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Review Article

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

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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 Several HERG-blockers have withdrawn post-approval surveillance [2-4].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].

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