Mechanism of HERG potassium channel inhibition by tetra-n-octylammoniumbromide,benzethonium chloride, domiphen bromide and didecyldimethylammonium bromide

Yan Long[1], Zuoxian Lin[1], Hongmao Sun[2], Menghang Xia[2], Wei Zheng[2], Li Zhiyuan[1*]

[1]Key Laboratory of Regenerative Biology, Guangzhou Institute of Biomedicine and Health, ChineseAcademy of Sciences, Guangzhou 510530, China

[2]NationalCenter for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD20892, USA

Abstract

Tetra-n-octylammoniumbromide, benzethonium chloride, domiphen bromide and didecyldimethylammonium bromide are synthetic quaternary ammonium salts that are widely used in hospitals and industries for the disinfection and surface treatment and as the preservative agent. Recently, the activities of HERG channel inhibition by these compounds have been found to have potential risks to induce the long QT syndrome and cardiac arrhythmia, although the mechanism of action is still elusive. This study was conducted to investigate the mechanism of HERG channel inhibition by these compounds using whole-cell patch clamp experiments in a CHO cell line stablyexpressingHERGchannels.Tetra-n-octylammonium bromide, benzethonium chloride, domiphen bromide and didecyldimethylammonium bromideexhibited concentration-dependent inhibitions of HERG channel currents with IC50 values of 4, 17, 9 and 5 nM, respectively, which were also voltage-dependent and use-dependent. Tetra-n-octylammonium bromide and benzethonium chloride shifted the channel activation I–V curves in a hyperpolarized direction for 10–15 mV and accelerated channel activation and inactivation processes by 2-fold. In addition, tetra-n-octylammonium bromide shifted the inactivation I–V curve in a hyperpolarized direction for 24.4 mV and slowed the rate of channel deactivation by 2-fold, whereas benzethonium chloride did not. Domiphen bromide and dodecyl

dimethylammonium bromide caused substantial negative shift of the activation curves, accelerated activated process, but had no effects on the deactivation and reactivation processes. The results indicate that these compoundsare open-channel blockers that inhibit HERG channels in the voltage-dependent, use-dependent and state-dependent manners.