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Review

Sex and sex hormones in cardiac stress—Mechanistic insights☆

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ABSTRACT

Important sex differences in the onset and characteristics of cardiovascular disease are evident, yet the mechanistic details remain unresolved. Men are more susceptible to cardiovascular disease earlier in life, though younger women who have a cardiovascular event are more likely to experience adverse outcomes. Emerging evidence is prompting a re-examination of the conventional view that estrogen is protective and testosterone a liability. The heart expresses both androgen and estrogen receptors and is functionally responsive to circulating sex steroids. New evidence of cardiac aromatase expression indicates local estrogen production may also exert autocrine/paracrine actions in the heart. Cardiomyocyte contractility studies suggest testosterone and estrogen have contrasting inotropic actions, and modulate Ca^{2+} handling and transient characteristics. Experimentally, sex differences are also evident in cardiac stress responses. Female hearts are generally less susceptible to acute ischemic damage and associated arrhythmias, and generally are more resistant to stress-induced hypertrophy and heart failure, attributed to the cardioprotective actions of estrogen. However, more recent data show that testosterone can also improve acute post-ischemic outcomes and facilitate myocardial function and survival in chronic post-infarction. The myocardial actions of sex steroids are complex and context dependent. A greater mechanistic understanding of the specific actions of systemic/local sex steroids in different cardiovascular disease states has potential to lead to the development of cardiac therapies targeted specifically for men and women.

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1. Introduction

Cardiovascular disease onset in women lags men by over a decade and is hence popularly presumed to be male-dominated, yet more women die than men from this disease each year. The conventional view of estrogen as a cardioprotective agent has been based on observational studies reporting significantly lower cardiovascular mortality in pre-menopausal women. In this context, the outcomes of the first clinical trials of hormone therapy were entirely surprising [1,2]. No benefit for postmenopausal women in primary or secondary prevention could be demonstrated, and indeed the Women's Health Initiative Study was terminated early due to a small but significant increase in ischemic cardiovascular events [1]. Beyond immediate clinical implications, these outcomes prompted recognition that at a fundamental mechanistic level, an understanding of myocardial sex steroid pathophysiology is

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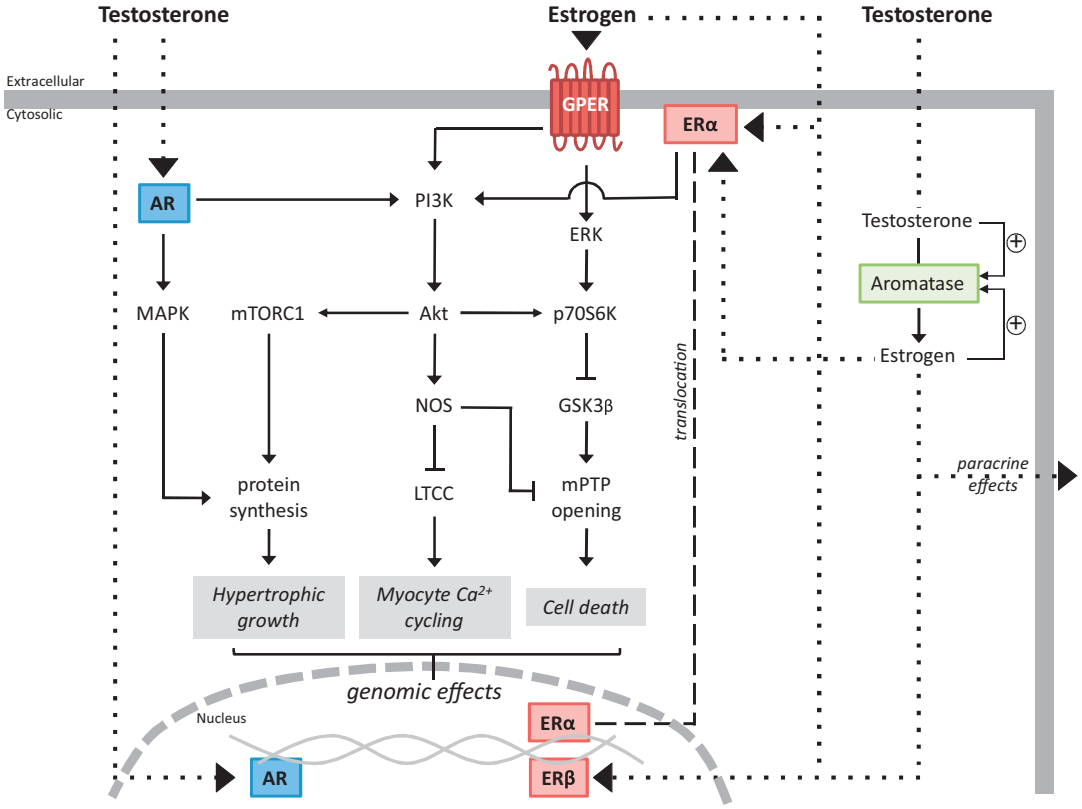

Fig. 1. Sex steroid signaling in the heart. The heart expresses both androgen and estrogen receptors, located at the sarcolemma, cytosol and nucleus. Binding of sex steroids to their receptors elicits both genomic transcriptional changes and more rapid non-genomic actions through activation of associated signaling intermediates. Genomic effects mediated by testosterone/estrogen on hypertrophy, myocyte Ca^{2+} cycling and cell death not specifically shown in the figure. The expression of aromatase in the heart, which itself may be influenced by local levels of testosterone and estrogen, suggests estrogen may be synthesized within the cardiomyocyte to exert autocrine/paracrine actions in the milieu of fluctuating circulating sex hormone levels. This figure includes sex steroid signaling pathways that are not fully established in the cardiomyocyte and referred to in the text/references. AR, androgen receptor; ERα, estrogen receptor α subunit; ERβ, estrogen receptor β subunit; GPER, G-protein coupled estrogen receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; NOS, nitric oxide synthase; LTCC, L-type Ca channel; mTOR, mammalian target of rapamycin complex 1; GSK3β, glycogen synthase kinase 3β; mPTP, mitochondrial permeability transition pore; ERK, extracellular signal-regulated kinase. Dotted line represents movement of sex steroids; dashed line represents translocation of ERα to nucleus.

lacking [3,4]. Considerable experimental research effort has since been invested and much revealed about estrogen and androgen signaling pathways and cardiac cellular actions. Yet still, more than a decade beyond the first unexpected trial outcomes, the challenge of understanding the sex specificity of myocardial pathophysiology remains unresolved. This review considers the influence of sex and sex steroids on the heart, and explores the mechanistic contribution of estrogen and testosterone to the development of stress-induced cardiac pathologies.

2. Systemic sex steroids and the heart

Systemic estrogen and testosterone levels increase substantially in women and men respectively from puberty, staying high through to middle-age. In menopause, estrogen declines rapidly at a time when cardiovascular disease becomes more prevalent in women, and findings of numerous observational studies have led to the inference of a link between estrogen and cardioprotection. In contrast, in men, the earlier onset of disease occurs when testosterone levels remain relatively high, suggesting testosterone may be a cardiovascular liability. Extensive evidence shows that sex steroids modulate blood lipid profiles in a manner that would support the view of estrogen protection and androgen detriment. Pre-menopausal women, and post-menopausal women administered hormone replacement therapy, exhibit lower LDL-cholesterol and triglyceride levels concomitant with higher HDL-cholesterol [5,6]; lipid profiles typically associated with less atherosclerotic plaque formation. Additionally, estrogen signaling through estrogen receptors in the coronary vasculature attenuates the response to vascular injury [7]; promoting endothelial repair and inhibiting vasculature remodeling to limit atherosclerotic plaque progression [6]. This estrogen-mediated maintenance of vascular function and reduction in luminal stenosis may contribute significantly to the delayed onset of ischemic heart disease in women, and hence the prevalence of ischemia-related contractile dysfunction, myocyte loss and compensatory tissue remodeling. However, beyond vascular influence, important considerations of the direct myocardial actions of estrogen arise, particularly in disease settings. It has been established for some time that the myocardium is functionally responsive to circulating androgens and estrogens and that cardiac tissues express both androgen receptors (AR; [8]) and multiple subtypes of estrogen receptor (ER; [9]); namely ERα, ERβ and the more recently described G-protein coupled estrogen receptor (GPER; [10]). Estrogen receptor subtype localization is relatively specific in the cardiac muscle cell, the cardiomyocyte (Fig. 1). ERα, ERβ, and AR are all reported to be localized in cytosolic and nuclear compartments [8]. In addition, evidence suggests ERα are expressed in the sarcolemma, particularly in t-tubular membranes (Ropero JMCC 2006). Receptor subtype expression and localization is similar in male and female ventricular tissue [11], though may be dependent on systemic sex steroid levels [9,11,12] and cardiovascular disease setting [13]. Binding of sex steroids to their respective receptors elicits genomic transcriptional changes (reviewed [8]) and also more rapid non-genomic

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