Review • Open Access •

Role of estrogen in angiogenesis in cardiovascular diseases

Oche Barnabas¹, Hong Wang¹,², Xiu-Mei Gao¹,³

¹Tianjin Key Laboratory of Traditional Chinese Medicine Pharmacology, Tianjin, China
²Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin, China; Key Laboratory of Pharmacology of Traditional Chinese Medical Formulas, Ministry of Education, Tianjin University of Traditional Chinese Medicine, Tianjin, China
³Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

Abstract

The formation of new blood vessels from existing ones is a major process of angiogenesis and it is most effective in the vascular systems. The physiological process like hypoxia inducible factors involved in the regeneration of damaged tissues varies within the vascular systems in the endothelium and could be limited due to some major angiogenic growth factors like vascular endothelial growth factor, fibroblast growth factors and epidermal growth factor among others which bring about this cellular vascular regrowth. These physiological processes leading to cellular vascular regrowth could be a major function for the treatment of cardiovascular diseases such as ischemia and atherosclerosis. Estrogens are one of the known factors within the cellular mechanisms that could initiate repairs to the damaged vascular tissues, since estrogens are known inducers of angiogenesis leading to this cellular regrowth. Research has also shown that this cellular regrowth is induced by vascular angiogenic growth factors via the estrogen receptors. In this review we will attempt to summarize the main angiogenic growth factors involved in these physiological processes leading to angiogenesis and possible new mechanisms that could lead to this vascular regrowth. And also we will try to summarize some reports on the effect of estrogen on these physiological processes leading to angiogenesis in cardiovascular diseases.

J Geriatr Cardiol 2013; 10: 377−382. doi: 10.3969/j.issn.1671-5411.2013.04.008

Keywords: Estrogen; Estrogen receptors; Angiogenesis; Vascular endothelial growth factor; Cardiovascular diseases

1 Introduction

The formation of new blood vessels from existing ones is referred to as Angiogenesis.[1] The proliferation of blood vessels could be aided by the mechanism of estrogens which are essential for the normal growth in adults mostly for the function of female reproductive organs. A form of angiogenesis referred to as physiological angiogenesis is suppressed in the adult tissues, thereby restraining capillary growth but could only occur in the state of cell abnormalities that results from cell damage in the physiological processes leading to wound healing, tissue re-growth, etc. These physiological processes are been regulated by some angiogenic growth factors under pathological conditions, but when lacking or insufficient, it could lead to various forms of cardiovascular diseases like atherosclerosis, menopause and other related diseases.[2]

2 Physiological processes leading to angiogenesis

Oxygen among other nutrients is essential in maintaining homeostasis in adults and it plays a pivotal role in the physiology and pathological growth of blood vessels. Thus oxygen is constantly being regulated by the circulatory system through some factors that lead to the regeneration of blood vessels, these processes are regarded as angiogenesis.[3] Low oxygen (hypoxia) could facilitate the angiogenic stimuli, which develops from tip cells on the endothelial cells which form vascular endothelial growth factor receptors (VEGFR) with notch signaling that induce high concentrated VEGF leading to formation of new capillaries. Hypoxia inducible factor (HIF-1) is also another physiological process responsible for the regulation of angiogenic growth factors like VEGF for the processes of angiogenesis in cardiovascular diseases.[4,5]

Other angiogenic growth factors responsible for angiogenesis include transforming growth factors-beta (TGF-β), fibroblast growth factors (FGFs), epidermal growth factor (EGF) and angiogenin. They are capable of altering the physiological processes of endothelial cells. Ang II (angio-
tensin II) is among the main bioactive peptide of the rennin-angiotensin system, it acts in controlling cardiovascular homeostasis, with effects on cardiovascular diseases.\[6\]

Estrogen plays a critical role in some physiological and pathological factors that lead to cardiovascular diseases in women mostly in the stage of pre-menopause.\[7\] Estrogen may act in modulating the inflammatory response system within vascular cells, aiding its metabolism, insulin sensitivity, hypertrophy development and stem cell death.\[8\] Estrogens activates gene regulation via estrogen receptors (ERs),\[9-11\] and when expressed enhances the pathophysiological processes of angiogenesis in endothelial cells. The role of estrogens is in the regulation of lipid and cholesterol levels, estrogens could directly affect the growth of vascular cells, and the recovery from vascular damage leading to cardiovascular diseases.\[12\] ERs may be involved in this protective effect. Estrogen is also known to increase HDL plasma levels \[13\] which response varies largely among women and may be part of genetic factors.\[14\]

### 3 Mechanisms of angiogenesis

Angiogenesis is the process of forming new blood vessels through sprouting and budding of new capillaries from existing blood vessels.\[15\] Endothelial cells (ECs) form the inner layer of blood vessels, however, the vascular endothelial cells and circulating endothelial cells play a very important role in the physiological and pathological processes leading to angiogenesis. Angiogenesis is essential for the functions of the circulatory system, including growth responses, responses to sustained exercise, estrus cycle, wound healing and ageing. Furthermore, the decrease in angiogenesis could act as natural and therapeutic mechanisms in conditions such as hypertension, coronary heart disease, tumor growth and menopause.\[16\] Some key factors could aid the mechanism that leads to the generation of angiogenesis within the endothelium. The stimulation of VEGF and its receptors is a key factor that leads to the formation of new blood vessels in ECs.\[17\] ECs release some enzymes matrix metallo-proteinases (MMPs) which degrade the surrounding extracellular matrix to form a sheath-like covering of blood vessels. This is followed by the initiation of intracellular signaling cascade that stimulates the formation of other building blocks of endothelial cell formation. The endothelial cells divide and pass through the dissolved openings of the basement membrane to where the new vessel will form. The sprouting of the newly developing vessel is aided by adhesion molecules known as integrin that bind and help pull the vessel into place. Meanwhile, other enzymes such as matrix metallo-proteinases degrade the surrounding extracellular matrix to make room for the growing vessel.\[18\] The endothelial cells join together to form individual capillary sprouts which are stabilized by smooth muscle cells and pericyte muscle cells, which develops into new capillaries. Many studies have also shown that estrogen play a significant role via angiogenesis in ischemic cardiovascular diseases.\[19,20\] In ovariectomy and estrogen treatment of female rabbits, estrogen mediated an increase in the density of blood vessels within two weeks of its supplementation period.

Further mechanisms of therapeutic angiogenesis using angiogenic growth factors and inhibitors in the treatment of cardiovascular diseases are still not fully understood. Therefore, it is most important to study more physiological and pathological mechanisms within ECs. High density lipoprotein (HDL) development in ECs is a major physiological factor leading to cardiovascular disease. HDL functions by binding to cholesterol in the peripheral tissues and moving the cholesterol to the liver. This action is induced by high affinity HDL receptor, scavenger receptor B type I (SR-BI). SR-BI could mediate angiogenesis by initiating signals in the endothelium through search which could promote endothelial NO synthase activity and cell migration.\[21\] Studies also suggest that endothelial cells function effectively by inducing cell migration via an adaptor protein PDZK1 which mediates the HDL and SR-BI.\[22\]

Others studies show that the mechanism of ARIA (Apoptosis regulator through modulating IAP expression) acts like a protein which functions in regulating apoptosis and angiogenesis in ECs.\[11\] ARIA through inhibitor of apoptosis (IAP) expression regulates PTEN/ phosphatidylinositol 3-kinase (P13K) pathways in ECs. It also mediates angiogenic growth factors in endothelial progenitor cells (EPCs) via P13K/Akt/endothelial nitric oxide synthase (eNOS) signaling. Akt may function as a mechanism used in inducing cell survival and growth through the parallel pathways leading to cell proliferation via Erk, therefore Akt activation can mediate cell proliferation.

### 4 Angiogenic growth factors and its signaling pathways

#### 4.1 VEGF signaling pathway in angiogenesis

Estrogen could play a vital role in the mediating of this angiogenesis via VEGF/eNOS/Akt\[23,24\] signaling pathway which is responsive through both ER-α and ER-β present in the endothelium. The activation of VEGF is critical in angiogenesis processes and it is dependent on the availability of ligands.\[25\] VEGFR2 serves as a critical signal transducing VEGF receptor for angiogenesis in endothelial cells.\[16\]
VEGF binds the receptor tyrosine kinase, VEGFR2, leading to different signaling pathways resulting in the up-regulation of genes involved in mediating the proliferation and migration of endothelial cells. VEGFR2 binding by homodimerization results in kinase activation and auto phosphorylation involving various isoforms of tyrosine. The signal transduction could be conducted by activation of some molecules like SRe and phosphatidylinositool 3-kinase (PI3k). PI3k activation stimulates the phosphorylation of Akt/PKB (Protein Kinase-B) which is actually downstream targets for inhibition.

Other growth factors involved in the processes of angiogenesis could be FGFs, which are small polypeptide growth factors with some structural characteristics of binding heparin in the ECs. FGFs functions by signaling peptides for secretion that binds to the heparin-like glycosaminoglycan’s (HLGAGs) of the extracellular matrix (ECM). FGFs could act on target cells, or may be released via active carrier proteins. FGFs may bind receptor tyrosine kinases in the presence of HLGAGs. The binding of FGF’s at this level induces receptor dimerization and stimulates the activation of various signal transductions to downstream signaling cascades. FGFs signaling play a critical role with estrogens in development of angiogenesis. In some other research reported, the use of fibril gel assay Knockdown of PCOLCE, Col1A1, SPARC, IGFBP7, and βig-h3 in pairs had little or no effect on EC sprouting, but the double-siRNA combinations of SPARC/Col1A1, IGFBP7/PCOLCE, IGFBP7/βig-h3, and PCOLCE/βig-h3 all significantly reduced EC lumen formation.

4.2 Role of estrogen in cardiovascular diseases

Many risk factors lead to cardiovascular diseases like unhealthy dietary habits, aging and smoking which bring about increasing blood lipid levels and inflammation in the arterial wall. Prevalence in the occurrence of these cardiovascular diseases in premenopausal women is low, including ischemic heart disease and heart failure. Consequently, the incidence increases with menopause have suggested an essential protective role of estrogens. Studies have shown that estrogen is essential for the regulation of vascular tone and in the pathophysiology of cardiovascular disease. Physiological effects of estrogen are mediated through estrogen receptors α (ERα) and β (ERβ), both expressed by different genes which possess a similar domain structure and are stimulated by ER agonist 17β-estradiol in a variety of cell types, including vascular smooth muscle cells and endothelial cells. ERβ plays a role in mediating systemic blood pressure by modulating endothelial independent vascular smooth muscles. In order to effectively understand the role of estrogen in cardiovascular disease, it is critical to examine the molecular mechanisms by which estrogen mediates the ERα & ERβ receptors in the vascular physiological and gene-regulatory pathways.

Recent research has also shown that endogenous estradiol (E2) could mediate physiological effects in G-protein-membrane coupled receptor 30 (GPR30) suggesting that GPR30 could act as a new form of the estrogen membrane receptor in ECs. GPR30 is a seven trans-membrane-associated G protein-co coupled receptor that is located at the plasma membrane and endoplasmic reticulum. GPR30 has been reported to induce physiological vasorelaxation effects by E2 through its receptors in rat aorta, and it mediates the actions of E2 in human epithelial cells.

Using wild type mouse exposed aorta, Zhai, et al. and Wang, et al. also reported that ERβ mediates myocardial protection by upregulation of PI3K/Akt stimulation with other factors in female hearts following ischemia-reperfusion. Therefore, it suggests that ERβ-mediated PI3K/Akt and anti-apoptotic signaling in the myocardium and may indicate insight on mechanistic pathways of cardiovascular diseases in males.

4.3 Mechanism of estrogen in angiogenesis

Estrogens are a group of steroid compounds, named for their function in the estrous cycle, and as primary female sex hormones. Estrogens are in three forms: E2, estrone (E1) and estriol (E3). E2 is the most essential compound among the estrogens and it stimulates endothelial cell migration, proliferation and survival in ECs. In the cardiovascular system, estrogen is activated by binding to estrogen receptors (ER) in the ECs. There are basically two classical estrogen receptor subtypes which are ERα and ERβ and a non-classical estrogen receptor GPR30. Estrogen receptors

http://www.jgc301.com; jgc@mail.sciencep.com | Journal of Geriatric Cardiology
functions in regulating the transcriptional processes in cells by binding to the ER in the nucleus which mediates dimerization and binding to specific response elements (ERE) to promote its target gene. Estrogen mediates protein reactions within the cell by binding to ERE through protein-protein interactions carried out in vitro and cultured UECs in-vivo. Physiological studies showed that ERα is more potent in stimulation of estrogen than ERβ ligands in vascular endothelial cells. ERα up-regulation in human dilated cardiomyopathies brings about increase in mRNA which was 17β-estradiol. The transcription factors in ER interact with cytoplasmic proteins and activate signaling pathways. Estrogen can interact with cytoplasmic proteins and activate signaling pathways. Estrogen could elicit its cardioprotective effect via ER-mediated non-genomic signaling pathways. Membrane ER binding results in rapid, non-genomic actions and are mediated by several pathways, such as receptor tyrosine kinases and protein kinases including PI3K, Akt, mitogen-activated protein kinase (MAPK), Src protein kinase A and C by increasing the concentration of intracellular calcium. With regard to cardiovascular events, direct membrane signaling causes vasodilatation through nitric oxide release and opening of the calcium-activated potassium channels through a NO and cyclic GMP pathway. A number of studies have suggested that acute addition of 17β-estradiol to either ovary-intact females or ovariectomized females reduces ischemic reperfusion. Some studies suggest location of ERα at the plasma membrane, where they could elicit rapid protective effects via the activation of non-genomic signaling pathways. Estrogen critically can bind at different receptors to initiate acute signaling pathway. It alters different levels of proteins and signaling pathways, leading to posttranslational modifications that alter protein activities. A direct protein-protein interaction between ligand-activated ERα and the regulatory subunit p58 of PI3K in endothelial cells through a non-genomic mechanism by which E2 rapidly stimulates eNOS via the activation of PI3K/Akt would lead to downstream activation of NOS/NO/SNO signaling. This clearly suggested that ERα activation of PI3K might play a role in cardiovascular diseases.

5 Conclusions

Angiogenesis plays an important role in the physiological and pathological process in cardiovascular diseases. ECs is a major physiological factor leading to these cardiovascular diseases which are most prominent in menopausal women. Therefore the understanding of the molecular mechanisms within the ECs is very important. The processes of cell migration and cell proliferation within the ECs determine the development of new vessels. Angiogenic factors like VEGF and FGF play very critical roles in the development of these new vessels. Some proteins like ARIA regulates PI3K pathways. VEGF and PI3K/Akt pathway in estrogen induction of VEGF expression in the endometrium. Another example of an estrogen mediated signaling pathway is tissue factory pathway inhibitor-1 (TFPI) as a physiological inhibitor of the tissue factor pathway of blood coagulation. TFPI may be involved in angiogenesis due to its stimulation with ER ligands. The regulation of TFPI involves post-transcriptional effects mediated by the amino-terminally truncated 45 kDa version of ERα. TFPI may affect angiogenesis through peptides within its carboxyl terminus which may directly block VEGF2 activation, thereby hindering the migration of endothelial cells. Estrogen could elicit its cardioprotective effect via ER-mediated non-genomic signaling pathways. Membrane ER binding results in rapid, non-genomic actions and are mediated by several pathways, such as receptor tyrosine kinases and protein kinases including PI3K, Akt, mitogen-activated protein kinase (MAPK), Src protein kinase A and C by increasing the concentration of intracellular calcium. With regard to cardiovascular events, direct membrane signaling causes vasodilatation through nitric oxide release and opening of the calcium-activated potassium channels through a NO and cyclic GMP pathway. A number of studies have suggested that acute addition of 17β-estradiol to either ovary-intact females or ovariectomized females reduces ischemic reperfusion. Some studies suggest location of ERα at the plasma membrane, where they could elicit rapid protective effects via the activation of non-genomic signaling pathways. Estrogen critically can bind at different receptors to initiate acute signaling pathway. It alters different levels of proteins and signaling pathways, leading to posttranslational modifications that alter protein activities. A direct protein-protein interaction between ligand-activated ERα and the regulatory subunit p58 of PI3K in endothelial cells through a non-genomic mechanism by which E2 rapidly stimulates eNOS via the activation of PI3K/Akt would lead to downstream activation of NOS/NO/SNO signaling. This clearly suggested that ERα activation of PI3K might play a role in cardiovascular diseases. The role of estrogens has been fully established in the proliferation of cells, which as we have shown is a key factor for angiogenesis. The two estrogen receptors, ERα and ERβ, play critical roles in the binding estradiol ligands which acts as agonists of several signaling pathways leading to angiogenesis. Studies have shown that the estrogen receptors are selective in their actions and ERα is more receptive to the binding of Estradiol.
Acknowledgements

This work was supported by the National Natural Science Foundation of China (81173592, 81125024), Tianjin Applied Basic Research and Frontier Technological Program (11JCZDJC21100), Program for New Century Excellent Talents in University of Ministry of Education of China (NCET-13-0935, “Major drug discovery”). National Science and Technology Major Project of the Ministry of Science and Technology of China (2012ZX09101212) and the Program for Changjiang Scholars and Innovative Research Team in University, PCSIRT (IRT0973IRT1276).

References

1. Ushio-Fukai M. Redox signaling in angiogenesis: role of NADPH oxidase. Cardiovasc Res 2006; 71: 226–235.
2. Boosani CS, Sudhakar YA. Proteolytically Derived Endo- neous Angiinhibitors Originating from the Extracellula Matrix. Pharmaceuticals (Basel). 2011; 4: 1551–1577.
3. Rey S, Semenza GL. Hypoxia-inducible factor-1 dependent mechanisms of vascularization and vascular remodelling. Cardiovasc Res 2010; 86: 236–242.
4. Ziello JE, Jovin IS, Huang Y. Hypoxia-Inducible Factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. Yale J Biol Med 2007; 80: 51–60.
5. Bellou S, Karali E, Bagli E, et al. The isoflavone metabolite 6-methoxyequol inhibits angiogenesis and suppresses tumor growth. Mol Cancer 2012; 11: 35.
6. Higuchi S, Ohtsu H, Suzuki H, et al. Angiotsensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci (Lond) 2007; 112: 417–428.
7. Iwakura A, Shastry S, Ludemann C, et al. Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9. Circulation 2006; 113: 1605–1614.
8. Murphy E. Estrogen signaling and cardiovascular disease. Circ Res 2011; 109: 687–696.
9. Shanle EK, Xu W. Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. Chem Res Toxicol 2011; 24: 6–19.
10. Tsutsumi S, Zhang X, Takata K, et al. Differential regulation of the inducible nitric oxide synthase gene by estrogen receptors 1 and 2. J Endocrinol 2008; 199: 267–273.
11. Liao WX, Magness RR, Chen DB. Expression of estrogen receptors-alpha and -beta in the pregnant ovine uterine artery endothelial cells in vivo and in vitro. Biol Reprod 2005; 72: 530–537.
12. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest 2006; 116: 561–570.
13. Srivastava N, Chowdhury PR, Averna M, et al. Estrogen increases hepatic lipase levels in inbred strains of mice: a possible mechanism for estrogen-dependent lowering of high density lipoprotein. Mol Cell Biochem. 2001; 220: 87–93.
14. Bagatell CJ, Knopp RH, Rivier JE, et al. Physiological levels of estradiol stimulate plasma high density lipoprotein2 cholesterol levels in normal men. J Clin Endocrinol Metab 1994; 78: 855–861.
15. Zhang K, Lu J, Mori T, et al. Baicalin increases VEGF expression and angiogenesis by activating the ERR [alpha]/PGC-1 [alpha] pathway. Cardiovasc Res 2011; 89: 426–435.
16. Secomb TW, Alberding JP, Hsu R, et al. Angiogenesis: an adaptive dynamic biological patterning problem. PLoS Comput Biol 2013; 9: e1002983.
17. Albrecht ED, Babischkin JS, Lisor Y, et al. Effect of estrogen on angiogenesis in co-cultures of human endometrial cells and microvascular endothelial cells. Hum Reprod 2003; 18: 2039–2047.
18. Vu TH, Web Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev 2000; 14: 2123–2133.
19. Ikeda K, Nakano R, Uraoka M, et al. Identification of ARIA regulating endothelial apoptosis and angiogenesis by modulating proteasomal degradation of cIAP-1 and cIAP-2. Proc Natl Acad Sci U. S. A. 2009; 106: 8227–8232.
20. Scarabin-Carre V, Canonico M, Brailly-Tabard S, et al. High level of plasma estradiol as a new predictor of ischemic arterial disease in older postmenopausal women: the three-city cohort study. J Am Heart Assoc 2012; 1: e001388.
21. Lin AD, Mannikarotu A, Kogan BA, et al. Estrogen induces angiogenesis of the female rabbit bladder. J Endocrinol 2006; 190: 241–246.
22. Zhu W, Sadar S, Seetharam D, et al. The scavenger receptor class B type I adaptor protein PDZK1 maintains endothelial monolayer integrity. Circ Res 2008; 102: 480–487.
23. Elkin M, Orgel A, Kleinman HK. An angiogenic switch in breast cancer involves estrogen and soluble vascular endothelial growth factor receptor 1. J Natl Cancer Inst 2004; 96: 875–878.
24. Jesmin S, Mowa CN, Sultana SN, et al. Estrogen receptor alpha and beta are both involved in the cerebral VEGF/Akt/NO pathway and cerebral angiogenesis in female mice. Biomed Res 2010; 31: 337–346.
25. Zachary I, Gliki G. Signal transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. Cardiovasc Res 2001; 49: 568–581.
26. Powars CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. Endocr Relat Cancer 2000; 7: 165–197.
27. Johns A, Freey AD, Fraser W, et al. Disruption of estrogen receptor gene prevents 17 beta estradiol-induced angiogenesis in transgenic mice. Endocrinology 1996; 137: 4511–4513.
28. Newman AC, Nakatsu MN, Chou W, et al. The requirement
for fibroblasts in angiogenesis: fibroblast-derived matrix proteins are essential for endothelial cell lumen formation. Mol Biol Cell 2011; 22: 3791–3800.

29 O’Lone R, Knorr K, Jaffe IZ, et al. Estrogen receptors alpha and beta mediate distinct pathways of vascular gene expression, including genes involved in mitochondrial electron transport and the generation of reactive oxygen species. Mol Endocrinol 2007; 21: 1281–1296.

30 Baruscotti I, Barchiesi F, Jackson EK, et al. Estradiol stimulates capillary formation of human endothelial progenitor cells: role of estrogen receptor-[alpha] / [beta], heme oxygenase 1, and tyrosine kinase. Hypertension 2010; 56: 397–404.

31 Masuda H, Kalka C, Takahashi T, et al. Estrogen-mediated endothelial progenitor cell biology and kinetics for physiological postnatal vasculogenesis. Circ Res 2007; 101: 598–606.

32 Jazbutyte V, Arias-Loza PA, Hu K, et al. Ligand-dependent activation of ER [beta] lowers blood pressure and attenuates cardiac hypertrophy in ovariectomized spontaneously hypertensive rats. Cardiovasc Res 2008; 77: 774–781.

33 Chakrabarti S, Davidge ST. G-protein coupled receptor 30 (GPR30): a novel regulator of endothelial inflammation. J Mol Endocrinol. 2013; 51: 191–202.

34 Lenhart PM, Broselid S, Barrick CJ, et al. G-protein-coupled receptor 30 interacts with receptor activity-modifying protein 3 and confers sex-dependent cardioprotection. J Mol Endocrinol. 2013; 51: 191–202.

35 Plante BJ, Lessey BA, Taylor RN, et al. G protein-coupled estrogen receptor (GPER) expression in normal and abnormal endometrium. Reprod Sci 2012; 19: 684–693.

36 Seok YM, Jang EJ, Reiser O, et al. 17beta-Estradiol induces vasorelaxation in a G-protein-coupled receptor 30-independent manner. Naunyn Schmiedebergs Arch Pharmacol 2012; 385: 945–948.

37 Zhai P, Eurell TE, Cooke PS, et al. Myocardial ischemia-reperfusion injury in estrogen receptor-alpha knockout and wild-type mice. Am J Physiol Heart Circ Physiol 2000; 278: H1640–H1647.

38 Wang M, Wang Y, Weil B, et al. Estrogen receptor beta mediates increased activation of PI3K/Akt signaling and improved myocardial function in female hearts following acute ischemia. Am J Physiol Regul Integr Comp Physiol 2009; 296: R972–R978.

39 Iseki T, Yuki K. Postoperative consideration of diagnostic value of ultrasonography and excretory urography on seven patients with renal calculi. Hinyokika Kiyo 1988; 34: 1557–1560.

40 Galimberti RL, Villalba I, Galarza S, et al. Itraconazole in Pityriasis versicolor: ultrastructural changes in Malassezia furfur produced during treatment. Rev Infect Dis 1987; 9 (Suppl 1): S134–S138.

41 Bjornstrom L, Sjoberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol Endocrinol 2005; 19: 833–842.

42 Jin X, Chen YC, Liu WQ, et al. Estradiol promote myocardial angiogenesis in a rat model of acute myocardial infarction through estrogen receptors. Sichuan Da Xue Xue Bao Yi Xue Ban. 2008; 39: 398–401.

43 Mahmoodzadeh S, Eder S, Nordmeyer J, et al. Estrogen receptor alpha up-regulation and redistribution in human heart failure. FASEB J 2006; 20: 926–934.

44 Kazi AA, Koos RD. Estrogen-induced activation of hypoxia-inducible factor-1alpha, vascular endothelial growth factor expression, and edema in the uterus are mediated by the phosphatidylinositol 3-kinase/Akt pathway. Endocrinology 2007; 148: 2363–2374.

45 Dahm AE, Iversen N, Birkenes B, et al. Estrogens, selective estrogen receptor modulators, and a selective estrogen receptor down-regulator inhibit endothelial production of tissue factor pathway inhibitor 1. BMC Cardiovasc Disord 2006; 6: 40.

46 Holroyd EW, Delacroix S, Larsen K, et al. Tissue factor pathway inhibitor blocks angiogenesis via its carboxyl terminus. Arterioscler Thromb Vasc Biol 2012; 32: 704–711.

47 Manavathi B, Nair SS, Wang RA, et al. Proliner-, glutamic acid-, and leucine-rich protein-1 is essential in growth factor regulation of signal transducers and activators of transcription 3 activation. Cancer Res 2005; 65: 5571–5577.

48 Deschamps AM, Murphy E, Sun J. Estrogen receptor activation and cardioprotection in ischemia reperfusion injury. Trends Cardiovasc Med 2010; 20: 73–78.

49 da Silva MB, Farges RC, Frode TS. Involvement of steroids in anti-inflammatory effects of PK11195 in a murine model of pleurisy. Mediators Inflamm 2004; 13: 93–103.

50 Lin J, Steenbergen C, Murphy E, et al. Estrogen receptor-beta activation results in S-nitrosylation of proteins involved in cardioprotection. Circulation 2009; 120: 245–254.