Cardiovascular Pharmacology: Open Access

Chen, Cardiovasc Pharm Open Access 2018, 7:4
DOI: 10.4172/2329-6607.1000246

Review Article Open Access

Mechanism of Gender-Related Differences in Vascular Function

Hua Chen*

Advanced Institute for Medical Sciences, Dalian Medical University, Dalian, China

***Corresponding author:** Hua Chen, Advanced Institute for Medical Sciences, Dalian Medical University, Dalian 116044, PR China, E-mail: chenhua@dmu.edu.cn

Received date: August 08, 2018; **Accepted date:** August 23, 2018; **Published date:** August 31, 2018

Abstract

Premenopausal women tend to have less metabolic diseases than age-matched men do. Agonist-induced endothelium-dependent constriction was significantly greater in arteries of male animals than that in female ones. Vascular protective effects of the female sex hormone estrogen have been suggested in this gender difference. This review discusses the important role of its downstream gene Phospholipase A2 group 1B (PLA2G1B) signaling in gender-related differences in vascular tone. The postulated mechanism is as follows: together with its "bottleneck" activation of cytosolic PLA2cPLA2, PLA2G1B can act on membrane phospholipids of endothelial cells to release arachidonic acid, thereby resulting in production of prostaglandins. Pharmacological inhibition of PLA2G1B may offer an attractive avenue for clinical intervention of metabolic diseases in men or menopausal women.

Keywords: Phospholipase A_2 group 1B; Gender differences; Estrogen; Arteries

Introduction

Many metabolic diseases including hypertension, diabetes, atherosclerosis, or stroke are associated with alterations in the function of arteries. Reduced dilations or increased contractions have been found in different vascular beds of many animal models of these metabolic diseases. It is known that premenopausal women tend to have less metabolic diseases than age-matched men do. Gender-related differences in arterial tone have been observed in both animals and humans, which is summarized in Table 1 [1,2].

Wire myography and pressure myography have been frequently used to investigate *in vitro* vasoconstriction or vasodilation to different agonists. Wire myography was developed in 1977 by Mulvany and Halpern to study the vascular responses of isolated small arteries [3,4]. Vessel rings are mounted through two parallel wires clamped at both ends. A micrometric screw is used to adjust the distance between the two wires, and a force transducer is used to record the isometric tension. With this method several arteries can be investigated simultaneously. Pressure myography was a method first introduced by Duling et al. in 1981 [5]. Vessel segments are cannulated at both ends with small glass pipettes and secured with sutures. During the experimental period vessel diameter changes can be measured continuously. Arteries under the more physiological isobaric conditions had higher sensitivity to noradrenaline than similar ones under isometric conditions [6,7].

Methods	Species	Sexes	Vessel	Outcome	References
Wire myography	Normotensive and SHR rats	Female, male	Thoracic aortas	Normotensive and hypertensive female rats had shown greater vasorelaxation to ACh compared with male counterparts.	Kauser et al. [8]
Wire myography	WKY and SHR rats	Female, male	Mesenteric arteries	Hypertensive female rats had shown greater vasorelaxation to ACh compared with males, but ACh-induced vascular responses were similar in female and male WKY rats.	Kahonen et al. [9]
Wire myography	Rats	OVX, OVX+EST	Mesenteric arteries	OVX+EST rats had greater vascular relaxation sensitivity to methacholine compared with OVX.	Davidge et al. [10]
Pressure myography	SHR rats	Female, OVX, OVX+EST	Mesenteric arteries	Female & OVX+EST SHR rats had greater vascular relaxation sensitivity to ACh and lower maximal response to NE compared with OVX SHR.	Dantas et al. [11]
Pressure myography	Mice	Female, male, OVX, OVX+EST	Cerebral arteries	Female & OVX+EST mice had lower vascular myogenic tone compared with male & OVX respectively.	Geary et al. [12]

Wire myography	WT and ERβKO mice	Female, male	Femoral arteries	ERβKO male mice had shown significantly enhanced vasoconstriction to PE compared with WT males, but not ERβKO female mice.	Luksha et al. [13]
Pressure myography	WKY and SHR-SP rats	Female, male	Cerebral arteries	Normotensive and hypertensive female rats had weaker vascular myogenic responses compared with male counterparts.	Ibrahim et al. [14]
Wire myography	Rats	Female, male	Mesenteric arteries	Female rats had more vasorelaxation to exogenous estradiol compared with male rats.	Lekontseva et al. [15]
Pressure myography	Mice	Female, male, sham, OVX	Mesenteric arteries	Female & sham mice had lower vascular myogenic tone compared with male & OVX respectively.	Chan et al. [16]
Pressure myography	Mice	Female, Male, sEH-KO female, sEH-KO male	Gracilis muscle arterioles	Female mice had stronger flow-induced vasodilations compared with males. sEH-KO mice had no such sex difference.	Qin et al. [17]
Wire myography	Rats	Female, male	Mesenteric arteries	Both male and nonestrous female rats with low-protein diet had the reduced sensitivity to sodium nitroprusside compared with normal-protein diet rats. Estrous female rats had no such difference between low- and normal-protein diet groups.	Black et al. [18]
Wire myography	WKY and SHR rats	Female, male	Thoracic aortas	Both WKY and SHR rats had weaker α-adrenergic constrictions of aortas in females than males.	Al-Gburi et al. [19]
Wire myography	Humans	Women, men	Mammary arteries	Human mammary arteries of women had weaker α-adrenergic constrictions than those of men.	Al-Gburi et al. [19]

SHR: Spontaneously hypertensive rats; WKY: Wista kyoto rats; Ach: Acetylcholine; OVX: Ovariectomized; EST: Estradiol; NE: Norepinephrine; PE: Phenylephrine; WT: Wild type; KO: Knockout; SHR-SP: Stroke prone spontaneously hypertensive rats; ERβKO: Estrogen receptor alpha knockout; sEH-KO: Soluble epoxide hydrolase knockout.

Table 1: Summary of gender differences in arterial tone in animals and humans.

Estrogen and Nitric Oxide (NO)

Estrogen and Prostanoids

Estrogen may modulate cross-talk between NO and prostanoids derived from NOS and cyclooxygenase respectively. Estradiol stimulated endothelial prostaglandin I_2 release through ERα [20-23]. In human endothelial cells estradiol inhibited thromboxane A_2 production under pro-inflammatory conditions, an effect mediated by GPER. Morever, in mouse carotid arteries endogenous estrogen blocked prostanoid-dependent vasoconstriction through GPER [24].

Estrogen and $[Ca^{2+}]_i$

The effects of estrogen on NO production appeared to be related to $[Ca^{2+}]_i$ in the vascular smooth muscle and endothelium. Endogenous estrogen bound GPER which then led to inhibition of ET-1-stimulated increase in $[Ca^{2+}]_i$ [25]. This was in accordance with previous observation that 17β-estradiol reduced VSMC $[Ca^{2+}]_i$ increases mediated by phenylephrine [26]. Experiments on uterine arteries of rats suggested estrogen replacement was associated with ACh-induced enhancement of endothelial $[Ca^{2+}]_i$ [27].

Estrogen and Protein Kinase C (PKC)

Treatment with estradiol caused downregulation of PKC signaling in sheep uterine arteries [28], which may provide an understanding of the mechanisms in estrogen regulation of vascular tone.

Although many factors have been shown to be the downstream targets of estrogen, this review will focus on the role of Phospholipase A2 group 1B (PLA2G1B) in gender-related differences in vascular function.

Role of PLA2G1B in Metabolic Diseases

Inactivation or pharmacological inhibition of the PLA2G1B gene suppressed diet-induced hyperlipidemia, atherosclerosis, obesity and diabetes in mice [29-31]. Moreover, PLA2G1B over-expression in pancreatic acinar cells promoted obesity and diabetes in transgenic mice [32]. So inhibition of the bioavailability of PLA2G1B may be a promising therapeutic target to prevent these metabolic diseases.

Role of PLA2G1B in Gender Differences

Eyster et al. firstly discovered in mesenteric arteries of rats the gene expression of PLA2G1B was significantly up-regulated by counteracting estrogen, whereas that of cPLA2 was not affected by it [33]. But in cultured rat ovaries inhibiting estrogen decreased PLA2G1B expression [34]. As reported recently, the PLA2G1B gene

was markedly down-regulated in trigeminal ganglia of female rats exposed to nerve injury but not in males [35]. The observations suggest that PLA2G1B might be involved in gender-related differences in vascular function as well.

General Properties of PLA2G1B

The PLA2G1B is a secreted extracellular phospholipase A_2 with Ca^{2+} binding sites. It is highly expressed in the acinar cells of the pancreas and to lesser extent in the lung and islet β-cells. So PLA2G1B has been thought to participate in hydrolysis of phospholipids in the digestive tract. PLA2G1B inhibition may protect against diet-induced metabolic diseases [36].

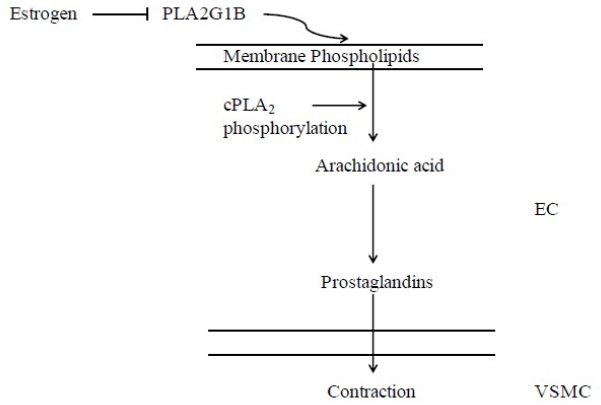

Figure 1: Postulated mechanism of gender-related differences in vascular function by which estrogen inhibiting PLA2G1B activity. PLA2G1B regulates the "bottleneck" phosphorylation of $cPLA_2$, hydrolyse membrane phospholipids to form arachidonic acid, thereby resulting in production of vasoconstrictor prostaglandins. EC, endothelial cell; VSMC, vascular smooth muscle cell; Phospholipase A_2 group 1_B, PLA2G1B; cytosolic PLA_2, $cPLA_2$. →stimulate; —l, inhibit.

Considering its presence in arteries [33], PLA2G1B may play an important role in gender-related differences in vascular function as follows: together with its "bottleneck" activation of cytosolic PLA2cPLA2, PLA2G1B can act on membrane phospholipids of endothelial cells to release arachidonic acid, thereby resulting in production of prostaglandins (Figure 1) [37,38]. Thromboxane A2, prostaglandin D2, prostaglandin E2, prostaglandin F2α, or high concentration of prostaglandin I2 can cause vascular smooth muscle constriction through TxA2/prostanoid receptors [39,40]. Thereforeestrogen may decrease agonist-induced vasoconstriction through inhibiting PLA2G1B activity. Recent observation showed that the upregulated cPLA2 phosphorylation (not cPLA2) and subsequently increased prostaglandin F2α release were involved in endothelium-dependent contractions of aorta from hypertensive mice, which was mediated by PKC activation. Nevertheless, the expressions of PLA2G1B were not investigated in this study [41].

Summary

Premenopausal women were at lower risk of hypertension, diabetes, atherosclerosis, or stroke than men of the same age. Agonist-induced endothelium-dependent constriction was significantly greater in arteries of male animals than that in female ones. Vascular protective effects of the female sex hormone estrogen have been suggested in this gender difference. Many factors, such as NO, prostaglandins, $[Ca^{2+}]_i$ and so on, have been related to vascular effects of estrogen. Inactivation of the PLA2G1B gene suppressed diet-induced metabolic diseases in mice, whereas PLA2G1B over-expression in pancreatic acinar cells promoted these diseases in transgenic mice. Regarding its presence in arteries, PLA2G1B may play an important role in gender-related differences in vascular function. Pharmacological inhibition of PLA2G1B may offer an attractive avenue for clinical intervention of metabolic diseases in men or menopausal women.

References

1. Rubanyi GM, Johns A, Kauser K (2002) Effect of estrogen on endothelial function and angiogenesis. Vascul Pharmacol 38: 89-98.
2. Egan KM, Lawson JA, Fries S, Koller B, Rader DJ, et al. (2004) COX-2-derived prostacyclin confers atheroprotection on female mice. Science 306: 1954-1957.
3. Mulvany MJ, Aalkjaer C (1990) Structure and function of small arteries. Physiol Rev 70: 921-961.
4. Mulvany MJ, Halpern W (1977) Contractile properties of small arterial resistance vessels in spontaneously hypertensive and normotensive rats. Circ Res 41: 19-26.
5. Duling BR, Gore RW, Dacey RG, Damon DN (1981) Methods for isolation, cannulation, and in vitro study of single microvessels. Am J Physiol 241: H108-H116.
6. Buus NH, VanBavel E, Mulvany MJ (1994) Differences in sensitivity of rat mesenteric small arteries to agonists when studied as ring preparations or as cannulated preparations. Br J Pharmacol 112: 579-587.
7. Dunn WR, Wellman GC, Bevan JA (1994) Enhanced resistance artery sensitivity to agonists under isobaric compared with isometric conditions. Am J Physiol 266: H147-155.
8. Kauser K, Rubanyi GM (1995) Gender difference in endothelial dysfunction in the aorta of spontaneously hypertensive rats. Hypertension 25: 517-523.
9. Kahonen M, Tolvanen JP, Sallinen K, Wu X, Porsti I (1998) Influence of gender on control of arterial tone in experimental hypertension. Am J Physiol 275: H15-H22.
10. Davidge ST, Zhang Y (1998) Estrogen replacement suppresses a prostaglandin H synthase-dependent vasoconstrictor in rat mesenteric arteries. Circ Res 83: 388-395.
11. Dantas AP, Scivoletto R, Fortes ZB, Nigro D, Carvalho MH (1999) Influence of female sex hormones on endothelium-derived vasoconstrictor prostanoid generation in microvessels of spontaneously hypertensive rats. Hypertension 34: 914-919.
12. Geary GG, Krause DN, Duckles SP (2000) Estrogen reduces mouse cerebral artery tone through endothelial NOS- and cyclooxygenase-dependent mechanisms. Am J Physiol Heart Circ Physiol 279: H511-519.
13. Luksha L, Poston L, Gustafsson JA, Aghajanova L, Kublickiene K (2005) Gender-specific alteration of adrenergic responses in small femoral arteries from estrogen receptor-beta knockout mice. Hypertension 46: 1163-1168.
14. Ibrahim J, Mc Gee A, Graham D, Mc Grath J C, Dominiczak AF (2006) Sex-specific differences in cerebral arterial myogenic tone in hypertensive and normotensive rats. Am J Physiol Heart Circ Physiol 290: H1081-1089.

15. Lekontseva O, Chakrabarti S, Jiang Y, Cheung CC, Davidge ST (2011) Role of neuronal nitric-oxide synthase in estrogen-induced relaxation in rat resistance arteries. J Pharmacol Exp Ther 339: 367-375.
16. Chan MV, Bubb KJ, Noyce A, Villar IC, Duchene J, et al. (2012) Distinct endothelial pathways underlie sexual dimorphism in vascular auto-regulation. Br J Pharmacol 167: 805-817.
17. Qin J, Kandhi S, Froogh G, Jiang H, Luo M, et al. (2015) Sexually dimorphic phenotype of arteriolar responsiveness to shear stress in soluble epoxide hydrolase-knockout mice. Am J Physiol Heart Circ Physiol 309: H1860-H1866.
18. Black MJ, Lim K, Zimanyi MA, Sampson AK, Bubb KJ (2015) Accelerated age-related decline in renal and vascular function in female rats following early-life growth restriction. Am J Physiol Regul Integr Comp Physiol 309: R1153-1161.
19. Al-Gburi S, Deussen A, Zatschler B, Weber S, Kunzel S, et al. (2017) Sex-difference in expression and function of beta-adrenoceptors in macrovessels: role of the endothelium. Basic Res Cardiol 112: p29.
20. Uwitonze AM, Uwambaye P, Isyagi M, Mumena CH, Hudder A (2018) Periodontal diseases and adverse pregnancy outcomes: Is there a role for vitamin D? J Steroid Biochem Mol Biol 180: 65-72.
21. Lekontseva O, Chakrabarti S, Jiang Y, Cheung CC, Davidge ST (2011) Role of neuronal nitric-oxide synthase in estrogen-induced relaxation in rat resistance arteries. J Pharmacol Exp Ther 339: 367-375.
22. Sobrino A, Oviedo PJ, Novella S, Laguna FA, Bueno C, et al. (2010) Estradiol selectively stimulates endothelial prostacyclin production through estrogen receptor. J Mol Endocrinol 44: 237-246.
23. Ospina JA, Duckles SP, Krause DN (2003) 17beta-estradiol decreases vascular tone in cerebral arteries by shifting COX-dependent vasoconstriction to vasodilation. Am J Physiol Heart Circ Physiol 285: H241-250.
24. Meyer MR, Fredette NC, Barton M, Prossnitz ER (2015) G protein-coupled estrogen receptor inhibits vascular prostanoid production and activity. J Endocrinol 227: 61-69.
25. Meyer MR, Field AS, Kanagy NL, Barton M, Prossnitz ER (2012) GPER regulates endothelin-dependent vascular tone and intracellular calcium. Life Sci 91: 623-627.
26. Castillo C, Ceballos G, Rodriguez D, Villanueva C, Medina R (2006) Effects of estradiol on phenylephrine contractility associated with intracellular calcium release in rat aorta. Am J Physiol Cell Physiol 291: C1388-C1394.
27. Burger NZ, Kuzina OY, Osol G, Gokina NI (2009) Estrogen replacement enhances EDHF-mediated vasodilation of mesenteric and uterine resistance arteries: role of endothelial cell Ca^{2+}. Am J Physiol Endocrinol Metab 296: E503-E512.
28. Xiao D, Huang X, Yang S, Zhang L (2009) Direct chronic effect of steroid hormones in attenuating uterine arterial myogenic tone: role of protein kinase c/extracellular signal-regulated kinase ½. Hypertension 54: 352-358.
29. Hui DY, Cope MJ, Labonte ED, Chang HT, Shao J (2009) The phospholipase A(2) inhibitor methyl indoxam suppresses diet-induced obesity and glucose intolerance in mice. Br J Pharmacol 157: 1263-1269.
30. Hollie NI, Konaniah ES, Goodin C, Hui DY (2014) Group 1B phospholipase A(2) inactivation suppresses atherosclerosis and metabolic diseases in LDL receptor-deficient mice. Atherosclerosis 234: 377-380.
31. Hollie NI, Hui DY (2011) Group 1B phospholipase A(2) deficiency protects against diet-induced hyperlipidemia in mice. J Lipid Res 52: 2005-2011.
32. Cash JG, Kuhel DG, Goodin C, Hui DY (2011) Pancreatic acinar cell-specific overexpression of group 1B phospholipase A2 exacerbates diet-induced obesity and insulin resistance in mice. Int J Obes (Lond) 35: 877-881.
33. Mark KCJ, Martin DS, Eyster KM (2011) Estrogens and selective estrogen receptor modulators regulate gene and protein expression in the mesenteric arteries. Vascul Pharmacol 55: 42-49.
34. Piasecka SJ, Blanco FF, Delman DH, Pixon DA, Geiser JL (2015) Tamoxifen prevents apoptosis and follicle loss from cyclophosphamide in cultured rat ovaries. Biol Reprod 92: p132.
35. Korczeniewska OA, Husain S, Khan J, Eliav E, Soteropoulos P (2018) Differential gene expression in trigeminal ganglia of male and female rats following chronic constriction of the infraorbital nerve. Eur J Pain 22: 875-888.
36. Hui DY (2012) Phospholipase A2 enzymes in metabolic and cardiovascular diseases. Curr Opin Lipidol 23: 235-240.
37. Rastogi P, Beckett CS, McHowat J (2007) Prostaglandin production in human coronary artery endothelial cells is modulated differentially by selective phospholipase A2 inhibitors. Prostaglandins Leukot Essent Fatty Acids 76: 205-212.
38. Murakami M, Taketomi Y, Sato H, Yamamoto K (2011) Secreted phospholipase A2 revisited. J Biochem 150: 233-255.
39. Feletou M, Huang Y, Vanhoutte PM (2011) Endothelium-mediated control of vascular tone: COX-1 and COX-2 products. Br J Pharmacol 164: 894-912.
40. Chen H (2018) Role of thromboxane A2 signaling in endothelium-dependent contractions of arteries. Prostaglandins Other Lipid Mediat 134: 32-37.
41. Li H, Kan H, He C, Zhang X, Yang Z (2018) TRPV4 activates cytosolic phospholipase A2 via Ca2+ -dependent PKC/ERK1/2 signalling in controlling hypertensive contraction. Clin Exp Pharmacol Physiol.