Constitutively Open HERG Mutant Channels Enable More Accurate and Efficient Drug Screening

Published date: March 14, 2017

Technology description

The human ether-a-go-go related gene (HERG) encodes a potassium channel that is expressed in the heart. Mutations in the HERG channel are a common cause of long QT syndrome, a disorder associated with delayed cardiac repolarization, prolonged electrocardiographic QT intervals, and the development of ventricular arrhythmias and sudden death. Therapeutic compounds can also block potassium channel activity, causing an acquired form of long QT syndrome.
Because it currently is not possible to predict if a compound will block HERG activity based on its structure, drugs, lead compounds and compound libraries commonly are screened for their effect on HERG channels early in development. Under normal conditions, HERG channels are in a closed or resting state where the drug-binding site is inaccessible. When the channels become active or open, drugs can access and bind to a domain within the channel pore to block it. However, most higher throughput screening assays do not fully activate HERG channels, leading to inaccurate measurements of compound potency. UW-Madison researchers have developed double mutant HERG channels that remain open at all times. They found that mutating two amino acid residues causes HERG channels to remain open under resting conditions—at physiological voltages the channel does not close. The channel pore is not altered (it remains potassium selective and has normal drug binding properties). Because these channels do not need to be activated before screening and still can be blocked by channel-blocking compounds, they could be used to screen drugs more efficiently and accurately.

Application area

Drug screening

Advantages

Provides a faster, simpler and more effective way to screen compounds for their effects on HERG channels
Eliminates a problematic and time-consuming step in screening assays, since the channels do not need prior activation
Cells expressing the mutant channels react more quickly and precisely to channel-blocking drugs than cells expressing wild type channels.

Institution

Wisconsin Alumni Research Foundation

Inventors

Christine Klemens
Brian Delisle