Available online at www.sciencedirect.com
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Pharmacology & Therapeutics 111 (2006) 434 – 475
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: P. Molenaar

Sex dimorphism in cardiac pathophysiology: Experimental findings, hormonal mechanisms, and molecular mechanisms

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Abstract

The higher cardiovascular risk in men and post-menopausal women implies a protective action of estrogen. A large number of experimental studies have provided strong support to this concept. However, the recent clinical trials with negative outcomes regarding hormone replacement therapy call for "post hoc" reassessment of existing information, models, and research strategies as well as a summary of recent findings. Sex steroid hormones, in particular estrogen, regulate numerous processes that are related to the development and progression of cardiovascular disease through a variety of signaling pathways. Use of genetically modified models has resulted in interesting information on diverse actions mediated by steroid receptors. By focusing on experimental findings, we have reviewed hormonal, cellular, and signaling mechanisms responsible for sex dimorphism and actions of hormone replacement therapy and addressed current limitations and future directions of experimental research.

Keywords: Heart disease; Estrogen; Androgen; Steroid hormone receptor; Sex difference

Abbreviations: β-AR, β-adrenergic receptor; ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; AR, androgen receptor; AT, angiotensin receptor; E2, 17β-estradiol; ECM, extracellular matrix; ER, estrogen receptor; ERE, estrogen response element; ERR, estrogen-related receptors; ERT, estrogen replacement therapy; HSP, heat shock protein; I/R, ischemia/reperfusion; LPL, lipoprotein lipase; LV, left ventricle or left ventricular; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; MI, myocardial infarction; MMP, matrix metalloproteinases; NCX, Na^+/Ca^{2+} exchanger; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; NPR-A, natriuretic peptide receptor-A; PKG, protein kinase G; PGC-1, PPARα-activated receptor γ coactivator-1; PPAR, peroxisome proliferator-activated receptor; RAS, renin-angiotensin system; SHBG, steroid hormone binding globulin; SHR, spontaneously hypertensive rats; SR, sarcoplasmic reticulum; TGF-β, transforming growth factor-β; VSMC, vascular smooth muscle cells.

Contents

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0163-7258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2005.10.016

1. Introduction

Sex-related differences in cardiovascular morbidity and mortality have long been recognized. The most striking difference is a 10- to 15-year delay in the prevalence of coronary artery disease in women than men. Under conditions of heart diseases, although younger women have less favorable outcomes than men after myocardial infarction (MI), prognosis is much worse in men than in women for heart failure (Vaccarino et al., 2001). Women with pressure overload have better preserved the left ventricular (LV) function but with a more marked concentric hypertrophy, whereas men tend to develop eccentric hypertrophy with LV dilatation (Aurigemma & Gaasch, 1995). Risk of sudden cardiac death is also lower in women than men according to the Framingham study (Kannel & Schatzkin, 1985).

Epidemiological studies show that men and post-menopausal women are at a higher risk for cardiovascular diseases than pre-menopausal women, suggesting that female steroid hormones, in particular estrogen, are cardioprotective (Mendelsohn & Karas, 1999; Dubey & Jackson, 2001b). Although changes in lipid profile occur depending on menstrual status or the use of hormone replacement therapy, direct actions of sex steroids on the heart and blood vessels account for about 50–70% of overall beneficial effects. These observations have resulted in estrogen replacement as the most frequently prescribed therapy to post-menopausal women in the last 2 decades. Indeed, cardiovascular protection by estrogen replacement therapy (ERT) in post-menopausal women has been suggested by numerous observational studies as well as large-scale clinical trials (Grodstein et al., 1997, 2000; Greendale et al., 1999) and by experimental studies. However, recent large-scale randomized trials (Grady et al., 2002; Manson et al., 2003) have provided evidence that ERT might actually increase the risk of cardiac disease.

While these findings are in contrast to those from the majority of observational clinical studies and animal studies, and are therefore surprising to researchers, they do suggest a fragmented knowledge on the mechanisms underlying sex differences in cardiovascular disease and perhaps misinterpretation of existing literature of clinical and experimental research. This calls for a timely overview of the database of experimental research on the hormonal and molecular mechanisms mediating sex dimorphism. This review is aimed to provide a comprehensive summary of experimental data on sex dimorphism in cardiac pathophysiology, lipid-independent hormonal mechanisms, sex steroid receptors, and molecular mechanisms that mediate sex differences, particularly recent findings in a range of in vitro and in vivo models.