CONTEMPORARY REVIEW

How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity

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Gender differences in cardiac repolarization and the arrhythmogenic risk of patients with inherited and acquired long QT syndromes are well appreciated clinically. Enhancing our knowledge of the mechanisms underlying these differences is critical to improve our therapeutic strategies for preventing sudden cardiac death in such patients. This review summarizes the effects of sex hormones on the expression and function of ion channels that control cardiac cell excitation and repolarization as well as key proteins that regulate Ca^{2+} dynamics at the cellular level. Moreover, it examines the role of sex hormones in modifying the dynamic spatiotemporal (regional and transmural) heterogeneities in action potential duration (eg, the arrhythmogenic substrate) and the susceptibility to (sympathetic) triggered activity at the tissue, organ, and whole animal levels. Finally, it explores the implications of these effects on the management of patients with LQTS.

KEYWORDS Long QT syndrome; Mechanisms of arrhythmogenesis; Dispersion of cardiac repolarization; Early afterdepolarizations; Gender differences; Sex hormones; Ion channels; Ca^{2+} cycling proteins; Adrenoceptors; Animal models

ABBREVIATIONS **APD** = action potential duration; **EAD** = early afterdepolarization; $\mathbf{I_{Ca,L}}$ = L-type Ca^{2+} current; $\mathbf{I_{K1}}$ = inward rectifier K^+ current; $\mathbf{I_{Kr}}$ = rapid delayed rectifier K^+ current; $\mathbf{I_{Ks}}$ = slow delayed rectifier K^+ current; **KCNE1** = β-subunit to KvLQT1 to form slow delayed rectifier K^+ current; **KCNE2** = β-subunit to HERG to form slow delayed rectifier K^+ current; **LQTS** = long QT syndrome; **LQT#** = LQT type #; **NCX** = sodium-calcium exchanger; **PLN** = phospholamban; **pVT** = polymorphic ventricular tachycardia; **QT/RR** = QT interval-to-RR interval ratio; **RyR2** = ryanodine receptor; **SCD** = sudden cardiac death; **SERCA** = sarcoplasmic reticulum ATPase; **SR** = sarcoplasmic reticulum

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A. Introduction

Women with inherited or acquired long QT syndrome (LQTS) have longer QT intervals and are more prone to develop additional drug-induced QT prolongation, polymorphic ventricular tachycardia (pVT), and sudden cardiac death (SCD) than men.[1,2] Several observations suggest an important role for sex hormones in conferring these gender differences; different phases of the menstrual cycle, pregnancy, and the postpartum period are all associated with changes in QT duration and the incidence of pVTs in patients with LQTS.[3,4]

This review explores the mechanisms underlying these gender differences and sex hormone effects at the cellular, tissue, organ, and whole animal levels in order to identify potential novel therapeutic approaches to prevent arrhythmias and SCD in patients with LQTS. Specifically, it recapitulates cellular sex hormone effects on the transcription, protein expression, posttranslational modification, and function of cardiac ion channels and Ca^{2+} cycling proteins. Moreover, this review explores sex hormone effects on the arrhythmogenic substrate and triggered activity and their modulation by sympathetic stimulation.

B. Cellular level: Mechanisms underlying gender differences and sex hormone effects on ion channels, Ca^{2+} cycling proteins, and triggered activity

The major determinants of the duration of cardiac repolarization include repolarizing voltage-gated rapid delayed rectifier K^+ current (I_{Kr}; α-subunit HERG), slow delayed rectifier K^+ current (I_{Ks}; α- and β-subunits KvLQT1 and KCNE1), and inward rectifier K^+ current (I_{K1}; Kir2.1) as

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well as depolarizing L-type Ca^{2+} current ($I_{Ca,L}$; α-subunit Cav1.2) and the activity of Na^+/K^+ ATPase. I_{Kr} and I_{K1} are lower in ventricular cardiomyocytes of female rabbits than in males.[5] The lower I_{Kr} in females that reduces the "repolarization reserve" is thought to be of major importance for females' higher sensitivity to I_{Kr}-blocking drugs and their prolonged action potential duration (APD).[5] The increased activity of cardiac Na^+/K^+ ATPase in female rats[6] that shortens the duration of cardiac repolarization, particularly at fast heart rates, may contribute to the steepening of the QT interval-to-RR interval ratio (QT/RR) slope in females. Recently, similar findings of gender differences in cardiac repolarizing ion currents have been detected in human cardiac tissue derived from nondiseased transplant donors. By using a high-throughput quantitative approach, Gaborit et al[7] demonstrated lower transcript and protein expression of several repolarizing K^+-channel subunits, such as HERG, KCNE1, and Kir2.3, in female cardiac tissue derived from right ventricular and left ventricular base regions as compared with analogous male tissue.

Sex hormone effects on the (regionally heterogeneous) expression and function of these ion channels may contribute to gender differences in the arrhythmogenic substrate. Sex hormones may influence the expression and function of cardiac ion channels via sex hormone receptor–mediated genomic modulation of their expression or of their post-translational phosphorylation state or by an acute, non-genomic regulation of ion current densities involving nitric oxide[8].

However, since the concentrations of sex hormones used and durations of hormone treatment vary, it is challenging to integrate data from all available studies into one concise picture. Ideally, sex hormone effects should be studied using physiological hormone dosages: for example, (1) estradiol concentrations could range from 15 to 350 pg/mL corresponding to the physiological levels in postpubertal premenopausal women during different phases of the normal menstrual cycle and could reach up to 7000 pg/mL as during pregnancy; (2) progesterone concentrations could range from 0.3 to 1.2 ng/mL corresponding to the physiological levels during the follicular phase, from 1.7 to 27 ng/mL as during the luteal phase, and could reach up to 340 ng/mL as during pregnancy; (3) dihydrotestosterone concentrations could range from 120 to 1000 pg/mL and testosterone concentrations could range from 3000 to 12,000 pg/mL corresponding to the physiological levels in healthy postpubertal adult men (reference ranges from the American College of Physicians and the Mayo Clinic). However, in the different studies available, estradiol concentrations ranging from 30 to 2000 ng/mL, progesterone concentrations from 0.3 to 3000 ng/mL, dihydrotestosterone concentrations from 200 to 900 pg/mL, and testosterone concentrations from 300 to 300 ng/mL were used. This is particularly important, since it is known (1) that sex hormone concentrations above naturally occurring physiological levels may exert differential, partially opposing effects on ion currents and channel expression (as demonstrated for estradiol's effects on I_{Kr}[9]) and (2) that acute and chronic hormone effects may counteract each other (as demonstrated for testosterone's effects on $I_{Ca,L}$[10]). Since rabbits have repolarizing ion current characteristics similar to those of humans and mimic human gender differences in LQTS-related arrhythmias and cardiac repolarization,[5,11,12] this review focuses mainly on rabbit studies investigating sex hormone effects on cardiac repolarizing currents at both the whole heart and animal levels.

I_{Kr} can be directly inhibited by estradiol[9,13] and can also be reduced indirectly by estradiol-induced increased transcription of the β-subunit KCNE2.[14] Moreover, estradiol and I_{Kr}-blocking drugs exert a synergistic effect on I_{Kr}.[13] In contrast, testosterone acutely increases I_{Kr} and I_{K1}[15], while other sex hormones have no direct effect on the inward rectifier current. Similarly, I_{Ks} can be acutely increased by testosterone or progesterone via a nongenomic pathway involving nitric oxide,[8] while estradiol indirectly reduces I_{Ks} by downregulating mRNA levels of the β-subunit KCNE1.[16] Thus far, sex hormone effects on the expression and activity of Na^+/K^+ ATPase have only been investigated in arteries (not in cardiomyocytes), demonstrating an estradiol-induced increased function and mRNA expression of its isoform 2.[17] Whether similar sex hormone effects may be found in cardiac muscle–specific isoforms remains to be investigated. All these hormone-induced alterations of ion current densities or the expression of its subunits result in a net estradiol-induced prolongation of APD and a net testosterone- and progesterone-induced shortening of APD (Table 1).

Reactivation of $I_{Ca,L}$ plays an important role in the formation and propagation of early afterdepolarizations (EADs).[18] In addition, Ca^{2+} cycling proteins such as the ryanodine receptor (RyR2), the sodium-calcium exchanger (NCX), the sarcoplasmic reticulum ATPase (SERCA) 2a pump, phospholamban (PLN), and the Ca^{2+}-calmodulin-dependent protein kinase II are known to contribute to or prevent the formation of EADs by altering cytoplasmic and sarcoplasmic reticulum (SR) Ca^{2+} concentrations, spontaneous Ca^{2+} release, and Ca^{2+} transient characteristics. An increased intracellular Ca^{2+} concentration or spontaneous SR Ca^{2+} release may thereby activate NCX in its forward mode, thus prolonging APD to allow the activation of the $I_{Ca,L}$ "window current" or the reactivation of sodium current I_{Na} in late phase 3 repolarization, thereby eliciting an EAD.

Sex hormone effects on the expression and function of Ca^{2+} cycling proteins may thus contribute to gender differences in the susceptibility to triggered activity (Table 1). Since protein kinase A or Ca^{2+}-calmodulin-dependent protein kinase II–mediated phosphorylation of these Ca^{2+} cycling proteins alters their function, for example, phosphorylation of L-type Ca^{2+} channel increases $I_{Ca,L}$, phosphorylation of PLN diminishes its inhibitory effects on SERCA, and phosphorylation of RyR2 increases its open probability, sex hormones may exert their effects on the activity of Ca^{2+}