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

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Abstract

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 (e.g., 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 LQTS patients.

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

Introduction

Women with inherited or acquired long-QT syndrome (LQTS) have longer QT intervals and are more prone to develop additional drug-induced QT prolongations, 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

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are all associated with changes in QT duration and the incidence of pVTs in LQTS patients[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 LQTS patients. Specifically, it recapitulates cellular sex hormone effects on the transcription, protein expression, post-translational 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.

Cellular level: Mechanisms underlying gender differences and sex hormone effects on ion channels, calcium cycling proteins, and triggered activity

Major determinants of the duration of cardiac repolarization include repolarizing voltage-gated rapid delayed rectifier current I_{Kr} (alpha-subunit HERG), slow delayed rectifier current I_{Ks} (alpha- and beta-subunits KvLQT1 and KCNE1), and inward rectifier current I_{K1} (Kir2.1), as well as depolarizing L-type Ca^{2+} current $I_{Ca,L}$ (alpha-subunit Cav1.2) and the activity of Na^+/K^+ ATPase. I_{Kr} and I_{K1} current densities are lower in ventricular cardiomyocytes of female rabbits than in males[5]. The lower I_{Kr} current density 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]. 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/RR slope in females. Recently, similar findings of gender differences in cardiac repolarizing ion currents have also been detected in human cardiac tissue derived from non-diseased transplant donors. 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 RV and LV base regions, 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 posttranslational phosphorylation state or by an acute, non-genomic regulation of ion current densities involving nitric oxide[8] (Table 1).

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; e.g., 1) Estradiol concentrations could range from 15 to 350 pg/ml corresponding to the physiological levels in post-pubertal premenopausal women during the different phases of normal menstrual cycle and could reach up to 7,000 pg/ml as during pregnancy, 2) Progesterone concentrations could range from 0.3 to 1.2 ng/ml corresponding to the physiological levels during follicular phase, from 1.7 to 27 ng/ml as during 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 post-pubertal adult men (ACP reference ranges, Mayo Clinic reference ranges). However, in the different studies available, estradiol concentrations ranging from 30 pg/ml up to 2,000 ng/ml, progesterone concentrations from 0.3 up to 3,000 ng/ml, dihydrotestosterone concentrations from 200 up to 900 pg/ml, and testosterone concentrations from 300 pg/ml up to 300 ng/ml were utilized. 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 humans and mimic human gender differences in LQT-related arrhythmias and cardiac repolarization[5, 11, 12], this review focuses mainly on rabbit studies investigating sex hormone effects on cardiac repolarizing currents on 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 beta-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 non-genomic pathway involving NO[8], while estradiol indirectly reduces I_{Ks} by downregulating mRNA levels of the beta-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 $I_{Ca,L}$ currents plays an important role in the formation and propagation of early afterdepolarizations (EADs)[18]. Additionally, Ca^{2+} cycling proteins such as the ryanodine receptor (RyR2), the sodium calcium exchanger (NCX), the sarcoplasmic reticulum ATPase 2a pump (SERCA), phospholamban (PLN), and the Ca^{2+}-calmodulin-dependent protein kinase-II (CaMKII) 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 action potential duration to allow the activation of the window $I_{Ca,L}$ current or the re-activation of 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 PKA- or CamKII-mediated phosphorylation of these Ca^{2+} cycling proteins alters their function – e.g., phosphorylation of L-type Ca^{2+} channel increases $I_{Ca,L}$ current, 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+} cycling proteins partly by altering their phosphorylation state. Moreover, since previous studies have demonstrated gender differences in intracellular Ca^{2+} transient characteristics with longer Ca^{2+} transient durations, as well as a slower rate of rise and a greater spatial Ca^{2+} transient variability in female rats' cardiomyocytes[19, 20], sex hormone effects on Ca^{2+} cycling proteins may also account for differences in Ca^{2+} transients. Indeed, estradiol increases Ca^{2+} transient amplitudes in rat cardiomyocytes[21], while testosterone shortens Ca^{2+} transient duration[22].

Since most studies investigating sex hormone effects on Ca^{2+} cycling properties and Ca^{2+} transients were performed on rodents, we have integrated this information into the review, despite the fact that rodents have different repolarization characteristics than human subjects and lack some of the gender differences in cardiac repolarization and arrhythmia vulnerability observed in human subjects[11, 23]. Moreover, $I_{Ca,L}$ recovery from inactivation, which is important for EAD formation, requires an action potential long enough to enable the reactivation of the L-type Ca^{2+} "window current" within its voltage range[24]. The AP in rodents, however, is too short for the reactivation of the $I_{Ca,L}$ window current. Thus, data on sex hormone effects on Ca^{2+} cycling properties from rodents may not necessarily reflect (all) sex hormone effects on Ca^{2+} dynamics and triggered activity in human subjects. Nevertheless, we added this information since these data may give some idea about the effects of sex hormones on Ca^{2+} dynamics that may contribute to their pro- or anti-arrhythmic effects.

Estradiol increases $I_{Ca,L}$ current density in rabbits, likely enhancing the propensity to develop EADs[25]. Acute and chronic progesterone and acute testosterone exposure, in contrast, decrease $I_{Ca,L}$ current densities[8, 10, 25]. The acute direct $I_{Ca,L}$-blocking effects of testosterone over the physiological range of concentrations will be dominant in the short-term time scale. Chronic exposure to testosterone, however, may eventually result in a contrasting increase in channel expression and $I_{Ca,L}$ current densities (at higher concentrations)[10, 26], though repeated acute exposure to testosterone could mask these chronic effects.

SERCA expression and activity in rats and rabbits are reduced by ovariectomy[27] and can be restored by progesterone and testosterone[25, 27, 28]. This progesterone-induced increased SERCA expression and activity[25] may contribute to progesterone's anti-arrhythmic effect by increasing the Ca^{2+} reuptake into the SR, thus shortening Ca^{2+} transient duration. Thr^{17}-phosphorylation of PLN, which inhibits phospholamban's SERCA-inhibitory effect, is reduced by ovariectomy in rats, resulting in a net reduction of SERCA activity[27]. This effect can be partly reversed by estradiol or progesterone replacement[27]. Ser^{16}-phosphorylation of PLN, in contrast, is reduced by estradiol via an ERβ-mediated mechanism involving PIK3, thus partly counteracting the above-described effects[29]. NCX expression can also be reduced by ovariectomy[30], while estradiol increases its transcription, protein expression, and activity in rabbits, rats, and the embryonic rat cardiomyoblast cell line H9C2[30, 31, 32]. This estradiol-effect may contribute to the increased EAD formation observed in female rabbits. Testosterone also increases NCX transcription and activity in rats[33]. However, increased function of NCX is accompanied and counteracted by testosterone-induced increased

function of SERCA[28], thus leading to a faster removal of Ca^{2+} from the cytosol and shortened Ca^{2+} transient duration (Table 1). In ovariectomized rats, PKA-mediated increased RyR2 activity leads to increased Ca^{2+} release from the SR into the cytosol[33]. Similarly, testosterone increases RyR2 activity[28]. Estradiol, however, increases the leakiness of RyR2 via an ERβ-mediated mechanism, thereby increasing the risk of pro-arrhythmic afterdepolarizations[34]. The net overall effects of sex hormones on Ca^{2+} transients and triggered activity, however, are hard to predict or model due to the lack of comprehensive studies that thoroughly investigated these different and partially opposing effects. There is ample evidence, however, that female gender and estradiol may at least increase $I_{Ca,L}$ currents[25, 32], NCX activity[32] and RyR2 leakiness[34] thus increasing the propensity for triggered activity, while testosterone and progesterone may increase SERCA activity either directly or by altering phospholamban phosphorylation[25, 27, 28] and acutely decrease $I_{Ca,L}$[8, 10, 25] thus reducing the likelihood for triggered activity.

There are known feedback mechanisms between Ca^{2+} transients and action potential duration, including an inactivation of $I_{Ca,L}$ currents induced by SR Ca^{2+} release that results in an APD shortening as well as an increase in NCX activity induced by SR Ca^{2+} release with the opposite (prolonging) effect on APD[35]. Consequently, any sex hormone effects on the activity of Ca^{2+} cycling proteins and Ca^{2+} transients may also indirectly affect APD and may have either synergistic or opposing effects on APD relative to the hormone's direct effects on ion currents. The testosterone-induced increased Ca^{2+} release via RyR2[28] may lead to a faster inactivation of $I_{Ca,L}$, creating a synergistic effect on APD with the testosterone-induced reduction of $I_{Ca,L}$[10]. Similarly, testosterone-induced increased Ca^{2+} release from the SR may enhance NCX activity, creating a synergistic effect with testosterone's direct effects on the transcription and activity of NCX[28], thereby partly counteracting the aforementioned APD-shortening effects. However, the effects of estradiol on the leakiness of RyR2[34] and the increased Ca^{2+} transient amplitudes in rat cardiomyocytes[23] may partly counteract the direct effects of estradiol on $I_{Ca,L}$ and thus on APD. Future studies of the effect of sex hormones on ion currents and Ca^{2+} dynamics should include modelling of these feedback mechanisms to reconcile and integrate sex hormone effects on AP duration and triggered activity.

Sympathetic α_1-adrenergic receptor-activation facilitates EAD formation and prolongs APD by reducing I_{Kr} and I_{K1}. Any sex hormone effects on the response to sympathetic α_1-adrenergic stimulation, such as an estradiol-induced increase in α_1-adrenoceptor responsiveness[36], may therefore affect APD and the susceptibility to EAD formation. β-adrenergic stimulation enhances I_{Ks} via G-protein-mediated phosphorylation of KvLQT1 and thereby shortens APD. Additionally, β-adrenergic stimulation enhances $I_{Ca,L}$ – which, because it occurs faster than that the increase of I_{Ks}, leads to an initial APD prolongation and increased EAD formation in a situation of short sudden sympathetic surge[37]. In the presence of the β-sympathomimetic drug isoproterenol, APD shortens upon faster pacing in male dogs, while the opposite is seen in females[38], strongly suggesting gender differences in the autonomic modulation of I_{Ks} and $I_{Ca,L}$. In rats, ovariectomy induces an upregulation[39] of β_1-adrenoceptor expression, while estrogen induces its downregulation[30, 40]. β_2-adrenoceptor expression, in contrast, is upregulated by estradiol[41] and is higher in female than in male rat cardiomyocytes[41], indicating that sex hormones may indeed modulate

cardiac responses to sympathetic stimulation by altering cardiac expression of β_1 and β_2-adrenergic receptors.

Tissue and organ level: Mechanisms underlying gender differences and sex hormone effects on the arrhythmogenic substrate and triggered activity

Regional and transmural spatial heterogeneities in APD as well as dynamic temporal APD changes, forming the so-called "arrhythmogenic substrate," are of major importance for re-entry formation in arrhythmias related to long QT[42]. Spatial and transmural heterogeneities in I_{Kr}, I_{Ks}, and $I_{Ca,L}$ current densities underlie these pronounced APD heterogeneities in LQTS[43, 44]. However, few studies have investigated gender differences and sex hormone effects on spatial APD heterogeneities and the underlying spatially heterogeneously expressed ion channels at the tissue and organ levels. In female rabbits but not in males, there is a transmural and base-to-apex gradient of $I_{Ca,L}$ with a higher conductance of $I_{Ca,L}$ in epi- than endocardial and basal than apical cells[44, 45]. Ovariectomy eliminates the transmural gradient, which reappears upon treatment with estradiol[44]. In contrast, there is no transmural gradient in orchiectomized rabbits even after exposure to estradiol[44], suggesting a potential gender difference in the mechanism of action of sex hormones. Moreover, estradiol increases the base-to-apex gradient of $I_{Ca,L}$ in rabbits[46]. However, to date, there are no experimental data available analyzing gender differences or sex hormone effects on transmural or base-to-apex distribution of I_{Ks} or I_{Kr} that might contribute to the observed gender differences in dispersion of repolarization.

Moreover, since sympathetic stimulation decreases the transmural dispersion of refractoriness[47], gender differences and sex hormone effects on (spatial inhomogeneities of) β_1 and β_2-adrenoceptor expression might produce marked discrepancies in APD and thereby facilitate ventricular arrhythmias. However, to date, no studies have investigated sex hormone effects on spatial differences in cardiac adrenoceptor expression and activity.

Animal models: Gender differences and sex hormone effects on the arrhythmogenic substrate in animal models of drug-induced and inherited LQTS

Similar to human subjects, rabbits exhibit pronounced gender differences in duration and dispersion of repolarization and are thus often used to explore such differences and their underlying mechanisms. Compared with males, female rabbits have longer QT intervals[5], a steeper QT/RR slope[48], and a more pronounced I_{Kr}-blocker induced QT prolongation and transmural APD dispersion[44].

Experiments involving castration and subsequent exposure to sex hormones can reveal the impact of different hormones on cardiac repolarization: Ovariectomized female and castrated male rabbits exhibit similar ventricular APD_{90}[44]. Moreover, orchiectomized rabbits have longer APD than intact males, while ovariectomized females have decreased drug-induced prolongation of APD compared to intact females[44], thus reversing the normal

gender differences in drug-induced APD or QT prolongation. The normal female phenotype can be mimicked by treating ovariectomized or orchiectomized rabbits with estradiol[16, 44]. Exposure to testosterone, in contrast, shortens QT and reduces the extent of drug-induced QT prolongation[44] (Tables 1 and 2).

In a transgenic LQT2 rabbit model over-expressing a loss-of-function pore mutation of the human HERG channel (HERG-G628S)[49], estradiol steepens the QT/RR slope by prolonging QT particularly at slow heart rates, while testosterone decreases QT/RR steepness[25], thereby mimicking the gender differences observed in human LQT patients (Table 2). Moreover, sex hormones differentially affect APD in different regions of the heart in transgenic LQT2 rabbits, and thus modify spatial APD dispersion. Estradiol induces a particularly pronounced APD prolongation in the LV and RV apex, increasing VF inducibility in estradiol-treated hearts[25]. In contrast, in prepubertal rabbits treated with the I_{Kr}-blocker E4031, male rabbits show a greater base-to-apex dispersion of repolarization and thus a higher incidence of EAD formation than do female rabbits[50], suggesting that other sex-related factors besides sex hormones might influence the extent of dispersion of repolarization during (prepubertal) development.

Animal models: Gender differences and sex hormone effects on triggered activity in animal models of drug-induced and inherited LQTS

Like women, female rabbits have a higher incidence of drug-induced pVTs than males[12]. Castration reverses these gender differences: Orchiectomy increases the incidence of I_{Kr}-blocker-induced EADs, while ovariectomy has the opposite effect[44]. The normal female phenotype can be mimicked by estradiol treatment[16], while combined treatment with estradiol and progesterone reduces the risk of drug-induced arrhythmias[51]. Similarly, testosterone reduces the risk of drug-induced EADs[44] (Table 2).

In transgenic LQT2 rabbits, which develop spontaneous pVT and SCD[49], estradiol exerts a pro-arrhythmic effect *in vivo*, while progesterone exerts an anti-arrhythmic, protective effect and completely abolishes pVTs and SCD[25] (Table 2). On the organ level, a reduced rate of EAD formation in response to sympathetic stimulation has been identified as the mechanism underlying the protective effect of progesterone[25].

Clinical observations: Gender differences in cardiac repolarization and arrhythmogenesis in patients with inherited or acquired LQTS

Patients with inherited LQTS demonstrate pronounced gender differences in cardiac repolarization and in arrhythmogenic risk: Adult women with LQT types 1 and 2 have longer QT intervals, a more pronounced transmural QT-dispersion, and a higher risk of pVTs and SCD than men[2, 52]. Moreover, female gender is a main independent risk factor for increased risk of life-threatening cardiac events during adulthood independent of the genotype or of the location of the mutation within the gene[2, 53]. Interestingly, in female patients with LQT2, the arrhythmogenic risk remains elevated after the onset of menopause[54], suggesting that other gender-related factors besides sex hormones may contribute to gender differences in arrhythmogenesis. Before puberty, however, the

incidence of arrhythmia (particularly in LQT1) is higher in boys than in girls, and the age at first cardiac event is younger in male than female LQT patients[55].

Similarly, drug-induced, acquired LQTS is also strongly influenced by gender. A variety of different drugs that block I_{Kr} currents (including antiarrhythmics, gastrokinetics, antipsychotics, antidepressants, antihistamines, and antibiotics) can cause this serious side effect (see complete list on www.QTDrugs.org). This risk and the extent of drug-induced QT prolongation and pVTs are significantly higher in women than in men, with two-thirds of reported drug-induced pVTs occurring in women[1, 56].

Clinical observations: Impact of sex hormones on the arrhythmogenic substrate and triggered activity in human subjects with inherited or acquired long-QT syndrome

Several observations suggest an important role for sex hormones in conferring these gender differences. The different phases of menstrual cycle, pregnancy, and the postpartum period are all associated with changes in QT duration and the incidence of pVT in patients with inherited and acquired LQTS. In acquired LQTS, drug-induced QT prolongation is more pronounced and the risk for pVTs is higher during menses and the follicular phase (with high estradiol serum levels) than during the luteal phase (with relatively higher progesterone levels)[3]. During pregnancy (with high progesterone levels), LQT2 patients have a reduced arrhythmogenic risk, while the risk markedly increases during the nine months postpartum[4]. These observations strongly suggest a pro-arrhythmic role for estradiol and an anti-arrhythmic effect of progesterone in humans. Additionally, other postpartum-related hormones such as oxytocin and prolactin may contribute to the heightened postpartal arrhythmogenic risk, as indicated in a recent study of transgenic LQT2 rabbits[57].

Conclusions

Observations in human subjects and animal models indicate that the sex hormones estradiol, progesterone, and testosterone are responsible for most of the gender differences observed in the arrhythmogenic substrate (cardiac repolarization), the susceptibility to (sympathetic) triggered activity, and the resulting gender differences in arrhythmia incidence in LQTS. Estradiol prolongs QT duration, increases the risk for additional drug-induced QT prolongation independently of gender, and exerts a pro-arrhythmic effect *in vivo* and *ex vivo*, whereas testosterone and progesterone shorten QT duration and exert an anti-arrhythmic effect with a reduced susceptibility to sympathetic stimuli. Some of the underlying mechanisms involved are: 1) an estradiol-induced decrease in I_{Kr} current densities as well as increases in $I_{Ca,L}$, NCX expression and activity, RyR2 leakiness, Ca^{2+} transient amplitude, and α1- and β2-adrenoceptor responsiveness; 2) a testosterone-induced increase in I_{Kr}, I_{Ks}, and I_{K1} current densities, increased SERCA activity, and shortened Ca^{2+} transient duration; and 3) a progesterone-induced increase in I_{Ks}, increased SERCA expression and activity, and decreased $I_{Ca,L}$ current densities with reduced Ca^{2+} oscillations upon sympathetic stimulation.

However, it is difficult to fully appreciate the complexity of sex hormone effects, not only on different single components of cardiac repolarization and excitability but also on the feedback interaction between Ca^{2+} transients and APD. This is because most studies have investigated hormone effects on only a very limited number of ion channels or Ca^{2+} cycling proteins. Moreover, comprehensive interpretation of data from studies of sex hormone effects on ion channels or Ca^{2+} cycling proteins is limited by the use of different sex hormone concentrations as well as different subject species. For example, mice and rats have different repolarization characteristics than human subjects and lack some of the gender differences in cardiac repolarization and arrhythmia vulnerability observed in human subjects[11, 23]. Rabbits have repolarizing ion currents similar to those of humans and mimic their gender differences in cardiac repolarization and arrhythmogenesis[5, 11, 12]. Ideally the effects of chronic sex hormone treatment should be studied using physiological hormone dosages, simultaneously targeting the activity of multiple ion currents, pumps, and Ca^{2+} dynamics in species with greater similarity to the human heart. Importantly, these studies should address such effects at the cellular, tissue, and organ levels.

Moreover, not all gender differences in cardiac repolarization and arrhythmogenesis can be completely recapitulated and explained by hormonal influences, as gender differences are also found in castrated and in prepubertal rabbits. Here, further investigations are warranted, focusing on possible genetic factors – or epigenetic modifications – responsible for these gender differences.

Clinical implications

As women with inherited LQTS are at higher risk for pVT, syncopes, and SCD than men and are particularly prone to develop lethal VTs during the postpartum phase[2, 4], particularly close clinical monitoring of female LQTS patients is mandatory – especially in phases associated with changing hormone levels. Similarly, as women generally have a higher risk for drug-induced pVTs than men[1], physicians should be particularly cautious when treating women with drugs with potential QT-prolonging properties.

Understanding the exact mechanisms that underlie sex hormone effects on cardiac repolarization and arrhythmogenesis in inherited and drug-induced LQTS will help to better discern the individual risk of LQTS patients and of healthy subjects treated with QT-prolonging drugs. Moreover, this understanding could help to develop future specific hormone-based anti-arrhythmic therapies. A recent community-based study determined that higher estradiol levels were associated with a higher risk for SCD in both sexes also in patients with ischemic heart disease. Those findings suggest an even broader potential impact of a deeper understanding of the exact mechanisms underlying sex hormone effects on arrhythmogenesis for risk stratification and treatment for a greater variety of arrhythmogenic diseases[58].

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List of Abbreviations

APD	action potential duration
EAD	early afterdepolarization
EST	estradiol
DHT	dihydrotestosterone
$I_{Ca,L}$	L-type Ca^{2+} current
I_{K1}	inward rectifier K^+ current
I_{Kr}	rapidly delayed rectifier K^+ current
I_{Ks}	slow delayed rectifier K^+ current
KCNE1	beta-subunit to KvLQT1 to form I_{Ks}
KCNE2	beta-subunit to HERG to form I_{Ks}
LQTS	long-QT syndrome
LV	left ventricle
NCX	sodium calcium exchanger
ORCH	orchiectomy
OVX	ovariectomy
PLN	phospholamban
PROG	progesterone
pVT	polymorphic ventricular tachycardia
RV	right ventricle
RyR	ryanodine receptor
SCD	sudden cardiac death
SERCA	sarcoplasmatic reticulum ATPase
QT/RR	QT-interval to RR-interval ratio steepness

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Table 1

Gender and sex hormone effects on cardiac repolarization and LQT-related arrhythmogenesis on cellular and whole-heart levels

Sex	Intervention	Ion currents	Magnitude of changes	Cardiac region	Level of changes	Species	Ca^{2-}cycling proteins	Magnitude of changes	Cardiac region	Level of changes	Species	APD in rabbits	EADs in LQT rabbits
Male	--------	**↑IKr** **↑IK1** compared to females [5]	**+ 30%** **+ 15%**	LV LV	current current	rabbit rabbit	**↓NCX** compared to females [32]	**−2.5-fold** **−55%**	LV base LV base	activity protein	rabbit rabbit	**↓APD** compared to females [5]	
	ORCH	**↓IKr** **↓IK1** [15]	**−40%** **−50%**	LV LV	current current	rabbit rabbit	**↓RyR2** **↓SERCA** **↓PLN-phos** **↓NCX** [28]	**−25%** **−30%** **−25%** **−15%**	LV LV LV LV	activity, ISO activity, ISO Ser16-phos activity, PE	rat rat rat rat	**↑APD** compared to males [15, 44]	
	ORCH+DHT	**↑IKr** **↑IKs** **↑IK1** **↓ICa,L** **↑ICa,L** [8, 10, 15, 44]	**+ 40%** **+ 45%** **+ 50–60%** **−40%** **−50%** **+ 2.5-fold** **+ 2-fold**	LV LV LV LV LV LV LV	current current, eNOS current current, acute current, acute current, chron protein, chron	rabbit guinea pig rabbit guinea pig rat rat rat	**↑RyR2** **↑SERCA** **↑NCX** [28]	**+ 25%** **+ 30%** **+ 15%**	LV LV LV	activity, ISO activity, ISO activity, PE	rat rat rat	**↓APD** compared to ORCH [15, 44]	
Female	--------	**↓IKr** **↓IK1** **↑ICa.L** (grad) compared to males/OVX [5, 44, 45]	**−30%** **−15%** **+ 30%** **+ 70%** **+ 3-fold**	LV LV LV base LV base LV base	current current current protein mRNA	rabbit rabbit rabbit rabbit rabbit	**↑NCX** compared to males [32]	**+ 2.5-fold** **+ 55%**	LV base LV base	activity protein	rabbit rabbit	**↑APD** compared to males [5]	**↑EADs** compared to DHT and PROG [25]
	OVX						**↑RyR2** **↓SERCA** **↓PLN-phos** **↓NCX** [27, 30, 33]	**+ 2-fold** **−15%** **−25%/−3-fold** **−30%** **−40%**	LV LV LV LV LV apex	activity activity protein/mRNA Thr17-phos protein	rat rat rat rat rat	**↓APD** compared to females [44]	**↑EADs** compared to DHT and PROG [25]
	OVX+EST	**↓IKr** **↑KCNE2** **↑IKs** **↓KCNE1** **↑ICa,L** [8, 9, 13, 14, 16, 25, 44]	**−25–35%** **+ 4.5-fold** **+ 35%** **no expr** **+ 30%** **+ 40–100%** **+ 20%** **+ 30 %**	LV LV LV LV LV apex LV base LV base LV base	current mRNA current mRNA current, chron current protein mRNA	guinea pig rat guinea pig rabbit rabbit rabbit rabbit rabbit	**↑RyR2 leak** **↑PLN** **↓PLN-phos** **↑PLN-phos** **↑NCX** [27, 29, 30, 31, 32, 34]	**+ 50%** **+ 30%** **−10-fold** **+ 30%** **+ 40%** **+ 20–25%** **+ 30%/+30%** **+ 60%/+20%**	LV LV apex LV LV LV apex - - LV base	leakiness mRNA Ser16-phos Thr17-phos protein activity, chron mRNA/protein activity/protein	rat rat rat rat rat rat H9C2 rat H9C2 rabbit	**↑APD** compared to OVX [16, 44]	**↑EADs** compared to DHT and PROG [25]
	OVX+DHT	**↑IKs** [25]	**+ 50%**	LV apex	current, chron	rabbit							**↑EADs**

Sex	Intervention	Ion currents	Magnitude of changes	Cardiac region	Level of changes	Species	Ca^{2-}cycling proteins	Magnitude of changes	Cardiac region	Level of changes	Species	APD in rabbits	EADs in LQT rabbits
													compared to females and compared to females and compared to females and
	OVX+PROG	**↑IKs** **↓ICa,L** [8, 25]	**+ 20–35%** **−30%**, cAMP **−25%**	LV LV LV apex	current, eNOS current, eNOS current, chron	guinea pig guinea pig rabbit	**↑ SERCA** **↑ PLN-phos** [25, 27]	**+ 50%** **+ 15%** **+ 30%**	LV apex LV LV	protein activity Thr17-phos	rabbit rat rat		**↓ EADs** compared to females and EST [25]

APD, action potential duration; EADs, early afterdepolarizations; ORCH, orchiectomy; OVX, ovariectomy; DHT, dihydrotestosterone; EST, estradiol; PROG, progesterone; I_{Kr}, rapidly delayed rectifier K^+ current; I_{Ks}, slow delayed rectifier K^+ current; I_{K1}, inward rectifier K^+ current; $I_{Ca,L}$, L-type Ca^{2+} current; KCNE1, beta-subunit to KvLQT1 to form I_{Ks}; KCNE2, beta-subunit to HERG to form I_{Ks},; NCX, sodium calcium exchanger; SERCA, sarcoplasmatic reticulum ATPase; RyR, ryanodine receptor; LV, left ventricle (region not further specified); grad, base-to-apex gradient. ↑ indicates an increase; ↓ indicates a reduction; ↑ APD indicates an APD prolongation; ↓ APD indicates an APD shortening. Chron, chronic hormone effects; Phos, phosphorylation; eNOS, acute eNOS-mediated mechanism; cAMP, under cAMP stimulated condition; PE, under phenylephrine stimulation; ISO, under isoproterenol stimulation; rat H9C2, rat H9C2 cell line

Table 2

Gender and sex hormone effects on cardiac repolarization and LQT-arrhythmogenesis in rabbit models *in vivo*

Sex	Intervention	Drug-induced QT-prolongation	Drug-induced EADs / pVT	QT/RR slope steepness in LQT rabbits	pVT / SCD in LQT rabbits
Male	--------	**↓ QT-prolongation** less pronounced than in females [5, 44]	**↓ EADs** fewer than in females [5]	**↓ QT/RR** less steep than in females [48]	
	ORCH	**↑ QT-prolongation** more pronounced than in males [15, 44]	**↑ EADs** more than in males [15, 44]		
	ORCH+DHT	**↓ QT-prolongation** less pronounced than in ORCH [15, 44]	**↓ EADs** reduced compared to ORCH [15, 44]		
Female	--------	**↑ QT-prolongation** more pronounced than in males [5, 44]	**↑ EADs** more than in males [5]	**↑ QT/RR** steeper than in males [48]	
	OVX	**↓ QT-prolongation** less pronounced than in females [16, 44]	**↓ EADs** reduced compared to females [16, 44]	**↓ QT/RR** less steep than in females [25]	
	OVX+EST	**↑ QT-prolongation** more pronounced than in OVX [16, 44]	**↑ EADs** more than in OVX [16, 44]	**↑ QT/RR** steeper than in OVX [25]	**↑ pVT, ↑ SCD** increased incidence of arrhythmias [25]
	OVX+DHT			**↓ QT/RR** less steep than in females and EST [25]	**no pVT, no SCD** decreased incidence of arrhythmias [25]
	OVX+PROG				**no pVT, no SCD** decreased incidence of arrhythmias [25]

EAD, early afterdepolarization; pVT, polymorphic ventricular tachycardia; SCD, sudden cardiac death; ORCH, orchiectomy; OVX, ovariectomy; DHT, dihydrotestosterone; EST, estradiol; PROG, progesterone; QT/RR, QT-interval to RR-interval ratio; ↑ indicates an increase; ↓ indicates a reduction.