The biological impact of estrogens on gender differences in congestive heart failure

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See also article by Pelzer et al. [14] (pages 604–612) in this issue.

Heart failure seems to be a different entity in women than in men because of gender-related differences in the cardiovascular system. Myocardial hypertrophy is one independent risk factor for heart failure and represents a very important health issue because of morbidity and mortality. Men under the age 50 have a greater risk of contracting cardiovascular disease than age-matched women. Women with heart failure very often have different clinical features than men, such as age of onset and comorbidities [1]. It is well documented that differences exist in remodeling and the response to injury when men are compared with women. The mechanisms underlying these gender-related differences, however, remain unresolved, and a large number of investigations have been initiated for the purpose of understanding the gender dependency in the pathogenesis of heart failure.

Pre-menopausal women have a reduced risk of contracting cardiovascular disease, and the incidence and severity of cardiovascular diseases strongly increase after menopause. Epidemiological, mostly observational studies showed less heart disease among women taking estrogens [2] (about a 50% reduction in cardiovascular disease). The pathophysiological mechanisms provided enough biological plausibility for hormone replacement therapy (HRT) [3] because estrogens are believed to have indirect and direct cardioprotective properties. But in 1998, the Heart and Estrogen/progestin Replacement Study (HERS) surprised everyone by finding no overall cardiovascular benefit. In fact, an increase in coronary heart disease was found during the first year [4], and within the Women’s Health Initiative (WHI) study, the estrogen–progestin replacement therapy for post-menopausal women was stopped because of increased cardiovascular risk for females. Thus, it was suggested that this increased cardiovascular risk may be a consequence of the thrombotic effects by progestin and not by the estrogens. For that reason, the main hypothesis of the WHI study was that the estrogen-alone trial would reduce the risk of coronary heart disease, but once again this did not happen (although it appeared less pronounced). To date, many comments on both trials (HERS and WHI) have been published [5]. They lead to the suggestion that estrogen alone in treating menopausal symptoms for a limited duration early in menopause is reasonable. Nevertheless, much speculation was raised about why the trials failed to show cardioprotection by estrogens. Besides the speculation on the impact of age at the beginning of treatment during menopause, the question arose concerning the plausibility of the suggested mechanism of the estrogens [5]. Therefore, more attention is now being paid to the characterization of the signaling pathways through estrogens, which should give new insights into the mechanisms underlying their mode of action in order to allow a better understanding of the use of estrogens in the treatment of cardiac hypertrophy.

In vitro and in vivo studies demonstrated attenuated development of myocardial hypertrophy by estrogens; i.e. it has recently been demonstrated that female ovariectomized mice develop a more robust left ventricular hypertrophy response in a model of pressure overload than ovariectomized mice with replacement of physiological levels of 17β-estradiol [6]. Estrogens seem to play a significant physiological role when hearts exhibit ischemia/reperfusion injury.

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Generally, estrogen action is mediated by specific estrogen receptors (ERs). The physiologically most important ERs are ERα and ERβ [7]. ERα and ERβ are both reported to be expressed in cardiac myocytes, fibroblasts, and coronary arteries. The ERs seem to be localized in a striated pattern within the cytoplasm of the cardiomyocyte [8,9].

ERs belong to the steroid hormone receptor superfamily, which can act as transcription factors on downstream target genes such as atrial natriuretic factor (ANF) or endothelial nitric oxide synthase (eNOS) with potential implications for cardiovascular function. Besides the genomic effects, estrogens can also exert rapid nongenomic effects possibly mediated by plasma membrane ERs [10]. Estrogenic compounds may rapidly activate early growth response gene-1 expression in cardiomyocytes via ERK 1 and 2 [10]. ERK signaling has been implicated in hypertrophy [10].

The direct genomic effect of an estrogen is the interaction of its receptor with specific target sequences of DNA (estrogen response elements, ERE) [7]. This interaction of ER with ERE can substantially be altered by differences in the ERE sequence, the ER subtype [7], and/or dimerization of ERs. Both ER subtypes (ERα and -β) are able to form homo- and heterodimers, and the different compositions of the dimer differentially regulate gene expression [11]. There are also data suggesting that ERβ can antagonize the action of ERα [12].

Gabel et al. [13] were stimulated to summarize all of these observations and raise the concept that selective estrogen receptor modulators (SERMs) might selectively activate estrogen-dependent protection in an organ such as the heart. They suggested that more studies are necessary to investigate the effects and the mechanism of action of ERα and -β in the cardiovascular system. The results of these studies would provide more evidence for ER specificity and functionality related to cardiovascular function and might have important therapeutic implications for the design of selective ER modulators effective in the prevention and treatment of cardiovascular disease [13].

In this issue of Cardiovascular Research, Pelzer et al. [14] were able to demonstrate that activation of ERα favorably affects cardiac hypertrophy, myocardial contractility, and gene expression in ovariecotomized spontaneously hypertensive rats (SHR). The selective ERα agonist 16α-L2 was sufficient in attenuating cardiac hypertrophy and in improving hemodynamic function in estrogen-deficient SHR, which was linked to differential expression patterns of cardiac myosin heavy chains. Furthermore, Pelzer et al. [15] have undertaken a study to determine the role of ERβ in the development of chronic heart failure following experimental myocardial infarction. Here, systemic deletion of ERβ in female mice increased mortality, which led to the hypothesis that selective activation of ERβ improves functional outcome after myocardial infarction.

The recent work by Gabel et al. [13] emphasized the physiological impact of the ERβ in the heart. ERβ was found to mediate cardioprotection in female mice after being subjected to ischemia and reperfusion. In conclusion, all of the recent studies shed more light into the function of ERβ and ERα in heart muscle disease. They considered the significance of the specificity and selectively of SERMs for cardioprotection. Nevertheless, more pharmacological studies are needed to investigate the indirect and direct cardioprotective properties of the recently developed selective ERα and ERβ agonists.

References