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Estradiol Regulation of Prostanoids Production in Endothelium

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1. Introduction

The endothelium is a continuous cellular monolayer lining the interior of the blood vessels and heart. Classically considered to exert its actions only as a mechanical barrier, also plays important roles in vascular physiology. Endothelium participates in numerous metabolic and regulatory functions such as the control of primary hemostasis, blood coagulation and fibrinolysis, interaction with lipoprotein metabolism, platelet and leukocyte interactions with the vessel wall, presentation of histocompatibility antigens, regulation of vascular tone and growth, and of blood pressure. The endothelium exerts these actions through the release of such vasoactive compounds as prostacyclin, thromboxane A₂, nitric oxide (NO), bradykinin, endothelin, angiotensin, and free radicals that control the functions of vascular smooth muscle cells and of circulating blood cells (Ross, 1999; Vapaatalo & Mervaala, 2001).

The integrity and functionality of the arterial endothelium play a crucial role in the physiology of circulation (Filipe *et al.*, 2008) and, as a consequence, in preventing the development of cardiovascular diseases, whose genesis is currently considered a consequence of the anatomical and functional disruption of the endothelium (Spyridopoulos *et al.*, 1997). When the ability of the endothelial cells to release relaxing is reduced, and in particular if the propensity to produce contractile factors is enhanced, endothelial dysfunction appears as a first step in the sequence of events that leads to atherosclerosis and coronary disease. Thus, no single mechanism is responsible for all endothelium dependent responses and their modulation by pathophysiological states leads to endothelial dysfunction characterized by an imbalance in endothelial regulators (Vanhoutte *et al.*, 2009).

Clinical and experimental data support the consideration of endothelium as a target for estradiol and other sexual hormones. A number of studies have demonstrated a favourable profile for estrogens in both experimental animal, as well as in *in vitro* models (Turgeon *et al.*, 2006). However, the protective effect detected in a considerable number of observational clinical studies (Barrett-Connor & Grady, 1998) has not been confirmed by randomized placebo-controlled trials (Hulley *et al.*, 1998; Grady *et al.*, 2002), which described clinical complications, such as thrombosis in veins and coronary arteries, developed in postmenopausal women during the administration of exogenous hormones (Cano *et al.*, 2007).

A number of studies have demonstrated that estrogens exert significant benefits on the cardiovascular system, and at least a part of these benefits are attributed to the direct effect of estradiol on vascular endothelial cells (Mendelsohn & Karas, 1999; Rubanyi *et al.*, 2002; Sader & Celermajer, 2002). Estradiol is able to stimulate endothelial NO production through several mechanisms, including increased expression of NO synthases (mainly endothelial NO synthase), increased L-arginine availability, non-genomic activation of second messengers (Simoncini, 2009), translocation to intracellular sites, modulation of NO degrading sites (Tostes *et al.*, 2003), and modulation of endogenous antagonist levels (Monsalve *et al.*, 2007).

Additionally, estradiol is able to exert antioxidant actions on endothelium (Shwaery *et al.*, 1998; Hermenegildo *et al.*, 2002), to modulate the renin-angiotensin system (Farhat *et al.*, 1996; Alvarez *et al.*, 2002), and to decrease endothelin-1 production (Mikkola *et al.*, 1995; Akishita *et al.*, 1998). Furthermore, estradiol regulates endothelial cell expression of adhesion molecules (Caulin-Glaser *et al.*, 1996; Abu-Taha *et al.*, 2009).

Estradiol has also been implicated on the regulation of prostanoids production in endothelial cells. Two main vascular prostanoids, prostacyclin and thromboxane A₂, play an essential role in the maintenance of vascular homeostasis. Prostacyclin is a vasodilator and an inhibitor of platelet aggregation; in contrast, thromboxane A₂ is a vasoconstrictor and a promoter of platelet aggregation. As a consequence of their opposing roles, an imbalance in prostacyclin or thromboxane production has been implicated in the physiopathology of many thrombotic and cardiovascular disorders. In this chapter, we will discuss clinical and experimental data that document the endothelial effects of estradiol on prostanoid production and regulation, and their vascular consequences.

2. Prostanoids in endothelium

Prostanoids are unstable lipid mediators that, after intracellular biosynthesis, are released outside the endothelial cell. It is believed that prostanoids work mostly locally in an autocrine or paracrine way. Prostanoids are ubiquitous compounds that coordinate a wide variety of physiological and pathological processes via membrane receptors on the surface of target cells (FitzGerald, 2002). Prostanoids include prostaglandins (such as prostaglandins D₂, E₂, F₂, F_{2α}, PGI₂ -or prostacyclin-) and thromboxanes (such as TXA₂) (Smith *et al.*, 2000; Linton & Fazio, 2002).

Prostanoids production is mainly regulated by the availability of free arachidonic acid and the activity of cyclooxygenases (COX). Release of arachidonate from cell membrane phospholipids is mediated through phospholipases, mainly phospholipase A₂. Once arachidonate is released, it is sequentially converted to prostaglandins G₂ and H₂ by two COX isoenzymes (COX-1 and COX-2). The unstable prostaglandin H₂ is then transformed into biologically active prostanoids by specific synthases in different cells. Prostaglandins interact with G-protein-coupled receptors, classified in function of their preferential affinity towards the five primary prostaglandins (Tsuboi *et al.*, 2002) (Figure 1).

COX isoenzymes (also known as prostaglandin endoperoxide synthases or prostaglandin H synthases) are the rate-limiting step in the formation of prostanoids from arachidonic acid and represent the main control mechanism for prostaglandin production (Smith *et al.*, 2000). Both enzymes have similar biochemical activity in converting arachidonic acid to PGH₂ in tissue or in recombinant enzyme systems (Vane *et al.*, 1998).

COX-1 and COX-2 are encoded by two different genes derived from human chromosomes 9 and 1, respectively. In spite of there is a 60 - 65% homology between the isoforms within

species, the activity and the pattern of gene expression of these enzymes are differentially regulated (Davidge, 2001).

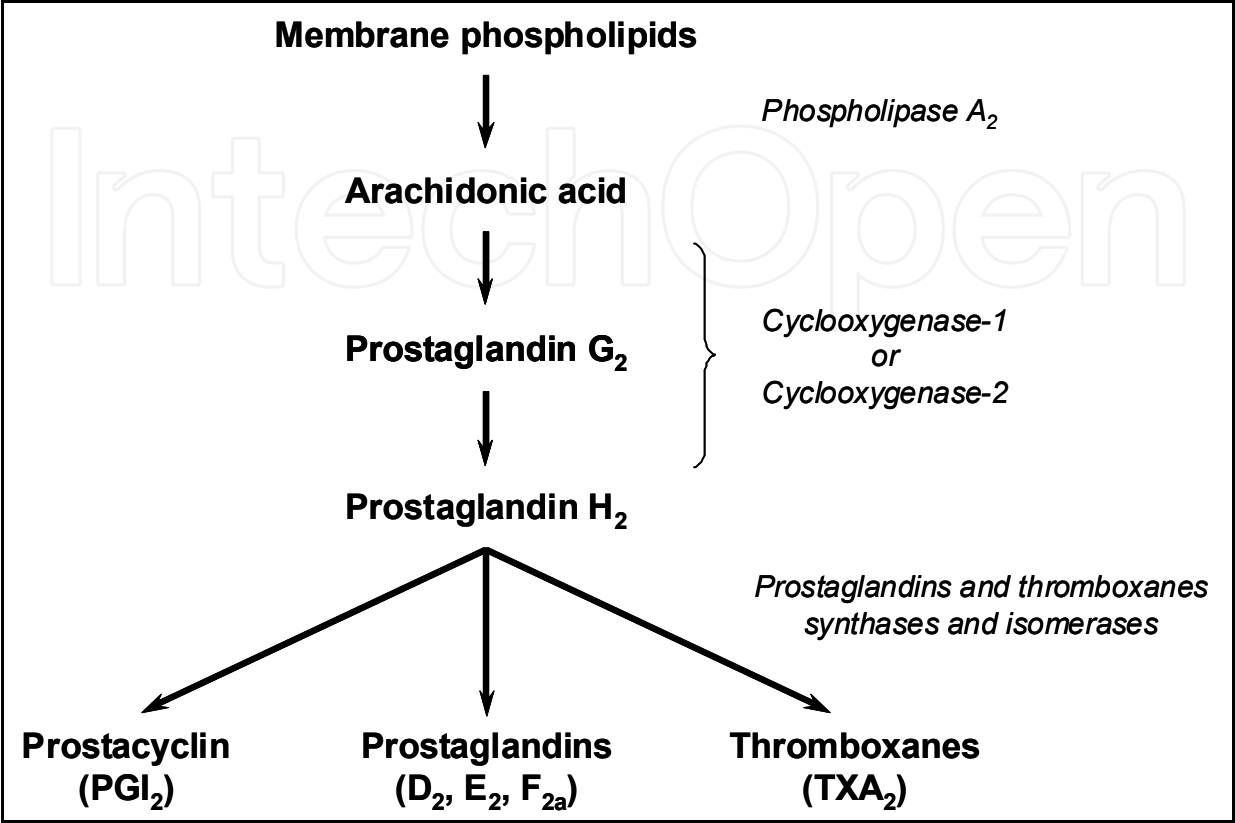


Fig. 1. Biosynthesis of prostaglandins and thromboxanes.

COX-1 has been considered to be the constitutively expressed protein, while COX-2 is induced at sites of inflammation. Following that hypothesis, COX-1 would generate prostaglandins for physiological, housekeeping functions like gastrointestinal mucosal integrity and regulation of renal blood flow, while COX-2 would form the prostaglandins responsible for inflammatory symptoms (Smith *et al.*, 2000; Parente & Perretti, 2003).

But this separation of functions is so not clear. For instance, COX-2 is constitutively expressed in some regions of the central nervous system, and in renal and uterus tissues, suggesting it may play a role under physiologic conditions (Kim *et al.*, 1999; FitzGerald, 2002; Cheng & Harris, 2004). In fact, both COX-1 and COX-2 are involved not only in physiological, but also in pathological processes. The importance of this topic has impelled many outstanding reviews (Vane *et al.*, 1998; Parente & Perretti, 2003; Cipollone *et al.*, 2008; Vanhoutte, 2009).

Regarding the vascular system, both isoenzymes are expressed in endothelium and smooth muscle cells. However, endothelial cells contain up to 20 times more COX than smooth muscle cells (DeWitt *et al.*, 1983). As mentioned before for other organs, COX-1 has usually been considered in endothelium as the constitutive isoform, while COX-2 is induced by a number of cardiovascular risk factors, such as cytokines, cholesterol, lipoproteins, and hypoxia. Actually, both COX isoenzymes share characteristics of constitutive and inducible enzymes in endothelium. Shear stress induces COX-1 gene expression in human umbilical vein endothelial cells (HUVEC) (Doroudi *et al.*, 2000), while clinical studies with a selective

inhibitor of COX-2 (celecoxib) have shown that this enzyme exerts control of most systemic prostacyclin production in healthy humans (McAdam *et al.*, 1999).

Although prostaglandins E_2 and $F_{2\alpha}$ can contribute to vascular phenotype, two main prostanoids play an essential role in vascular physiology: thromboxane A_2 and prostacyclin. On the one hand, in the cardiovascular system, thromboxane A_2 is predominantly derived from platelet COX-1, but can also be produced by other cell types including the endothelial cells. The stimulation of thromboxane receptors elicits not only platelet aggregation and smooth muscle contraction, but also the expression of adhesion molecules and the adhesion and infiltration of monocytes/macrophages (Nakahata, 2008). As platelets are anucleate, there can be no induction of COX-2 enzyme synthesis (Patrignani *et al.*, 1999). Thromboxane A_2 can also be synthesized from endothelial cells (Sellers & Stallone, 2008). The third possibility is a transcellular formation of thromboxane A_2 by platelets from prostaglandin H_2 released by endothelial cells (Camacho & Vila, 2000). Thromboxane A_2 promotes irreversible platelet aggregation, vasoconstriction, and smooth muscle proliferation and, consequently, plays an important role as a mediator of not only haemostasis, but also of acute vascular occlusive events and atherogenesis (FitzGerald, 2002; Weir *et al.*, 2003).

On the other hand, in most blood vessels prostacyclin is the main prostanoid produced by endothelial cells, and the endothelium is its major source (Moncada & Vane, 1978). Both COX-1 and COX-2 isoenzymes contribute to the production of endothelial prostacyclin. By stimulating its preferential receptor, prostacyclin is a potent inhibitor of platelet adhesion to the endothelial cell surface and of platelet aggregation, and generally acts as an endothelium-derived vasodilator and an inhibitor of vascular smooth muscle migration and proliferation (Moncada & Vane, 1978; Fetalvero *et al.*, 2007).

Under physiological conditions, endothelial prostacyclin is a counterregulatory influence to platelet-derived thromboxane, and eicosanoids produced by the COX pathways generally induce vasorelaxation. Nevertheless, in some pathologic circumstances, such as oxidative stress and dyslipidemia, there may be an imbalance where COX-dependent vasoconstrictors and platelet aggregation become more predominant. Reactive oxygen species, such as superoxide anion and hydrogen peroxide are derived from multiple sources within inflammatory leukocytes and vascular tissues including NADPH oxidase, uncoupled endothelial and inducible endothelial NO synthase, xanthine oxidase, cyclooxygenases, lipoxygenases, cytochrome P450 monooxygenases and excess substrate utilization by mitochondria. Additionally, NO reacts with superoxide anion to form the extremely potent oxidant, peroxynitrite. Low concentrations of peroxynitrite selectively nitrate and inactivate prostacyclin synthase, which not only eliminates the vasodilatory, growth-inhibiting, antithrombotic, and antiadhesive effects of prostacyclin, but also increases release of the potent vasoconstrictor, prothrombotic, growth- and adhesion-promoting agents, prostaglandin H_2 and thromboxane A_2 being in general deleterious to vascular function (Zou *et al.*, 2004; Schildknecht & Ullrich, 2009; Feletou *et al.*, 2010).

3. Estrogens actions on endothelium

Estradiol is the most potent estrogen in humans, and exerts its actions mainly through binding and activation of estrogen receptors (ER). Two major subtypes of ER (ER α and ER β) have been identified. These receptors vary not only in their tissue distributions, but also in their agonist/antagonist profile of several compounds (Cano & Hermenegildo, 2000). Both

types of ER belong to the class of intracellular receptors classically defined as nuclear ligand-activated transcription factors. Activation of these receptors by the corresponding hormones affects gene expression by acting on specific sequences in the target genes, known as estrogen-response elements, and by modulating transcriptional events.

The contribution of both receptors to the regulation of vascular effects is still under study. There is controversy about whether estrogenic effects are mediated through ER α , ER β or both. In the cardiovascular system, ER α and ER β have been identified by different techniques in the endothelium, smooth muscle cells and adventitia and on adrenergic nerve endings of arteries from various territories and several species, including humans (Karas *et al.*, 1994; Kim-Schulze *et al.*, 1996; Venkov *et al.*, 1996; Register & Adams, 1998). Although it has been reported cultured endothelial cells do not express ER α (Toth *et al.*, 2008), other investigators have demonstrated the presence of both ER α and ER β mRNA in endothelium (Wagner *et al.*, 2001) and data from our group demonstrate the protein expression of both ER α and ER β in HUVEC (Sobrinho *et al.*, 2009; Sobrinho *et al.*, 2010).

Although the relative significance of both ER subtypes in the vascular actions of estrogens is still under study, data from mice lacking either ER α (Pare *et al.*, 2002; Arnal *et al.*, 2010) or ER β (Zhu *et al.*, 2002), and also from a non-functional mutation of ER α in a male patient (Sudhir *et al.*, 1997), reveal an impaired vascular function. Therefore, ER α is probably critical for the production of estrogen vascular protective actions (Favre *et al.*, 2010), but ER β may have relevant functions at the vascular level too (Simoncini *et al.*, 2004). The changes in vascular cell gene and protein expression mediated by those ER α and/or ER β produce the classic, and better known, longer-term effects of estrogen (Cano & Hermenegildo, 2000).

ER act in the nucleus as ligand-activated transcription factors that regulate gene expression in response to hormone binding. ER can also regulate vascular cell gene expression in the absence of estrogen following activation by growth factor signalling pathways, a process referred to as ligand-independent transcriptional activation. In addition, ER are able to signal rapidly (from seconds to minutes), in an apparently non-nuclear manner, resulting in downstream activation of specific kinases and their effectors molecules (Mendelsohn & Karas, 2010).

The rapid effects of estrogens have been also explained by ER-independent mechanisms of action. For instance, the G protein-coupled receptor GPR30 has been proposed to be a third form of ER, although it is controversial whether GPR30 is a biologically-relevant ER or a collaborator in non-nuclear functions of the classical ER in certain contexts (Levin, 2009). Moreover, even though GPR30 is expressed in certain endothelial cells, there is currently a lack of clear evidence of a role for the receptor in estrogen action in endothelium (Wu *et al.*, 2011).

Rapid actions of estradiol include several endothelial pathways, being the activity of endothelial nitric oxide synthase the most studied (Chow *et al.*, 2010). Other signalling pathways acutely activated by estradiol in endothelium are several kinases, such as phosphatidylinositol 3-kinase (PI3K) (Razandi *et al.*, 2000), protein kinase C (PKC) (Akarasereenont *et al.*, 2000) and Rho-associated kinase (ROCK) (Simoncini *et al.*, 2006; Oviedo *et al.*, 2011). Rapid actions are responsible for the acute and potent vasorelaxation induced by estradiol both at physiological (Teoh *et al.*, 2000; Tep-areenan *et al.*, 2003) or supraphysiological (Naderali *et al.*, 2001; Salom *et al.*, 2002) concentrations, and it has been demonstrated in isolated vessels from animals such as rats (Tep-areenan *et al.*, 2003), pigs (Teoh *et al.*, 2000), rabbits (Salom *et al.*, 2002), guinea pigs (Naderali *et al.*, 2001), and even from human beings (Chester *et al.*, 1995).

In addition, steroid hormone genomic and non-genomic effects may occur simultaneously and may act at different levels, revealing the complexity of estrogen regulation of vascular function (Tostes *et al.*, 2003).

4. Estrogens actions on prostanoids vascular regulation

The actions of estrogens on prostanoids vascular production will be presented in two sections: first, those experimental data that are rapid in onset and short in duration (within minutes; “non-genomic” effects); second, those experimental data that are delayed in onset and prolonged in duration (require from hours to days to occur; “genomic” effects).

4.1 Rapid effects of estrogens on prostanoids vascular production

Physiological concentrations of estradiol cause a rapid stimulation of prostacyclin synthesis (within 15 min) in two types of cultured endothelial cells, ovine fetal pulmonary artery endothelial cells (PAEC) (Sherman *et al.*, 2002) and HUVEC (Alvarez *et al.*, 2002). In both cases, the use of the ER-antagonist ICI182780 reveals that the increased prostacyclin production is mediated through ER activation. In ovine PAEC, it seems mediated through ER β , since prostacyclin stimulation with estradiol was fully blocked by the ER β - antagonist RR-tetrahydrochrysene. Moreover, in ovine PAEC, the increased prostacyclin production is not related to changes in COX-1 or COX-2 protein abundance, thus reinforcing the implication of non-genomic mechanisms (Table 1) (Sherman *et al.*, 2002).

COX-pathway activity is involved in the acute relaxation afforded by estradiol. In rat mesenteric vessels and aorta, COX inhibition with indomethacin enhances the vasodilator potency of estradiol, suggesting an endogenous release of vasoconstrictor prostanoids (Tepareenan *et al.*, 2003). But estradiol also indirectly affects vasoreactivity to contracting and relaxing substances. In epicardial porcine coronary arteries activation of ER α , but not of ER β , reduces thromboxane A₂ vasoconstriction, indicating another indirect and vasodilator function of ER α (Traupe *et al.*, 2007). Other data suggest that the estrogen-dependent constrictor prostanoid mechanism in the vascular wall may play an important role in the regulation of vascular tone in the female, in both normal and pathophysiological states. In that way, endogenous estrogen acts as an important regulator of constrictor prostanoid function in female rat aorta, involving the potentiation of COX-2 and thromboxane synthase expression in vascular wall (Li *et al.*, 2008).

Data from studies performed on postmenopausal women also supports the importance of COX-pathway in acute estrogen-induced vasodilation. Estradiol induces a rapid increase of cholinergic cutaneous vasodilation, which is eliminated in women treated for 6 weeks with celecoxib, suggesting that the COX-2 pathway plays a specific role in the rapid estradiol-induced vasodilation in postmenopausal women (Calkin *et al.*, 2002).

Some studies have been performed at times that do not clarify whether the observed effects are genomic or non-genomic actions. Estrogen stimulates rat aortic endothelial cell release of prostacyclin after 1 hour of incubation without affecting COX-1 levels (Myers *et al.*, 1996). That stimulation could be mediated by NO, since endogenous NO increased production of prostacyclin and thromboxane A₂ in bovine coronary microvascular endothelial cells within 1 hour, without affecting COX-1 or COX-2 expressions (Davidge *et al.*, 1995). At molecular level, exposure of HUVEC for 40 min to estradiol significantly increases the expression of roughly 250 genes, measured by DNA microarray analysis. Among them, the COX-2 gene was the strongest up-regulated by estradiol. In fact, estradiol induced COX-2 gene

expression and new COX-2 protein synthesis by 40 and 60 min, respectively, and quickly stimulated the secretion of prostacyclin and prostaglandin E₂ in an ER-dependent manner (Pedram *et al.*, 2002). A similar, significant induction of COX-2 mRNA levels is obtained in human placental villous endothelial cells exposed to estradiol up to 1 hour, without an increased protein production (Su *et al.*, 2009).

Cell type	Time	E ₂ (nM)	Prostacyclin production	COX-1	COX-2	Reference
Rapid effects						
Ovine fetal PAEC	15 min	10	↑ 52 %	↔	↔	(Sherman <i>et al.</i> , 2002)
HUVEC	15 min	1	↑ 57 %	NA	NA	(Alvarez <i>et al.</i> , 2002)
HUVEC	30 min	1	↑ 134 %	NA	NA	(Alvarez <i>et al.</i> , 2002)
Delayed effects						
HUVEC	24 h	10	↑ 26 %	NA	NA	(Mikkola <i>et al.</i> , 1995)
HUVEC	24 h	0.1	↑ 16 %	NA	NA	(Mikkola <i>et al.</i> , 1996)
HUVEC	24 h	1	↑ 78 %	↔	↑	(Akarasereenont <i>et al.</i> , 2000)
HUVEC	24 h	1	↑ 30 %	↑	↔	(Sobrino <i>et al.</i> , 2009)
HUVEC	24 h	10	↑ 33 %	↑	↔	(Sobrino <i>et al.</i> , 2010)
Human coronary EC	24 h	100	↑ 45 %	NA	NA	(Mueck <i>et al.</i> , 2002)
Bovine coronary EC	24 h	1	↓ 83 %	↔	↔	(Stewart <i>et al.</i> , 1999)
Ovine fetal PAEC	48 h	10	↑ 64 %	↑	NA	(Jun <i>et al.</i> , 1998)

Table 1. Summary of estradiol effects on cultured cell production of prostacyclin. E₂: concentration of estradiol in nM. Prostacyclin production is expressed as increased (↑) or decreased (↓) percentage of control values. COX-1 and COX-2 expression: increased (↑), decreased (↓), unchanged (↔) or not available (NA). PAEC: pulmonary artery endothelial cells. HUVEC: human umbilical vein endothelial cells. EC: endothelial cells.

4.2 Delayed (genomic) effects of estrogens on prostanoids vascular production

Estrogen also exerts vascular delayed effects on the metabolism of prostaglandins and the activity of COX, as has been demonstrated in studies performed both in cultured cells, as well as in isolated vascular preparations. A time-course analysis performed in HUVEC, demonstrates that estradiol effects on prostacyclin production were evident only after 8 or 24 hours (10 and 1 nM estradiol, respectively), suggesting an ER-mediated genomic effect (Sobrino *et al.*, 2010). Moreover, physiological concentrations of estradiol stimulate the production of prostaglandins, mainly

prostacyclin, in a variety of cultured endothelial cells, such as ovine fetal PAEC (Jun *et al.*, 1998), HUVEC (Mikkola *et al.*, 1995; Mikkola *et al.*, 1996; Akarasereenont *et al.*, 2000; Sobrino *et al.*, 2010), and human coronary endothelial cell (Mueck *et al.*, 2002). In the vast majority of experiments, cells were exposed to estradiol during 24-48 hours, and the increase of prostacyclin above control values ranged from 16 % to 78 % (Table 1).

In addition, it has been shown that estradiol stimulates production of prostaglandins in a variety of preparations of arteries, including ovine uterine arteries (Vagnoni & Magness, 1998; Janowiak *et al.*, 1998; Habermehl *et al.*, 2000), mesenteric arteries from ovariectomized rats (Davidge & Zhang, 1998; Armstrong *et al.*, 2002), rat cerebral blood vessels (Ospina *et al.*, 2002; Ospina *et al.*, 2003), and aorta from ovariectomized monkeys (O'Sullivan *et al.*, 2001). The increase of prostacyclin production is of a similar magnitude to that obtained with cultured endothelial cells.

Concerning endothelial production of thromboxane A₂ under estradiol, the literature indirectly suggests that estrogen would have a beneficial effect by decreasing the production of thrombogenic compounds. In men, there is a decrease in the formation of thromboxane A₂ after the use of high dosage intra-muscular estrogen therapy (Henriksson *et al.*, 1996). Moreover, the ratio of *in vivo* prostacyclin to thromboxane A₂ formation increases 2-fold during estrogen replacement therapy (Mueck *et al.*, 2001). Nevertheless, it has also been documented that estrogen increases platelet activation with the liberation of thromboxane A₂ in women treated with hormone replacement therapy (Oliveira *et al.*, 2005) and that estrogen enhances the constrictor prostanoid function in female rat aorta (Li *et al.*, 2008). However, in cultured endothelial cells, thromboxane A₂ production remains unchanged when measured after exposure to estradiol (Sobrino *et al.*, 2010).

The regulatory role of estradiol on the biosynthesis pathway of prostanoids in endothelium (Figure 1) has been scarcely studied, with the only exception of COX-1 and COX-2 expressions. Concerning the first enzyme, soluble phospholipase A₂ is highly expressed in HUVEC and umbilical smooth muscle cells (Ost *et al.*, 1998), but it does not appear to be regulated by estradiol. Phospholipase A₂ expression remains unchanged after exposure to estradiol in HUVEC (Sobrino *et al.*, 2010) or in human myometrial cells prepared from second trimester pregnant women (Korita *et al.*, 2004).

The roles of COX-1 and/or COX-2 isoenzymes in endothelial cells exposed to estradiol have been studied in some cases, and both enzymes have been implicated in estradiol effects. In ovine fetal PAEC after exposure to estradiol, both COX-1 mRNA and protein expressions were up-regulated (Jun *et al.*, 1998), whereas in HUVEC estradiol only induces COX-2 expression protein (Akarasereenont *et al.*, 2000). Genome-wide analysis performed in HUVEC exposed to estradiol for 24 hours demonstrated that COX-1 was among the 5 % of proteins which expression was changed more than 1.5 fold-times compared to controls, data that was verified by western blot analysis (Sobrino *et al.*, 2009).

Prostacyclin increased levels after vessel stimulation with estradiol have been mainly associated with enhanced expression of COX-1. In this way, COX-1 protein content is increased in rat (Ospina *et al.*, 2002) and mice (Geary *et al.*, 2001) cerebral blood vessels, and in ovine uterine arteries in response to treatment with estrogen (Rupnow *et al.*, 2002). Indeed, COX-1 (but not COX-2) expression is increased in the endothelium of the ovine uterine artery during the follicular phase of the ovarian cycle and during pregnancy, where estrogen levels are highest (Janowiak *et al.*, 1998; Habermehl *et al.*, 2000). In spite of the classic consideration of COX-2 as an inducible enzyme, it seems that COX-2 does not contribute to the estradiol-increased prostacyclin production. Estrogen has even been found

to decrease COX-2 expression in mesenteric arteries from ovariectomized aged rats (Armstrong *et al.*, 2002). However, similar experiments have occasionally produced contradictory results. Exposure of culture bovine coronary microvascular endothelial cells to physiological concentrations of estradiol for 24 hours reduced both prostacyclin and thromboxane A₂ production (Stewart *et al.*, 1999). In the case of whole tissue experiments, arteries respond in a different way to estradiol. This is the case of artery segments from different vascular beds (thoracic aorta, pulmonary artery, ear artery and coronary arteries) from adult male rabbits in which estradiol may cause both vasorelaxation and vasoconstriction (Saetrum *et al.*, 2002). Moreover, in thoracic aorta the contractile effects of estrogen are mediated through the release of vasoconstrictor prostaglandins (Saetrum *et al.*, 2002). These discrepancies could indicate a difference in the effects of estrogen depending on its previous serum concentration, the reproductive condition of the animal and/or the vascular bed being studied (Armstrong *et al.*, 2002; Saetrum *et al.*, 2002; Tostes *et al.*, 2003).

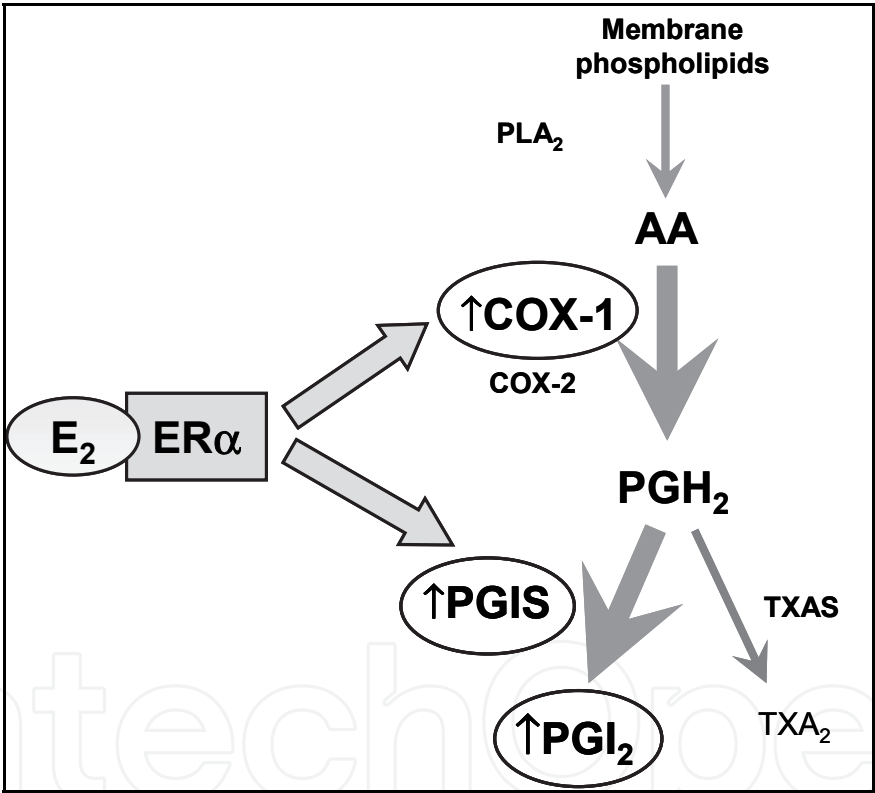


Fig. 2. Estradiol-induced modifications on prostanoid pathway through ERα. Estradiol (E₂), acting on ERα, increased cyclooxygenase-1 (COX-1) and prostacyclin synthase (PGIS) expression, resulting in an increased prostacyclin (PGI₂) production. Phospholipase A₂, cyclooxygenase-2 (COX-2) and thromboxane synthase (TXAS) expressions, along with thromboxane A₂ production (TXA₂), remained unchanged after exposure to estradiol.

The regulatory actions of estradiol on the prostanoids biosynthesis pathway are mediated through ER activation. The use of ICI182780, a non-selective ER-antagonists, completely blocks estradiol-stimulated prostacyclin production in ovine fetal PAEC (Jun *et al.*, 1998), HUVEC (Sobrinho *et al.*, 2009), and tamoxifen blocked it in HUVEC (Mikkola *et al.*, 1995; Mikkola *et al.*, 1996).

Moreover, data support a specific role for ER α on estradiol-stimulated prostacyclin production. Recently, selective ER α agonist 1,3,5-tris(4-hydroxyphenyl)-4-propyl-1h-pyrazole (PPT), selective ER β agonist (diarylpropionitril; DPN), and selective ER α antagonist, methyl-piperidino-pyrazole (MPP), have become available (Krom *et al.*, 2007). With their use, it has been demonstrated that estradiol increased prostacyclin production, and COX-1 and prostacyclin synthase protein and gene expressions through ER α , whereas COX-2, phospholipases and thromboxane synthase expression remained unaltered (Sobrino *et al.*, 2010). The regulatory role of estradiol through ER α is supported by other studies. Estradiol increases levels of COX-1 in cerebral blood vessels from wild-type mice but was ineffective in ER α knockout mice (Geary *et al.*, 2001) and also increases COX-1 expression through ER α in ovine endothelial cells transfected with the human COX-1 promoter (Gibson *et al.*, 2005).

5. Conclusion

Remarkable progress has been made in elucidating the effects of estrogens on the vascular system, and the cellular and molecular mechanisms by which those effects are achieved. The analysis of published data supports estradiol increases prostacyclin vascular production in accordance with experimental and clinical research. This effect seems to be mediated mainly through ER α -dependent pathways which involve an increase in COX-1 and, in some cases, COX-2 activation and/or expression, and an augment in prostacyclin synthase expression, without affecting thromboxane A2 production. As a consequence, estradiol may reduce vascular tone and improve endothelium-dependent vasodilation (Figure 2).

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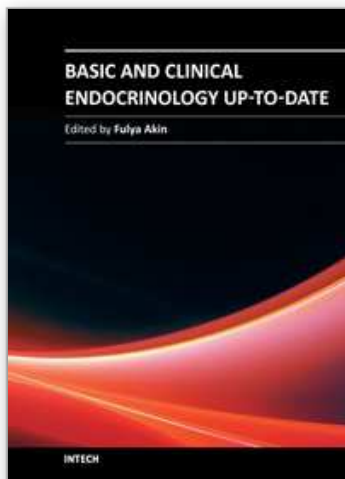
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This book provides the most up-to-date information on the basic and clinical aspects of endocrinology. It offers both researchers and clinicians experts, gold-standard analysis of endocrine research and translation into the treatment of diseases such as insulinoma, endocrine disease in pregnancy and steroid induced osteoporosis. Investigates both the endocrine functions of the kidneys and how the kidney acts as a target for hormones from other organ systems. Presents a uniquely comprehensive look at all aspects of endocrine changes in pregnancy and cardiovascular effects of androgens.

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