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Influence of sex on cardiovascular drug responses: role of estrogen

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In this review we discuss the sex/estrogen-specific modulation of cardiovascular function and responses to current therapeutics. We discuss how anatomical differences such as a smaller kidney size, and lower glomerular filtration rate in females, reduce the clearance and increase the toxicity of some drugs in females. Other important sex differences include the dampening effect of estrogen on central sympathetic and renin angiotensin systems. Further, we discuss how a shift in myocardial redox status leads to paradoxical transformation of estrogen into a pro-inflammatory hormone. Finally, the review, along with cited recent publications, identify some areas that need further investigation to advance our understanding of the sex differences in cardiovascular disease outcomes to help develop female specific interventions for these anomalies.

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Background

In recent years, there is evidence of significant reductions in cardiovascular-related mortalities [1,2], which is attributed to a better understanding of cardiovascular pathology and the development of new interventions against these pathologies. Nonetheless, it is disconcerting that women have benefited less from these advances because they exhibited a substantially lower decline in cardiovascular-related mortality compared to men [1,3]. This discrepancy has led to concerted efforts to increase funding of preclinical and clinical research to conduct studies in female experimental animals and women. These efforts, pioneered by the American Heart Association and the National Institutes of Health, will lead to generating parallel robust female-specific data from studies that are traditionally conducted in men or in male experimental animals. In this short review, we will focus on the current understanding of the role of the female sex hormones, particularly estrogen, in cardiovascular health and disease as well as how estrogen impacts cardiovascular therapy (Figure 1).

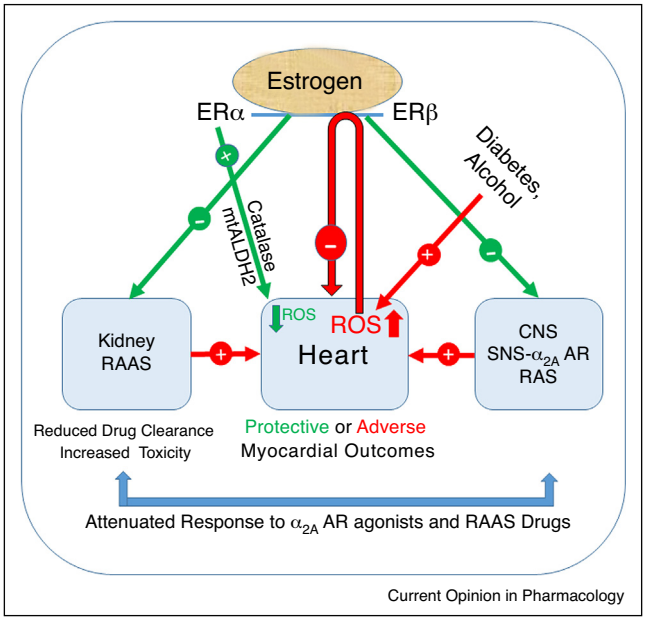
Estrogen modulation of cardiovascular function

Organ-dependent effects

Estrogen plays a fundamental role in regulating cardiac and vascular function via its classical estrogen receptor (ER)-dependent genomic mechanism. We and others have shown that estrogen plays a causal role in the enhanced myocardial eNOS activity in sexually mature cycling female, compared to ovariectomized, rats [4,5]. These biological effects of estrogen, which influence cardiac function and reflexes, are mediated by two mechanisms. First, estrogen-mediated increase in the expression of myocardial eNOS. Second, estrogen induces calmodulin, and inhibits caveolin-3, expression; two allosteric proteins that bind with eNOS to increase, and decrease, its activity, respectively [4]. More recently, we have shown that estrogen can also enhance the activity of an important antioxidant enzyme, catalase, within minutes, in ovariectomized rats, which supported a role for nongenomic ER signaling in myocardial redox regulation [6]. It is noteworthy that despite these favorable cellular effects of estrogen, there are reported situations in which estrogen mediates detrimental effects.

The elucidation of the ER subtype(s) implicated in a paradoxical transformation of E_2 into a pro-inflammatory hormone in the presence of conditions that promote cellular oxidative stress [7] is important for understanding the molecular mechanisms of the sex (E_2)-dependent regulation of the cardiac redox status. All 3 ER subtypes, ERα, ERβ and GPER, are distributed throughout the cardiovascular system [8,9]. These ERs mediate favorable redox and functional cardiac effects under physiopathological conditions via both genomic and rapid signaling mechanisms [10,11]. In support of this premise are the findings that in OVX rats, acute E_2 administration enhances the activity of two cardiac enzymes, catalase and mitochondrial aldehyde dehydrogenase 2 (mitALDH2) [6], which serve antioxidant roles [12–14].

Figure 1



Summary of major signaling events that determine the sex/estrogen-dependent differences in cardiovascular/renal function, and the responses to some prescribed therapeutics. Anatomically and functionally, a smaller kidney size, and a lower glomerular filtration rate in females, compared to males, may reduce the clearance of drugs that are excreted by the kidney, and potentially increase their toxicities. Estrogen dampening of the peripheral renin-angiotensin-aldosterone (RAAS) and central RAS as well as sympathetic activities (green arrows) confer cardiovascular protection, and might explain the lower incidence of hypertension in premenopausal women. However, these sex differences might also explain the attenuated hypotensive responses to some centrally acting sympatholytic drugs and RAAS inhibiting drugs. Importantly, under conditions that create cardiovascular oxidative stress (*e.g.*, diabetes or heavy alcohol consumption), the cellular environment becomes conducive to a paradoxical transformation of estrogen into a pro-inflammatory hormone. The latter might explain, at least partly, some puzzling adverse cardiovascular outcomes associated with estrogen replacement therapy in some clinical studies.
ER, estrogen receptor; **mtALDH2**, mitochondrial aldehyde hydrogenase; **CNS**, central nervous system; **ROS**, reactive oxygen species; **AR**, adrenergic receptor.

Central estrogen-mediated regulation of cardiac reflexes

Our findings, which were among the first to show an unexpected and unexplained lower baroreflex sensitivity in young women, compared to men [15], raised the possibility that estrogen dampens the cardiac baroreflex response. This possibility was initially supported by the ability of testosterone to enhance this response [16]. Nonetheless, the findings that postmenopausal, compared with premenopausal, women exhibit lower cardiac baroreflex response [17], and the replication of these findings in a rodent model of surgical menopause [18,19] suggested that estrogen and testosterone share the ability to enhance the cardiac baroreflex response. There are differences, however, between the two hormones because estrogen enhances baroreflex sensitivity, at least partly, via a central site of action [18] and dampens central sympathetic tone [20]. These central estrogen effects might explain the lower incidence of hypertension in premenopausal women and female rats [21,22]. More studies are needed to understand the mechanism of these estrogen-dependent effects and the implicated ER subtype(s).

Sex differences in cardiovascular pathology outcomes

A recent scientific statement from the American Heart Association indicates that, compared to men, women exhibit worse cardiovascular consequences of diabetes [23•]. This unexplained phenomenon might extend to other diseases or the engagement in specific lifestyle paradigms such as alcohol consumption. Therefore, more research is needed to understand this sexually dimorphic cardiovascular outcome, which is most likely attributable to a paradoxical transformation of estrogen from an anti-inflammatory to a pro-inflammatory hormone.

Cellular microenvironment determines the cardiovascular role of estrogen

Under healthy conditions, estrogen confers favorable cardiovascular effects that include improved cardiac redox status and coronary artery vasodilation [24]. The estrogen-dependent improvement of cardiac redox status is supported by the increase in myocardial oxidative stress in ovariectomized rats and the mitigation of the latter by chronic or even acute estrogen replacement [6,25]. This favorable redox effect is mediated, at least partly, by estrogen enhancement of the catalytic activity of two cardiac antioxidant enzymes, catalase and mitochondrial aldehyde dehydrogenase [6,26]. Interestingly, our recent studies showed that the effect of estrogen on these two cardiac enzymes is ER subtype-dependent because a highly selective ERα agonist replicated the effect of estrogen while ERβ or GPER activation caused a reduction in ALDH2 activity [27]. The latter finding and the GPER-mediated relaxation of the coronary artery [24] support the tissue specificity of estrogen actions and underscores the complexity of estrogen regulation of cardiovascular function.

It is imperative to note that the cardiovascular biological effects of estrogen will be drastically influenced by coexisting conditions that modify the cellular redox status. For example, the vasodilating effect of estrogen under normal conditions [7,24] is transformed into a vasoconstrictor effect in the presence of oxidative stress *in vitro* [7]. These findings might explain, at least partly, the exacerbated deleterious cardiovascular consequences of diabetes in women [23•] because diabetes is associated with oxidative stress [28]. This concept gains credence from our findings, which established a causal link between