

RESEARCH ARTICLE

Electrophysiological evaluation of an anticancer drug gemcitabine on cardiotoxicity revealing down-regulation and modification of the activation gating properties in the human rapid delayed rectifier potassium channel

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Abstract

Gemcitabine is an antineoplastic drug commonly used in the treatment of several types of cancers including pancreatic cancer and non-small cell lung cancer. Although gemcitabine-induced cardiotoxicity is widely recognized, the exact mechanism of cardiac dysfunction causing arrhythmias remains unclear. The objective of this study was to electrophysiologically evaluate the proarrhythmic cardiotoxicity of gemcitabine focusing on the human rapid delayed rectifier potassium channel, hERG channel. In heterologous hERG expressing HEK293 cells (hERG-HEK cells), hERG channel current (I_{hERG}) was reduced by gemcitabine when applied for 24 h but not immediately after the application. Gemcitabine modified the activation gating properties of the hERG channel toward the hyperpolarization direction, while inactivation, deactivation or reactivation gating properties were unaffected by gemcitabine. When gemcitabine was applied to hERG-HEK cells in combined with tunicamycin, an inhibitor of N-acetylglucosamine phosphotransferase, gemcitabine was unable to reduce I_{hERG} or shift the activation properties toward the hyperpolarization direction. While a mannosidase I inhibitor kifunensine alone reduced I_{hERG} and the reduction was even larger in combined with gemcitabine, kifunensine was without effect on I_{hERG} when hERG-HEK cells were pretreated with gemcitabine for 24 h. In addition, gemcitabine down-regulated fluorescence intensity for hERG potassium channel protein in rat neonatal cardiomyocyte, although hERG mRNA was unchanged. Our results suggest the possible mechanism of arrhythmias caused by gemcitabine revealing a down-regulation of I_{hERG} through the post-translational glycosylation disruption possibly at the