

Electrophysiological cardiac safety assessment in drug discovery and development



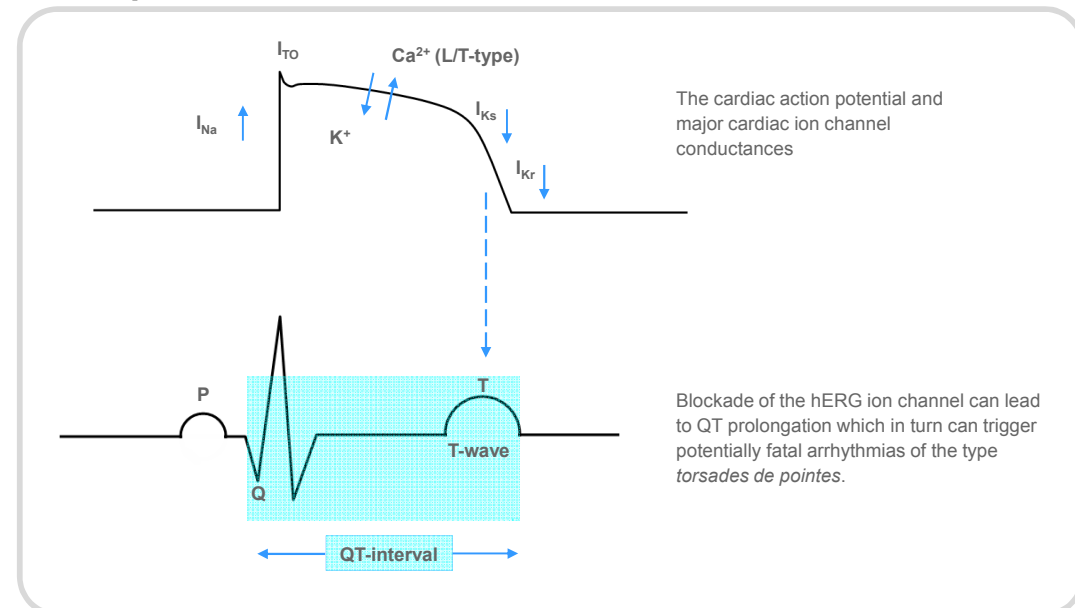
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Introduction

In recent years the cardiac human ether-à-go-go related gene (hERG) potassium ion channel was identified as a notorious off-target with the potential to induce life threatening arrhythmias of the type *torsades de pointes* (TdP). Liability for the hERG ion channel has been shown for compounds with diverse chemical structures, stemming from different therapeutic areas. Testing of drugs for potential hERG interactions has thus become standard in drug discovery and development.

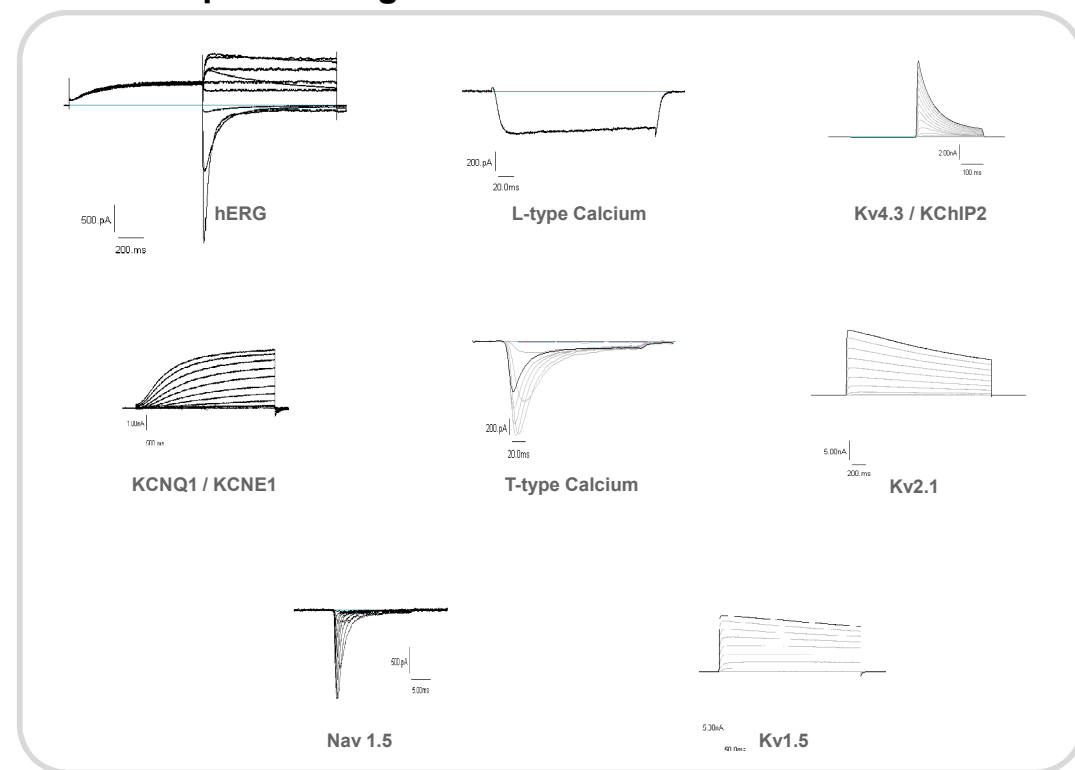
With an increased understanding of the molecular players of the cardiac action potential, and the physiology involved in cardiac function, new test systems that deliver information on cardiac safety beyond pure hERG blockade are being developed. Here we present electrophysiological measurements of stem cell derived cardiac myocytes as a valuable tool for cardiac safety assessment of drugs.

A complex concert of ion channels shapes the cardiac action potential

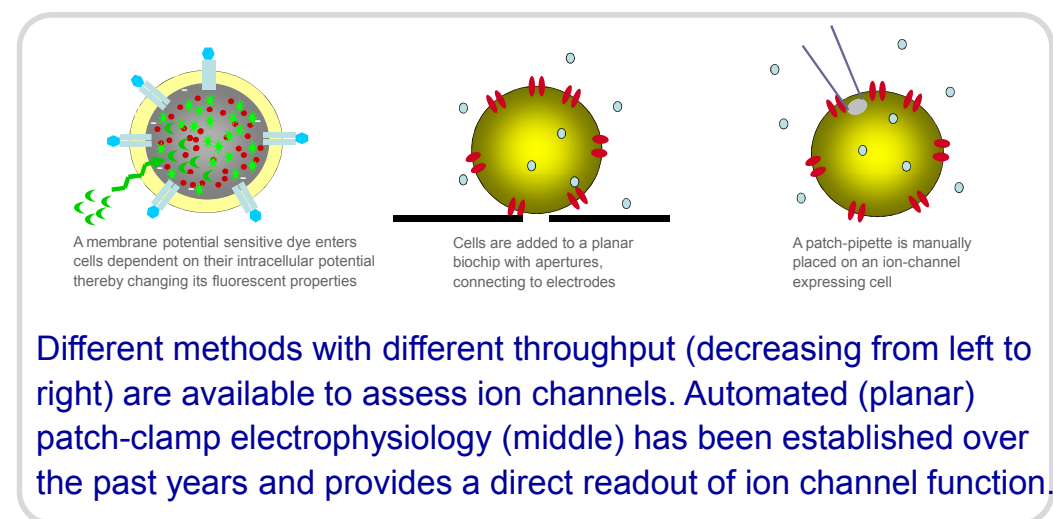


Many compounds have been shown to interact with the hERG ion channel, however not all of these compounds have been observed to induce arrhythmias. On the other hand, compound-induced cardiac side effects have been observed without the hERG ion channel being affected. One reason for this is that interactions with cardiac ion channels in addition to hERG blockade can mitigate or exacerbate hERG effects.

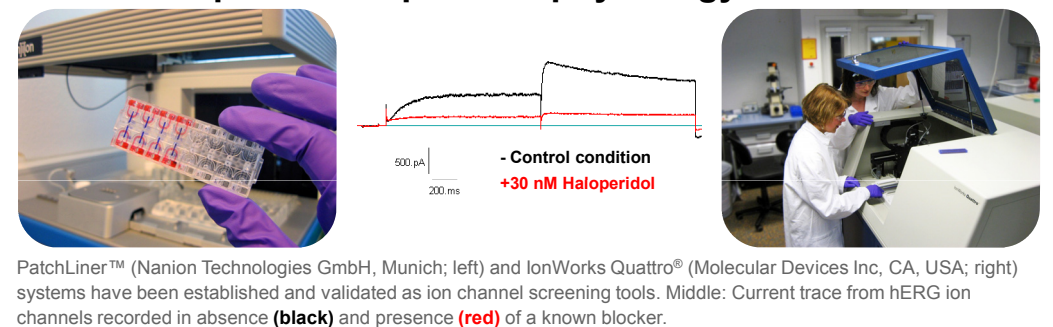
Patch clamp recordings from cardiac ion channels



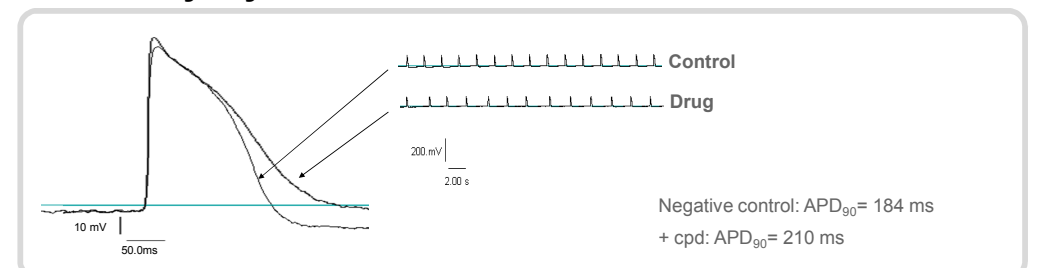
Methods to assess ion channel function



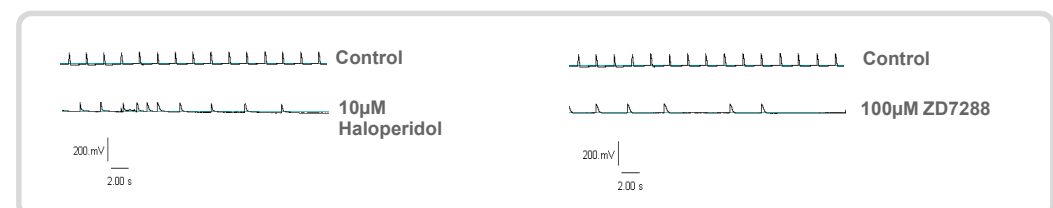
Automated patch-clamp electrophysiology hardware



Action potential recordings in stem cell derived cardiac myocytes



Current-clamp recordings from spontaneously beating cardiac myocytes (from mouse; Cor.AT® cells, Axiogenesis AG, Cologne) have been performed, and action potentials measured. At low concentrations of certain pro-arrhythmic reference compounds, a prolongation of the action potential can be observed (top). At increased concentrations, the continuous beating of the myocytes was disturbed, corresponding to obvious arrhythmias (bottom).



Summary

hERG interaction is a major concern in drug discovery and development. However, interactions with cardiac ion channels in addition to hERG blockade can mitigate or exacerbate hERG effects. Therefore, it is not only essential to identify hERG interacting compounds early during the drug discovery and development process, e.g. by automated patch-clamp electrophysiology, but also to understand the potential effects of compounds on the cardiac action potential. We show here that stem cell derived cardiac myocytes as homogenous cell populations are amenable to electrophysiological analysis of compound effects on the cardiac action potential. Investigations of compound effects using these cells will certainly help to improve our understanding of compound effects on the cardiac action potential, thus increasing the safety for patients and avoiding costs due to failure of projects in later phases.