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Influence of Sex on Cardiovascular Drug Responses: Role of Estrogen

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Abstract

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.

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 (Fig. 1).

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1. Estrogen modulation of cardiovascular function

i. 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 caveolins-3, expression; two allosteric proteins that bind with eNOS to increase, and decreases, 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 E₂ 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 (E₂)-dependent regulation of the cardiac redox status. All 3 ER subtypes, ER α , ER β 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 E₂ administration enhances the activity of two cardiac enzymes, catalase and mitochondrial aldehyde dehydrogenase 2 (mitALDH2) (6), which serve antioxidant roles (12-14).

ii. Central estrogen-mediated regulation of cardiac reflexes

Our findings, which were amongst 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 such 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).

2. 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 disease 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.

3. 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 ER α agonist replicated the effect of estrogen while ER β 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 oxidative stress and estrogen-dependent deleterious cardiac effects in vivo because: (i) the alcohol-evoked myocardial oxidative stress is tolerated in the absence of estrogen in ovariectomized and male rats, and (ii) such resilience is lost, and is transformed into myocardial dysfunction, when estrogen is co-administered with ethanol in both sexes (6, 29**, 30). Current evidence implicates the ER α and ER β subtypes in mediating these estrogen-dependent adverse cardiac effects of ethanol (27, 29**), at least partly, via the PI3K-Akt-NOS pathway (29**, 31, 32). More mechanistic studies are warranted in this area of research given the widespread use of alcohol by young women (33, 34). Further, this complex estrogen-ethanol interaction might influence the therapeutic outcomes of clinically prescribed cardiovascular drugs.

4. Estrogen influences cardiovascular responses to drug therapy

As discussed above, estrogen-dependent inhibition of central sympathetic tone (18, 20) might influence the response of females to antihypertensive medications that lower blood pressure by a central sympatho-inhibitory mechanism of action. Radiotelemetry studies in ovariectomized rats treated with estrogen releasing pellets or placebo showed that estrogen dampens centrally (clonidine), but not peripherally (hydralazine), mediated hypotensive responses (35). In that study, the clonidine-evoked hypotension in sham-operated rats was enhanced in OVX rats and restored to sham-operated levels in estrogen-treated OVX rats. These findings suggest that estrogen dampens centrally evoked hypotension, and implicate the cardiovascular autonomic control in the enhanced hypotensive response to clonidine in OVX rats (35). These findings led to another study that examined the potential specificity of estrogen towards central signaling pathways that determine the hypotensive response to first and second generation centrally acting sympatholytics. This was important because the equipotent agonist activity of clonidine at central α_2 - and imidazoline I_1 -receptors made it difficult to identify which receptor was targeted by estrogen in the previous study (35). A selective I_1 -receptor agonist, rilmenidine, or a virtually pure α_2 -receptor agonist, alpha-methyldopa, was administered to sham-operated rats and to ovariectomized (OVX) rats with or without estrogen replacement. In sham-operated rats, rilmenidine and alpha-methyldopa elicited similar hypotension. Ovariectomy enhanced the alpha-methyldopa, but not rilmenidine, evoked-hypotension. This differential effect was estrogen dependent because estrogen replacement dampened the alpha-methyldopa evoked hypotension, and highlights a role for the cardiac autonomic control in alpha-methyldopa estrogen interaction (36). These findings might be clinically important because alpha-methyldopa is the drug of choice for treatment of hypertension associated with pregnancy. More studies are needed to elucidate the mechanism of estrogen mediated inhibition of central α_2 adrenergic receptor signaling.

A very recent review summarized the progress in current understanding of sex differences in susceptibility to spontaneous and drug-induced arrhythmias (37). The authors also highlighted the importance of investigating the mechanisms of the higher susceptibility of women to drug-induced arrhythmia, and possible contribution of the acute effects of female sex hormones to the risk of drug-induced arrhythmias. As discussed above, acute estrogen influences myocardial redox status via ER subtype-dependent modulations of major antioxidant enzymes such as catalase and mitochondrial ALDH2. However, the direct and indirect links between these changes in redox status and cardiac electrophysiology remain elusive.

5. Sex differences in kidney function determines different therapeutic outcomes

Caution has to be exercised when women are prescribed medications that are excreted by the kidney as the active drug or its active metabolite. For example, anticoagulant drugs, such as lepirudin, which are excreted by the kidney, exhibit a substantially longer half-life in women, compared to men. The result is the presence of the drug in women's circulation for

up to 48, compared to 2, hours in men, which increases the potential of bleeding in women. This sex difference in potential drug toxicity is best explained by the lower normalized glomerular filtration rate in women (38), and can be resolved by prescribing medications that are not influenced by kidney function such as argatroban. The same problem extends to some fibrinolytic drugs that are used post myocardial infarction, and are associated with greater bleeding risk in women.

It is important to recognize the role of the kidney in the attenuated renin-angiotensin system (RAS) in women and in female animals for two reasons. First, the kidney, the major source of renin-mediated synthesis of the angiotensin II precursor, angiotensin I, is smaller in women (39). Second, the estrogen-dependent reduction of central sympathetic tone (20) is expected to further reduce the norepinephrine-mediated renin release from the kidney's juxtaglomerular cells. Nonetheless, it is also important to consider an important and less studied dampening effects of estrogen on central RAS, which directly (via AT₁ receptor) and indirectly (via neuronal oxidative stress) activates central sympathetic tone (40, 41**) as well as peripheral AT₁ receptor signaling (42**).

Conclusions

The effects of sex/estrogen on cardiovascular and kidney function regulation need to be considered at the integrative as well as organ/tissue specific levels. Current knowledge suggests an important cardiovascular protective role for estrogen, at least partly, via its dampening effects on central sympathetic tone and peripheral AT₁R signaling (Fig. 1). These and other estrogen-mediated effects such as enhancement of the catalytic activities of myocardial antioxidant enzymes (catalase and ALDH2) might explain the reduced propensity of premenopausal women to cardiovascular oxidative stress and subsequent anomalies. Nonetheless, evidence suggests that induction of cellular oxidative stress paradoxically transforms estrogen into a pro-inflammatory hormone. It is also noteworthy that the lower kidney function in females might account for the increased toxicity caused by anticoagulant and fibrinolytic drugs that are excreted by the kidney. Further, the estrogen-mediated inhibitions of central sympathetic tone and AT₁R signaling likely lead to attenuated antihypertensive effect of clinically prescribed drugs that target those systems in women. Therefore, more research is needed to advance our understanding of the sex/estrogen-specific cardiovascular pathophysiological and therapeutic implications.

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Highlights

- Oxidative stress transforms estrogen into a pro-inflammatory hormone.
- Estrogen receptor-alpha signaling enhances cardiac catalase and mtALDH2 activities.
- Kidney function influences therapeutic outcomes and toxicity in females.

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.