Testosterone-mediated upregulation of delayed rectifier potassium channel in cardiomyocytes causes abbreviation of QT intervals in rats

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Abstract
Men have shorter rate-corrected QT intervals (QTc) than women, especially at the period of adolescence or later. The aim of this study was to elucidate the long-term effects of testosterone on cardiac excitability parameters including electrocardiogram (ECG) and potassium channel current. Testosterone shortened QT intervals in ECG in castrated male rats, not immediately after, but on day 2 or later. Expression of Kv7.1 (KCNQ1) mRNA was significantly upregulated by testosterone in cardiomyocytes of male and female rats. Short-term application of testosterone was without effect on delayed rectifier potassium channel current ($I_{Ks}$), whereas $I_{Ks}$ was significantly increased in cardiomyocytes treated with dihydrotestosterone for 24 h, which was mimicked by isoproterenol (24 h). Gene-selective inhibitors of a transcription factor SP1, mithramycin, abolished the effects of testosterone on Kv7.1. Testosterone increases Kv7.1-$I_{Ks}$ possibly through a pathway related to a transcription factor SP1, suggesting a genomic effect of testosterone as an active factor for cardiac excitability.

Keywords Testosterone · Electrocardiogram · QT interval · Potassium channel · Kv7.1

Abbreviations
DHT Dihydrotestosterone
TdP Torsades de pointes
QTc Corrected QT intervals
JTc Correlated JT interval
Kv Voltage-gated potassium channel
Kir Inwardly rectifying potassium channel
KCNQ1 Potassium voltage-gated channel subfamily Q member 1
$I_{K1}$ Anomalous inwardly rectifying potassium current
$I_{to}$ Transient outward potassium currents
$I_{Kr}$ Rapidly activating delayed rectifier potassium currents
$I_{Ks}$ Slowly activating delayed rectifier potassium current
ISO Isoproterenol
CREB cAMP response element binding protein
Sp1 Specificity protein 1

Introduction
Clinical studies have identified striking differences between men and women in the incidence of many different cardiovascular diseases including arrhythmias. Torsades de pointes (TdP) arrhythmia is a potentially fatal form of polymorphic ventricular tachycardia that typically occurs in a setting of prolonged QT interval duration measured from electrocardiogram (ECG) recordings [1–4]. Female gender is an independent risk factor for developing drug-related TdP [5]. Evidence from clinical studies suggest that the gender-dependent differences in rate-corrected QT intervals (QTc) may be primarily due to the impact of male sex steroid hormones [6–8] because QTc intervals of prepubertal boys and girls are similar to those found in adult women, whereas postpubertal males generally have shorter QTc intervals. A clinical study demonstrated that the correlated JT interval (JTc) in the castrated male group were significantly longer.