Another jigsaw piece in the complex picture of hormonal regulation of cardiac repolarization

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This editorial refers to ‘Estradiol regulates human QT-interval: acceleration of cardiac repolarization by enhanced KCNH2 membrane trafficking’, by L. Anneken et al., on page 640.

Albert Einstein once said, ‘The important thing is not to stop questioning . . . It is enough if one tries merely to comprehend a little of this mystery every day’. In this spirit, in their study presented in this issue, Anneken et al.1 tried to add another jigsaw piece in the intriguing and complex puzzle of sex hormones and cardiac repolarization.

For quite a while, sex differences in cardiac repolarization, with longer QT intervals in adult women than in men, have been appreciated clinically. This phenomenon can be found in healthy subjects and in patients with inherited long QT syndrome (LQTS) harbouring mutations in repolarizing ion channel genes.2 In addition, changes in QT duration and the concomitant long QT–related arrhythmic risk have been observed during the menstrual cycle, pregnancy and the post-partum phase,3,4 strongly suggesting a major role of sex hormones in regulating cardiac repolarization.

The more we investigate potential mechanisms underlying these sex hormone effects, however, the more complex is the picture that emerges4 (Figure 1). This may be partly due to the fact that studies have been performed in various species using various hormone concentrations,5 which can exert opposing effects on cardiac repolarization and arrhythmogenic risk,6,7 and partly due to the fact that most studies focus on one ion channel/current at a time without systematically assessing and integrating data on all ion currents.

Based on studies in rabbits and guinea pigs, it has been postulated that sex differences in repolarizing voltage-gated rapid delayed rectifier current (HERG, KCNH2) are of major importance for the observed sex differences in cardiac repolarization. Larger IKr current densities have been observed in males than in females due to a testosterone-mediated increase in IKr and an oestradiol-mediated decrease in IKr,6 causing a longer QT/action potential duration (APD) and a higher propensity of female hearts for long QT–related arrhythmia. Similarly, in human cardiac tissue, reduced mRNA and protein expression of KCNH2/HERG has been demonstrated in females compared vs. males.8 In addition, sex hormone effects on voltage-gated slow delayed rectifier current (IKs and ICa,L) and the consecutive QT/APD shortening are thought to mainly account for the observed changes of QT interval during the menstrual cycle and pregnancy.

Here, another seemingly diverging piece is introduced to this complex picture by Anneken et al.1 In their detailed, elegantly performed study, they investigate the effect of oestradiol (physiological levels during pregnancy and post-partum and high oestradiol levels during clomiphene stimulation for infertility) on QT duration in human subjects and assess oestradiol effects on IKr and KCNH2/HERG channel trafficking in vitro in human embryonic kidney (HEK) cells. Unexpectedly, and in contrast to our current knowledge, they identify a QT shortening with increasing oestradiol levels along with increased KCNH2/HERG channel trafficking to the membrane and increased IKr current densities. Even more intriguingly, no such effect on QT duration is seen with increasing progesterone ones, although the data of patients during pregnancy suggest a negative correlation between progesterone levels and QT duration. Here, further studies in larger patient cohorts are clearly warranted.

This study, and its pronounced differences compared with previous studies in animal models, demonstrates the importance of investigating mechanisms of sex hormone effects on repolarization in human subjects and human tissue/cells to solve the complex riddle of hormonal regulation of cardiac repolarization and arrhythmogenic risk. In the future, novel techniques such as induced pluripotent stem cell–derived cardiomyocytes might further help us to reveal sex hormone effects in a ‘cardiomyocyte-like’ environment rather than in heterologous expression systems.

The clinically observed distinct sex differences in cardiac repolarization and known sex hormone effects on various repolarizing ion...
channels/currents suggest that, in the future, sex hormone–based drugs might be utilized as novel anti-arrhythmic therapies. The authors also state that the observed oestradiol-induced QT shortening could potentially be exploited as a therapeutic approach in LQTS. However, this suggestion should be considered very cautiously and might even be premature since oestradiol also exerts a contrasting pronounced pro-arrhythmic effect, increasing the incidence of ventricular arrhythmia and sudden cardiac death in transgenic LQT2 rabbits due to increased ICa,L currents and early afterdepolarization formation.12 Before we better understand this complex interaction and species-dependent variations, it might be too early to exploit hormonal treatment as an anti-arrhythmic therapeutic option. Moreover, in general, it will be challenging to establish future sex hormone–based anti-arrhythmic therapies due to potential systemic side effects via steroid receptors expressed in other organs and since different synthetic hormone derivatives may have unspecific actions via other sex hormone receptors. Several cases and clinical studies have demonstrated that in contrast to pure progesterone,12 synthetic progesterone derivatives that have additional partial oestradiol-mimicking effects lack any anti-arrhythmic effects14 and that combined oestradiol–gestagene treatment as it is used for contraception lacks effects on cardiac repolarization and arrhythmogenic risk.15

Overall, the complex hormonal impact on all major repolarizing ion channels/currents and Ca2+ handling proteins, and their partly contrasting and thus (simultaneously) pro- and anti-arrhythmic effects, clearly warrant further detailed investigation. This article adds an interesting, yet only partially fitting, piece to the puzzle. However, if we listen to Isaac Asimov, who said ‘The most exciting phrase to hear in science. . . . is not ‘Eureka!’ but ‘That’s funny. . . .’’ exciting times are ahead.

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References


