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Estrogens and Heart, A Subcellular Relationship

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Sex Steroid Hormones and the Cardiovascular System

Given the differences in cardiovascular disease between the sexes and potential protective effect of estrogen on the cardiovascular system, there is considerable interest in understanding the effects of sex steroid hormones on the cardiovascular system. The primary sex steroid hormones are estrogen, progesterone, and testosterone. [1]. The estrogens in humans are estrone, estriol, and the most active form 17β -estradiol [1]. While all three estrogens may affect cardiovascular function, most studies have focused on the actions of 17β-estradiol on the heart and vasculature.

Estrogens act through the two forms of the estrogen receptor (ER-α and ER-β) that are highly homologous. The ligand-binding and DNA-binding domains are highly conserved between them [2]. These receptors have been shown to signal via both genomic and non-genomic pathways [1]. There is also evidence that a G-protein coupled receptor with a high affinity for estrogen (known as GPER or GPR30) is present in the heart, and may modulate rapid signaling events [3].

To initiate genomic signaling, estrogen binds to the ligand-binding domain of the ERs [1,2]. In the absence of hormone, the ERs are localized in the cytosol. Estrogen binding causes a conformational change in the ERs, leading to their dimerization and translocation to the nucleus [1,2]. Once in the nucleus, the ERs bind to estrogen response elements (EREs) on DNA. In turn, ERs recruit the transcriptional machinery, coactivators and corepressors resulting in an increase or decrease in gene expression [1,2]. In genes that are regulated by the ER but do not contain an ERE, ER can bind to DNA indirectly via transcription factors [2]. The ER can also be phosphorylated allowing it to bind to ERE or bind DNA indirectly via transcription factors to regulate gene transcription even in the absence of ligand binding [1].

Nuclear ER-α and ER-β can also signal in a non-genomic manner. This mechanism of action is similar in ER-α and ER-β isoforms. Estrogen can bind to ERs localized to the plasma membrane and activate the phosphatidylinositol 3-kinase (PI3K) signaling pathway [4]. In brief, PI3K activates protein kinase B(Akt). Akt can subsequently activate nitric oxide synthase (NOS) to produce nitric oxide (NO) [5,2]. No can then modulate components of the EC-coupling pathway, such as ion channels [5]. PI3K has also been shown to regulate cAMP levels, which would modulate PKA activity within ventricular myocytes [6,7].

Estrogen can also bind to ERs to activate a second non-genomic signaling pathway that acts through mitogen-activated protein kinases (MAPK), specifically the extracellular signal-regulated kinases (ERK) [8,9].

When ERK becomes activated, it translocates to the nucleus and activates transcription factors required for gene expression [5]. Recently, it has been shown that estrogen also binds to an orphan G-protein-coupled receptor known as GPER [10], and that GPER is expressed in cardiac tissue [2,3]. When estrogen binds to GPER, it can also activate the PI3K and MAPK non-genomic signaling pathways [2]. The binding of estrogen to the various ERs in the heart is thought to have important effects on cardiac function as outlined in the next section.

Estrogens and the Heart

Many studies have shown that estrogens have important effects on the structure and function of the heart in the setting of cardiovascular disease. Estrogens have been shown to decrease apoptosis and prevent cardiac remodeling in myocardial infarction [2]. Adult myocytes isolated from infarcted rat hearts showed less apoptosis and greater survival in culture when treated with estrogen when compared to untreated controls [11]. Other studies have shown that 17β -estradiol treatment of ovariectomized (OVX) mice reduces cardiomyocyte apoptosis following coronary artery-ligation induced myocardial infarction [12]. Further, studies in OVX rabbits have shown that in vivo administration of estrogen prior to coronary artery-ligation

induced myocardial infarction can reduce infarct size [13]. This may be due to the ability of estrogen to activate survival signals within cardiomyocytes. Pressure overload in OVX rats results in a significant decrease in the prosurvival kinase, Akt, when compared to sham controls [14].

Conversely, treatment of cultured neonatal rat cardiomyocytes with 17β -estradiol has been shown to rapidly increase the activation of Akt [12]. Increased activation of Akt also occurs in vivo in mice supplemented with 17β -estradiol prior to coronary artery ligation [12]. Further, premenopausal women have greater Akt activity in their cardiac myocytes when compared to men or to postmenopausal women [15]. Together, these studies suggest that the increased expression of the prosurvival kinase Akt in the female heart may contribute to the cardio protection observed in cardiovascular disease models. Estrogen has also been shown to prevent cardiac hypertrophy. In female mice, less cardiac hypertrophy occurs in comparison to males after transaortic constriction, which induces pressure overload [16,17].

Interestingly, studies also show that knockout of ER-β, but not ER-α, in female mice abolishes the protective effects of female sex on cardiac hypertrophy [16,17]. Similarly, OVX and ER-α knockout female mice treated with 17β-estradiol showed reduced cardiac hypertrophy after transaortic constriction in comparison to untreated controls [18-20]. However, 17β-estradiol had no effect on cardiac hypertrophy in ER-β knockout mice [18]. It has been suggested that estrogen may prevent induction of the calcineurin stress response pathway that leads to an hypertrophic response. Studies have shown that 17β-estradiol activates the calcineurin antagonist known as the modulatory calcineurin-interacting protein 1 (MCIP1) [21,22]. Additionally, OVX mice treated with 17β-estradiol showed a reduction in calcineurin A levels in comparison to placebo-treated females [14]. Treatment with an ER antagonist or knockout of ER-β prevented 17β-estradiol mediated decreases in calcineurin levels and activity [19,22]. Overall, these findings suggest that 17β-estradiol acts through the estrogen receptor to prevent cardiomyocyte apoptosis and hypertrophy. This likely occurs by activating anti-apoptotic Akt signaling and inhibiting stress response signaling through the calcineurin pathway.

Estrogen has also been shown to affect cardiac function. As mentioned above, contractile function in intact hearts and cardiac tissue is greater in male than in female rats [23-27]. Interestingly, a recent study also showed that the degree of left ventricular fractional shortening as determined by echocardiography is greater in rats subjected to OVX than in controls [28]. These findings suggest estrogen may suppress contractility. Similar effects are evident at the level of the individual myocyte. Cellular contractions from OVX animals are significantly larger when compared to sham-controls [23,24]. OVX has also been shown to increase the size of Ca2+ transients [23,29,30,24]. In addition, the speed of contractile responses is faster in myocytes from OVX animals [23]. OVX also increases the rates of rise and decay of the Ca2+ transient when compared to sham [23,29] Interestingly, the enhanced responses observed with OVX are reversed with estrogen replacement [23,24,29]. Taken together, these findings suggest that removal of ovarian-derived estrogen increases the speed and size of contractile responses and Ca2+ transients in the female heart.

Estrogen may affect cardiac contractile function by modulating the underlying EC-coupling pathway. Estrogen has been shown to affect ion channels in the heart. Acute application of estrogen to isolated ventricular myocytes from guinea pigs has been shown to reduce ICaL [31]. Studies of chronic estrogen reduction have shown that ICaL and L-type Ca2+ channel density is increased in ER knockout mice in comparison to control [32]. Further, OVX increases the expression of Cav1.2, the main L-type Ca2+ channel subunit in rat ventricular myocytes [33]. Estrogen may also affect potassium channels. ER knockout mice show an increase in APD and a prolongation of the QT interval without significant changes in PQ or QRS intervals [32]. Estrogen has also been shown to downregulate Kv1.5 and Kv4.3 subunits resulting in smaller transient outward (ITO) and delayed rectifier (IKur) potassium currents [34,35], which would prolong APD. Taken together these finding suggest that estrogen may regulate Ca2+ and K+ channels by decreasing channel expression and ionic current density in the female heart.

Estrogen may also affect Ca2+ storage and Ca2+ removal mechanisms. One study has shown that OVX significantly increased the size of intracellular Ca2+ stores in the SR [29]. This suggests that reduced estrogen levels may promote SR Ca2+ loading. Investigation of proteins involved in Ca2+ removal have shown that while SERCA2a, PLB, and NCX expression are unchanged or in some instances reduced with OVX, the activity of the NCX may be elevated [36,37,23,29]. As responses become faster when estrogen is removed, changes in NCX activity may contribute to enhanced decay rates observed in OVX animals.

Taken together, these findings suggest that estrogen suppresses cardiac contractile function at the level of the individual cardiomyocyte by modulating components of the EC-coupling pathway. However, our knowledge of the effects of estrogen on specific EC-coupling mechanisms in cardiomyocytes is still limited. As premenopausal women have a lower incidence of cardiovascular disease in comparison to postmenopausal women [1,38], female sex steroids may play a role in protecting the aging heart. One possibility is that estrogen suppresses Ca2+ release, which prevents Ca2+ overload and Ca2+ dysregulation in the setting of cardiovascular disease.

Estrogens and Mitochondria

By all the things mentioned above it is accepted that women suffer cardiovascular diseases (CVD) especially after menopause and at an older age than men, in such way sex and age are considered now as major risk factors in the development of CVDs [39,40] It is thought that steroid sex hormones play a substantial role in sexual dimorphism in CVDs [41]. Specially estrogens that

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are important participants in metabolic regulation, different studies have shown that estrogens play a regulatory role in mitochondrial function modulating ATP production, generation of mitochondrial membrane potential, mitochondrial biogenesis and regulation of calcium concentrations [42,43] in such way the loss of the main circulating estrogen, 17β-estradiol, due to either natural or surgical menopause has effects that go beyond reproductive health.

Different studies have shown the ER´s presence in mitochondria [44] and specific binding of estrogens to sites inside [45] so, it is possible to think that estrogens influence mitochondrial function by altering mitochondrial ROS formation and induce antioxidant responses [42].

It has been shown that cardiac mitochondria in female Wistar rats have higher phosphorylation capacity than males of 15-month old [46] and higher activities of mitochondrial complexes III-V in heart of female monkeys compared to males [47]. In this sense in MCF-7 cells, mitochondrial oxygen consumption was increased 4-6 days after estrogens treatment, following increased expression of the mitochondrial respiratory chain components [48] besides, rats with normal estrous cycles have enhanced mitochondrial respiration, compared with ovariectomized rats [42] a condition that in women occurs in menopausal age, when they suffer from low energy levels, reduced exercise capacity, tiredness and susceptibility to weight gain.

Mitochondrial dysfunction also has been linked with CVDs, for example mutations in nuclear and mitochondrial genes encoding mitochondrial proteins associated with oxidative phosphorylation have been shown to cause cardiomyopathy and cardiac defects due to impaired mitochondrial energy production and increased reactive oxygen species (ROS) production [49] conditions that our group reproduced in isolated heart mitochondria of castrated female rats [42].

Another condition linked to cardiac pathology is altered fatty acid oxidation activity within mitochondria. It has been suggested that mitochondrial dysfunction in cardiomyocytes could lead to decreasedenergy production, reduced contractility, altered electrical properties and cell death [50]. In heart failure (HF) a complex clinical syndrome characterized by impaired contractile performance of the myocardium leading to inability of the heart to supply adequate amounts of blood to meet the metabolic needs of peripheral tissues, cardiac energy deficits have been reported,due to impairment of all components of cardiac bioenergetics [51]. Both, mitochondrial biogenesis and function are affected, exhibiting a biphasic pattern with an early increase and a late decline that coincides with the transition from hypertrophy to heart failure [52]. Female gender and old age are associated with adverse outcomes in HF [53-57].

The molecular mechanisms underlying sex-based differences in development of CVDs are multi factorial, however, evidence involve the possible participation of mitochondria and its failure when estrogens are absent [58-64].

References

1. Czubryt MP, Espira L, Lamoureux L, Abrenica B (2006) The role of sex incardiac function and disease. Can J PhysiolPharmacol 84(1): 93-109.
2. Murphy E (2011) Estrogen signaling and cardiovascular disease. Circ Res 109(6): 687-696.
3. Deschamps AM, Murphy E (2009) Activation of a novel estrogen receptor, GPER, is cardioprotective in male and female rats. Am J Physiol Heart Circ Physiol 297(5): H1806-H1813.
4. Simoncini T, Hafezi-MA, Brazil DP, Ley K, Chin WW, et al. (2000) Interaction of oestrogen receptor with the regulatory subunit ofphosphatidylinositol-3-OH kinase. Nature 407(6803): 538-541.
5. Furukawa T, Kurokawa J (2008) Non-genomic regulation of cardiac ion channels by sex hormones. Cardiovasc HematolDisord Drug Targets 8(4): 245-251.
6. Kerfant BG, Gidrewicz D, Sun H, Oudit GY, Penninger JM, et al. (2005) Cardiac sarcoplasmic reticulum calcium release and load are enhanced by subcellular cAMP elevations in PI3Kgamma-deficient mice. Circulationresearch 96(10): 1079-1086.
7. Kerfant BG, Rose RA, Sun H, Backx PH (2006) Phosphoinositide 3-kinase gamma regulates cardiac contractility by locally controlling cyclic adenosine monophosphate levels. Trends Cardiovasc Med 16(7): 250-256.
8. Endoh H, Sasaki H, Maruyama K, Takeyama K, Waga I, et al. (1997) Rapid activation of MAP kinase by estrogen in the bone cell line. Biochem Biophys Res Commun 235(1): 99-102.
9. Watters JJ, Campbell JS, Cunningham MJ, Krebs EG, Dorsa DM (1997) Rapidmembrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene transcription. Endocrinology 138(9): 4030-4033.
10. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER (2005) A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science 307(5715): 1625-1630.
11. Brinckmann M, Kaschina E, Altarche-XW, Curato C, Timm M, et al. (2009) Estrogen receptoralpha supports cardiomyocytes indirectly through post-infarct cardiac c-kit+ cells. J Mol Cell Cardiol 47(1): 66-75.
12. Patten RD, Pourati I, Aronovitz MJ, Baur J, Celestin F, et al. (2004) 17beta-estradiol reduces cardiomyocyte apoptosis in vivo and in vitro viaactivation of phospho-inositide-3 kinase/Akt signaling. Circ Res 95(7): 692-699.
13. Booth EA, Marchesi M, Kilbourne EJ, Lucchesi BR (2003) 17Beta-estradiol as areceptor-mediated cardioprotective agent. J Pharmacol ExpTher 307(1): 395-401.
14. Bhuiyan MS, Shioda N, Fukunaga K (2007) Ovariectomy augments pressureoverload-induced hypertrophy associated with changes in Akt and nitric oxidesynthase signaling pathways in female rats. Am J Physiol Endocrinol Metab 293(6): E1606-E1614.
15. Camper-KD, Welch S, Walker A, Shiraishi I, Setchell KD, et al. (2001) Myocardial Akt activation and gender: increased nuclear activity in females versus males. Circ Res 88(10): 1020-1027.
16. Fliegner D, Schubert C, Penkalla A, Witt H, Kararigas G, et al. (2010) Female sex and estrogen receptor-beta attenuate cardiac remodeling and apoptosis in pressure overload. Am J Physiol Regul Integr Comp Physiol 298(6): R1597-R1606.
17. Skavdahl M, Steenbergen C, Clark J, Myers P, Demianenko T, et al. (2005) Estrogen receptor-beta mediates male-female differences in

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the development of pressure overload hypertrophy. Am J Physiol Heart Circ Physiol 288(2): H469-H476.

18. Babiker FA, Lips D, Meyer R, Delvaux E, Zandberg P, et al. (2006) Estrogen receptor beta protects the murineheart against left ventricular hypertrophy. ArteriosclerThromb Vasc Biol 26(7): 1524-1530.

19. Donaldson C, Eder S, Baker C, Aronovitz MJ, Weiss AD, et al. (2009) Estrogen attenuates left ventricular and cardiomyocyte hypertrophy by an estrogen receptor-dependent pathway that increases calcineurin degradation. Circ Res 104(2): 265-275.

20. van Eickels M, Grohe C, Cleutjens JP, Janssen BJ, Wellens HJ, et al. (2001) 17beta-estradiol attenuates the development of pressure overload hypertrophy. Circulation 104(12): 1419-1423.

21. Pedram A, Razandi M, Aitkenhead M, Levin ER (2005) Estrogen inhibits cardiomyocyte hypertrophy in vitro. Antagonism of calcineurin-related hypertrophy through induction of MCIP1. J Biol Chem 280(28): 26339-26348.

22. Pedram A, Razandi M, Lubahn D, Liu J, Vannan M, et al. (2008) Estrogen inhibits cardiac hypertrophy: role of estrogen receptor-beta to inhibit calcineurin. Endocrinology 149(7): 3361-3369.

23. Curl CL, Delbridge LM, Wendt IR (2008) Sex differences in cardiac muscle responsiveness to Ca2+ and L-type Ca2+ channel modulation. Eur J Pharmacol 586(1-3): 288-292.

24. Wu Q, Zhao Z, Sun H, Hao YL, Yan CD, et al. (2008) Oestrogen changed cardiomyocyte contraction and beta-adrenoceptor expression in rat hearts subjected to ischaemia-reperfusion. Exp Physiol 98(9): 1034-1043.

25. Leblanc N, Chartier D, Gosselin H, Rouleau JL (1998) Age and gender differences in excitation-contraction coupling of the rat ventricle. J Physiol511(Pt 2): 533-548.

26. Petre RE, Quaile MP, Rossman EI, Ratcliffe SJ, Bailey BA, et al. (2007) Sex-based differences in myocardial contractile reserve. Am J Physiol Regul Integr Comp Physiol 292(2): R810-R818.

27. Schaible TF, Scheuer J (1984) Comparison of heart function in male and female rats. Basic Res Cardiol 79(4): 402-412.

28. Stice JP, Chen L, Kim SC, Jung JS, Tran AL, et al. (2011) 17beta-Estradiol, aging, inflammation, and the stress response in the female heart. Endocrinology 152(4): 1589-1598.

29. Kravtsov GM, Kam KW, Liu J, Wu S, Wong TM (2007) Altered Ca(2+) handling by ryanodine receptor and Na(+)-Ca(2+) exchange in the heart from ovariectomized rats: role of protein kinase A. Am J Physiol Cell Physiol 292(5): C1625-C1635.

30. Ma Y, Cheng WT, Wu S, Wong TM (2009) Oestrogen confers cardio protection by suppressing Ca2+/calmodulin-dependent protein kinase II. Br J Pharmacol 157(5): 705-715.

31. Jiang C, Poole-WPA, Sarrel PM, Mochizuki S, Collins P, et al. (1992) Effect of 17 beta-oestradiol on contraction, Ca2+ current and intracellular free Ca2+ in guinea-pig isolated cardiac myocytes. Br J Pharmacol 106(3): 739-745.

32. Johnson BD, Zheng W, Korach KS, Scheuer T, Catterall WA, et al. (1997) Increased expression of the cardiac L-type calcium channel in estrogen receptor-deficient mice. J Gen Physiol 110(2): 135-140.

33. Chu SH, Goldspink P, Kowalski J, Beck J, Schwertz DW (2006) Effect of estrogen on calcium-handling proteins, beta-adrenergic receptors, and function in rat heart. Life Sci 79(13): 1257-1267.

34. Saito T, Ciobotaru A, Bopassa JC, Toro L, Stefani E, et al. (2009) Estrogen contributes to gender differences in mouse ventricular repolarization. Circ Res 105(4): 343-352.

35. Trepanier-BV, St-Michel C, Tremblay A, Fiset C (2001) Gender-based differences in cardiac repolarization in mouse ventricle. Circ Res 89(5): 437-444.

36. Bupha-IT, Laosiripisan J, Wattanapermpool J (2009) Moderate intensity of regular exercise improves cardiac SR Ca2+ uptake activity in ovariectomized rats. J Appl Physiol 107(4): 1105-1112.

37. Bupha-IT, Wattanapermpool J (2006) Regulatory role of ovarian sex hormones in calcium uptake activity of cardiac sarcoplasmic reticulum. Am J Physiol HeartCirc Physiol 291(3): H1101-H1108.

38. Luczak ED, Leinwand LA (2009) Sex-based cardiac physiology. Annu RevPhysiol 71: 1-18.

39. Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, et al. (1997) Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association. Writing Group. Circulation 96(7): 2468-2482.

40. Kong WK, Regeer MV, Ng AC, McCormack L, Poh KK, et al. (2017) Sex differences in phenotypes of bicuspid aortic valve and aortopathy: insights from a large multicenter, international registry. Circ Cardiovasc Imaging 10(3): Pii: e005155.

41. Mahmoodzadeh S, Fliegner D, Dworatzek E (2012) Sex differences in animal models for cardiovascular diseases and the role of estrogen. Handb Exp Pharmacol 214: 23-48.

42. Pavon N, Cabrera-OA, Gallardo-PJC, Uribe-AC, Rivero-SNA, et al. (2017) In female rat heart mitochondria, oophorectomy results in loss of oxidative phosphorylation. J Endocrinol 232(2): 221-235.

43. Duckless PS, Krause ND, Stirone C, Procaccio V (2006) Estrogen and mitochondria. A new paradigm for vascular protection? Mol Interv 6(1): 26-35.

44. Yang SH, Liu R, Perez EJ, Wen Y, Stevens SM, et al. (2004) Mitochondrial localization of estrogen receptor beta. Proc Natl Acadsci USA 101(12): 4130-4135.

45. Noteboom WD, Gorski J (1965) Stereospecific binding of estrogens in the rat uterus. Arch Biochem Biophys 111(3): 559-568.

46. Colom B, Oliver J, Roca P, Garcia-PFJ (2007) Caloric restriction and gender modulate cardiac muscle mitochondrial H_2O_2 production and oxidative damage Cardiovasc Res 74(3): 456-465.

47. Yan L, Ge H, Li H, Lieber SC, Natividad F, et al. (2004) Gender-specific proteomic alterations in glycolytic and mitochondrial pathways in aging monkey hearts. J Mol Cell Cardiol 37(5): 921-929.

48. Mattingly AK, Ivanova MM, Riggs AK, Wickramasinghe, Barch MJ, et al. (2008) Estradiol stimulates transcription of nuclear respiratory factor-1 and increases mitochondrial biogenesis. Mol Endocrinol 22(3): 609-622.

49. Lenefsky EJ, Moghaddas S, Tandler B, Kerner J, Hoppel CL (2001) Mitochondrial dysfunction in cardiac disease: ischemia-reperfusion, aging and heart failure. J Mol Cell Cardiol 33(6): 1065-1089.

50. Rosenberg P(2004) Mitochondrial dysfunction and heart disease. Mitochondrion 4(5-6): 621-628.

51. Stanley WC, Recchia FA, Lopaschuk GD (2005) Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 85(3): 1093-1129.

52. Rosca MG, Hoppel CL(2013) Mitochondrial dysfunction in heart failure. Heart Fail Rev 18(5): 607-622.

53. Nozaki A, Hata N, Kobayashi N, Okazaki H, Matsushita M, et al. (2016) The prognostic impact of gender in patients with acute heart failure-An evaluation of the age of female patient with severely decompensated acute heart failure. J Cardiol Pii: S0914-5087(16) 30316-1.

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54. Curl CL, Wendt IR, Canny BJ, Kotsanas G (2003) Effects of ovariectomy and17 beta-oestradiol replacement on [Ca2+]i in female rat cardiac myocytes. Clin Exp Pharmacol Physiol 30(7): 489-494.

55. Gavin KM, Seals DR, Silver AE, Moreau KL (2009) Vascular endothelial estrogen receptor alpha is modulated by estrogen status and related to endothelial function and endothelial nitric oxide synthase in healthy women. J Clin Endocrinol Metab 94(9): 3513-3520.

56. Goldstein J, Sites CK, Toth MJ (2004) Progesterone stimulates cardiac muscle protein synthesis via receptor-dependent pathway. Fertil Steril 82(2): 430-436.

57. Grohe C, Kahlert S, Lobbert K, Stimpel M, Karas RH, et al. (1997) Cardiac myocytes and fibroblasts contain functional estrogen receptors. FEBS Lett 416(1): 107-112.

58. Grohe C, Kahlert S, Lobbert K,Vetter H (1998) Expression of oestrogen receptoralpha and beta in rat heart: role of local oestrogen synthesis. J Endocrinol 156(2): R1-R7.

59. Lizotte E, Grandy SA, Tremblay A, Allen BG, Fiset C (2009) Expression,distribution and regulation of sex steroid hormone receptors in mouse heart. Cell Physiol Biochem 23(1-3): 75-86.

60. Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, et al. (1998) Androgen receptors mediate hypertrophy in cardiac myocytes. Circulation 98(3): 256-261.

61. Nordmeyer J, Eder S, Mahmoodzadeh S, Martus P, Fielitz J, et al. (2004) Upregulation ofmyocardial estrogen receptors in human aortic stenosis. Circulation 110(20): 3270-3275.

62. Pavón N, Martínez-AE, Hernández L, Gallardo-PJC, Alvarez-DC, et al. (2012) Sexual hormones: effects on cardiac and mitochondrial activity after ischemia-reperfusion in adult rats. Gender difference. J Steroid Biochem Mol Biol 132(1-2): 135-146.

63. Purohit A, Reed MJ (2002) Regulation of estrogen synthesis in postmenopausal women. Steroids 67(12): 979-983.

64. Simpson ER (2003) Sources of estrogen and their importance. J Steroid Biochem Mol Biol 86(3-5): 225-230.

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