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HERG1 Channel Agonists and Cardiac Arrhythmia

Michael Sanguinetti, PhD
Department of Internal Medicine, Nora Eccles Harrison Cardiovascular Research & Training Institute, University of Utah, 95 South 2000 East, Salt Lake City, Utah 84112, Voice: 801-581-3058

Michael Sanguinetti: sanguinetti@cvrti.utah.edu

Abstract

Type 1 human ether-a-go-go-related gene (hERG1) potassium channels are a key determinant of normal repolarization of cardiac action potentials. Loss of function mutations in hERG1 channels cause inherited long QT syndrome and increased risk of cardiac arrhythmia and sudden death. Many common medications that block hERG1 channels as an unintended side effect also increase arrhythmic risk. Routine preclinical screening for hERG1 block led to the discovery of agonists that shorten action potential duration and QT interval. Agonists have the potential to be used as pharmacotherapy for long QT syndrome, but can also be proarrhythmic. Recent studies have elucidated multiple mechanisms of action for these compounds and the structural basis for their binding to the pore domain of the hERG1 channel.

Introduction

Long QT syndrome (LQTS) is an inheritable disorder of ventricular repolarization that predisposes affected individuals to ventricular arrhythmia and sudden death. Current pharmacotherapy for congenital LQTS is administration of β-blockers. These drugs significantly reduce the risk of life-threatening cardiac events [1]. However, failure of β-blocker therapy (observed as recurrent syncope) is significant in young children and women and implantable cardioverter-defibrillator (ICD) therapy has been recommended for high risk LQTS patients [2]. ICDs are effective, but expensive and not available to all patients in need. Thus, there remains a need for the discovery and development of additional pharmacotherapies. Currently, no drugs directly treat the reduced hERG1 (Kv11.1) or KCNQ1 (Kv7.1) delayed rectifier K^+ channel function that underlies the majority of clinical cases of congenital LQTS. Cromakalim, nicorandil and pinacidil increase the open probability of ATP-sensitive K^+ (K_{ATP}) channels and shorten action potential duration (APD), but cause postural hypotension and excessive shortening of action potentials with attendant risk of ventricular fibrillation [3]. In 2005, the first hERG1 channel agonist (RPR260243) was shown to shorten action potentials prolonged after pretreatment of cells with a hERG1 blocker by slowing the rate of channel closure [4]. Many additional hERG1 agonists have since been discovered and their mechanisms of action defined. In vivo characterization of these new compounds has revealed both antiarrhythmic and proarrhythmic activity.

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Mutations in *KCNH2* and hERG blockers can increase risk of cardiac arrhythmia

In cardiac myocytes, the rapid delayed rectifier K^+ current, I_{Kr} is a key regulator of action potential duration [5,6] and is conducted by hERG1 channels [7,8]. In response to membrane depolarization (e.g., upstroke of action potential), most hERG K^+ channels are open for only a very brief period before they inactivate (enter a non-conducting state). During the plateau phase of the cardiac action potential, outward currents including I_{Kr} are balanced by inward current conducted by L-type Ca^{2+} channels. Reduction of outward I_{Kr}, either by drug-induced channel block (e.g., dofetilide) or by a loss of function mutation in the hERG1 gene (*KCNH2*) [9], lengthens APD of cardiomyocytes and prolongs QT interval, a body surface measure of ventricular repolarization. Enhancement of I_{Kr}, either by a drug (e.g., hERG agonist) or by a gain of function mutation in *KCNH2* shortens APD and the QT interval. The unusual biophysical properties and structural basis of hERG1 channel gating and modulation of its function by drugs and inherited mutations is expertly summarized in a recent review [10].

LQTS is most often caused by loss of function mutations in *KCNH2* or *KCNQ1* K^+ channel genes [11]. The physiological consequence is decreased outward K^+ current and prolonged ventricular repolarization that can induce torsades de pointes (TdP), the signature arrhythmia of LQTS that can degenerate into lethal ventricular fibrillation. Slow heart rates and hypokalemia increases the likelihood of early afterdepolarizations (EADs), considered to be a cellular trigger of TdP. Gain of function point mutations in *KCNH2* cause short QT syndrome (SQTS), a rare disorder that hastens cardiac repolarization and increases risk of ventricular and atrial fibrillation. The two point mutations in *KCNH2* known to cause SQTS increase outward hERG1 current by shifting the voltage dependence of inactivation gating to more positive potentials. The voltage required to cause 50% of channels to inactivate ($V_{0.5}$) is shifted by +102 mV by N588K [12] and +50 mV by T618I [13]). Reduced inactivation may increase I_{Kr} more in the ventricle than in Purkinje fibers and the resulting disparity in APD could create the arrhythmogenic substrate responsible for ventricular fibrillation [12]. HERG1-3 channels are also highly expressed in the central nervous system and primary tumors of several tissues. These topics and more in-depth discussions of hERG1 and cardiac arrhythmias are the subjects of recent reviews [10,14].

Delayed ventricular repolarization, EADs, TdP and increased risk of arrhythmia can also be an unintended side effect of treatment with many common medications. Only when used by large numbers of patients were such drugs discovered to possess significant proarrhythmic risk. In the past decade, several drugs were withdrawn from the market, or their approved use severely restricted when their link to ventricular arrhythmia was elucidated [15]. Risk assessment of drug-induced TdP [16] has since been routinely assessed by screening of compounds for hERG1 activity because most drugs that induce TdP preferentially target these channels. This screening effort resulted in the serendipitous discovery of numerous hERG1 agonists.

Multiple mechanisms of action of hERG1 channel agonists

The extent of APD shortening induced by hERG1 agonists varies widely. These differences are undoubtedly related to the specific or multiple channel gating properties that are affected by a given compound. However, when APD is first prolonged (e.g., by partial block of I_{Kr} or I_{Ks}), then all agonists accelerate the rate of action potential repolarization. To date, four distinct agonist mechanisms have been described: 1) slowed rate of channel deactivation, 2) attenuation of C-type inactivation, 3) shift of channel opening to more negative potentials, and 4) increase in channel open probability. With few exceptions, most compounds alter

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multiple components of channel gating. The chemical structures and biophysical effects on hERG1 gating for several known hERG1 agonists are presented in Figure 1 and Table 1, respectively. Individual compounds are considered next.

RPR260243 and ginsenoside Rg3 slow the rate of hERG1 channel deactivation

The first synthetic activator of hERG channels, RPR260243 was reported in 2005. The compound caused a profound slowing in the rate of deactivation without any significant effect on the voltage dependence of activation or inactivation of hERG1 channels heterologously expressed in Chinese hamster ovary (CHO) cells [4]. In isolated guinea pig myocytes, RPR260243 slowed I_{Kr} deactivation, but only shortened APD in these myocytes at a high (30 μM) concentration or at lower concentrations after pretreatment with the I_{Kr} blocker dofetilide. Ex vivo evaluation in Langendorff-perfused, isolated guinea pig hearts, revealed that RPR260243 at 5 μM increased the amplitude of T-waves, prolonged the PR interval, and shortened the QT interval. RPR260243 did not affect heterologously expressed KCNQ1/KCNE1 (I_{Ks}) or $Na_V1.5$ (I_{Na}) channel currents, but suppressed I_{CaL} in myocytes [4].

Ginsenoside Rg_3 isolated from the root of *Panax ginseng* plants also slows the rate of hERG1 channel deactivation with an EC_{50} of 0.4 μM [17]. However, unlike RPR260243 it also induced channel opening at more negative potentials by causing a −14 mV shift in the $V_{0.5}$ for activation and a 2-fold increase in peak outward current at 3 μM. The compound was without effect on C-type inactivation. Rg_3 inhibits KCNQ1 and activates KCNQ1/minK channels [18] and likely has multiple effects on other ion channels.

ICA-105574 attenuates C-type inactivation

ICA-105574 increases outward hERG1 currents (EC_{50} of 0.5 μM, Hill slope of 3.3) far more than any other known agonist [19]. The more than 10-fold enhancement of current is caused by a profound positive shift (+182 mV at 2 μM) in the voltage dependence of C-type inactivation. In addition, the $V_{0.5}$ for activation is shifted by −11 mV at 3 μM with an expected slowing of deactivation. In guinea pig ventricular cardiac myocytes, 3 μM ICA-105574 shortens APD by ~70% [19] and has similar effects on QTc intervals in Langendorff-perfused guinea-pig hearts and in anesthetized dogs [20]. In isolated guinea pig hearts, pretreatment with the compound prevented TdP subsequently induced by hypokalemia and the I_{Kr} blocker moxifloxacin and I_{Ks} inhibitor chromanol 293B, but was ineffective if TdP was initiated by these drugs before administration of ICA-105574 [21].

Mallotoxin and KB130015 shift the voltage dependence of hERG1 channel opening to more negative potentials

Mallotoxin, an alkaloid isolated from the tree *Mallotus phillippinensis*, increases hERG1 current amplitude by causing a hyperpolarizing shift in the voltage dependence of channel activation, with a maximum shift of −24 mV at 10 μM and an EC_{50} of 0.5 μM [22]. Associated with the shift in activation gating, the toxin also accelerated the rate of activation and slowed the rate of deactivation, but had no effect on $V_{0.5}$ for inactivation.

KB 130015 is a derivative of amiodarone. Whereas both compounds block hERG1 channels, only KB 130015 enhances current, and only at voltages negative to 0 mV (EC_{50} = 12 μM) due to accelerated onset of activation and a negative shift in the $V_{0.5}$ for activation (-16 mV at 10 μM) [23]. The binding site for the agonist effect of this compound has not been defined, but in excised membrane patches it only activated channels when applied to the

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cytosolic side. The finding that the agonist effect of KB 130015 was competitively antagonized by amiodarone suggests that the binding site(s) for the inhibitory and agonist activities of the compound overlap or are functionally coupled [23].

PD-118057 increases the open probability of hERG1 channels

PD-118057 shortened APD and QT interval, suppressed EADs induced by dofetilide in a rabbit ventricular wedge preparation without major effect on other cardiac currents, and doubled the magnitude of hERG1 tail current in HEK293 cells at 10 μM without affecting the voltage dependence and kinetics of gating [24]. This compound does not alter single channel conductance or gating currents, indicating that increased hERG1 current magnitude must result from an increase in single channel open probability (Po) [25].

hERG1 agonists with multiple mechanisms of action

Most hERG1 agonists have multiple mechanisms of action. A-935142 shifted $V_{0.5}$ for inactivation by +15 mV, accelerated the rate of activation and slowed the rate of deactivation consistent with a −9 mV shift in the $V_{0.5}$ for activation [26]. PD-307243 slowed the rate inactivation and increased hERG tail currents by 3.4-fold at 10 μM, but had no effect on rates of channel activation or deactivation [27] [28]. NS1643 induced a maximum 300% increase in hERG1 at 10 μM, accelerated the rate of activation and shifted $V_{0.5}$ for activation by −27 mV [29]. The shift in $V_{0.5}$ develops slowly over time and in oocytes, only occurs at much higher drug concentrations [28] [30]. NS1643 also causes a left-ward shift of the activation curve of ERG2 [31] and ERG3 channels [32]. In addition, NS1643 slows the rate of inactivation with either no shift (CHO cells) [29] or a positive shift in $V_{0.5}$ for inactivation (oocytes) [30]. In conscious guinea pigs NS3623 (50 mg/kg, iv) shortened QTc interval by 30% and normalized QT that was prolonged by E4031 [33]. NS3623 also prolonged QRS duration and slowed cardiac conduction at 10 μM in Langendorff-perfused guinea pig hearts, an effect that was reversed by the I_{Kr} blocker E4031 [34].

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Molecular determinants of agonist activity

A-935142 does not compete with ^{3}H-dofetilide binding, nor does it exhibit functional competition with other hERG1 blockers (terfenadine or sotalol) [35]. Scanning mutagenesis of hERG1 and functional characterization of heterologously expressed mutant channels also suggests that the binding sites for hERG1 blockers and agonists differ. Small molecule blockers bind to residues that line the central cavity [36,37], whereas agonists that have been characterized to date bind to a hydrophobic pocket located outside of the central cavity and formed by the pore helix, S5 and S6 segments of two adjacent subunits [38] [25,39] [40]. A molecular model of ICA-105574 bound to the pore domain of a hERG1 channel is shown in Fig. 2A-B. Based on mutagenesis experiments, PD-118057 interacts with L646 of one hERG1 subunit and F619 of an adjacent subunit [25], whereas ICA-105574 interacts with L622C in the pore helix, F557L in the S5 segment, and Y652A in the S6 segment (Fig. 2B) [40]. Fig. 2C compares the residue interaction map for three different hERG1 agonists and illustrates that compounds with different structures bind to a similar, but not identical binding pocket. With three exceptions, the specific amino acids that form the putative binding pocket for ICA-105574 in hERG1 are conserved in EAG1, yet the compound inhibits EAG1 channels [41]. Mutations introduced into EAG1 to replicate the binding site in hERG1 did not alter the functional response to ICA-105574, suggesting that it binds to the same site in both channels to elicit opposite functional effects on inactivation gating [42]. There are four identical putative agonist binding sites per channel; all may need to be occupied to elicit a maximal effect on channel gating.

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HERG1 channel agonists and proarrhythmia risk

A short electrical refractory period provides a substrate for re-entry based arrhythmia. Although it has not been systematically investigated, hERG1 agonists will likely differ with respect to their propensity to cause excessively short APD and refractoriness and some agonists have even been used to create drug-induced models of SQTS. Removal of inactivation by ICA-105574 mimics the gating effects caused by hERG1 mutations that cause SQTS and would therefore be expected to be proarrhythmic at high concentrations. PD-118057 shortened APD, increased spatial dispersion of repolarization, and a single premature stimulus induced fibrillation in coronary-perfused canine right atria [43] and polymorphic ventricular tachycardia in left ventricular wedge preparations [44]. In isolated guinea pig hearts, NS1643 provided some protection against moxifloxacin-induced arrhythmia in the setting of hypokalemia [21], and suppressed arrhythmias induced by infusion of dofetilide to methoxamine-sensitized rabbits or by atrioventricular block with ventricular bradypacing in rabbits [45]. However, in a transgenic rabbit model of LQTS1, NS1643-induced shortening of QTc was accompanied by an increased incidence of arrhythmia [46]. Proarrhythmic risk needs to be assessed for any hERG1 agonist proposed for clinical use.

Concluding remarks

At present, insufficient information is available regarding the efficacy and safety of hERG1 agonists. However, this new class of drugs could potentially cause a paradigm shift in the clinical management of LQTS or perhaps other disorders where hERG1 channel function is implicated. The most obvious safety concern is that hERG1 agonists will be proarrhythmic due to excessive shortening of the QT interval. A drug that has a limited intrinsic maximal efficacy that normalizes, but does not cause excessive shortening of ventricular repolarization in the targeted patient population is a goal for future discovery and development of hERG1 agonists.

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• of special interest

•• of outstanding interest

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Highlights

- hERG1 potassium channels mediate repolarization of cardiac action potentials.
- hERG1 agonists alter channel gating to shorten action potential duration and QT interval.
- There are four identical agonist binding sites per hERG1 channel.
- hERG1 agonists can either prevent or promote cardiac arrhythmia

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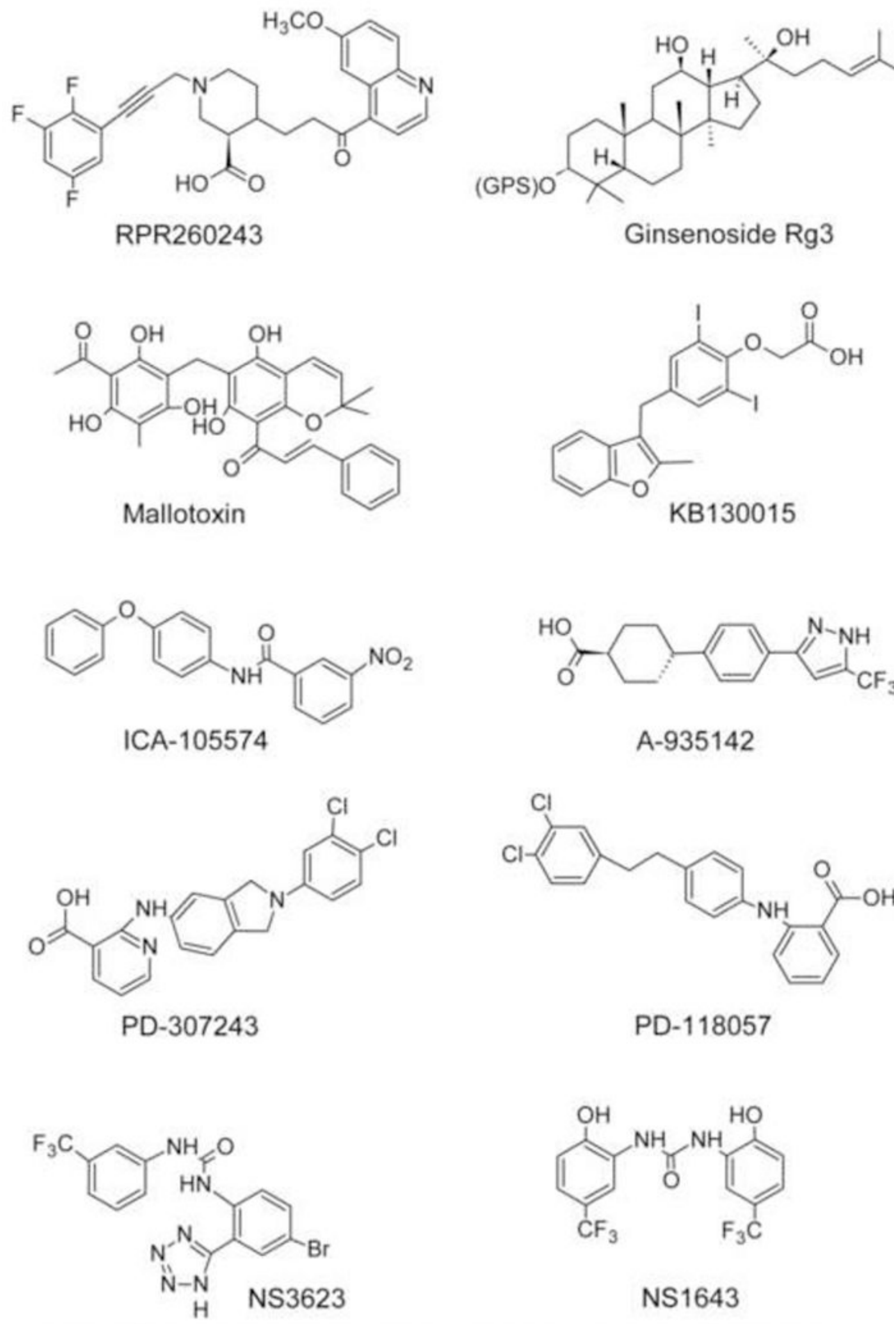

Figure 1. Chemical structures of hERG channel agonists

*for Ginsenoside Rg3, GPS = β-D-glucopyranosyl-β-D-glucopyranoside

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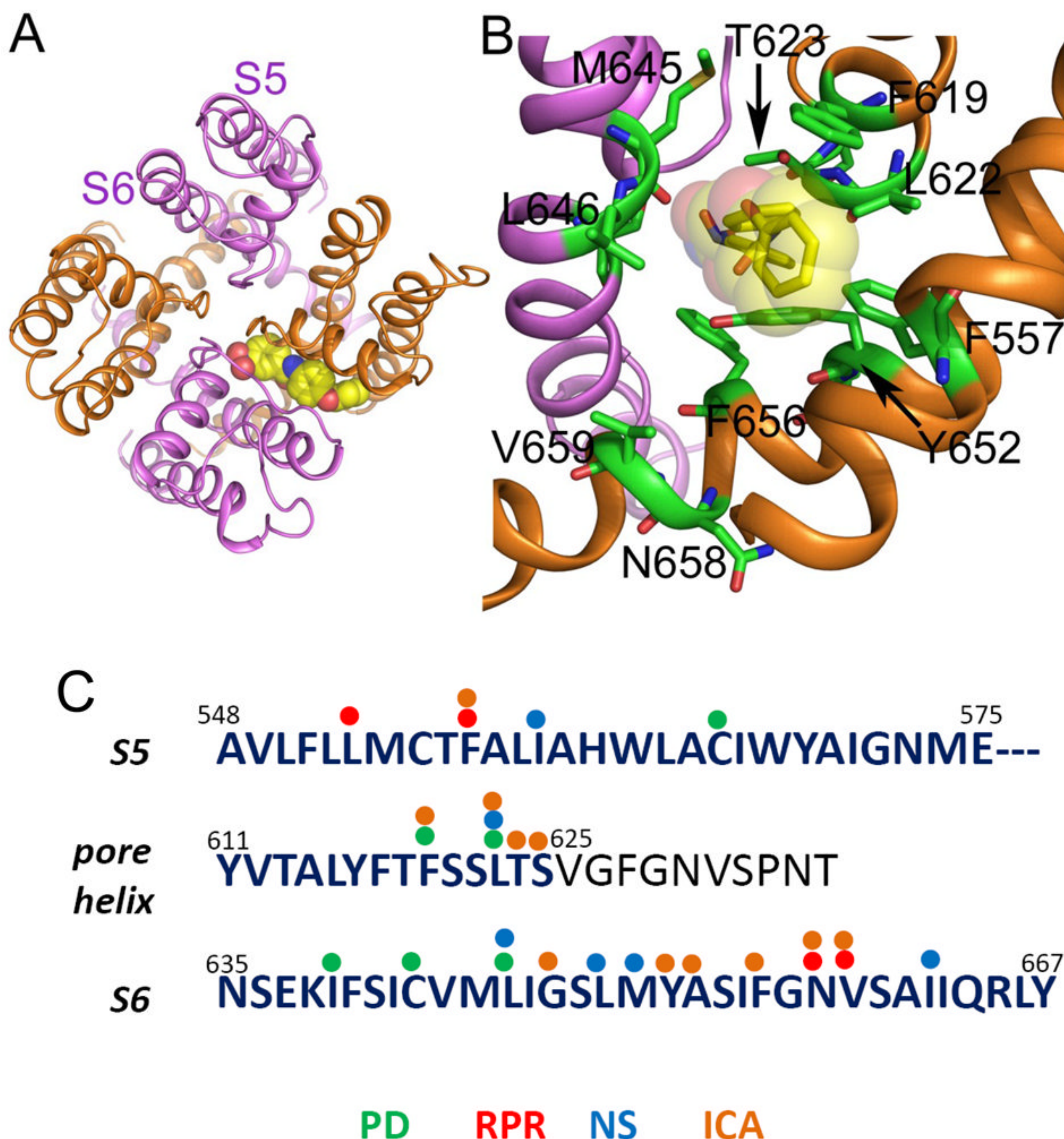

Figure 2.

Agonists bind to a hydrophobic pocket located between two adjacent hERG1 subunits. (A) Molecular model of ICA-105574 molecule (atoms depicted as spheres) bound to the pore domain of a hERG1 channel in the open state as viewed from the extracellular side of the membrane. The S5 and S6 segments (shown as ribbons) of one of the four idential subunits are labeled. (B) Close-up view showing ICA-105574 (yellow) and key binding residues (green) determined from site-directed mutagenesis and functional analysis of mutant channels. (C) Location of pore domain residues that interact with four different hERG1 agonists. Circles denote residues in the S5 segment, pore helix and S6 segment that when individually mutated (usually to Ala) reduced the agonist activity of RPR260243 (●), PD-118057 (●), NS1643 (●), or ICA-105574 (●). Numbering indicates the position of

specific residues within a hERG1 subunit relative to the N-terminus. The residues S624 to G628 located C-terminal to the pore helix comprise the K^+ channel signature sequence. Panels A and B originally published in [40].

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Table 1

Mechanisms of action of hERG1 channel agonists.

Compound	Effect on hERG1 channel				
	Slows rate of deactivation	Positive shift in V-dependence of inactivation	Negative shift in V-dependence of activation	Increases open probability (P_o)	EC_{50} (cell type)
RPR260243	+++	+			*n.d. (~3 μM)(CHO)[4]
Ginsenoside Rg3	+++		+		0.4 μM(X. o.)[17]
ICA-105574	+	+++	+		0.5 μM(HEK)[47]
Mallotoxin	+		++	+	0.4 μM(CHO)[22]
KB130015	+		++		12 μM(HEK)[23]
PD-118057		+		++	n.d. (~10 μM)(HEK)[24]
PD-307243		+		+	n.d. (~2 μM)(CHO)[27]
NS1643		+/-	++		10.4 μM (X. o.)[30]
NS3623		+		+	79 μM(X. o.)[48]
A-935142	+	+	+		n.d. (>20 μM)(HEK)[26]

* n.d., not determined; CHO, Chinese hamster ovary cells; X. o., *Xenopus* oocytes; HEK, HEK293 cells