QT interval and risk of long QT-related arrhythmias exhibit gender difference: however, underlying mechanisms are not fully understood. We examined the acute effects of sex hormones on cardiac ion channels, and the underlying molecular mechanisms. Testosterone, progesterone, and high concentration of estrogen shortened action potential duration (APD) by activating IKs in the basal condition, and inhibited ICa,L in cAMP-stimulated condition, both via nitric oxide (NO) produced through the non-genomic pathway. IKs activation was due to s-nitrosylation of KCNQ1 in the C-terminus in a calmodulin-dependent manner, while ICa,L inhibition via cGMP-dependent activation of phosphodiesterase and cAMP breakdown. The non-genomic generation of NO occurred in a signal pathway localized in lipid raft/caveola. N-terminal truncated form of sex hormone receptors appeared to be involved. High concentration of estrogen prolonged APD by directly inhibiting IKr independent of estrogen receptor. Incorporation of these effects in a computer simulation model recapitulated longer QT interval and higher incidence of torsade de pointes (TdP) in women, especially in luteal phase of menstrual cycle. Thus, the non-genomic regulation of cardiac K+ and Ca2+ channels by sex hormones may be involved, at least in part, in gender difference in long QT-related arrhythmias.

Keywords: long QT, sex hormone, nitric oxide