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The Role of Sex Hormones
in the Cardiovascular System

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1. Introduction

In developed countries heart disease is the primary cause of death in men and in women over the age of 60. While premenopausal women have a low incidence of cardiovascular disease as compared to men, the mortality among post-menopausal women rises to the same frequency or even exceeds the rates of men (Adams et al., 1995; Fraser et al., 2000; Gray et al., 2001; Wild & Bartholemew, 1988). This significant gender difference is mostly attributed to the beneficial role of estrogens (Collins et al., 1993; Gray et al., 2001). Many studies have suggested that females have reduced incidence of cardiovascular diseases due to the beneficial effects of estrogen on both the lipid profile and on the vasculature. Lately, many new mechanisms are discovered in cardiovascular diseases and research has been focused on the role of both estrogen and testosterone, as well as some other androgens, but also on the estrogen receptor GPER, which shows an important role in the cardioprotection of both, males and females (Deschamps &Murphy, 2009).

The sex hormones in the cardiovascular system might be viewed at as biomarkers for cardiovascular health status, as well as by itself, as protective agents against myocardial diseases. The estrogens in premenopausal women are modulating health in the regular menstrual cycle. Testosterone is lacking such cycle activity and is probably more expressed in the physically active population. The effects of testosterone are increasing muscle mass induced by higher physical activity, and higher adrenal and hypophysis activity resulting in potential cardiovascular system damage. However, when testosterone or its derivatives are missused, ventricular hypertrophy, diastolic dysfunction and myocardial stiffening appear and the potential risk for infarction increases (Malkin et al., 2010).

The sex hormones, i.e. estrogen, progesterone and androgens and their receptors, ERs, PRs and ARs, have been studied as candidates to mediate sex-specific effects observed in gender related responses of the cardiovascular system and related diseases. Above all estrogen has received major attention, while testosterone is at present studied for its potential beneficial and cardioprotective mechanism of action. However, within several cardiovascular diseases like myocardial infarction, coronary artery disease and other ischemia related diseases, heart failure, ECG gender specific differences, the focus was already turned to the gender related sex hormones differences. These studies presented new approaches and specificities in

gender related pathways responses. Recently, most of the approaches of cardiovascular diseases focused on non-genomic action of sex hormones.

1.1 Non-genomic estrogen action

Since estrogens in premenopausal women with regular menstrual cycle are established as a natural protection against cardivoascular diseases, nuclear and non-nuclear mechanisms are evaluated for their mode of action. The non-nuclear modality of estrogens action is for example ascribed to their direct vascular effects, antioxidative activity and a new pathway discovered in the last years shows that the plasma membrane G protein estrogen receptor (GPER1) is involved in cardioprotection of both in females as in males.

1.2 Testosterone and its non-genomic role

For decades, the research reports proposed only cardiotoxic and deleterious effect of testosterone in the cardiovascular system. This was based on epidemiologic human studies, where direct testosterone treatment, especially in supra-physiological androgen abuse, showed an increase in left ventricular mass and hypertrophy, causing myocardial stiffness and diastolic disfunction. Animal studies with castrates showed similar deleterious effects from adrogen receptor antagonist studies. However, later, with the use of better designed studies it was shown that testosterone, in optimal levels, may enable significant and profound cardioprotection expressed in e.g., diminished reperfusion injuries, decreased arrhythmias. It is now obvious that testosterone must posses the comparable non-nuclear activity, at cytoplasmatic level, similar to the non-genomic action of estrogen, through yet unknown mechanism(s).

2. Sex hormones and heart protection

In the cardiovascular tissues the protective effects of estrogen and testosterone are manifested through the instantly responsive arteries of the coronary artery system, which estrogen directly relaxes via the endothelial nitric oxide (NO) mechanism (Dai et al., 2004; Santos et al., 2004; Woodman et al., 2004). It is probable that testosterone relaxes these arteries via a different mechanism, maybe even a non-genomic pathway, which does not involve the nuclear androgen receptors and is independent of the vascular endothelium. This testosterone response is initiated at specific binding sites in the cell membranes of smooth muscles. For example, testosterone directly inhibits voltage-gated calcium channels, with an additional inhibitory action of calcium store-operated calcium channels (Jones et al., 2004; Yildiz et al., 2005). In the myocardium the estrogens reduce the incidence of postischemic ventricular arrhythmias by reducing the accumulation of intracellular Ca^{2+}, protecting mitochondrial structures, inhibiting apoptosis, having antioxidant action and interacting with heat stress proteins, thus protecting the heart from injuries (Fraser et al., 2000; Kim et al., 1998; Knowlton & Sun, 2001; Zhai et al., 2000). Further, both the mitogen activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) are believed to be involved in the regulation of NO synthesis by estrogen (Gray et al., 2001). The acetylcholine-induced and flow-dependent vasodilation are preserved or potentiated by estradiol by increasing the endothelial production of NO and prostacyclin. Estradiol also promotes the endothelial healing and angiogenesis through the activation of estrogen receptor-α, which

shows that the protective mechanism in the cardiovascular system is linked to the estrogen activation of ER receptors (Arnal et al., 2010).

In the past the action of androgens on the cardiovascular system has received relatively little attention and authors disagree about possible detrimental or protective effects of testosterone on the heart (Pugh et al., 2000). Later studies showed that cardioprotective effects of testosterone are mediated by a yet not identified androgen-dependent pathway, but only after chronic administration of testosterone (Kuhar at al., 2007; Borst et al., 2010).

2.1 Coronary flow, acute and chronic effects of sex hormones

Direct application as well as estradiol pretreatment increased the coronary flow in isolated female hearts after the onset of reperfusion as well as testosterone pretreated male hearts (which was equally effective to female hearts), showing the vasodilatative effects of sex hormones (Kuhar et al., 2007). The coronary flow was increased after direct application of estradiol, while direct testosterone administration lacked such a vasodilatatory effect (Kuhar et al., 2007). Estradiol is reported to possess a direct artery relaxant action and also a direct effect on myocardium. Similarly, testosterone influenced coronary flow directly and the effects were both beneficial and deleterious (Pugh et al., 2000). Estradiol improved coronary flow of rats directly through the stimulation of NO release from endothelial cells (Dai et al., 2004; Fraser et al., 2000; Santos et al., 2004; Woodman et al., 2004). The vasodilatatory effects of testosterone are mediated by opening the large conductance, calcium-activated potassium channels (Deenadayalu et al., 2001). The short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease, which may be related to its direct coronary relaxing effect (Rosano et al., 1999).

In physiological conditions, both estrogens as well as androgens may elicit very rapid effects to keep the homeostasis balanced, without manifesting RNA and protein synthesis (Dechering et al., 2000; Revelli et al., 1998). For example, the plasma membrane estrogen receptor was shown to respond rapidly to estrogen (Peitras & Szego, 1977), while there is no clear evidence yet of a similar effect for androgens.

2.2 Endothelium, estrogen and the heart

The sex hormones in the endothelium were generally believed to have mainly non-genomic effects. The endothelial estrogen receptor-α (ERα) in the endothelium as a whole, is considered one of the most important targets of cardioprotection. The endothelium and, in particular, the endothelial ER-α appear to be a key cellular and molecular targets of the protective actions of estradiol against ischemia/reperfusion (I/R)-induced coronary endothelial dysfunction. The activation of the endothelial estrogen receptor (ER) by estradiol, triggers a protective action on the coronary endothelial structure and function, which, in turn, limits the size of the infarct. This protection may be in part due to reduced cardiac oxidative stress, demonstrated by the decreased production of reactive oxygen species observed during early reperfusion. The signaling mechanisms of cardioprotection are to a great extent dependent on NO, which signals in cardiomyocytes via protein kinases and may possibly protect mitochondria, resulting in decreased cardiomyocyte death. Another indirect effect the reduced neutrophil-mediated cardiomyocyte injury may also play a role as endothelial protection and thus in cardioprotection (Favre et al., 2010).
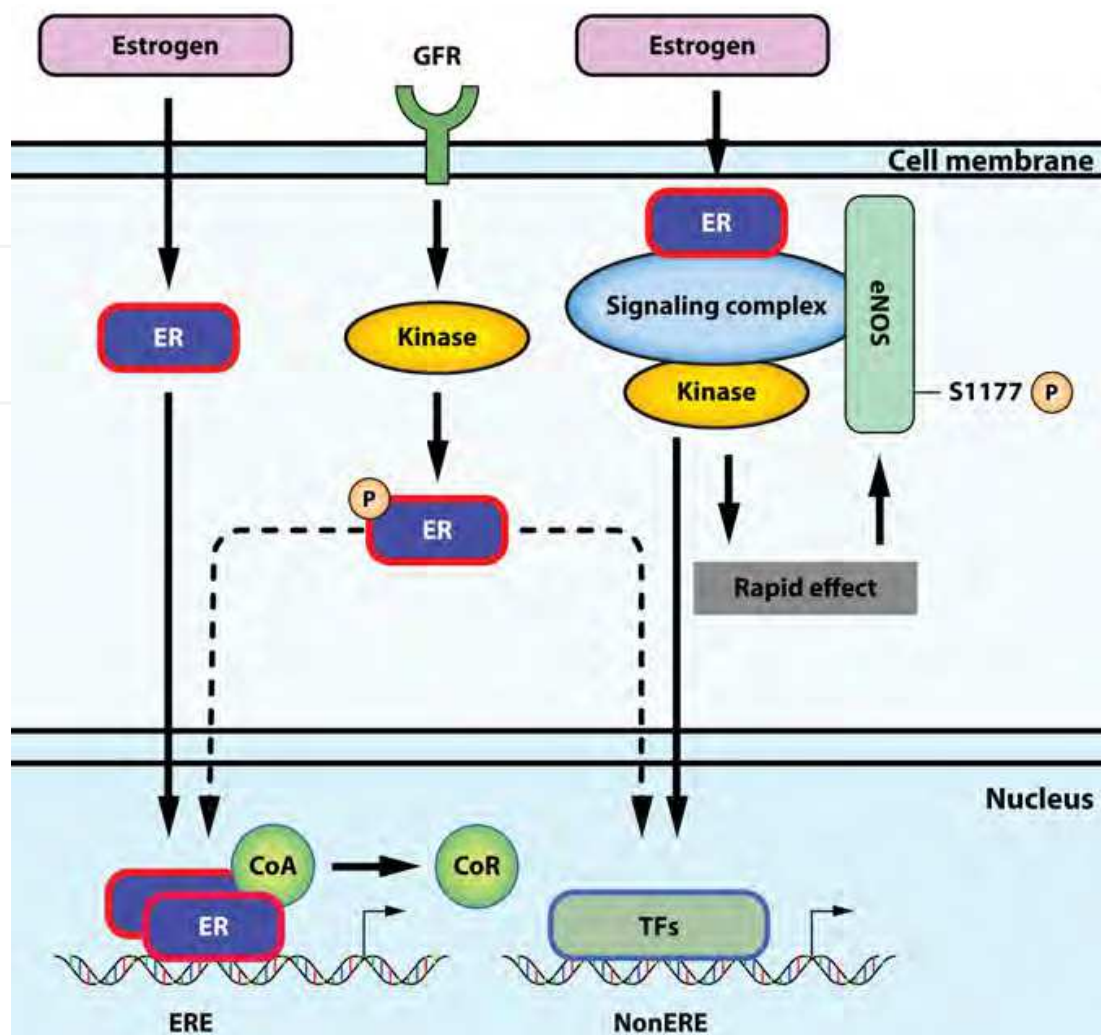
Fig. 1A. Endothelial estrogen-mediated responses. Adopted from Wu et al., (2011).
Left: The first signaling pathway in vascular endothelial cells by estrogen receptor (ER) represent the cytosolic receptors, that are ligand-activated transcription factors, that regulate gene expression. After translocation to the nucleus receptor dimerizes and binds to specific DNA sequences called estrogen response elements (ERE), recruiting coactivator (CoA) proteins, displacing corepressors (CoR) from the DNA, and activating gene expression.
Center: The second signaling pathway are the ERs that can be transcriptionally activated via ligand-independent pathways in which growth factor receptor (GFR) activation leads to activation of specific kinases that directly phosphorylate (circled P) the ER, again leading to altered gene expression, either directly by the ER or via ER interactions with other transcription factors (TFs).
Right: The third signaling pathway is mediated by non-nuclear ERs. In this pathway, estrogen induces a cell membrane–associated ERs to form a signaling complex that results in rapid activation of specific kinases, which in turn phosphorylate and enzymatically activate endothelial nitric oxide synthase (eNOS).

Another important endothelial, cardioprotection factor is the vascular endothelium growth factor (VEGF) and its basic signal molecules (VEGF receptor, Akt, eNOS). ERα knockout mice showed a marked decrease of capillary density, and the absence of receptor β has minimal effect, while the levels of the VEGF receptor, phosphorylated Akt and eNOS in the

ERα knockouts were reduced to half of the values in control group. This leads to the conclusion that VEGF is supposed to act mainly via ERα to regulate VEGF transcription and elements of basic VEGF signaling, which makes it is crucial in the development of microvasculatures in the heart (Jesmin et al., 2010).

2.3 Heart failure

The inability of the heart to supply sufficient cardiac output and blood flow to meet the needs of the body and lungs is defined as a heart failure. The causes of heart failure are myocardial infarction, ischemic heart disease in general, hypertension, valvular heart disease, and cardiomyopathy, with symptoms being shortness of breath, leg swelling,
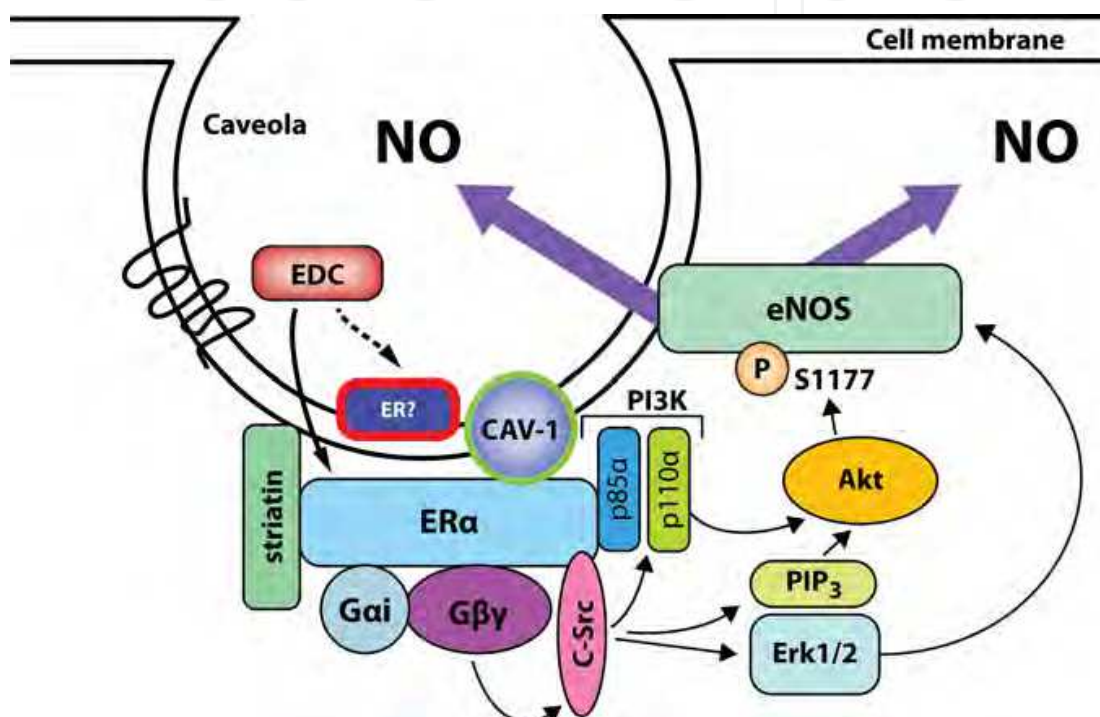

Fig. 1B. Non-nuclear estrogen receptor signaling in vascular endothelial cell caveolae. Adopted from Wu et al., (2011).

The non-nuclear estrogen receptors (ERs) localize to the endothelial cell membrane invaginations called caveolae by direct binding to the caveolar proteins, including the scaffold protein striatin, which is bound to the major caveolar structural protein, caveolin-1 (Cav-1). Upon estrogen binding (EDC), signaling complexes assemble that include the ERs and the G protein $G\alpha_i$, $G\beta\gamma$ and sequentially activate the tyrosine kinase src (C-src), the serine/threonine kinase, phosphoinositide-3 protein kinase (PI3K), consisted of subunits p85a and p110a, that produce phosphatidylinositol (3,4,5)-triphosphate (PIP_3), and the kinase Akt. Akt is serine/threonine protein kinase that plays a key role in multiple cellular processes such as cell proliferation, apoptosis, transcription, cell migration as well as in angiogenesis. Akt then directly phosphorylates endothelial nitric oxide synthase (eNOS) on serine 1,177, leading to its enzymatic activation and the production of nitric oxide (NO). Also, Akt activate extracellular signal-regulated kinases (Erk1/2) or MAP kinases, involved in differentiation of cells, but also in regulation of eNOS. The position of the assembling complex - on the internal or the external side of the cell membrane – remains unclear. This non-nuclear ER dependent pathway confers protection against vascular injury.

exercise intolerance and the overall body becomes congested with fluid. Heart failure is a complex state of progressive multisystem diseases with significant morbidity and mortality and its clinical picture is defined by pathology of the cardiovascular system and is influenced by peripheral cytokine, hormonal, and musculoskeletal dysfunction. The cytokines, catecholamines, and hormones during heart failure have a maladaptive response that leads to a proinflammatory state tipping the metabolic balance toward catabolism. In addition to this procatabolic combination, chronically high levels of catecholamines, angiotensin II, and aldosterone eventually may contribute to testosterone deficiency, which blunts the anabolic compensatory pathways.

Present medical treatments for heart failure have proven to decrease mortality and include treatment with β-adrenergic receptor antagonists, which target adrenergic hyperstimulation of the failing myocardium; angiotensin converting enzyme inhibitors and angiotensin receptor blockers, which attenuate left ventricular remodeling; and aldosterone blockers, which blunt myocardial fibrosis.

Several studies have shown that more than ¼ of men is affected with chronic heart failure are deficient in testosterone. Thus testosterone is directly or indirectly involved in its pathology. Androgen deficient men without heart failure often report similar typical symptoms, such as shortness of breath, fatigue, deterioration of muscle mass, decline in strenght and endurance (Naghi et al., 2011). In male, but not female mice, G protein estrogen receptor GPR30-deficient mice manifested impaired left-ventricular cardiac function, indicating that non-genomic estradiol signalling is important in heart failure. Further, also regulation of vascular tone by GPER1 is indicated to play a role in heart failure (Delbeck et al., 2011).

2.4 Ischemic heart disease and acute myocardial injuries

The protective action of estradiol in cardiac ischemia/reperfusion (I/R) was demonstrated in several animal studies, but most of the cellular targets involved in this protection still need to be defined. Usually, in control animals after cardiac I/R the following are evoked: structural endothelium injuries, including necrosis, associated with altered coronary endothelial NO production. The long-term activation of the endothelial ERα by estradiol protected both the coronary endothelial and myocardial layers and endothelial structures associated with the NO-mediated coronary endothelial response (Favre et al., 2007). However, this was not the case for ovariectomized female mice and male mice, which during I/R showed endothelial dysfunction (Favre et al., 2007). More precisely, the ERα deficiency worsens global I/R-induced alteration in coronary flow and cardiac NO release in male mice and also abolishes the endogenous cardiac protection displayed in intact female mice (Favre et al., 2007).

Genomic pathway for cardioprotection by estrogen receptor (ER) activation is upregulated with chronic ERβ stimulation. This pathway is ligand-activated by transcription factors that, after translocation to the nucleus, bind to DNA sequences and regulate gene expression, resulting in for example modulators of both the NO system and apoptosis processes.

Stimulation of the nuclear G-protein coupled membrane bound estrogen receptor (GPER1) by tyrosine kinase src (C-src) results in activation of matrix metalloproteinase (MMP) leading to the release of epidermal growth factor (EGF) that can transactivate epidermal growth factor receptors (EGFRs). EGFR activation leads to multiple downstream events including activation of kinases within the phosphoinositide-3 protein kinase/ Akt pathways (PI3K/Akt).
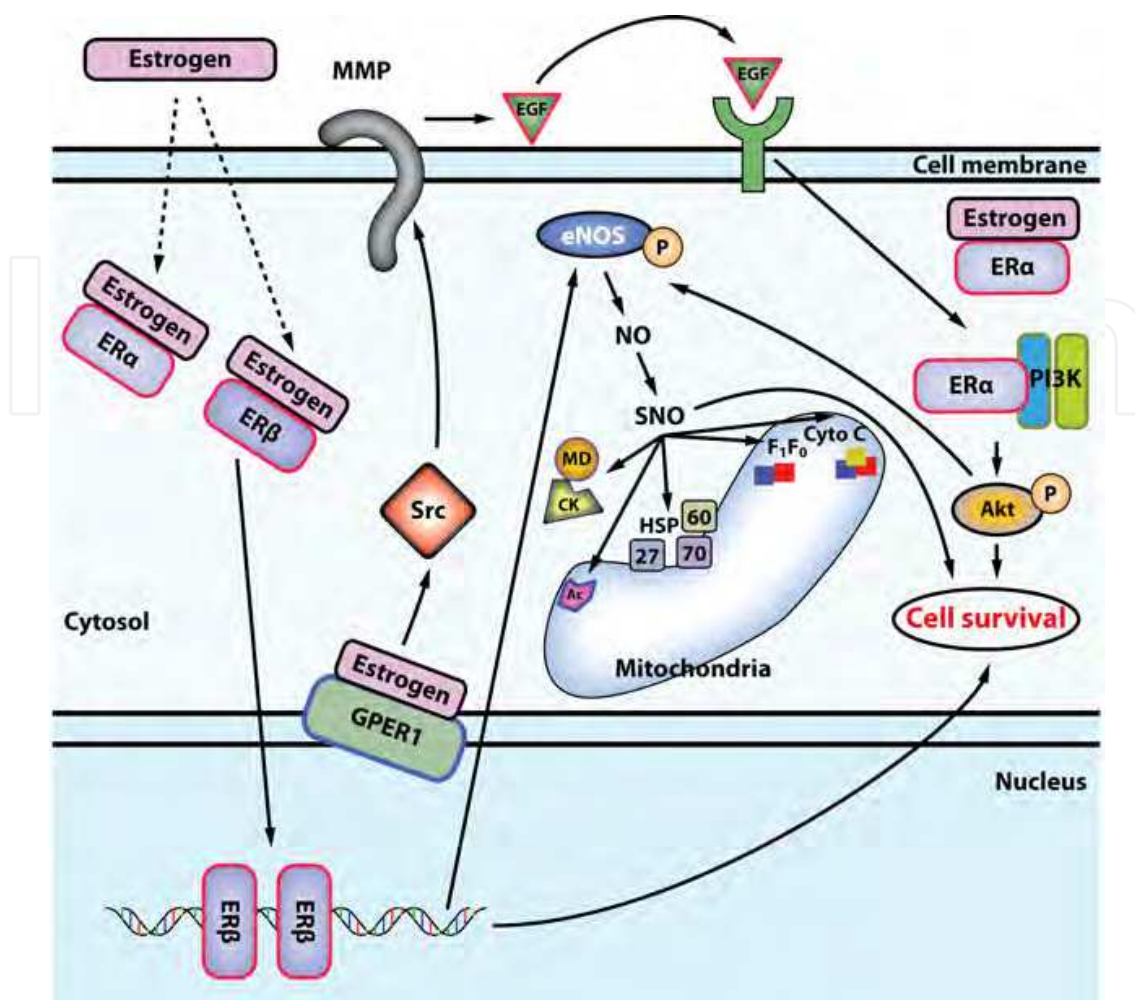
Fig. 2. Cardioprotective signalling pathways induced by estrogen receptor activation. Adopted from Deschamps, Murphy & Sun (2010).

Following after the activation of both PI3K/Akt, nitric oxide (NO) signaling and the chronic activation of ERβ comes a significant increase in S-nitrosylated proteins (SNO) in the mitochondria including F_1F_0-ATPase, aconitase (Ac), cytochrome c oxidase (Cyto C), heat shock proteins (HSP27/60/70), and cytosol like creatine kinase (CK), and malate dehydrogenase (MD). The acute and moreover chronic activation of these pathways leads to enhanced cell survival resulting in cardioprotection.

2.4.1 Amelioration of ischemia and reperfusion induced myocardial injuries

The anti-ischemic effects of sex hormones are considered to protect due to improvement of the coronary flow and due to the reduced incidence of arrhythmias and established cytoprotection during reperfusion. Both estradiol and testosterone in supraphysiological levels significantly decreased ischemia-reperfusion injuries of isolated rat hearts. The reperfusion injuries were reduced both by the direct application of sex hormones, and pretreatment prior to the isolated heart experiment. However, protective effects against ischemia-reperfusion injuries were only observed in the male hearts of animals pretreated with testosterone in a comparable effective way as in estradiol pretreated female hearts. The direct testosterone application was not comparable to the protection by the directly applied estradiol (Kuhar et al., 2007).

Further, in female animals direct administration of estradiol showed protection against cell injuries, and no protection was shown in estradiol pretreatment. In male hearts cytoprotective effects were found only in testosterone pretreated animals, while estradiol lacks direct cytoprotective effects in isolated heart (Kuhar et al., 2007). Amelioration of ischemia and reperfusion induced myocardial injuries has also been demonstrated in some experimental animal models (Delyani et al., 1996). For estradiol a profound protective effect against stroke-like ischemic injuries in female rats was found (Wise et al., 2001), while also the cytoprotective effect of estradiol to hypoxia–reoxygenation induced injuries in cardiac cells has been reported (Jovanovic et al., 2000). Chronic estradiol treatment does show some cardioprotective effects which can be attributed to over expression of heat-shock proteins (HSPs), which is generally regarded as protective against cardiac injury. HSP90 is known to bind the intracellular hormone receptors and therefore it was suggested that the interaction between HSP90, the receptors, and heat-shock factor-1 (HSF-1) was an important element in the activation of HSF-1 by hormones (Knowlton & Sun, 2001). It is known that after treatment of cardiac myocytes with 17β-estradiol or progesterone the HSP90 redistributes. However, testosterone did not effect HSP levels and pretreatment of males with testosterone did not elicit protective effects (Knowlton & Sun, 2001). This is in accordance with the discovery that androgen receptors are absent in cardiac myocytes.

Morover, testosterone acutely and directly depolarizes and oxidizes cardiac mitochondria in a K-dependent, ATP-sensitive, and testosterone receptor-independent manner, by activation of mitochondrial K^+ channels, while it does not activate sarcolemal K^+ ATP channels. Thus, mitochondrial K^+ channels play a key role in cardioprotection during ischemia and via this mechanism testosterone protects cardiomyocytes from ischemic cell death (Er et al., 2004). In contrast, cell injury tests did not confirm the direct protective effects of testosterone in ischemia/reperfusion induced myocardial injuries, which may be due to the limited electrolyte capacity of the mitochondria. To conclude, the action of the sex hormones is attributable not only due to its direct action on coronary arteries, but also due to other non-genomic properties.

The demonstration that estrogen exert a cardioprotective effect in male animals showed, that in vivo supplemental estrogen treatment of male mice reduces the prevalence of cardiac rupture during the acute phase of myocardial infarction (Cao et al., 2011). In other short-term (acute) and long-term (chronic) cardiac function study, myocardial infarction-induced male mice treated with estrogen and female mice treated with testosterone, showed opposing chronic cardiac remodeling and function effects, with favorable (protective) effects exerted by estrogen and detrimental effects exerted by testosterone (Cavasin et al., 2003). During the acute phase of myocardial infarction, however, estrogen appeared to offer no or little protection against acute myocardial infarction-induced cardiac rupture. The castration alone could slightly reduce the prevalence of cardiac rupture in male mice. While a lower prevalence of cardiac rupture was observed in estrogen-treated mice as compared to placebo-treated ones (Cao et al., 2011), no difference was observed in another study (Cavasin et al., 2003).

The observation on the obligatory role of the endothelium for cardiomyocyte protection may appear contradictory to a direct protective action of estradiol on hypoxia/reoxygenation-mediated death of isolated cardiomyocytes. First, the in vitro data used large amounts of immediately administered estradiol and thus with these pharmacological doses, it is

possible to elicit direct effects that can not be observed in cardiomyocites. Second, the mechanisms of reperfusion injury to cardiomyocytes in vivo markedly differ from those involved in vitro. The immediate inflammatory response associated with severe oxidative stress appears to be operative in vivo but not in vitro and this phenomenon centrally involves the endothelium as both a target and a trigger of the inflammatory response. Third, another important aspect of reperfusion injury is the no-reflow phenomenon that may worsen I/R injury and that is likely to be reduced by estradiol secondary to endothelial protection (Favre et al., 2010).

2.4.2 Delayed cardioprotection by testosterone

Cardioprotection also can be achieved by preconditioning, a process that can be assesed pharmacologically, by ischemia, or by other stressors. Preconditioning increases the resistance to subsequent longer stress. Among the most important benefits are reduction of reperfusion injuries, diminished arrhythmia, prevention of myocardial stunning and post-ischemic contractile dysfunction, marked limitation and decrease of infarct size, and reduction of endothelial injury (Geršak & Drevenšek, 2002). The receptors involved in preconditioning are mainly coupled to protein kinase C. In mice with removed testicles, the immediate cardioprotection of ischemic preconditioning is abolished, thus testosterone is needed for the acute cardioprotection of preconditioning. In the absence of testosterone, the preconditioning with metabolic inhibition in vitro or k-opioid agonist in vivo, failed to establish delayed cardioprotection against ischemic insult in ventricular myocytes or isolated perfused male rat hearts, respectively (Liu et al., 2006). This was the first evidence that testosterone at physiological concentrations is needed for the delayed cardioprotection of preconditioning.

3. Atherogenesis, sex hormones and gender differences

Estrogen is known to relax arteries directly via endothelial NO and thus exert potential antiatherogenic effects (Dai et al., 2004; Santos et al., 2004; Woodman et al., 2004). Also, estradiol prevents early atheroma through endothelial-mediated mechanisms (Arnal et al., 2010). Androgens on the other hand, have been associated with possible proatherogenic effects and an increased cardiovascular risk by adversely affecting the plasma lipid and lipoprotein profile, increasing the risk of thrombosis and cardiac hypertrophy (Adams et al., 1995). On the contrary, short-term administration of testosterone causes vasodilatation in a range of species including humans (Costarella et al., 1996; Crews & Khalil, 1999; Honda et al., 1999; Perusquia et al., 1996; Yue et al., 1995). However these beneficial early on atherogenesis effects of testosterone were not explained by changes in lipid levels. Besides, estradiol administration to orchidectomized males attenuated lesion formation to the same extent as testosterone administration. These results indicate that testosterone attenuates early atherogenesis and that this is most likely be caused by being converted to estrogens by the enzyme aromatase expressed in the vessel wall (Nathan et al., 2000). The latest study in an androgen receptor knockout mice on apolipoprotein E-deficient basis, showed acceleration of atherosclerosis, while testosterone treatment reduced this atherosclerosis. In conclusion, the male mice showed testosterone atheroprotection which has both androgen receptor-dependent and androgen receptor-independent components (Bourghardt et al., 2010).
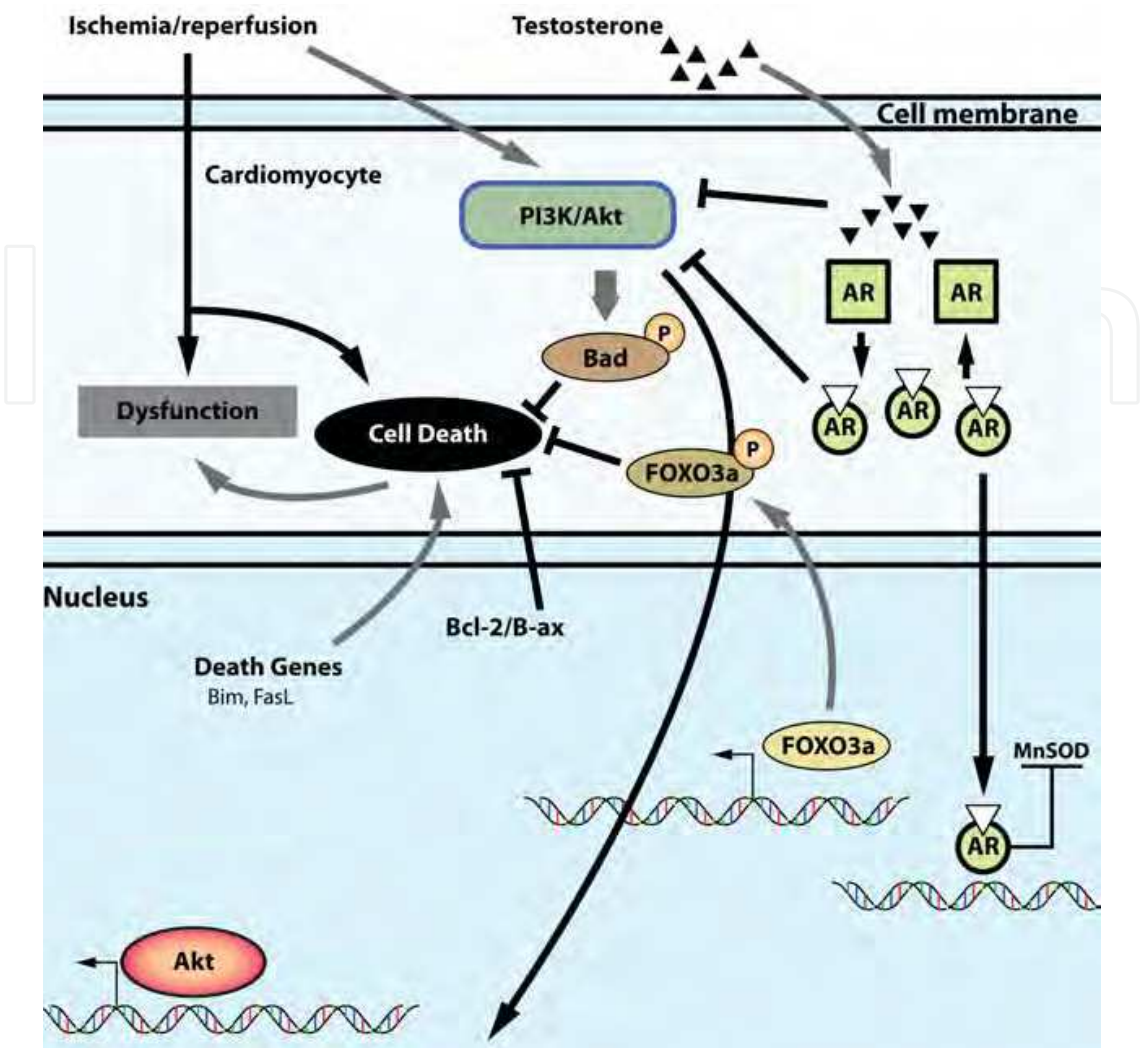
Fig. 3. Acute ischemia/reperfusion induced testosterone signalling pathways in cardiomyocites during androgen receptor activation. Adopted from Huang et al. (2010). The activation by myocardial Akt in PI3K/Akt downstream signaling after activation of androgen receptor (AR) due to ischemia reperfusion causes increased release of cell death signals (Bad, Bcl-2, FOXO3a) and decrease apoptotic mediator FasL. The Akt protein at normal sex hormone status is more active in female then in male hearts and thus in this pathway testosterone is a negative factor in cardioprotection processes.
The genomic actions of the AR activation consist out of changes in gene expression involved in cardiac protection/injury, like modulators of the superoxide dismutase (MnSOD) system, apoptotic and death genes. Besides, testosterone in acute ischemia down-regulates FOXO3a, a trigger protein for apoptosis, and decreases antiapoptotic activator targets as Bim and FasL that are probably post-translational products with little or no influence on acute ischemia/reperfusion injuries. Overall, genomic pathway probably leads to testosterone induced cardioprotection.

4. Arrhythmias

The ventricular arrhythmias, mostly being the malignant ones of all arrhythmias, show important gender differences. Torsades de pointes, a ventricular tachyarrhythmia that can

lead to ventricular fibrilation, is associated with long QT syndrome and is more common in females than in males. The long QT syndrome can be inherited as congenital mutations of the ion channels that carry the cardiac action potential or acquired as a result of drugs that block these cardiac ion currents. The higher male incidence of the Brugada syndrome is associated with the early phase of ventricular repolarization, that is larger in the right ventricular epicardium of males than in females, resulting in a characteristic ST elevation in males. The early repolarization syndrome is characterized by a prominent J wave and by elevation of the ST-segment in the left precordial leads; it is most commonly seen in young males (Ezaki et al., 2010).

The evaluation of arrhythmias during ischemic-reperfusion induced injuries using high doses of hormones, showed that cardioprotection with testosterone is established only after pretreatment (Kuhar et al., 2007), but no protective effect was detected when testosterone was applied directly to the isolated animal hearts. Animals pretreated with testosterone as well as with estradiol showed high level of cardioprotection against post-ischemic injuries. Most of the beneficial effects shown in post-ischemic hearts were expressed as improved coronary flow, decreased release of lactate dehydrogenase rate and shorter lasting arrhythmias (Kuhar et al., 2007). The increased coronary flow in the hearts of pretreated animals of both sexes with estradiol and testosterone may be the result of induced NO production. The diminished arrhythmias in chronically treated hearts in rats of both sexes could be the consequence of both, vasodilatation and the direct cardioprotective effects of the hormones. The reduced lactate dehydrogenase release rate in the estradiol pretreated group showed more complex activity; cardioprotection might be induced also due to HSP activation with estradiol.

During reperfusion in the hearts of the animals pretreated with both testosterone and estradiol, all types of arrhythmias were reduced compared to the directly treated groups (Kuhar et al., 2007). The heart arrest was most severely decreased followed by, decreasing intensities in ventricular fibrilation, and ventricular premature complexes (Kuhar et al., 2007). The protective effect of sex hormones against the appearance of arrhythmias, fibrillation and ventricular tachycardia, was proposed by some other studies (Kim et al., 1998; Zhai et al., 2000).

4.1 Electrocardiogram, QTc and ST

The QT interval in the electrocardiogram (ECG) is defined as the interval from the onset of the QRS complex to the end of the T wave (Figure 4), it is the sum of ventricular myocardial action potential duration and the ventricular repolarization. The ST segment of the ECG represents the duration of ventricular repolarization only, with -J, -M, and –E segment representing the right and left ventricles and are measured by the ECG leads V2 and V5 respectively. The sex hormones, like estrogens, progesterones and androgens, can modulate a variety of ionic currents and are reported to influence the duration of the ECG (James et al., 2007).

4.1.1 Molecular basis for QTc differences

The QTc represents the rate-corrected QT interval that is calculated using the method of Fridericia (QTc=QT/RR1/3, Schwartz et al., 2011). On molecular level, the duration of the QT interval is the net effect of the activity of multiple ion-channels and transporters. The

combined activity of two delayed rectifier currents I_{Kr} (rapid delayed rectifier potassium channel) and I_{Ks} (slow delayed potassium channel) account for the majority of phase 3 repolarization of the ventricles. Several mutations in genes regulating these channels are responsible for the more common forms of inherited long QT syndromes. But also acquired conditions such as cardiac disease, electrolyte derangements (e.g. hypokalemia, hypocalcemia), and renal insufficiency (Genovesi et al., 2008), and iatrogenic causes, as cardiac as well as non-cardiac drugs are known to prolong the QT interval (Roden, 2004). Moreover, I_{ks}, but not I_{kr}, is highly influenced by β-adrenergic stimulation and blockade.

4.1.2 Gender related QTc differences

In men left ventricular mass is greater than in women (Hayward et al., 2001) and besides, the hearts from a small number of young and middle-aged non-diseased women showed reduced expression of a variety of K^+ channel subunits (HERG, mink, Kir2.3, Kv1.4, Kir6.2, KchIP2, SUR2) as compared to male hearts (Gaborit et al., 2010). In general, the QT interval durations of men are generally shorter than of women. The androgen receptors expressed in the heart muscle cells might play an important role in gender-dependent heart function differences, in particular the electrical activity of the left ventriculum. The QT interval at birth is comparable between genders (Stramba-Badiale et al., 1995) and up to 10 years of age, then at puberty it shortens by some 20 msec in young males (Pham & Rosen, 2002). The normal upper limit for QTc in men is 440 msec (Schwartz et al., 2011) and the shorter the QT interval the more it protects men from developing malignant ventricular arrhythmias such as Torsade de pointes (Abi-Gerges et al., 2004). Women which have a faster heart rate and thus a shorter QT interval show a higher incidence of Torsade de pointes. So the QT differences can be attributed to gender.

In women, repolarization lasts longer and proceeds slower compared with men and, indeed, surface ECG reveals longer QT interval and lower T-wave amplitude in adult women of all ages as compared with men (Bidoggia et al., 2000a). Also, the method of Fridericia to correct the QT intervals for heart rate (QTc) showed longer QTc intervals in women (about 1%) compared with men (Kadish et al., 2004; Schwartz et al., 2011). Moreover, the gender difference in QT interval is larger at long cardiac cycle lengths (Genovesi et al., 2007). The gender-related differences in QTc interval and T-wave amplitude are not present at birth (Stramba-Badiale et al., 1995) and during childhood, but appear during the teenage years (Pham & Rosen, 2002; Surawicz & Parikh, 2002), and decrease at older ages suggesting that this gender related QT difference of cardiac repolarization can be attributed to the life cycle: first an increase followed by a decrease of the sex hormones. The average sex differences in QTc intervals range from 10–15 ms (approximately 2-6 %). Besides, the longitudinal assessment of QT interval is independent of the menstrual cycle of women (Burke et al., 1996; Surawicz & Parikh, 2002), whereas in men the QT intervals shorten by some 20 msec at puberty (Surawicz & Parikh, 2002), and in both men and women testosterone levels directly shorten the QT interval independently of the heart rate (Schwartz et al., 2011), with differences in men of about 4% between high and low testosterone levels (Charbit et al., 2009; Pecori Giraldi et al., 2010). Further, these differences were larger than expected in older men and women during decreased hormonal status, where for women, testosterone decreased QT and QTc intervals but were longer in comparison with men (Schwartz et al., 2011). Moreover, a direct shortening of QT intervals by testosterone in older men and older women or hypogonadal status is known to exist independent of heart rate changes

(Schwartz et al., 2011). Male hypogonadism is associated with an increased prevalence of prolonged QT interval, over 2.5%, as compared to the control and the healthy population (Schwartz et al., 1993), and hence, a higher risk for fatal ventricular arrhythmias. The QTc interval in the hypogonadal state is prolonged and by hormone replacement therapy normalized (Pecori Giraldi et al., 2010). This evidence led to the conclusion that testosterone is the main determinant of gender-related differences in the ventricular refractory periods (James et al., 2007), and several experimental studies support this hypothesis.

In vitro and data on animals showed that sex hormones increased the QTc intervals in females, or conversely, decreased the QTc intervals in males (Fülöp et al., 2006). Women with excess androgen secretion present shorter and faster repolarization (Bidoggia et al., 2000b). In orchiectomized rabbits testosterone administration shortens the QT interval and drug-induced QT prolongation (Liu et al., 2002).

4.1.3 Gender related ST differences

Gender differences in the ST segment are known for healthy subjects and the ST level is elevated in young males compared to females (Ezaki et al., 2010). Also females showed longer JT intervals than males. These differences of ventricular repolarization are not observed in early childhood, but they become apparent after puberty (Ezaki et al., 2010), suggesting an important role of sex hormones. After puberty the leads that represent the right and left ventricles show that the J point amplitude is higher and besides that the ST segment and angle is steeper in males.

Brugada syndrome has higher incidence in young males than in females and causes sudden death by ventricular fibrillation: in the early phase of the ventricular repolarization of males, the transient outward potassium current I_{to} is stronger and contributes more largely to the repolarisation of the right ventricular epicardium. In the early repolarization syndrome an important elevation of the J wave and ST-segment is detected in males (Ezaki et al., 2010).

In pre-pubescent subjects of age 5–12 years, there is no significant gender differences in the ST levels. In males, the ST levels from both leads increase significantly after puberty and reach a maximum after 20 to 29 years of age and decrease during the 3rd decade of life (Nankin & Calkins, 1986). While for females, with increasing age there was a reduction in lead V5 only and irrespective of female age, from lead V2 the ST levels remained low and almost constant. For both sexes, all 3 ST segments were significantly higher in lead V2, which shows a more potent left ventricle. After puberty, the ST levels from both leads V2 and V5 were significantly higher in males than in females, suggesting that the effect of sex hormones on ST levels might be smaller in females than in males (Ezaki et al., 2010). In males, androgen-deprivation therapy significantly lowered all 3 ST segments and they closely resembled the ST segments of age-matched control females (Ezaki et al., 2010). Further, the J point amplitude was significantly lower in males with secondary hypogonadism and in castrated males.

These significant age- and gender differences in the ST segment suggest that sex hormones modulate the early phase of ventricular repolarization (Ezaki et al., 2010). For example, in healthy adults, estrogen prolongs the repolarization (ST segment), while testosterone shortens it (James et al., 2007). Sex differences in the ST segment elevation showed an important role for the male hormone testosterone. Since the plasma testosterone concentration increases around puberty, reaches peaks at 20–30 years of age, and decreases gradually due to the physiologic effects of aging in both males and females, the ST segment

fluctuation with age is correlated to the level of testosterone. In contrast, the female sex hormone, which also increases around puberty, has little effect on the ST levels because it does not change the ST segment in pubescent females (Ezaki et al., 2010).
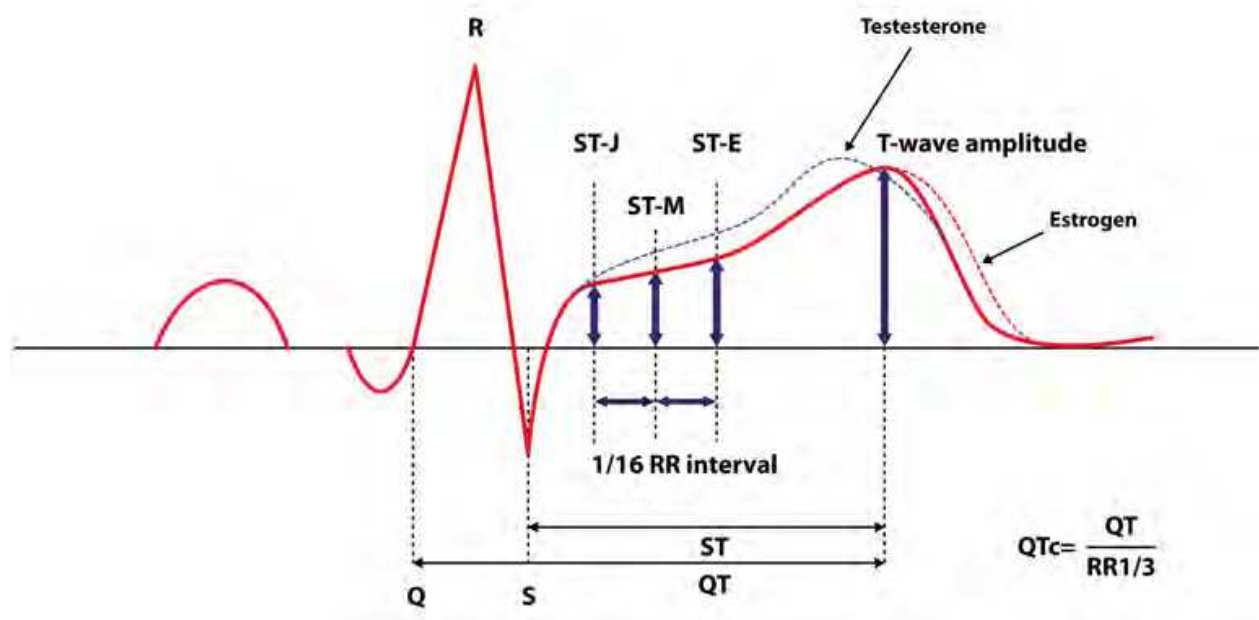

Fig. 4. Electrocardiogram of the heart

ST-J: The J point level at the end of the QRS complex with respect to the baseline. The middle or **ST-M** level is the level at 1/16th of the preceding RR interval of the following ST segment. **ST-E**: The level at 2/16th of the preceding RR interval of the following ST segment. T-wave amplitude is defined as the absolute distance from the baseline from the S point to the apex of the T-wave. In men the level of repolarizarion (ST) is elevated in all 3 segments and the duration is shortened (blue hatched line), while testosterone deprivation therapy in men decreases the elevation of these segments. The duration of the repolarization (ST) is prolonged by estrogens (red hatched line). The method of Fridericia for calculating the rate-corrected QT interval: QTc=QT/RR1/3 is described in text. Adopted from Ezaki et al. (2010) and James et al. (2007).

5. Sex hormone receptors and their role in the cardiovascular system

Androgen receptors are expressed both in the atria and the ventricles, while estrogen receptors are more pronounced in atrial myocytes (Lizotte et al., 2009). Anti-androgen drugs inhibit the androgen receptors of cardiac ventricular myocytes and decrease the hormonal modulation of ventricular repolarization (Ezaki et al., 2010). The actions of estrogen are mediated through (1) receptor-α and –β, (2) an unknown cytosolic membrane receptor and (3) another membrane based GPER1. ERα directly modulates transcription of target genes through two activation functions, AF1 and AF2. ERα demonstrates to have a prominent role in vascular biology, i.e., an AF1-deficient ERα isoform can be physiologically expressed in the endothelium and appears sufficient to mediate most of the vasculoprotective actions of estradiol (Arnal et al., 2010). Pretreatment of cardiac myocytes with estradiol protects

against cell death during ischemia and decreases the extent of cell death (Wise et al., 2001). Testosterone is known to act via nuclear receptors and regulate protein synthesis (Reid et al., 2003), and experimental data also indicates a non-genomic pathway of testosterone action on the cardiovascular system, i.e. direct testosterone mediated vasodilatation (English et al., 2002).

5.1 Estrogen receptors
At present, there are three known estrogen receptors. The two »classical« nuclear estrogen receptors, ERα and ERβ, are ligand-activated nuclear transcription factors that bind regulatory response elements in the promoters of genes (Carroll & Brown, 2006). The third estrogen receptor, GPER1 or GPER (previously GPR30) was identified as an orphan 7-transmembrane G protein-coupled receptor (GPCR) with low homology to other known GPCRs (Carmeci et al., 1997; Kvingedal & Smeland, 1997; O'Dowd et al., 1998; Takada et al., 1997).

Although the distinction between the modes of cellular activation, rapid signaling versus transcription, there exists extensive overlap between these artificially defined categories. Classical estrogen receptors are traditionally thought of as regulators of transcription, however, there is extensive evidence of their ability to mediate rapid signaling events (Moriarty et al., 2006). In addition, rapid signaling events, whether initiated by nuclear steroid receptors, growth factor receptors or GPCRs, result in the modification of transcriptional activity of conventional transcription factors (Ma & Pei, 2007). Thus the cellular effects of estrogen will depend on the specific receptors expressed and the integration of their stimulatory and inhibitory signaling pathways.

5.1.1 ERα
In cardiomyocytes ERα is distributed in the cytosolic, nuclear and membrane compartments (Lizotte et al., 2009), in T-tubular membranes (Ropero et al., 2006) and in the caveolae (Chung et al., 2009), which suggests that the ERα is localized in these complexes as an estrogen non-genomic rapid signaling, and its cytosolic and nuclear distribution suggest a genomic signaling. Moreover, ERα is more densely expressed in ventricular tissue as compared to the atrium, having higher densities in men than in women (Lizotte et al., 2009).

Estradiol induces the translocation of ERα to the PI3K regulatory domain and results in endothelial NOS (eNOS) activation (Simoncini et al., 2000). In an in vivo rabbit ischemia/reperfusion (I/R) model, acute treatment with estradiol significantly decreases the infarct size in female hearts after ischemia (Booth et al., 2005), suggesting that activation of ERα is required for the acute cardioprotective effects of estrogen. Also an in vivo study with ovariectomized female rats found that acute estrogen-mediated cardioprotection, following I/R, is mimicked by pretreatment with an ERα agonist and unaffected by ERβ antagonist pretreatment (Jeanes et al., 2008). In a model of ERα knockout mice cardioprotection in the ischemia model was blocked in female animals (Zhai et al., 2000). Subchronical estradiol pretreated female rats showed cardioprotection comparable, but lower, than the protection of directly applied estradiol (Kuhar et al., 2007). In conclusion, the importance of ERα in cardioprotection is confirmed in many models, despite being controversial and more protection is dedicated to direct estrogen effects.
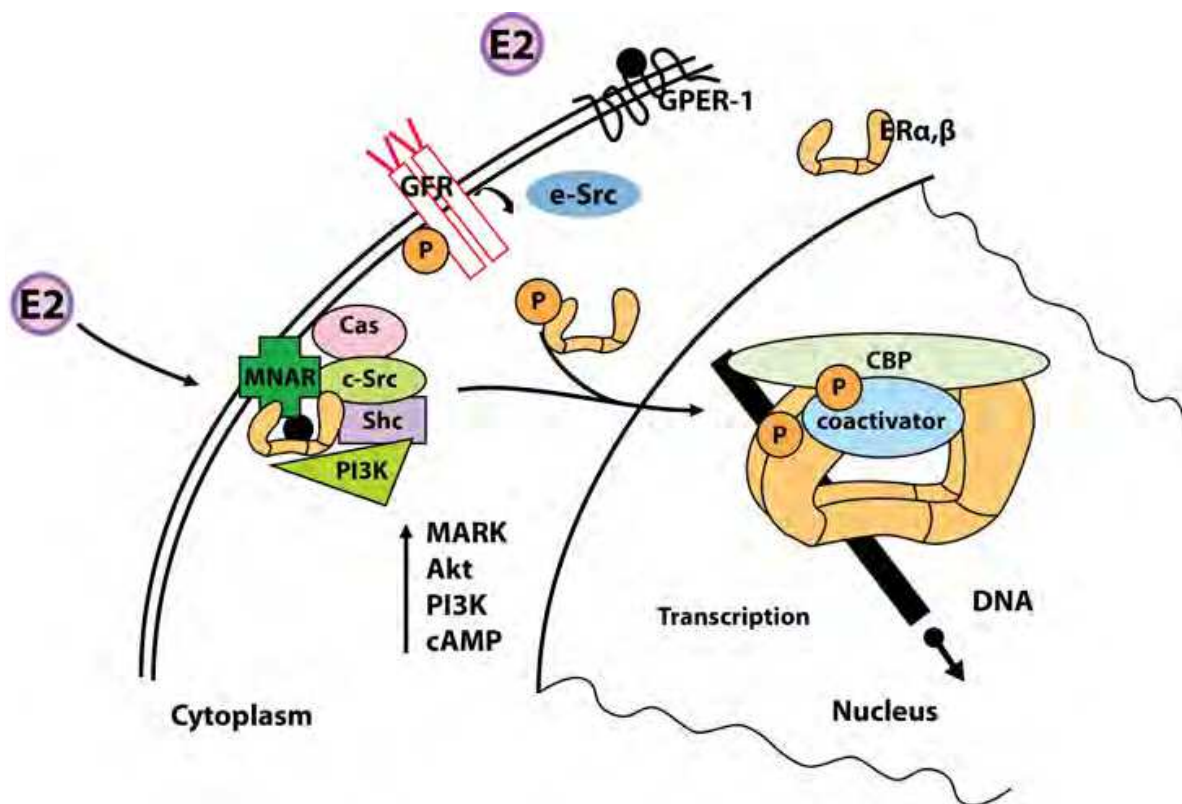
Fig. 5. Overview of genomic and non-genomic action of estrogen receptors
Estradiol stimulates cytoplasmic as well as nuclear signaling. Estradiol (E2) binds to the estrogen receptors (ERα, ERβ), stabilizes ER dimers, and stimulates direct interaction with growth factor receptors (GFR), association with proto-oncogenic tyrosine kinase Src (c-Src) and adaptor molecules: modulator of non-genomic activity of the estrogen receptor (MNAR), apoptotic protein (Shc), cellular apoptosis susceptibility protein, an exportin (Cas), and stimulation of common cytoplasmic signaling pathways via phosphoinositide-3 protein kinase (PI3K). ER can also initiate gene transcription in the absence of estradiol via phosphorylation (circled P) and activation of receptors and coactivators (cAMP-response element-binding protein - CBP), by growth factor signaling cascades, or by a ligand-stimulated mechanism. Testosterone stimulates, probably similarly to estrogens, both cytoplasmic and nuclear androgen receptors. Adopted from Fox et al. (2009) and Huang et al. (2010) and Wu et al. (2011).

5.1.2 ERβ

ERβ is predominantly localized in the nucleus and cytosol of adult murine cardiomyocytes (Lizotte et al., 2009), and has been reported to be localized in the mitochondria (Yang et al., 2004). Being primarily found in the sarcolemma, the possible ERβ-mediated effects will depend mostly on gene transcription. ERβ is evenly distributed in the heart (Lizotte et al., 2009), with females showing a higher density than males. Direct application of a specific ERβ agonist showed no antiischemic effects (Booth et al., 2005) thus suggesting that acute activation of ERβ is lacking cardioprotection.

Most studies have found that female ERβ knockout mice had more I/R injury than control (Wang et al., 2008). However, the knockouts showed increased damage, i.e., decreased gene expression of fatty acids and nitric oxide (NO) production (Gabel et al., 2005), and further

reduced activation of the PI3K/Akt proteins (Wang et al., 2009). In ovariectomized female mice long-term treatment with ERβ agonists has been shown to be cardioprotective and reduce I/R injury. The gene profiling of this experimental model showed that a number of protective genes were upregulated, i.e., encoding the NO biosynthesis and the anti-apoptotic proteins. Through activation of ERβ, estrogen plays a cardioprotective role against I/R injury (Nikolic et al., 2007). Other reported that estrogen-mediated cardioprotection following I/R is unaffected by an ERβ antagonist and is activated by ERα agonists (Jeanes et al., 2008). The chronic treatment with estradiol and/or ERβ activation leads to activation of protein-S nitrosylation and cardioprotection, which could be blocked by NOS inhibition (Lin et al., 2009), suggesting that chronic estrogen exposure protects the hearts largely via activation of ERβ and NO signaling.

5.2 GPER receptors

The G protein-coupled estrogen receptor (GPR30 or now GPER-1) was initially identified as an orphan G-protein coupled receptor (GPCR), and were traditionally recognized as mediating rapid changes in the levels of second messengers and to regulate various pathways of kinases (Luttrell, 2006). Then estrogen was identified as an endogenous ligand, and estradiol binding to GPER1 was found to result in Gbg activation of Src and resulting in the matrix metalloproteinase (MMP) cleavage of heparan-bound epidermal growth factor (EGF). Subsequently, the activated EGF receptor results in acute PI3K and ERK activation (Filardo et al., 2000). Thus, as a transmembrane estrogen receptor, GPER1 activation may mediate rapid cell signaling (Prossnitz et al., 2008). GPER1 is expressed in both the ventricles and the atria of the human heart, although more in ventricles than in atria, and besides, in the atrioventricular sinus and aorta. It is absent in the atrioventricular node and in the heart apex (Lizotte et al., 2009).

5.2.1 GPER1 and ischemia

GPER1 appears to be present in all tissues where ischemic injuries takes place. Under hypoxic conditions the up-regulation of GPER1 in estrogen receptor-negative HL-1 cardiomyocytes is activated by HIF-1-responsive elements located within the promoter region of GPER1 (Recchia et al., 2011), and required for this cardiomyocyte pathway is the ROS-induced activation of EGFR/ERK signaling. Thus the adaptive cell responses to hypoxia induced by estrogen are most likely GPER mediated (Recchia et al., 2011). In Langendoff perfused male and female rat hearts, the acute activation of GPER1 by its specific agonist G-1 reduced the myocardial infarct size and improved the functional recovery of contractility when compared to control (Deschamps & Murphy, 2009). Besides, less myocardial inflammation was found, indicated by decreased levels of tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and IL-6 (Wang et al., 2006). Also increased phosphorylation of both Akt and ERK were found, which could be reversed by the use of the PI3K/Akt inhibitor (Filardo et al., 2000). Moreover, the mitochondria permeability transition pore opening was inhibited through the activation of the extracellular signal regulated kinase (ERK) pathway (Bopassa et al., 2010). Further, administration of G1 prior to global ischemia also improved the cardiac contractility function, while the improvements were abolished both by co-administration of GPER1 specific antibodies, or an inhibitor of the PI3K pathway (Deschamps & Murphy, 2009). Further, the acute administration of G-1 causes the activation of the ERK pathway, inducing phosphorylation of eNOS (Filice et al., 2009).

In ovariectomized rats, G-1 was able to prevent an elevation in systolic blood pressure that occurs due to estrogen depletion, and in a GPER1 deficient mouse model, female mice develop a significant increase in mean arterial blood pressure (Mårtensson et al., 2009).

5.2.2 GPER1 and other pathways

Under hypoxic conditions the GPER1 may also mediate additional effects that are separate from those of both genomic and nongenomic classic ERs signaling. From isolated female mouse hearts with knockout mutations for ERα or ERβ, the role for both of these receptors in mediating the protective effects of estrogen through GPER1 against I/R injury was established (Wang et al., 2009; Weil et al., 2010). The upregulation of protein kinase A and the following inhibition of apoptosis was contributed to GPER1 and not to the ER. The acute administration of estradiol in the isolated rat heart was protective against acute I/R injury, and both ERα and/or ERβ may mediate these effects. ERβ mediates the upregulation of extracellular receptor kinase (ERK)-signaling and the antiapoptotic PI3K/Akt pathways and ERα mediates the downregulation of proapoptotic c-Jun N-terminal kinase (JNK) pathways. The GPER1 activation provides cardioprotection by decreasing inflammation, including activation of proinflammatory cellular pathways, upregulation of protective mitogen activated kinase (p38 MAPK) and/or JNK pathways (Weil et al., 2010), in addition to decreasing cellular apoptosis, and to promote survival.

5.2.3 GPER mediates cardioprotection

These results show that the G protein estrogen receptor GPER1 plays an important role in mediating the acute cardioprotective effects of estrogen against global ischemia/reperfusion. They can be upregulated by ischemia and mediate protection through adaptation to low oxygen and reactive oxygen species generation conditions and may contribute to progression of disease in the metabolic function, impulse cell proliferation and improve the contractility of myocites (Patel et al., 2010; Recchia et al., 2011). It is suggested that these mechanisms of protection by GPER1 activation are mediated through the EGF receptor/extracellular signal regulated kinase (ERK) and the PI3K/AKT, and eNOS signaling pathways (Filardo et al., 2000; Filice et al., 2009).

Just like ERα and ERβ the membrane estrogen receptor GPER1 is involved in estradiol induced cardiac activity. The cardiotropic effects induced by estrogen include the ERK, PI3K and PKA transduction cascades. A potential functional interactivity between GPER1, ERα and ERβ, might exert their combined cardioprotection, and involves all of the ERK, PI3K, PKA pathways and converge downstream on the eNOS transduction pathway, suggesting that NO production plays a central role in the response of male heart to estrogen stimulation (Filice et al., 2009).

5.3 Androgens
5.3.1 Angiogenesis

The androgen receptors have independent of their genomic function, which changes gene transcription, a second mode of action, in which cytoplasmic androgen binding to androgen receptors causes rapid changes in cell function, such as changes in ion transport. The most potent natural androgen is dihydrotestosterone (DHT), that in contrary to testosterone, cannot be aromatised to estradiol and thus no secondary estrogen receptor mediated effects can be produced. Endothelial cells exposed to DHT produce a dose-dependent increase in
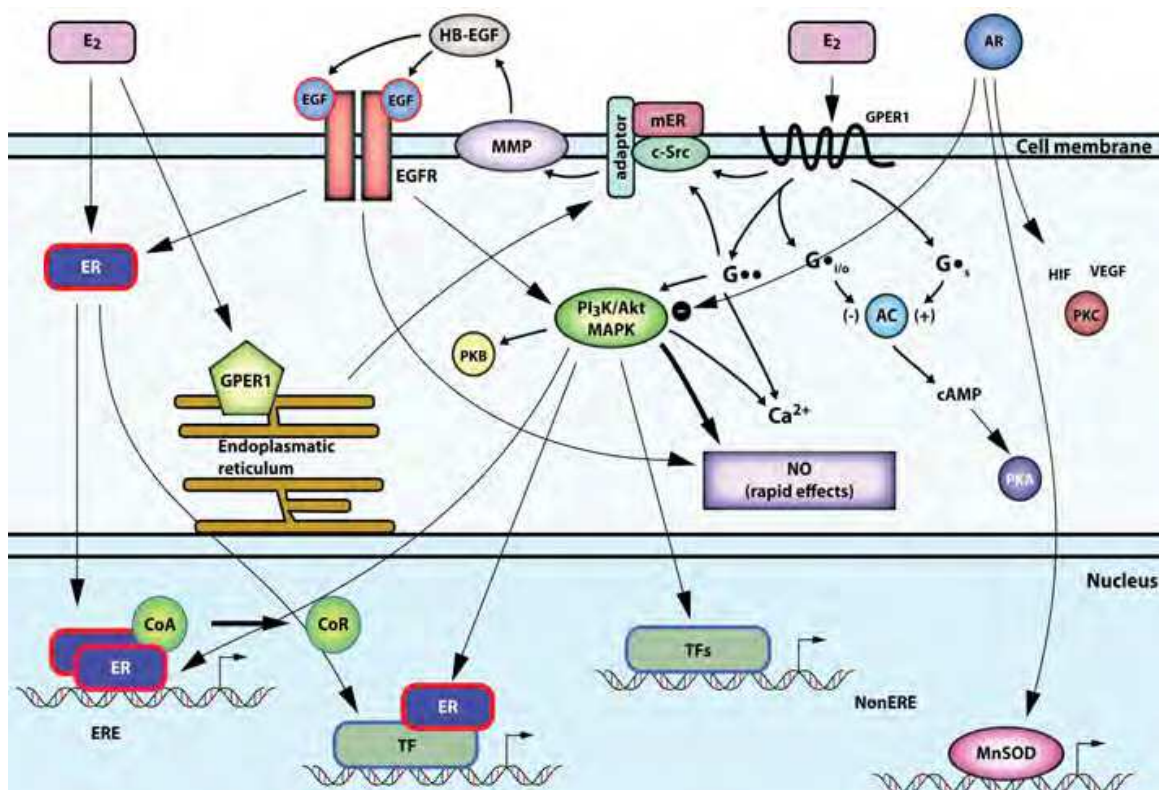
Fig. 6. Signaling pathways activated by estrogens and androgens. Adopted from Meyer et al. (2009) and Nilsson et al. (2011).

Specific cellular actions of estradiol (E2) are activated through both genomic and non-genomic transduction pathways. In the primary genomic pathway (left), activated estrogen receptors (ER) influence the nuclear transcription as well as rapid signaling by nitric oxide (NO) and phosphoinositide-3 protein kinase (PI3K) /Akt activation. In the secondary (center) non-genomic pathway, stimulation of membrane bound G protein-coupled estrogen receptor (GPER1) activates G proteins, which trigger multiple effectors. Both pathways activate $G\alpha_{i/o}$ proteins and activate adenylate cyclase (AC) to either, positively or negatively regulate the cAMP level and the subsequent cAMP-dependent protein kinase (PKA) activity. Also, the stimulation of $G\alpha_{i/o}$ leads to activation of PI3K and subsequent Akt/PKB protein kinase (Akt/PKB). Activation of c-Src protein kinase, forming the complex with adaptor protein, activaties matrix metalloproteinase (MMP), that liberate heparin-bound epidermal growth factor (HB-EGF) and activates the EGF receptor (EGFR). The EGFR activation leads to multiple downstream events including activation of mitogen activated protein kinases (MAPK) and PI3 kinases (PI3K), which increase expression of transcription factors (TFs). Besides, the GPER1 stimulation also leads to elevation of intracellular Ca^{2+} through unknown mechanisms that involve either primary signaling through G proteins or secondary signaling through EGFR transactivation. Moreover, the estrogen stimulation can lead to the expression of target genes whose promoters do not contain steroid response elements (nonEREs). The combined effects of these signaling and transcriptional events often lead to cell cycle progression and cell proliferation.

The androgen receptors (AR, right) are known to activate hypoxia induced factors (HIF), vascular endothelium growth factor (VEGF) and effects resulting in activation of protein kinase C (PKC), and besides AR activation leads to deactivation of PI3K, thus leading also to diminished cardioprotection, and direct effects on calcium metabolism is also described.

the production of vascular endothelial growth factor (VEGF), a key angiogenic growth factor and show increased messenger RNA expression of VEGF receptors 1 and 2 (Flt-1 and KDR respectively, Sieveking et al., 2010). This suggests that the proangiogenic effects of DHT in male endothelial cells are VEGF dependent. Besides, it is known that KDR is the main mediator of the mitogenic/angiogenic action of VEGF in endothelial cells, while Flt-1 is a negative regulator of VEGF action and Flt-1 mRNA is indeed expressed less upon DHT exposure. This upregulated anti-VEGF action, and also the activated inhibitor of phosphoinositol 3-kinase (PI3K), a key enzyme in the PI3K– AKT pathway of VEGF signaling, both inhibited DHT-mediated tubulogenesis genes (Sieveking et al., 2010). In comparison, estrogen receptor α and β are both involved in the cerebral VEGF/Akt/NO pathway in angiogenesis in female mice, while VEGF signaling is disrupted in the hearts of mice lacking estrogen receptor α (Jesmin et al., 2010a, b).

Also, orchidectomy markedly decreased in vivo vascularization in males, and in females this angiogenesis is not dependent on the presence of dihydrotestosterone (Sieveking et al., 2010). In ischemia induced angiogenesis, the endogeneous androgens modulate recovery in ischemic hindlimbs, and in orchidectomized animals DHT enhances recovery from ischemia. The orchidectomy significantly reduced the expression of hypoxia-inducible factor 1α (HIF-1α), which is the key subunit to HIF-1, a critical, genome-wide transcription regulator responsible for oxygen homeostasis and responsive to hypoxic stress. HIF-1 drives the expression of more than a hundred genes, including the genes associated with angiogenesis (e.g., VEGF and its receptors). In conclusion, the endogenous androgens play an important role in the coordination of ischemia-mediated angiogenesis by the regulation of key angiogenesis-related genes (Sieveking et al., 2010).

5.3.2 Vascular tone

The castration of animals causes reduced arterial pressure and reduced responses to angiotensin II (Song et al., 2010). In the castrated animals, treatment with testosterone restored the response to angiotensin II. It is concluded that long term effects of testosterone is pressor-related to angiotensin II responses. Treatment of the castrates with a protein kinase C (PKC) inhibitor attenuated the differences in arterial pressure to angiotensin II. Also, mRNA expression of PKCδ and PKCε are attenuated by castration, but are restored by testosterone. The expression of protein kinase C (CPI-17) and phospho-CPI-17 was decreased in the castrated group, whereas drug replacement of testosterone in castrated rats reversed this effect (Song et al., 2010). These findings suggest that in genetically hypertensive rats the PKC/CPI-17 pathway may contribute to androgenic potentiation of the pressor and renal vascular responses of angiotensin II (Song et al., 2010).

6. Pathway basis of sex hormones action in cardiovascular system

The estrogen binding to GPER1 activates downstream PI3K, MAPK, and NOS along a similar path as the non-genomic signaling of the classic ERs-mediated signaling. However, the GPER1 also may mediate additional effects that are separate from those of both genomic and non-genomic signaling mediated by the classic ERs. For example, it seems that GPER1 and not ERα is responsible for the upregulation of protein kinase A and the inhibition of apoptosis.

6.1 NO and protein S-nitrosylation

Most of the present cardioprotective effects are dedicated to the NO-related mechanisms that play a role in the regulation of cardiovascular function. Beside the activation of cyclic guanosine monophosphate (cGMP)-dependent pathway, NO also regulates cell function through protein S-nitrosylation. This is a reversible redox-sensitive posttranslational protein modification, which involves the attachment of a NO moiety to the nucleophilic protein sulfhydryl, resulting in S-nitrosothiol (SNO) formation. It is very likely that the protein S-nitrosylation plays an important role in cardioprotection (Sun & Murphy, 2010).

Estrogen-induced protein S-nitrosylation has been shown to be involved in a murine model of I/R resulting in a cardioprotection (Lin et al., 2009). During the Langendorff model of I/R, hearts of ovariectomized female mice pretreated with estradiol and/or ERβ-selective agonists, showed increased post-ischemic recovery. This protection was blocked by a NOS inhibitor (Lin et al., 2009), suggesting that increased NO signaling contributes to the cardioprotection. These chonic estradiol or ERβ agonist exposed hearts showed increased S-nitrosylated proteins and this protein S-nitrosylation could be abolished by pretreating hearts with the NOS inhibitor (Lin et al., 2009). These data suggest that chronic estrogen treatment and activation of ERβ would indeed lead to increased NO/SNO signaling, playing an essential role in cardioprotection.

Many of the S-nitrosylated proteins found in ERβ-selective agonist-treated hearts (Lin et al., 2009) have also been shown to be increased in preconditioned hearts (Sun et al., 2007), including the mitochondrial F_1F_0-ATPase, aconitase, malate dehydrogenase, creatine kinase, cytochrome c oxidase and heat shock proteins (HSP 27, 60, and 70). The protein S-nitrosylation might also elicit cardioprotective effects by regulating intracellular Ca^{2+} handling, apoptosis, and post-infarct myocardial remodeling (Sun & Murphy, 2010).

Estradiol, the naturally occuring major form of estrogen, increases protein S-nitrosylation levels in cultured endothelial cells and besides in intact endotheliums where, the estradiol was shown to act through ERα, activates eNOS and generates NO which leads to S-nitrosylation (Sun & Murphy, 2010). The S-nitrosylation also mediates the inhibitory effects of estradiol on endothelial ICAM-1 expression by angiotensin II (Chakrabarti et al., 2010). It is a post-translational protein modification induced by both, endogenous NO, generated by NOS in endothelium, and exogenous NO in a variety of cells. Over 100 different cellular proteins have been shown to be S-nitrosylated in processes that reduce the generation of harmful free radicals on one hand, and activate the free radical scavengers on the other (Chakrabarti et al., 2010). Both processes contributing to a reduction in oxidative stress, but also reducing pro-inflamatory signaling, processes which are crucial in I/R injury protection (Chakrabarti et al., 2010).

6.2 PI3K/Akt pathway and its activation by sex hormones

The Akt pathway is considered as one of the most important molecular kinase that mediates cardioprotection during ischemia reperfusion (Wang et al., 2009). Female hearts have higher level of Akt activity and thus, compared to male hearts, have better protection against I/R injuries and better heart recovery. Indeed, male hearts showed lower Akt activity and worse I/R recovery. In ovariectomized rat hearts the Akt activity is reduced, the recovery decreased (Huang et al., 2010), and supposedly the occurance of apoptosis during the myocardial infarction is one of the potential reasons.
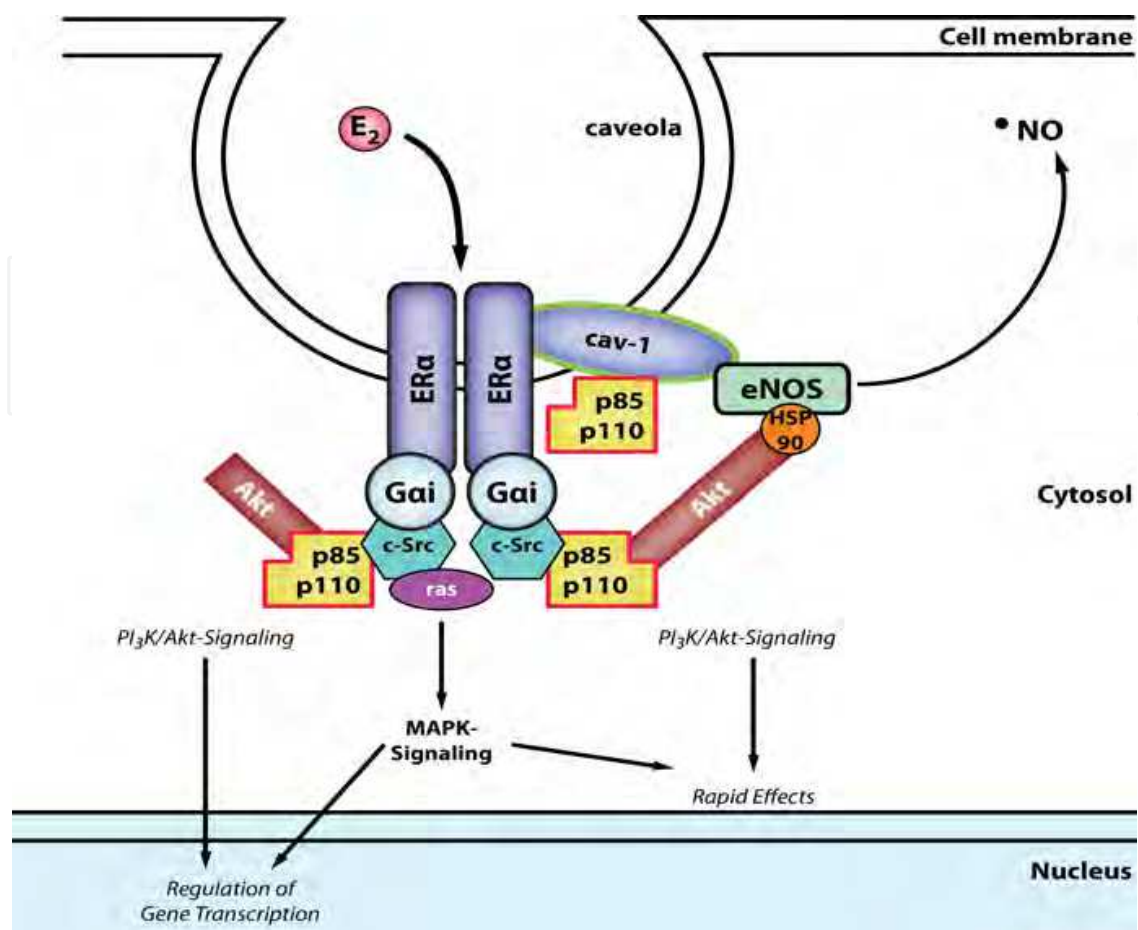
Fig. 7. Integrative model of putative mechanism of non-genomic estrogen signaling. Modified from Meyer et al. (2009) and Moriarty et al. (2006).

Caveolae, invaginations of the endothelial plasma membrane, are centers for signaling processing, providing localization for the molecules involved. Here, estradiol (E2) binds to the estrogen receptor α (ERα) and the "modulator of non-genomic activity of the ER" (MNAR) promotes complex formation with ERα, c-Src, and p85, the regulatory subunit of phosphoinositide-3 protein kinase (PI3K; with subunits p85 and p110), facilitating activation of the PI3K/Akt-signaling. Alternatively, c-Src activates the monomeric GTPase p21ras (ras), which is capable of directly recruiting downstream the mitogen activated protein kinases (MAPK) pathway. Essential for the activation of c-Src is the direct interaction of the G protein Gα$_i$ with ERα. Once activated, both PI3K/Akt- and MAPK-pathways can modulate gene transcription, and besides in endothelial cells, alternatively, the activation of PI3K/Akt-signaling leads to the phosphorylation of endothelial nitric oxide synthase (eNOS) protein, which is localized to caveolae through interaction with caveolin-1 (cav-1), a protein that also targets ERα. The molecular chaperone heat shock protein 90 (Hsp90) enhances the PI3K/Akt-eNOS interaction. Once eNOS is activated, the release of nitric oxide (NO) induces rapid cellular effects.

The ablation of ERβ significantly decreased postischemic functional recovery in female, but not in male hearts (Wang et al., 2009), and besides, a reduced activation of PI3K/Akt was noted in the female ERβ knockout hearts. Since, females show higher densities in cardiac ERβ expression in women than in men, the activation of the PI3K/Akt signaling cascade

plays a crucial role in the cardioprotection against I/R injury through an acute gender-dependent ER-mediated and gender-independent GPER1 signaling.

6.2.1 Estrogen

At present, PI3K seems to be the most important activation pathway in the cardioprotection of sex hormones. This pathway involves further Akt and NOS activation. Both in vivo and in vitro studies show that acute estradiol treatment reduces cardiomyocyte apoptosis and elicits cardioprotection via ERα activation and PI3K/Akt signaling (Patten et al., 2004). In endothelial cells a direct protein-protein interaction between ligand-activated ERα and the regulatory subunit p85 of PI3K through a nongenomic mechanism is suggested (Simoncini et al., 2000), by which estradiol rapidly activates eNOS via the activation of PI3K/Akt.

6.2.2 Testosterone

Decreased testosterone in castrated animals showed increased myocardial Akt activation (Huang et al., 2010), so some researchers suggested its negative role in I/R induced injuries and others confirmed increased Akt activity. In isolated rat hearts, testosterone used in acute ischemia reperfusion caused gender differences in myocardial Akt activation and its dowstream signaling molecules (p-Bad, Bcl-2, p-FOXO3a). Bad and Bcl are triggers for apoptosis and once these levels increase, apoptosis is suppressed. FOXO, another downstream target of Akt pathway, enables cell survival by inducing death genes. Also, the use of the testosterone antagonist flutamide or castration of the animals prior to the experiment showed an increase in myocardial Akt pathway and increased all three markers (p-Bad, Bcl-2, p-FOXO3a) in the male hearts. Moreover, the effect of castration in the activation of the Akt pathway can be reversed by some agonists, but not by dihydrotestosterone (Huang et al., 2010).

6.3 Matrix metalloproteinase in ischemia

The degradation of the extracellular matrix by metalloproteinases (MMPs) is involved in post-myocardial infarction processes of healing and remodeling. Knockout mice targeting the MMP-9 gene (the primary MMP protein functioning in post-myocardial infarction cardiac remodeling) were reported to have a reduced prevalence of cardiac rupture and attenuated left ventricular remodeling compared to control mice. Also a temporal change in the expression of MMP-9 and MMP-2 after myocardial infarction has been found (Tao et al., 2004). With estrogen treatment a significant reduction in MMP-9 expression was exerted regardless of castration status, and no reduction was observed in the MMP-2 protein. The decreased activity of matrix MMP-9 by estrogen induced cardioprotection in males after acute myocardial infarction was accompanied with increased Akt-Bcl-2 anti-apoptotic signaling (Cao et al., 2011).

6.4 Apoptosis in cardiac ischemia-reperfusion

Apoptosis of cardiomyocytes in infarct zones can be determined by the anti-apoptotic protein marker Bcl-2. Estrogen treated mice showed higher amounts of Bcl-2 expression during myocardial infarction as compared to control mice (Cao et al., 2011). This study has established a pivotal role for the Akt gene in estrogen-induced inhibition of apoptosis. However, which of the ER isoforms (α or β) play a role is uncertain.

To established the protective effects of estrogen on hypoxia-induced apoptosis cells with minimal ERα expression were used (Cao et al., 2011), and it was revealed that 17β-estradiol protects against apoptosis induced by H_2O_2-induced oxidative stress through the glutathione/glutaredoxin-dependent redox regulation of the Akt protein. After estrogen treatment, the activity of the pro-apoptotic Akt (P-Akt) began to decrease, while the expression of the anti-apoptotic Bcl-2 began to increase. Cell-cycle analyses indicated that hypoxia-induced apoptosis was efficiently inhibited through supplemental of 17β-estradiol, which shows that ERβ is at least partly involved in the estrogen-mediated cardioprotection (Cao et al., 2011).

6.5 Gonadotrophin releasing hormone as a new target in the heart

Among the other potential hormones acting in the heart, gonadotrophin releasing hormone is the potential cardiac marker, responsible for the release of luteinizing hormone and follicle-stimulating hormone from the anterior pituitary, that is synthesized and released from neurons in the hypothalamus. Treatment may be associated with an increased risk of cardiac dysfunction that is attributed to the accompanying androgen deprivation. Gonadotrophin releasing hormone by itself may be a major contributor to the cardiac pathology. The chronically administered agonists may prolong QT interval in men and in women and reduce cardiac index, and decreased blood pressure. The potential pathway of activation is the PKA pathway and not the PKC pathway, that leads to gonadotrophin releasing hormone-mediated increased contractility. The PKA-mediated pathway has targets for phosphorylation, promotes cardiomyocyte contractile function, including the L-type Ca^{2+} channel on the sarcolemma and components of the contractile apparatus. Besides, PKA also phosphorylates the ryanodine receptor and Ca^{2+} release channels in the cardiomyocytes, which in turn regulates channel opening and leads to increased sensitivity to Ca^{2+}-induced activation. Higher doses of gonadotrophin releasing hormone elevated resting intracellular Ca^{2+} and may be a reflection of increased sarcoplasmic reticulum Ca^{2+} release and cardiac contractility (Dong et al., 2011).

6.6 Other potential mechanism of sex hormones mediated protection

Some other potential mechanisms may contribute to the cardioprotective effects of sex hormones. For example, it has been reported that estrogen exerts cardioprotective effects by modulating the cardiac expression of tumor necrosis factor-α (TNFα) and its receptor (Xu et al., 2006). Additionally, nitric oxide synthase (NOS) has also been shown to mediate estrogen-induced cardioprotection (Lin et al., 2009). Therefore, the entire mechanism may be far beyond our current knowledge. Also, understanding the exact functional relationship between estrogen and androgen in the cardiovascular system should be the goal of future research.

7. Conclusion

Many studies of the last years focused not only on estrogen, but also on testosterone for a role in cardiovascular diseases. Importantly, as a new approach of non-nuclear modulation of cardioprotection the estrogen receptor GPER1 was mentioned.

The actions of estrogen are mediated by estrogen receptors -α and –β, by two cytosolic receptors and another, membrane bound receptor GPER1. In the cardiovascular system the

ERα demonstrates to have a more prominent role compared to ERβ, which might be gender-related. ERα is widely distributed in cardiomyocytes (Lizotte et al., 2009), thus indicating its important role, and its membrane position suggests important estrogen non-genomic rapid signaling, while its cytosolic and nuclear distribution suggest genomic signaling. Among the rapid signalling effects, estradiol induces the translocation of ERα to the PI3K regulatory domain and shows NOS (eNOS) activation in endothelium (Simoncini et al., 2000) as one of the most important effector product. Also, GPER1 activation results in matrix metalloproteinase cleavage of heparin-bound epidermal growth factor, that is able to activate the EGF receptor, that subsequently results in acute PI3K and ERK activation (Filardo et al., 2000). Besides, being a transmembrane estrogen receptor, GPER1 activation mediates rapid cell signaling too (Prossnitz et al., 2008). GPER1 deactivation of the PI3K pathway was confirmed by abolishing the agonist-mediated protective effect, suggesting that the more important mechanism of protection by GPER1 activation is through the PI3K/AKT pathway. The activation of the PI3K pathway by GPER1-mediated transactivation of the EGF receptor (Filardo et al., 2000), leads not only to activation of PI3K but also to activation of ERK. Also, HIF-1 in hypoxic conditions activates the up-regulation of GPER1 in cardiomyocytes and ROS-induced activation of EGFR/ERK signaling is required for this pathway. Hypoxia-induced expression of GPER1 may be included among the mechanisms involved in the anti-apoptotic effects elicited by estrogens. Blocking the PI3K activation resulted in reduced phosphorylation of Akt and in reduced recovery and larger infarct sizes compared to agonist-treated hearts. The acute activation of the estrogen receptor GPER1 is gender-independent cardioprotective (Deschamps & Murphy, 2009).

Androgenes, mostly testosterone, have been known up till now for their deleterious effects in cardiovascular system, and are supposed to potentiate ischemic/reperfusion injuries; but those effects are present only in acute heart injuries. Rapid androgen receptor activation, analogous to estrogen receptor cytosolic activation, probably enable yet unknown cardioprotective pathways, which are expressed as diminished ischemic effects, and decreased arrhythmias. Most of such protective effects, beyond their nuclear cardioprotection pathway, are proposed to be mainly long-term activated. Also, endothelial cells exposed to dihydrotestosterone, produced a dose-dependent increase in the production of a key angiogenic growth factor - vascular endothelial growth factor, and further increased the expression of VEGF receptors Flt-1 and KDR. VEGF receptor KDR is the main mediator of the mitogenic/angiogenic action of VEGF in endothelial cells, and VEGF receptor Flt-1 is a negative regulator of VEGF action, so dihydrotestosterone plays a proangiogenic role for VEGF signaling. Anti-VEGF action inhibits tubulogenesis, and also the inhibitor of phosphoinositol 3-kinase (PI3K), a key enzyme in the PI3K–AKT pathway of VEGF signaling, inhibited dihydrotestosterone-mediated tubulogenesis.

The main pathways for cardioprotection are known to be PI3K-mediated. Estradiol induces the translocation of ERα to the PI3K regulatory domain and results in endothelial NOS (eNOS) activation (Simoncini et al., 2000). ERβ activation leads to protein S-nitrosylation and thus cardioprotection, which could be blocked by NOS inhibition, suggesting that chronic estrogen exposure protects hearts largely via activation of ERβ and NO signaling (Lin et al., 2009). The role for the Akt gene in estrogen-induced inhibition of apoptosis is probably a crucial step. However, which ER isoform plays the major role, ERα or ERβ, and whether gender-dependent, is uncertain. In short, ERα and GPER1 might be more important in acute protection, and ERβ in more long term, estrogen chronically exposed conditions.

Cardioprotective effects induced by estrogen involved ERK, PI3K and PKA transduction cascades. In endothelial cells, ERα activation culminates in two major signal transduction events, one is the ERK pathway, and a second is increased PI3K/Akt activity. In both pathways, the final event involves a rapid NO production by eNOS. A potential functional interactivity between GPER1, ERα and ERβ leads to cardioprotective action, responsible for estrogen involvement in ERK, PI3K, PKA and eNOS. Gender-independent GPER1 activation of eNOS plays a central role in the response to estrogen stimulation (Filice et al., 2009). Testosterone on the other hand, is known to act via PKC; PKC inhibition attenuates the differences in arterial pressure to Ang II. Also, expression of PKCδ and PKCε are attenuated by castration, but are restored by testosterone. Undoubtly, testosterone cardioprotection is the focus of present studies and search for its protective pathways, independent from nuclear action.

Of course, some clinical findings predicts even more potential clinical protection by sex hormones, by yet unknown mechanisms. A review analysis of physiologic responses to critical illnesses and injury as well as their relative rates of survival and recovery, proposed estrogen to have protective effects in numerous conditions ranging from global ischemic insults and massive systemic inflammatory responses to devastating focal injury and apoptosis in vital organs. Furthermore, the authors suggested even exogenous infusion of estrogen, not only as a direct therapeutic agent, that can benefit in some instances, but proposed estrogen administration for synergism with other resuscitative interventions (Wigginton et al., 2010).

8. Acknowledgement

9. References

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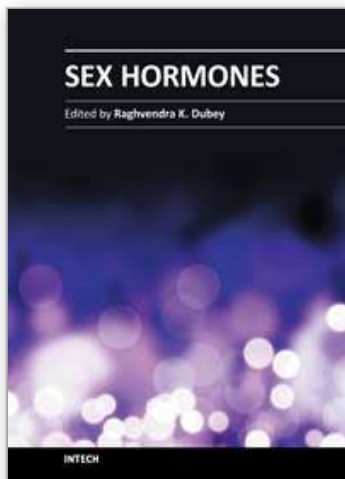
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Sex Hormones

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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

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