative Affinity of Antipsychotic Drugs for Dopamine D₂ Receptors and hERG K⁺ Channels

<table>
<thead>
<tr>
<th>Drug</th>
<th>D₂ Receptor, Kᵣ nmol/l</th>
<th>hERG K⁺ Channel, IC₅₀, nmol/l</th>
<th>Relative Potency, hERG IC₅₀/D₂ Kᵣ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimozide</td>
<td>0.7⁵</td>
<td>18⁴–55⁶</td>
<td>26–78</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.7⁴</td>
<td>27⁵–100⁶</td>
<td>38–1429</td>
</tr>
<tr>
<td>Sertindole</td>
<td>1.2⁴</td>
<td>3³–15⁶</td>
<td>2–12</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1.3⁵</td>
<td>21 600⁷</td>
<td>16 615</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.7⁴</td>
<td>148⁵–167⁶</td>
<td>87–98</td>
</tr>
<tr>
<td>Thioridizine</td>
<td>2.3⁴</td>
<td>33⁵–19¹⁵</td>
<td>14–83</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>6.4⁴</td>
<td>231⁵–601³⁹</td>
<td>36–940</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>8.4⁵</td>
<td>125⁶–169³⁹</td>
<td>15–20</td>
</tr>
<tr>
<td>Clozapine</td>
<td>82⁴</td>
<td>320⁶–250⁶</td>
<td>4–30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>155⁴</td>
<td>5765³⁹</td>
<td>37</td>
</tr>
</tbody>
</table>

⁴[³H]-raclopride or [³H]-spiropenol.
⁵Displacement from cloned human dopamine D₂ receptors, hERG channel current.
⁶Malmberg et al. (1993).²⁵
⁷CHO cells, Kang et al.²²
⁸HEK293 cells, Ekins et al.¹⁸
⁹Kapur and Seeman (2000).²⁶
¹₀Xenopus oocytes, Suessbrich et al.²¹
¹¹CHO cells, Kongsamut et al.¹⁹
¹²HEK293 cells, Rampe et al.²⁴
¹³Xenopus oocytes, Thomas et al.²⁰
¹⁴Seeger et al. (1995).²⁷
¹⁵HEK293 cells, Lee et al.²³

hERG K⁺ Channels in the Brain

In addition to being ubiquitously distributed in cardiac tissue, the gene encoding K₁,11.1 K⁺ channels in the heart (erg-1) is also strongly expressed in mammalian brain.²³ Two additional erg genes (erg-2 and erg-3) and their respective K⁺ channels (K₁,11.2 and K₁,11.3) have recently been identified and shown to be distributed exclusively within the central nervous system (CNS).³⁸ Individual members of the erg family are expressed in different levels and patterns throughout the CNS. mRNA encoding erg-1, erg-2, and erg-3 is distributed in the cerebral cortex, hippocampus, reticular nucleus of the thalamus, paraventricular nucleus of the hypothalamus, cerebellum, and several brain stem nuclei.⁴⁰ Moderate to high levels of the erg-1 transcript and all 3 ERG proteins are also expressed in neurons within the pars compacta of the substantia nigra.⁴¹ In most regions, the level of expression of erg-1 and erg-3 exceeds that of erg-2. While all 3 transcripts appear to be weakly expressed in pyramidal neurons, in the rat, erg-1 is expressed alone and in high levels in parvalbumin-labeled interneurons in the cingulate and retrosplenial cortex, selective interneuronal populations in the hippocampus, and in aspiny interneurons in the caudate.⁴⁰ The spatial distribution of ERG K⁺ channels in the CNS generally parallels the distribution of erg transcripts.⁴¹ Notably, ERG proteins are not only expressed in neuronal cell bodies but also in dendritic and axonal compartments,⁴¹ and the high degree of overlap in the expression of erg-1, erg-2, and erg-3 mRNA in the mammalian brain suggests that native channels are likely to be heteromultimeric. This is an important consideration given that the kinetic properties of K₁,11.3 channels are appreciably different from those associated with channels encoded by erg-1 and erg-2.³⁸

The contribution of native ERG K⁺ current (I_{ERG}) to the intrinsic electrical properties of CNS neurons that express the conductance is for the most part poorly

accumulate in myocardium.³³ While there are clear differences in the propensity of individual antipsychotics to cause LQTS,³⁴ it has also been difficult to establish a causal relationship between drug-induced QT prolongation and torsade de pointes or sudden cardiac death.³⁵ Approximately 8%–10% of individuals treated with atypical antipsychotic drugs exhibit clinical evidence of QT prolongation, while the incidence of arrhythmogenic disorders in the same population occurs with a frequency of only 1 in 10 000 individuals.³⁰,³⁴ Deaths attributed to drug-induced torsade de pointes amount to less than 1 in 100 000 patients.³⁰ With the possible exception of thioridizine, most instances of antipsychotic drug-induced torsade de pointes are associated with high dosing regimens, intentional drug overdose, synergistic drug interactions, or other predisposing factors, including diabetes, hypokalemia, or cardiac ischemia.³⁰,³³,³⁴,³⁶
understood. One exception is the cerebellar cortex, where Purkinje cells have been shown to exhibit an inwardly rectifying K⁺ current with the biophysical and pharmacological characteristics of an ERG channel.⁹ I_{ERG} in these neurons is characterized by slow deactivation, a fast recovery from inactivation, and is potently suppressed by the ERG-selective blocker WAY-123,398. Blockade of I_{ERG} in Purkinje cells increased neuronal excitability and suppressed spike frequency adaptation without altering the duration of individual action potentials. Loss of I_{ERG} also prolonged the duration of complex spikes elicited by activation of climbing fiber inputs. These data support the proposition that pharmacological blockade of I_{ERG} in the CNS could result in a change in neuronal excitability that would alter synaptic integration.

**Antipsychotic Drugs and I_{ERG} in the CNS: Therapeutic Implications**

The discovery of ERG K⁺ channels in CNS neurons together with preliminary evidence that they can influence neuronal excitability raises the intriguing question of whether blockade of these channels by antipsychotic drugs contributes in some way to their therapeutic actions or neurological side effects. Although the ERG-blocking capabilities of antipsychotic drugs have focused almost exclusively on Kv11.1 (hERG) channels, there is evidence to suggest that these drugs also block additional ERG channel subtypes in the CNS (Kᵥ11.2 and Kᵥ11.3). Cloned human Kᵥ11.3 channels expressed in CHO cells produce an ERG current that is inhibited by sertindole and pimozide at concentrations comparable to their Kᵦ values at D₂ dopamine receptors.⁴² Rispiridone, haloperidol, thioridazine, and clozapine but not metoclopramide block native ERG currents in cloned pituitary GH₃ cells.⁴³ Notably, these channels play a prominent role in controlling burst duration and prolactin release from pituitary lactotrophs.⁴⁴,⁴⁵ Haloperidol has also been shown to block I_{ERG} in cerebellar Purkinje neurons.⁹

Midbrain dopamine-containing neurons, cells strongly implicated in both the therapeutic and side effects of antipsychotic drugs, also appear to express functional ERG K⁺ channels that are blocked by these compounds. Using intracellular recording techniques in conjunction with a brain slice preparation, Steen Nedergaard⁴⁶ identified an ERG-like slow, voltage-activated K⁺ current responsible for a long-lasting afterhyperpolarization termed AHPₚ. AHPₚ in dopamine neurons is calcium independent, activated by prolonged depolarization, and inhibited by local application of low micromolar concentrations of haloperidol. The effects of haloperidol could not be attributed to blockade of dopamine or sigma receptors as neither (–)sulpiride, (+)SKF110047, nor pентazocine had any effect on AHPₚ. By contrast, terfenadine, a potent blocker of ERG K⁺ channels, effectively inhibited AHPₚ in dopamine neurons.

The most prominent physiological effect associated with blockade of the putative ERG current in dopamine neurons was a reduction in the duration of a pause in spontaneous firing that occurs at the end of a train of stimulus-evoked spiking.⁴⁶ This “poststimulus inhibitory period,” resembles the characteristic pause in spontaneous activity that follows a burst of spikes.⁴⁷,⁴⁸ Bursting activity in dopamine neurons has been implicated in a variety of physiological processes, including the encoding of reward, modulation of dopamine release, and the induction of “depolarization block” following chronic administration of antipsychotic drugs.⁴⁹–⁵¹ Although the neurobiological basis of bursting activity in dopamine neurons is not yet understood, it is likely to involve an interaction between afferent inputs and the intrinsic properties of the cell, including the voltage and ligand-gated ion channels expressed in the soma and dendrites of these neurons.⁵²,⁵³ The ability of haloperidol and terfenadine, both potent ERG K⁺ channel blockers, to reduce the inhibition inactivity following episodes of high-frequency firing, suggested that these channels could contribute to the process underlying burst termination. In support of this hypothesis, Canavier et al.⁵⁴ demonstrated that addition of an ERG K⁺ conductance to a computational model of oscillatory activity in dopamine neurons faithfully reproduced the time course of membrane potential changes and somatic calcium oscillations observed during plateau potentials induced experimentally by the calcium chelator 1,2-bis(2-aminophenoxy)ethane N,N,N',N'-tetraacetic acid (BAPTA). These data suggested that I_{ERG} is capable of terminating plateau potentials in dopamine neurons and implied that the current may be important in the generation of bursting activity by preventing induction of acute depolarization inactivation.⁸ The predictions of the computational model were tested experimentally by obtaining intracellular recordings from spontaneously active dopamine neurons under conditions similar to those used to simulate plateau potential oscillations in the model. As illustrated in figure 2A, and in accordance with previous studies,⁵⁴,⁵⁵ bursting was induced by partially blocking an SK-type Ca²⁺-activated K⁺ conductance. The plateau potential oscillations underlying this type of bursting activity are clearly visible when tetrodotoxin is applied to block spiking (figure 2B and C, black traces). Addition of haloperidol, at a concentration previously shown to block the putative I_{ERG} in dopamine cells (5 µM), prolonged the plateau potentials exhibited by these neurons in the presence of tetrodotoxin (TTX)⁸ (figure 2C, gray trace). Comparable results were not observed in response to sulpiride (2 µM, figure 2B, gray trace). At these concentrations, both drugs would have effectively antagonized D₂ dopamine receptors; however, only haloperidol would have also reduced I_{ERG} activated during the prolonged plateau depolarization.

While it has yet to be determined whether plateau potentials triggered by blockade of SK channels in vitro are involved in “natural” bursting activity exhibited by
dopamine neurons in vivo, plateau properties are importantly involved in regulating the activity of a variety of CNS neurons. The unique kinetic properties of ERG channels including their rapid inactivation and large regenerative outward current would appear to make them uniquely suited for limiting the duration of plateau potentials. It is interesting to note in this regard that many of the CNS neurons expressing high levels of erg transcripts, including subthalamic, hypothalamic para-ventricular, cerebellar Purkinje, cortical pyramidal, and subicular neurons also exhibit regenerative plateau potentials.

In summary, ERG K\(^+\) channels exhibit a unique set of biophysical properties that are well suited for their prominent physiological role in repolarizing plateau potentials both in the heart and the brain. First- and second-generation antipsychotic drugs block ERG channels in the heart resulting in LQTS and an increased liability for developing life-threatening arrhythmias. However, the discovery of ERG K\(^+\) channels in brain suggests that central actions of antipsychotic drugs could include alterations in the intrinsic electrical properties of neurons expressing this conductance. Indeed, it seems quite possible that partial block of ERG K\(^+\) channels in dopamine neurons by antipsychotic drugs could increase neuronal excitability, facilitate bursting activity, and promote the induction of “depolarization inactivation,” a phenomenon that has been implicated in the therapeutic effects of these agents.\(^{50,61,62}\) Given that Kv11.2 and Kv11.3 channels are expressed solely in the CNS, it should be possible to develop centrally active blockers of I\(_{\text{ERG}}\) that are both regionally selective and devoid of significant cardiotoxicity.\(^{63}\) A more complete understanding of the functional role played by ERG K\(^+\) channels in CNS neurons and the degree to which clinically relevant doses of antipsychotic drugs modify these effects could provide new insights into the therapeutic mechanism of action of these drugs.

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