of contraception in at-risk populations, such as young females.

Much of our inability to define the biological role of these cofactors in HIV-1 susceptibility comes from a lack of understanding of the initial events in HIV-1 infection (*7*). HIV-1 is transmitted to women primarily via heterosexual contact, and the virus must therefore penetrate the mucosal barrier to establish a systemic infection. Ulcerative STDs increase the risk of HIV-1 infection, which implies that breaches in mucosa enhance HIV-1 transmission. Additionally, STDs increase the presence of inflammatory cells, a result that provides more potential targets for the virus. Fundamental questions regarding the biology of HIV-1 transmission have been difficult to answer, because it is hard to examine relevant cells and tissue at the time of HIV-1 acquisition, when the initial pivotal events are occurring.

Susceptibility to HIV-1 also varies throughout a woman's reproductive life. Adolescent girls appear to be the population most vulnerable to HIV-1, either because of behavioral high-risk activities or because of the physiological properties of an immature genital tract with increased cervical ectopy or exposed columnar epithelium. In addition, recent studies have shown a twofold increase in the risk of HIV-1 acquisition during pregnancy and the early postpartum period, even after adjustments have been made for changes in sexual behavior and social and demographic factors (*8*). Factors that could increase susceptibility during pregnancy include high levels of progesterone, which has been shown to enhance susceptibility in nonhuman primate models of HIV-1 (*9*), and increased ectopy. The mechanisms by which female hormones may affect HIV-1 susceptibility include increases in the number of target cells and the suppression of immune responses, but these mechanisms remain poorly defined.

If hormonal changes play a key role in HIV-1 susceptibility and the magnitude of the immune response to infection, then it is critical that vaccine trial design consider possible gender differences in outcome. Indeed, some preliminary findings from the only phase-III HIV-1 vaccine trial conducted to date suggested that there may be differences in the humoral immune responses to the vaccine generated in women and men (*10*). However, this difference was not detected in an analysis of smaller phase-I/II vaccine trials (*11*).

This growing "feminization" of the HIV-1 pandemic reflects women's greater social and biological vulnerability (*12*). Because gender norms shape attitudes toward information on sex, sexuality, sexual risk-taking, and fidelity, they play a critical role in determining the course of the epidemic. Because the risk of HIV-1 infection in women has been linked to the regional norms that affect power in interpersonal relationships (*12*), controlling the HIV-1 pandemic requires intensive attention to gender-related issues driving the epidemic. Interventions must be multifaceted and should include making both female and male condoms accessible to all in ways that do not stigmatize; prioritizing the development of female-initiated methods of protection such as microbicides; defining the influence of hormones on disease progression and response to treatment; and educating women and men about HIV-1 and other STDs, including how to negotiate safe sex, and encouraging them to seek testing and treatment.

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REVIEW

Molecular and Cellular Basis of Cardiovascular Gender Differences

Michael E. Mendelsohn* and Richard H. Karas

Cardiovascular diseases (CVDs), the major cause of morbidity and mortality for both men and women, occur uncommonly in premenopausal women, but their incidence rises sharply after the menopausal transition. Cardiovascular gender differences are apparent long before CVDs appear in men and women, and improved understanding of the biology underlying these differences has the potential to advance the diagnosis and treatment of CVDs in both sexes. This review considers gender differences in the molecular and cellular physiology of the heart and blood vessels in health and disease, highlighting understudied areas that can help resolve the current controversy regarding hormone replacement therapy and improve cardiovascular health in women.

Sex Steroid Hormones, Receptors, and Gender Differences

Women develop heart disease later in life than men. This difference has been attributed to the loss of female sex steroid hormones at the time of menopause, but the biological explanations for gender differences in cardiovascular diseases (CVDs) are more complex. Recent advances in research on cardiovascular gender differences have increased our understanding of the biology responsible; however, a synthesis of the underlying mechanisms that explain these differences has not yet been possible. The current controversy that has arisen from the Women's Health Initiative (WHI) trials of the cardiovascular effects of hormone replacement therapy (HRT) on CVD (*1*) is a case in point. This controversy is in part due to an underappreciation of the relationship between the timing of HRT initiation and differences in the underlying vascular biology that exist between perimenopausal and older women. Resolving this controversy will require a more complete understanding of the molecular and cellular physiology of each of the sex steroid hormones and their receptors in the cardiovascular system and a greater focus on how the extent of underlying atherosclerosis affects the response to HRT.

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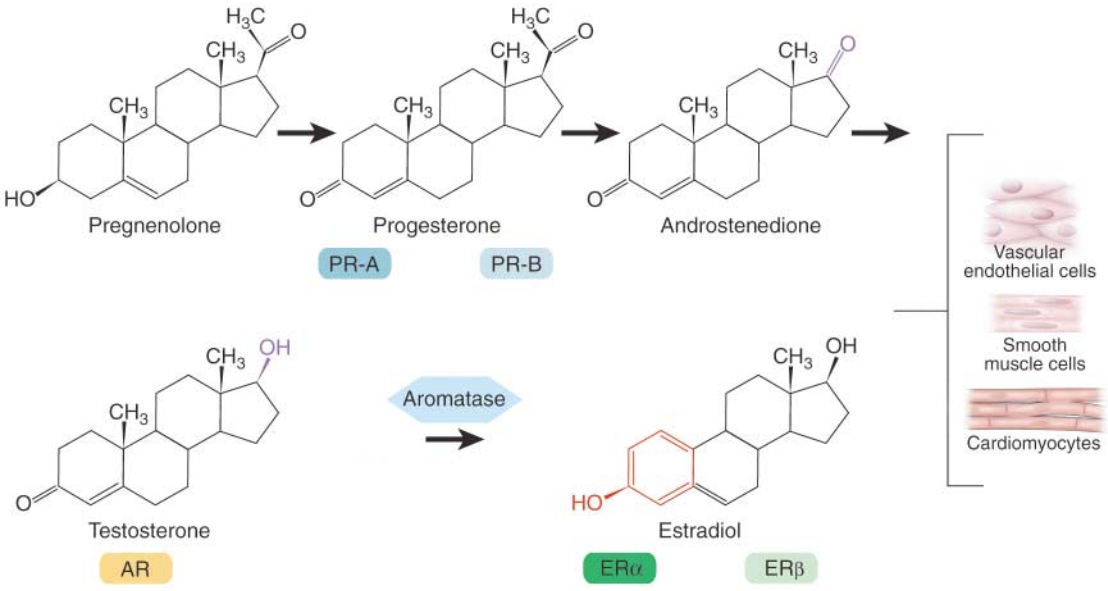

Fig. 1. Sex steroid hormones and sex steroid hormone receptors. Synthesis of the three gonadal sex steroid hormones, estrogen, progesterone, and testosterone, from pregnenolone. Pregnenolone gives rise first to progesterone, which serves as the intermediate for the synthesis of androgens and estrogens. Estrogens are synthesized from androgens by the formation of an aromatic A ring, which is catalyzed by the enzyme aromatase (Cyp19). Steroid hormones bind to and activate specific members of the nuclear hormone receptor superfamily of ligand-activated transcription factors. All of the sex steroid hormone receptors, and the enzyme aromatase, are expressed in vascular endothelial cells, vascular smooth muscle cells, and cardiomyocytes (right).

Sex steroid hormones (SSHs) and their receptors are critical determinants of cardiovascular gender differences. Most research has focused on the effects of estrogen and estrogen receptors (ERs) on cardiovascular physiology and disease, whereas progesterone and testosterone and their receptors (PR and AR), and the enzyme aromatase, which converts testosterone to estrogen in specific tissues (Fig. 1), have received far less attention. Steroid hormones activate their cognate receptors, members of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Ligand-bound sex steroid hormone receptors (SSHRs) dimerize and bind to specific DNA response elements, and engage the general transcriptional apparatus, as reviewed previously (*2*, *3*). Several newer SSHR signaling concepts with implications for cardiovascular physiology have emerged recently (Fig. 2, points 1 to 6).

First, steroid hormone receptors do not act alone, but interact with a broad array of coregulatory proteins to alter transcription (Fig. 2, point 1). Cell-specific expression of coactivator and corepressor proteins and their regulation by post-translational modifications allow for exquisite tissue-specific and temporal regulation of SSHR-mediated transcription (*2*, *4*). Understanding coregulator biology is important to the development of cardiovascular-selective estrogen receptor modulators (SERMs) and modulators for other SSHRs. Examples of cardiovascular coregulator specificity include the role of the ER coactivator protein steroid receptor coactivator 3 (SRC3) in mediating estrogen inhibition of vascular injury (*5*) and the relatively specific myocardial AR coactivator, FHL2 (*6*). However, little is known about the differential expression and function of coregulatory molecules in myocardial and vascular cells. SSHRs also participate in rapid cellular activation pathways that at least initially do not alter gene expression (Fig. 2, point 2), such as rapid stimulation of vascular endothelial nitric oxide synthase (NOS) and vascular dilatation mediated by activated ER (*3*, *7*, *8*). Rapid signaling pathways can also converge on genomic pathways, activating transcription of genes lacking SSH response elements (*8*, *9*). ER and PR in vascular cells also can be activated in the absence of ligand by growth factor pathways (*3*, *8*) (Fig. 2, point 3). In addition, SSHRs cross-regulate expression of one another in vascular cells (*8*, *10*) (Fig. 2, point 4). These pathways all add substantial combinatorial complexity to the physiological effects of SSHs in target tissues. Genetic SSHR variants influence individual responses to SSHs (Fig. 2, point 5) and are associated with altered cardiovascular risk in both sexes (*11*, *12*), but the physiological consequences of such variants are unexplored. Finally, SSHRs can regulate non-SSH nuclear receptors such as the peroxisome proliferator-activated receptor α (PPARα), and the liver X receptors (LXRs), which govern metabolic pathways directly relevant to CVD (*13*, *14*) (Fig. 2, point 6). These newer concepts of SSHR action (Fig. 2) require greater attention in all target tissues, including the cardiovascular system.

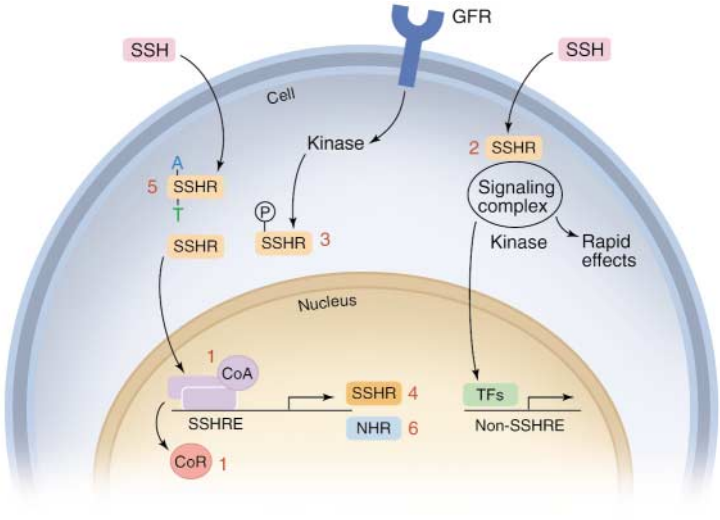

Fig. 2. Emerging concepts in sex steroid hormone receptor signaling of potential importance in cardiovascular physiology. Newer concepts in SSHR action that are relatively unexplored in cardiovascular cells and tissues are depicted (see text). Abbreviations: GFR, growth factor receptor; SSHR, sex steroid hormone receptor; SSHRE, SSH response element; CoA, coactivator; CoR, corepressor; NHR, non-SSHR nuclear receptors; TFs, transcription factors.

Gender Differences in Blood Vessels

Vascular SSHR and aromatase. The expression of SSHRs and aromatase in the vasculature is well recognized (*3*, *15*), but how the expression of these proteins in cardiovascular cells varies with gender, vascular bed, and the presence of car-

diovascular risk factors or CVD is unclear. AR and the two PR isoforms (PR-A and PR-B) are expressed in the vasculature, but little is known about their functions in cardiovascular physiology. In mouse models, ERα mediates most of the protective effects of estrogen on injured blood vessels, including promoting reendothelialization (*16*) and inhibiting smooth muscle cell proliferation and matrix deposition following vascular injury (*17*), and attenuating atherosclerotic plaque progression (*18*, *19*). ERα-mediated protection in low density lipoprotein (LDL) receptor–deficient female mice is in part due to E2-ERα–dependent production of the atheroprotective molecule prostacyclin (*19*).

Studies of cardiovascular gender differences have focused mainly on later life stages, but mammalian hypothalamic-pituitary-gonadal axis function begins in utero, when testosterone is first produced (*20*). Ovarian endocrine activity begins shortly after birth, and estradiol (E2) levels are significantly higher in prepubertal girls than in boys (*20*, *21*). At puberty, gonadotropin secretion rises, stimulating gonadal SSH production. The cyclic variation in estrogen and progesterone then continues for nearly four decades in women, when the perimenopausal transition begins. The need to study cardiovascular gender differences during premenopausal years and the perimenopausal transition is now gaining attention (*22*).

Vascular tone and blood pressure. Hormone-dependent gender differences exist in vascular function. Estrogens cause vasodilatation through both rapid increases in NO production and induction of NOS genes (*3*, *8*, *23*). Blood pressure is lower in adolescent and premenopausal women than in age-matched men, and rises following menopause (*24*, *25*). Vasodilatation and blood pressure are both affected by fluctuations in circulating estrogen levels during the menstrual cycle, pregnancy, or E2 supplementation (*24*–*26*). In men, short-term estrogen administration has little effect on vascular relaxation, whereas longer-term administration improves vasodilatation (*25*). HRT does not lower blood pressure to premenopausal levels, suggesting a role for unopposed androgens in blood pressure regulation following menopause (*26*). Progesterone lowers blood pressure, whereas synthetic progestins can raise blood pressure (*24*). ERβ is required for normal vasodilatation and blood pressure in both males and females, with loss of ERβ causing more substantial hypertension in males (*27*).

Lipids. Lipid abnormalities contribute substantially to atherosclerosis and are regulated both by SSH and HRT, principally by way of hepatic effects on lipoprotein metabolism [reviewed in (*3*, *28*, *29*)]. The liver expresses ERα, PR, and AR, but not ERβ, which influences cardiovascular effects of HRT formulations and SSHR modulators. In clinical and animal studies, E2 inhibition of atherosclerosis is only partly explained by lipid changes (*3*, *30*). After menopause, LDL and triglyceride levels rise, and high density lipoprotein (HDL) levels fall. HRT has antiatherogenic effects on lipids, lowering LDL and raising HDL (*3*, *28*, *29*), but paradoxically also elevates triglycerides. HRT alters hepatic synthesis and/or clearance of many lipoproteins (*3*, *29*). In both male and female apolipoprotein E–deficient mice, E2 inhibits atherosclerotic lesion formation in a manner not fully explained by changes in lipids (*30*). Testosterone's effects on lipids are discussed below.

Hemostasis and thrombosis. HRT causes an increase in venous thromboembolic events, but the effects of SSH on coagulation, fibrinolysis, and arterial thrombosis are understudied (*28*, *31*). Oral HRT and contraceptives increase levels of Factor VII, but decrease circulating fibrinogen and plasminogen activator inhibitor–1 (*31*). Genetic variants like the common variant Factor V Leiden may predispose to thrombosis in the setting of HRT (*12*, *31*). Megakaryocytes express ERβ and AR, but not ERα or PR (*32*). Platelet aggregation and secretion change with sexual maturity differently in females and males (*33*). Further studies are needed of coagulation/fibrinolysis and platelet function in gonadectomized animals, mice

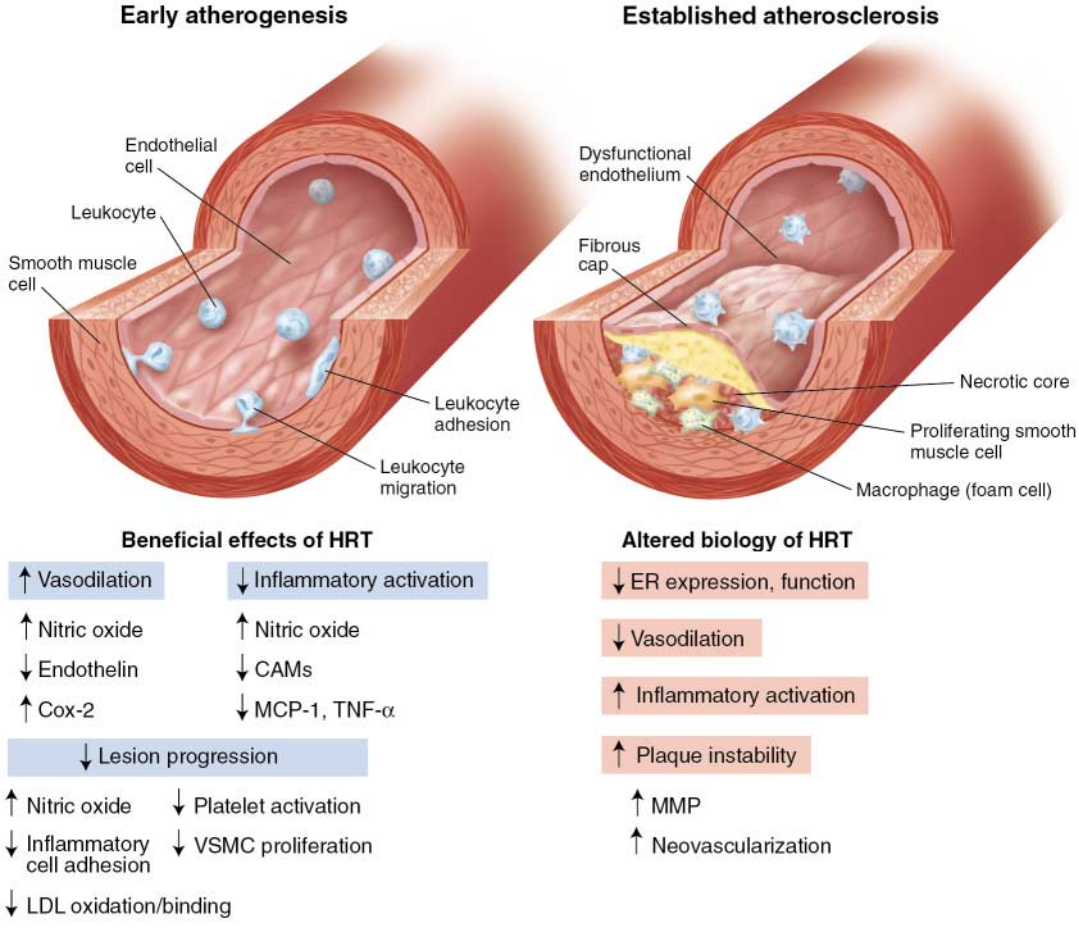

Fig. 3. The timing hypothesis: differential effects of HRT on early and later stages of atherosclerotic disease. Atherosclerosis is characterized by the gradual loss of vascular protective mechanisms and the emergence of advanced, unstable lesions (*38*). SSH effects on the endothelium and its protective functions, vascular smooth muscle cells, and inflammatory cells differ, depending on the stage of atherosclerosis in the underlying blood vessel (*3*, *8*, *24*, *35*, *39*, *40*). LDL, low density lipoprotein; CAMs, cell adhesion molecules; MCP-1, monocyte chemoattractant protein 1; TNF-α, tumor necrosis factor–α; VSMC, vascular smooth muscle cell; MMP, matrix metalloproteinase; COX-2, cyclooxygenase 2.

harboring SSHR disruptions, and humans on HRT.

Evolution of atherosclerosis and the timing of HRT. Observational studies consistently show that CVD risk decreases with HRT use and increases with premature menopause (*1*, *3*, *29*), supporting evidence that estrogen/progesterone loss and/or unopposed androgen promotes postmenopausal CVD. In contrast, the WHI and other randomized trials of HRT fail to show an HRT effect in lowering cardiovascular events (*1*). This discordance remains widely misinterpreted as strong or definitive evidence that HRT does not afford cardioprotection. Both methodological and biological issues contribute to the differences between observational and randomized clinical trials (*34*), but the age at which women initiate HRT is likely critical. Studies in primates (*35*) and other animal models (*36–38*) support evidence that the beneficial effects of HRT in preventing atherosclerosis occur only if HRT is initiated before the development of advanced atherosclerosis (the timing hypothesis) (Fig. 3). Atherosclerosis is a complex, progressive inflammatory process characterized by the gradual loss of vascular atheroprotective mechanisms and the emergence of susceptibility to plaque instability and rupture (*39*, *40*). The timing hypothesis states that SSHs alter the biology of vessel wall cells and the inflammatory cells that accrue as atherosclerosis progresses differently in the early versus later stages of the disease (Fig. 3). Early, physiological levels of SSH replacement can improve or reverse the endothelial dysfunction that occurs before the development of more advanced atherosclerotic lesions [reviewed in (*3*, *8*, *24*, *35*, *40*)] (Fig. 3). In advanced atherosclerotic lesions, however, a different cellular biology exists that provides an altered substrate, which in response to the late initiation of HRT is more susceptible to inflammatory and hemostatic abnormalities (Fig. 3).

Failure to account for timing data contributes to the present confusion in interpreting trials of the effect of HRT on CVD. Most women in observational studies initiated HRT during the perimenopause (*41*), whereas the WHI trial included too few younger women to examine whether women starting HRT during the menopausal transition achieve cardioprotection (*42*). There are proven therapies for CVDs in women that continue to receive insufficient attention and use in the midst of this controversy, such as HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins), which prevent and reverse atherosclerosis and decrease cardiovascular events (*43*). Preclinical data supporting the timing hypothesis have not yet been adequately considered and incorporated into clinical trial study designs. Two prospective clinical studies to directly address the HRT timing hypothesis are currently enrolling patients: the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE).

Cardiovascular effects of testosterone. In both sexes, testosterone levels decline with age, but at a more gradual rate than estrogen and progesterone decreases in women following menopause. In men, circulating estrogen levels are quite low, but appear to be physiologically relevant, because estrogen deficiency in males increases testosterone levels (*44*). In male mice, testosterone inhibition of atherosclerosis is abrogated by aromatase inhibition (*45*). Aromatase inhibitors disrupt normal vascular relaxation in healthy human males, and aromatase knockout mice have abnormal vascular relaxation, supporting evidence that conversion of testosterone to estrogen in males by aromatase helps maintain normal vascular tone [reviewed in (*46*)]. However, effects of aromatase inhibitors on vascular function in females have not yet been examined, despite their widespread use in breast cancer therapy. Androgen replacement therapy (ART) is controversial in both sexes, but in general is not associated with increased cardiovascular risk (*47*, *48*). Several ART studies suggest a beneficial cardiovascular effect, especially on vasomotion (*47–50*). ART can improve cardiac ischemic indices in men, but not ischemia caused by peripheral arterial disease (*49*). Androgens have variable effects on lipoproteins and other risk factors, depending on the hormone formulation used and population studied. Exogenous androgens generally lower HDL-C and lipoprotein (a) [Lp(a)], with only modest effects on LDL-C (*50*), and facilitate both macrophage lipoprotein uptake and efflux of cellular cholesterol to HDL (*50*). ART in men with coronary artery disease enhances coronary blood flow and endothelial function (*51*). Testosterone activates both AR and ER (by aromatase conversion to E2) in cardiovascular tissues, but the relative importance of ER and AR for vascular androgen effects and the specific cardiovascular genes regulated by these receptors are not yet known. Normal ER function is required in both males and females for normal cardiovascular development and function (*27*, *44*, *46*, *52*). A man lacking functional ERα has impaired vascular function and early coronary arterial calcification (*52*). Although interest in the potential for ART in both sexes has increased in recent years (*47*, *48*), randomized trials of ART in either gender are lacking (*47–50*).

Gender Differences in the Heart

SSHR and aromatase all are expressed in the heart (Fig. 1) [reviewed in (*3*, *15*, *53*)]. Recent controversy has arisen as to whether murine hearts express ERβ (*54*), but functional ERα and ERβ have been detected in animal and human cardiomyocytes (*3*, *15*, *53*). Gender differences exist in normal heart function. Cardiac contractility is greater in healthy women than in age-matched men, and HRT withdrawal in women decreases contractility (*55*, *56*). As men and women age, myocardial mass is better preserved in women (*57*), which may be related to differences in cardiac expression of glycolytic and mitochondrial metabolic enzymes (*58*) and/or to prosurvival effects of E2-ER on cardiomyocytes mediated by ERα- and phosphatidylinositol 3-kinase–Akt–dependent pathways (*59*).

Gender differences also exist in cardiac electrophysiological function [reviewed in (*60*)] and in both inherited and acquired abnormalities of the heart muscle. Some familial hypertrophic cardiomyopathies are more severe in males than in females (*61–63*). Hearts of women with aortic stenosis are more hypertrophied and have better contractile function than those of men with this disorder (*64*). In heart failure studies, female gender is associated with improved cardiac function and survival (*65*, *66*). Animal studies of ischemia and reperfusion injury show that female gender confers protection, which requires ERβ (*67*). Estrogen benefits but testosterone worsens cardiac function in a mouse model of myocardial infarction in both males and females (*68*), suggesting that myocardial ER and AR may mediate opposing effects on the myocardial response to injury. Further study of these two SSHRs in normal and diseased myocardium of peri-and postmenopausal women is needed. SSHR-mediated changes in the levels and regulation of myocardial calcium-contractility coupling proteins in the heart are likely involved in the effects of SSH on myocardial hypertrophy and heart failure (*69*, *70*) and also need greater study.

Summary

New, better tailored hormone replacement therapies and selective SSHR modulators of use in preventing and treating CVD are needed. To improve diagnosis and treatment of CVD in women, it will be necessary to strengthen interactions between preclinical and clinical scientists, improve our understanding of the biology of gender differences and the perimenopause, and reconsider the paradigm of and singular focus on untailored postmenopausal HRT that has dominated the past several decades. To accomplish these goals, greater focus on understanding the molecular and cellular physiology of each of the SSHs and their receptors in the cardiovascular system will be required.

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SPECIAL SECTION

REVIEW

The Pains of Endometriosis

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Endometriosis is a disease defined by the presence of endometrial tissue outside of the uterus. Severe pelvic pain is often associated with endometriosis, and this pain can be diminished with therapies that suppress estrogen production. Many women with endometriosis also suffer from other chronic pain conditions. Recent studies suggest that mechanisms underlying these pains and sensitivity to estrogen involve the growth into the ectopic endometrial tissue of a nerve supply, which could have a varied and widespread influence on the activity of neurons throughout the central nervous system.

Endometriosis is a common disorder that occurs mainly in women of reproductive age. Because ectopic endometrial implants respond to natural or induced decreases in estrogen levels, the disorder is considered "estrogen dependent" (*1*). Symptoms of endometriosis include reduced fertility and several types of pain such as severe dysmenorrhea (excessive menstrual pain), deep dyspareunia (pelvic pain with coitus), dyschezia (pelvic pain with defecation), and chronic pelvic pain. In some women, pain can be exacerbated by the co-occurrence of other severe chronic pain conditions such as irritable bowel syndrome, interstitial cystitis, repetitive kidney stones, vulvodynia, temporomandibular syndrome, migraine, and fibromyalgia (*2*–*4*). Little is known about the association between the ectopic implants and pain; however, recent studies of women and animal models are beginning to provide clues.

The most common pharmacological treatment for endometriosis uses a class of drugs called gonadotropin-releasing hormone (GnRH) agonists. Because these drugs down-regulate GnRH receptors, they suppress pituitary gonadotropin secretion and sex steroid production, thereby producing a systemic hypoestrogenic state. This treatment results in the elimination or reduction in size of the implants in women (*5*) as well as in a rat model of endometriosis (*6*). In addition, optimized treatment with GnRH agonists is effective in reducing endometriosis-related pain symptoms in women (*5*).

Because GnRH agonists reduce both implant size and the pains associated with endometriosis, these pains may be due to the presence of the abnormal implants. Numerous studies, however, have failed to find a correlation among pain scores, types of pain, and various aspects of the anatomy and biochemistry of the implants (*7*). In addition, although surgical removal of the ectopic implants alleviates pain symptoms in many women, the surgery can fail to alleviate the pain and/or pain may recur even without evidence of residual or recurrent disease or any other identifiable visceral or somatic pathology (*8*).

On the other hand, correlations have been found between pain severity and both the depth of "infiltration" into peritoneum or pelvic organs and the proinflammatory cytokines, pros-

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