Patanè S, J Cardiol Neuro Cardiovasc Dis 2014, 1: 004
DIO: 10.24966/CNCD-8860/100004

HSOA Journal of Cardiology and Neurocardiovascular Diseases

Review Article

Human ether-a-go-go-related gene K(+) channels [HERG] in neurocardiology field

Salvatore Patanè

Cardiologia Ospedale San Vincenzo - Taormina (Me) Azienda Sanitaria Provinciale di Messina,Contrada Sirina, 98039 Taormina (Messina), Italy

Abstract

Human ether-a-go-go-related gene K(+) channels [HERG] (hERG; Kv11.1, KCNH2) encode the rapid delayed-rectifier K^+-current (I_{Kr}) and are expressed in various tissue including heart, various brain regions and a wide range of tumor cell lines Further investigations are needed to elucidate the pathologic and non-pathologic role of HERG in neurology and cardiology as well in other tissue and diseases and to highlight the co-occurrence in neurocardiovascular diseases such as Long QT Syndrome (LQTS) and Epilepsy.

Keywords: Cardiology, Cancer, Drug interactions, HERG, Neurology, Torsade de Pointes arrhythmia (TdP)

Human ether-a-go-go-related gene K(+) channels [HERG](hERG; Kv11.1, KCNH2) encode the rapid delayed-rectifier K^+-current (I_{Kr}) and are expressed in various tissue including heart, various brain regions and a wide range of tumor cell lines [1]. The heart HERG slow activation and deactivation kinetics, coupled to their rapid voltage-dependent inactivation and recovery from inactivation, is crucial for determining the duration of the action potential plateau phase and also contribute to pacemaking activity in sinoatrial (SA) and atrioventricular node cells and to diastolic depolarization [1]. Extra-cardiac HERG role has suggested in cancer, and in spike-frequency adaptation and burst duration regulation in neurons as well as in regulation of resting membrane potential and action potential firing frequency in smooth muscle and endocrine cells [1]. Heart HERG –blockade can lead to QT prolongation with increased risk of potentially life-threatening torsade de pointes arrhythmia (TdP). Several HERG-blockers have withdrawn post-approval surveillance [2-4]. HERG-blockers interactions among antiarrhythmic and non-antiarrhythmic drugs including antipsychotic agents as well as drug interactions with inhibitors of the CYP-mediated metabolism have been also shown to prolong cardiac repolarization predisposing to Tdp [5-13]. The risk may be increased by underlying risk factors such as cardiac disease and electrolyte disturbance [5-15]. Moreover in the heart the HERG-GENE is involved in chromosome 7-associated long QT syndrome (LQTS) [1] and research suggests that *Loss-of-function* mutations in HERG cause type 2 long QT syndrome (LQT2) [11] increasing the risk of episodes of sudden death due to ventricular fibrillation. HERG are over-expressed in a wide range of human cancers controlling cell proliferation, migration and death and nowadays new findings are emerging regarding actions and use of HERG-Blockers drugs as HERG-Targeted therapy in both cancer and cardiovascular system [2-4]. Research has also suggested that HERG are widely expressed in the brain where they contribute to setting the frequency and the discharge stability of neurons, and to adapting their intrinsic properties to signal processing [16]. HERG also modulate the excitability of dopaminergic and GABAergic neurons [17-19]. Research also has suggested that herg+ dopamine neuron plays an important role in limiting excitability and in minimizing HERG depolarization inactivation in the central nervous system representing a possible novel target for central nervous system drugs development [17]. Moreover the induction of inflammation-associated genes in schizophrenia and epilepsy has suggested the possibility that HERG expression might also be induced in neurologic conditions as a secondary consequence of tissue damage in the nervous system [17,21,22]. Notably, LQT syndrome is closely associated with seizure and frequently it is misdiagnosed as epilepsy. Sudden unexpected death in epilepsy is the most frequent epilepsy-related cause of death for which an underlying arrhythmogenic predisposition has been suggested. Several clinical reports have recently described seizures and arrhythmic events in LQT2 triggered by visual or acoustic stimuli [21,23-25]. Considering that HERG channels control several neuronal electrical features, including discharge dynamics [18,20], these clinical findings raise the possibility that alteration in HERG may confer susceptibility for epilepsy and cardiac LQT2 arrhythmia[21]. Further investigations are needed to elucidate the pathologic and non-pathologic role of HERG in neurology and cardiology as well in other tissue and diseases and to highlight the co-occurrence in neurocardiovascular diseases such as Long QT Syndrome (LQTS) and Epilepsy[17-22].

References

1. Vandenberg JI, Perry MD, Perrin MJ, Mann SA, Ke Y, et.al. (2012) hERG K(+) channels: structure, function, and clinical significance. Physiol Rev 92: 1393-1478.
2. Patanè S (2014) HERG-targeted therapy in both cancer and cardiovascular system with cardiovascular drugs. Int J Cardiol 176: 1082-1085.
3. Patanè S (2014) Heart Failure and Breast Cancer: Emerging Controversies Regarding Some Cardioprotective Strategies. J Card Fail 20: 456-457.
4. Patanè S (2014) Is there a role for quinazoline-based α (1)-adrenoceptor antagonists in cardio-oncology? Cardiovascular Drugs and Therapy.
5. Patanè S (2011) Torsade de pointes, QT interval prolongation and renal disease. Int J Cardiol 149: 241-242.

***Corresponding author:** Salvatore Patanè, Cardiologia Ospedale San Vincenzo - Taormina (Me) Azienda Sanitaria Provinciale di Messina, Italy, Contrada Sirina, 98039 Taormina (Messina), Italy, Tel: +393402783962; E-mail: patane-@libero.it

Citation: Patanè S (2014) Human Ether-a-go-go-Related Gene K(+) Channels [HERG] in Neurocardiology Field. J Cardiol Neuro Cardiovasc Dis 1: 004.

Received: September 03 2014; **Accepted:** November 27, 2014; **Published:** December 11, 2014

6. Patanè S, Marte F, Di Bella G, Currò A, Coglitore S (2008) QT interval prolongation, torsade de pointes and renal disease. Int J Cardiol 130: 71-73.

7. Patanè S, Marte F, Di Bella G (2009) QT interval prolongation and torsade de pointes. Int J Cardiol. 131: 51-53.

8. Sun H, Xia M, Shahane SA, Jadhav A, Austin CP, et.al. (2013) Are hERG channel blockers also phospholipidosis inducers? Bioorg Med Chem Lett 23: 4587-4590.

9. Leung JY, Barr AM, Procyshyn RM, Honer WG, Pang CC (2012) Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol Ther 135: 113-122.

10. Keller GA, Ponte ML, Di Girolamo G (2010) Other drugs acting on nervous system associated with QT-interval prolongation. Curr Drug Saf 5:105-111.

11. Keller DI, Grenier J, Christé G, Dubouloz F, Osswald S, et.al. (2009) Characterization of novel KCNH2 mutations in type 2 long QT syndrome manifesting as seizures. Can J Cardiol 25: 455-462.

12. Alvarez PA, Pahissa J (2010) QT alterations in psychopharmacology: proven candidates and suspects. Curr Drug Saf 5: 97-104.

13. Roberto La Rocca, Giulia Ferrari-Toninelli G, Selvatore Patane (2014) Widened QRS interval and left ventricular systolic depression after propafenone and promazine exposure. International Journal of Cardiology 177: 57-60.

14. La Rocca R, Foschi A, Preston NM, Ceriani C, Materia V, et al. (2012) QT interval prolongation and bradycardia in lithium-induced nephrogenic diabetes insipidus. Int J Cardiol 162: 1-2.

15. Hu C, Yan C, Lin J, Liu S, Li Y (2011) Down-regulation of the human ether-a-go-go-related gene in rat cardiac hypertrophy. Am J Med Sci 341: 119-125.

16. Ji H, Tucker KR, Putzier I, Huertas MA, Horn JP, et al. (2012) Functional characterization of ether-à-go-go-related gene potassium channels in midbrain dopamine neurons - implications for a role in depolarization block. Eur J Neurosci 36: 2906-2916.

17. Pessia M, Servettini I, Panichi R, Guasti L, Grassi S, et al. (2008) ERG voltage-gated K^+ channels regulate excitability and discharge dynamics of the medial vestibular nucleus neurones. J Physiol 586: 4877-4890.

18. Nedergaard S (2004) A $Ca2^+$-independent slow afterhyperpolarization in substantia nigra compacta neurons. Neuroscience 125: 841-852.

19. Canavier CC, Oprisan SA, Callaway JC, Ji H, Shepard PD (2007) Computational model predicts a role for ERG current in repolarizing plateau potentials in dopamine neurons: implications for modulation of neuronal activity. J Neurophysiol 98: 3006-3022.

20. D'Adamo MC, Catacuzzeno L, Di Giovanni G, Franciolini F, Pessia M (2013) K(+) channelepsy: progress in the neurobiology of potassium channels and epilepsy. Front Cell Neurosci 7: 134.

21. Yu N, Tucker KR, Levitan ES, Shepard PD, Canavier CC (2014) Implications of cellular models of dopamine neurons for schizophrenia. Prog Mol Biol Transl Sci 123: 53-82.

22. Omichi C, Momose Y, Kitahara S (2010) Congenital long QT syndrome presenting with a history of epilepsy: misdiagnosis or relationship between channelopathies of the heart and brain? Epilepsia 51: 289-292.

23. Tu E, Bagnall RD, Duflou J, Semsarian C (2011) Post-mortem review and genetic analysis of Sudden Unexpected Death in Epilepsy (SUDEP) cases. Brain Pathol 21: 201-208.

24. Zamorano-León JJ, Yañez R, Jaime G, Rodriguez-Sierra P, Calatrava-Ledrado L (2012) KCNH2 gene mutation: a potential link between epilepsy and long QT-2 syndrome. J Neurogenet 26: 382-386.

25. Babcock JJ, Li M (2013) hERG channel function: beyond long QT. Acta Pharmacol Sin 34: 329-335.