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Review

Cytokines, angiogenic, and antiangiogenic factors and bioactive lipids in preeclampsia

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ABSTRACT

Preeclampsia is a low-grade systemic inflammatory condition in which oxidative stress and endothelial dysfunction occurs. Plasma levels of soluble receptor for vascular endothelial growth factor (VEGFR)-1, also known as sFlt1 (soluble fms-like tyrosine kinase 1), an antiangiogenic factor have been reported to be elevated in preeclampsia. It was reported that pregnant mice deficient in catechol-*O*-methyltransferase (COMT) activity show a preeclampsia-like phenotype due to a deficiency or absence of 2-methoxyoestradiol (2-ME), a natural metabolite of estradiol that is elevated during the third trimester of normal human pregnancy. Additionally, autoantibodies (AT1-AAs) that bind and activate the angiotensin II receptor type 1 a (AT1 receptor) also have a role in preeclampsia. None of these abnormalities are consistently seen in all the patients with preeclampsia and some of them are not specific to pregnancy. Preeclampsia could occur due to an imbalance between pro- and antiangiogenic factors. VEGF, an angiogenic factor, is necessary for the transport of polyunsaturated fatty acids (PUFAs) to endothelial cells. Hence reduced VEGF levels decrease the availability of PUFAs to endothelial cells. This leads to a decrease in the formation of anti-inflammatory and angiogenic factors: lipoxins, resolvins, protectins, and maresins from PUFAs. Lipoxins, resolvins, protectins, maresins, and PUFAs suppress insulin resistance; activation of leukocytes, platelets, and macrophages; production of interleukin-6 and tumor necrosis factor-α; and oxidative stress and endothelial dysfunction; and enhance production of prostacyclin and nitric oxide (NO). Estrogen enhances the formation of lipoxin A_4 and NO. PUFAs also augment the production of NO and inhibit the activity of angiotensin-converting enzyme and antagonize the actions of angiotensin II. Thus, PUFAs can prevent activation of angiotensin II receptor type 1 a (AT1 receptor). Patients with preeclampsia have decreased plasma phospholipid concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), the precursors of lipoxins (from AA), resolvins (from EPA and DHA), and protectins (from DHA) and prostaglandin E_1 (PGE_1 from DGLA: dihomo-γ-linolenic acid) and prostacyclin (PGI_2 derived from AA). Based on these evidences, it is proposed that preeclampsia may occur due to deficiency of PUFAs and their anti-inflammatory products: lipoxins, resolvins, protectins, and maresins.

Introduction

Preeclampsia (PE) is a disorder of pregnancy characterized by hypertension and albuminuria and usually occurs in the third trimester of pregnancy [1]. In severe disease there may be hemolysis, thrombocytopenia, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. PE increases the risk for poor outcomes for both the mother and the baby. If left untreated, PE may result in seizures, at which point it is known as eclampsia. Risk factors for PE include obesity, prior hypertension, older age, and diabetes mellitus and are more frequent in primi (first pregnancy) and in women who are carrying twins. The underlying mechanism involves abnormal formation of blood vessels in the placenta, as well as other factors [1]. Preeclampsia affects between 2% and 8% of

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pregnancies worldwide. Women who have had PE are at increased risk for heart disease later in life.

Of the several factors suggested that could cause preeclampsia; none of which are yet proven to be causative in vivo, the strongest is the soluble receptor for vascular endothelial growth factor (VEGFR)-1, also known as sFlt1 (soluble fms-like tyrosine kinase 1), which binds VEGFs and placental growth factor (PlGF) and deprives systemic endothelium of essential survival factors [2,3]. sFlt1 is antiangiogenic but is not specific to pregnancy nor is it raised in every affected woman [4]. Because preeclampsia affects about 2% to 8% of women and has the potential to kill mother or baby or both, more effective methods of detection, prevention, and therapeutic approaches are urgently needed.

Antiangiogenic molecules in preeclampsia

Trophoblast invasion, fetoplacental vascular development, and maternal vascular remodeling are key events for the formation of the hemochorial placenta in humans. Human placental trophoblasts make direct contact with maternal blood to mediate efficient gas and nutrient exchange between mother and fetus. Failure in the aforementioned key events will compromise placental function and lead to the onset of preeclampsia. Clinical features of preeclampsia include hypertension, proteinuria, endothelial dysfunction (due to the action of proinflammatory cytokines) and placental defects. Advanced-stage clinical symptoms include cerebral hemorrhage, renal failure, and HELLP (hemolysis, elevated liver enzymes, and low platelets). Although the etiologic factors of preeclampsia are currently unknown, shallow trophoblast invasion and poor maternal vascular remodeling have been reported in preeclamptic placentas. These defects impair the development of the fetal–maternal vasculature and result in placental ischemia and hypoxia, which contribute to the pathogenesis of preeclampsia [5]. This is supported by the observation that expression of the antiangiogenic protein soluble Flt-1 (Fms-like tyrosine kinase-1) is elevated, whereas expression of the proangiogenic VEGF and PlGF is decreased in preeclampsia [6–8]. Pregnant women who showed higher ratio between circulating levels of sFlt-1 and PlGF were found to have significantly higher chances of developing preeclampsia [7,8]. This implies that an imbalance between pro- and antiangiogenic factors may contribute to the development of preeclampsia.

VEGF, sFlt1, and endoglin in preeclampsia

It has been reported that sFlt1 is elevated in preeclampsia, which by binding to VEGFs and PlGF decreases systemic endothelium of essential survival factors, implying an important role for VEGF in this condition [6]. Placenta-derived soluble transforming growth factor (TGF)-β co-receptor, endoglin (sEng), which is elevated in the sera of preeclamptic individuals, correlates with disease severity and falls after delivery. sEng inhibited formation of capillary tubes in vitro (using human umbilical vein endothelial cells) and enhanced vascular permeability and induced hypertension in vivo [7]. The actions of sEng are amplified by coadministration of sFlt1, which can result in the development of severe preeclampsia, including the HELLP syndrome, and restrict fetal growth [7,8]. Eng can impair binding of TGF-β1 to its receptors and decrease activation of endothelial nitric oxide synthase (eNOS), which results in impaired peripheral vasodilation and might explain development of the hypertension seen in preeclampsia [7,8]. These results led to the suggestion that sEng may act in concert with sFlt1 to induce severe preeclampsia. It is noteworthy that infusion of anti-VEGF antibody causes hypertension and proteinuria, the typical features of preeclampsia. VEGF participates in the transport of polyunsaturated fatty acids (PUFAs) to endothelial cells [9], implying that reduced VEGF levels may decrease the availability of PUFAs to endothelial cells. It is noteworthy that PUFAs form precursors to potent anti-inflammatory molecules such as lipoxins, resolvins, protectins, and maresins, which have vasodilator, platelet antiaggregator actions, and suppress the production of proinflammatory interleukin (IL)-6 and tumor necrosis factor (TNF)-α and enhance the synthesis of endothelial nitric oxide (eNO). Hence, decreased availability of PUFAs to endothelial cells and other tissues may lead to reduced formation of lipoxins, resolvins, protectins, and maresins. As a result, endothelial dysfunction (due to deficiency of NO that leads to peripheral vasoconstriction), increased production of IL-6 and TNF-α due to the absence of negative feedback regulation exerted by lipoxins, resolvins, protectins, and maresins would occur that ultimately leads to the onset of preeclampsia.

COMT and 2-ME in preeclampsia

However, preeclampsia occurs in some women with low sFlt-1 and high PlGF levels [8,10] suggesting that other factors, which may affect the vasculature, play a role as a result of placental hypoxia in preeclampsia [11,12]. This is supported by the observation that pregnant mice deficient in catechol-*O*-methyltransferase (COMT) show a preeclampsia-like phenotype. COMT deficiency leads to an absence or decrease of 2-methoxyoestradiol (2-ME), a natural metabolite of estradiol, which is normally elevated during the third trimester of normal human pregnancy [13]. Administration of 2-ME ameliorated several of the preeclampsia-like features without toxicity in the $Comt^{-/-}$ pregnant mice. 2-ME suppresses placental hypoxia, hypoxia-inducible factor-1α expression, and sFlt-1 elevation. In pregnant women with preeclampsia, the plasma levels of COMT and 2-ME were reported to be significantly lower [13]. These results imply that plasma levels of 2-ME may be used as a diagnostic marker for preeclampsia. However, the mechanism by which deficiency of 2-ME will lead to the onset of preeclampsia is not known.

Angiotensin-1 receptor in preeclampsia

Women with preeclampsia possess autoantibodies, termed *AT1-AAs*, that bind and activate the angiotensin II receptor type 1 a (AT1 receptor). Several key features of preeclampsia, including hypertension, proteinuria, glomerular endotheliosis (a classical renal lesion of preeclampsia), placental abnormalities, and small fetus size occurred in pregnant mice after injection with either total immunoglobulin (Ig)G or affinity-purified AT1-AAs from women with preeclampsia. These features were prevented by coinjection with losartan, an AT1 receptor antagonist. These results indicate that preeclampsia may be a pregnancy-induced autoimmune disease in which key features of the disease result from autoantibody-induced angiotensin receptor activation [14]. This evidence supports the contention that soluble factors other than sFlt-1 and sEng may have an important role in the pathogenesis of preeclampsia.

It is evident from the preceding discussion that various pathways play key roles in inducing placental disease; these include deficient heme-oxygenase expression [15,16], placental hypoxia, genetic factors, oxidative stress, inflammation, altered natural killer cell signaling, and deficient COMT [6–8,10–13,17–22].

The underlying events, however, that activate the vicious cycle of placental damage and antiangiogenic factor production remain unknown. It is also not clear as to how various mediators identified to play a role in preeclampsia converge on a common pathway, if there is one, to initiate the onset of preeclampsia. Identifying such a common pathway is important to develop relevant preventive and therapeutic strategies in the management of preeclampsia. One such pathway could be the occurrence of deficiency of NO (either absolute or relative) that results in endothelial dysfunction and development of hypertension and insulin resistance (IR) seen in preeclampsia. In this context, I propose that altered metabolism of PUFAs could be the common pathway through which various mediators involved in preeclampsia converge.

Feedback regulation among PUFAs and their metabolites, NO, cytokines, and oxidative stress and its relevance to preeclampsia

Several studies showed that both plasma and cord blood concentrations of PUFAs such as arachidonic acid (AA, 20:4 ω-6), eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3) are reduced in patients with preeclampsia [23–30]. It has been reported that increased formation of platelet aggregator and vasoconstrictor thromboxane A_2 (TXA_2) and decreased levels of prostacyclin (PGI_2), a potent platelet antiaggregator and vasodilator, occurs in preeclampsia [31–37], though not all studies are in support of this contention [32–36]. This implies that TXA_2 and PGI_2 may have a role in some patients with preeclampsia but not all and indicates a role for an altered metabolism of AA in this condition.

In this context, it is noteworthy that AA is metabolized into a variety of products by cyclo-oxygenases, lipoxygenases, and cytochrome P450 enzymes as shown in Figures 1–4. The conversion of dietary essential fatty acid linoleic acid (LA, 18:2 ω-6) to AA depends on the activities of Δ^6 and Δ^5 desaturases and respective elongases [38,39]. Furthermore, for the normal activities of both desaturases, a variety of cofactors are needed that include vitamins, minerals, and hormones [38,39]. This suggests that whenever these cofactors are not available in adequate amounts, a decreased formation of AA and consequently an imbalance in the formation of its metabolites could occur. This is particularly interesting in light of the observation that whenever the plasma or tissue levels of AA are low, the formation of proinflammatory eicosanoids is enhanced, whereas when the stores of AA are adequate, formation of beneficial metabolite such as PGI_2 is preferred. For instance, in children with type 1 diabetes mellitus (DM) mean levels of plasma PGE_2 and $PGF_{2\alpha}$ were high and serum dihomo-γ-linolenic acid (DGLA; 20:3 ω-6) and AA were low, whereas those of plasma thromboxane B_2 (TXB_2) levels were similar to those seen in control [40]. These patients showed increased platelet aggregation, which led to the suggestion that in children with diabetes there could occur a disturbance in the formation of DGLA from its precursor cis-linoleic acid (LA; 18:2 ω-6) leading to a decrease in the formation of prostaglandins of series 1 (e.g., PGE_1), which have platelet antiaggregatory action. Thus, in type 1 DM there is an increase in the formation of PGE_2 and $PGF_{2\alpha}$ despite decreased availability of their precursor AA. A similar scenario is seen in those with inflammatory conditions such as pneumonia, sepsis, and colitis, who have enhanced plasma PGE_2 levels but decreased AA in their plasma phospholipid fraction [41–45]. It is likely that increased PGE_2 formation in instances of AA deficiency is a compensatory mechanism. Further support of this paradoxical relationship between decreased tissue or plasma levels of AA and enhanced formation of PGE_2 is derived from the report that dietary supplementation of AA increased AA content and formation of lipoxin A_4 (LXA_4) but did not enhance PGE_2 formation [45]. These results imply that when plasma and tissue concentrations of AA are normal, more of anti-inflammatory products such as LXA_4 and less proinflammatory PGE_2 are formed.

Additionally, conditions in which oxidative stress is high were also found to be associated with low tissue or plasma concentrations of AA and altered PGE_2 metabolism. For example, increased oxidative stress is seen in DM, hypertension, and coronary heart disease (CHD) [46–54] in which IL-6 and TNF-α and plasma PGE_2 levels are high, whereas plasma and/or tissue AA concentrations are low [40–42,52–68]. These data suggest that IR (which is common in type 2 DM, hypertension, and CHD), type 2 DM, hypertension, and CHD are low-grade systemic inflammatory conditions with altered AA and PGE_2 metabolism [69–74]. Preeclampsia is also characterized by IR [73,74], hypertension, and elevated levels of proinflammatory cytokines [75,76], and incidence of type 2 DM is high in them [77,78]. This indicates that preeclampsia is a disease in which factors that are involved in the pathogenesis of IR, hypertension, type 2 DM, and low-grade systemic inflammation play a significant role. Thus, preeclampsia can be considered a low-grade systemic inflammatory condition characterized by peripheral IR, hypertension, and a prediabetic-like state.

In addition to the increased formation of platelet aggregator and vasoconstrictor TXA_2 and a deficiency of PGI_2 that are derived from AA [31–37], decreased formation and/or action of NO [22,79–82] associated with enhanced oxidative stress, and reduced antioxidants [22,81,82] have also been described in preeclampsia. Decreased NO levels appear to be due to decreased levels of its precursor L-arginine; a deficiency of eNOS enzyme, including its genetic polymorphism; enhanced levels of asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of NO formation; and/or increased activity of arginase [83,84].

VEGF and renin–angiotensin–aldosterone system in preeclampsia

The renin–angiotensin–aldosterone system (RAS) is involved in the regulation of salt, water, and blood pressure (BP). As normal pregnancy is associated with an increase in blood volume without an increase in BP, it is expected that RAS may have a role in preeclampsia. It was reported that in normotensive patients, renin activity, plasma aldosterone, and progesterone concentrations showed consistent and progressive increases from the sixth week of pregnancy, whereas plasma renin activity did not show such a progressive rise. In both hypertensive groups (pregnant patients in whom hypertension became manifest only during pregnancy and patients with chronic hypertension antedating pregnancy), plasma renin activity and aldosterone concentration were significantly suppressed during the last trimester of pregnancy, although both renin substrate and progesterone were not significantly different than those observed in normotensive pregnancy. These results suggest that suppression of renin and plasma aldosterone concentrations in toxemia is not due to a decrease in renin substrate [85].

It was noted that in women with chronic hypertension in whom preeclampsia did not develop, BP decreased and the RAS was stimulated, beginning in the first trimester and continuing throughout pregnancy and plasma estradiol and progesterone levels also increased progressively [86]. On the

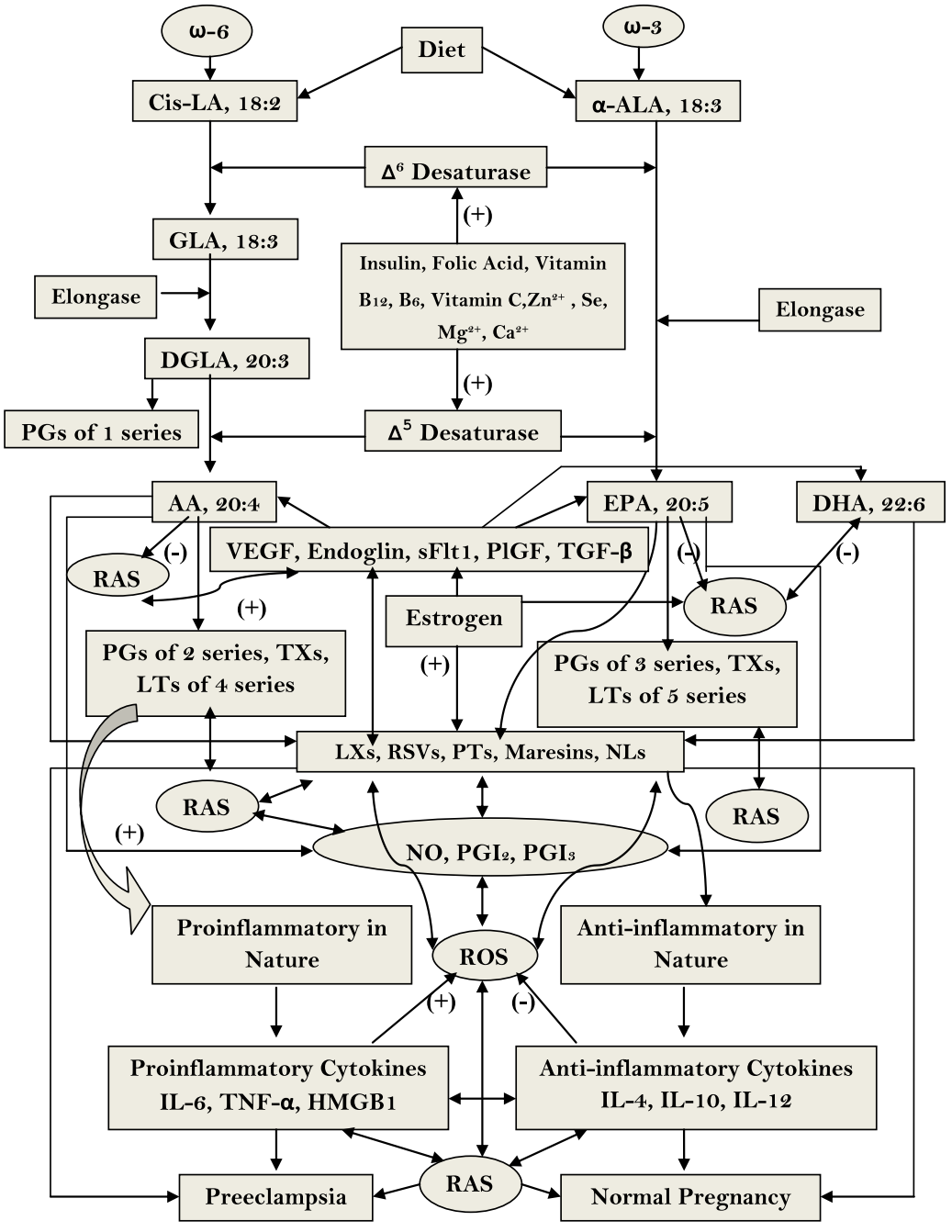

Fig. 1. Scheme showing metabolism of essential fatty acids and their role in preeclampsia. (+) indicates increase in synthesis and/or action; (−) indicates decrease in synthesis and/or action. Dietary EFAs LA, and ALA are converted by Δ^6 and Δ^5 desaturases and elongases to their long-chain metabolites. LA is converted to γ-linolenic acid (GLA, 18:3 ω-6), dihomo-GLA (20:3 ω-6), and AA and ALA to EPA and DHA. Desaturases are the rate-limiting step in the formation of AA, EPA, and DHA. Both desaturases and elongases need several cofactors such as insulin, folic acid, vitamins B_{12}, B_6, and C, zinc, selenium, magnesium, and calcium for their optimum action. Thus, lack or deficiency of these cofactors will lead to reduced formation of GLA, DGLA, AA, EPA, and DHA. Estrogen enhances the formation of lipoxins and possibly, resolvins, protectins and maresins that may explain its anti-inflammatory nature. DHA can be retroconverted to EPA. Lipoxins derived from AA; resolvins formed from EPA and DHA; protectins and maresins formed from DHA have potent anti-inflammatory actions. Unsaturated fatty acids react with NO to form nitrolipids that have potent anti-inflammatory, platelet antiaggregatory, and vasodilator actions. Nitrolipids have short half-life (few seconds to minutes) and can be detected in the blood and urine. AA, EPA, and DHA also give rise to respective prostaglandins, leukotrienes, and thromboxanes that are predominantly proinflammatory in nature. But, both PGE_1 (formed from DGLA) and PGI_2 (from AA) are known to have anti-inflammatory, vasodilator, and platelet antiaggregatory actions. Under normal physiological conditions, a balance is maintained between pro- and anti-inflammatory products of AA/EPA/DHA. When this balance is tilted more toward proinflammatory molecules, it could lead to initiation and progression of inflammatory events. Lipoxins, resolvins, protectins, maresins, and nitrolipids suppress production of IL-6, TNF-α and other pro-inflammatory cytokines and enhance that of anti-inflammatory IL-10. RAS (renin-angiotensin-aldosterone system) has pro-inflammatory actions and enhance IL-6, TNF-α production and free radical generation. NO generation is augmented by AA, EPA, DHA, lipoxins, resolvins, protectins, maresins, and nitrolipids. ROS inactivate NO, and reduce the formation of lipoxins, resolvins, protectins, maresins, and nitrolipids, whereas these bioactive lipids can suppress ROS. VEGF, endoglin, sFlt1, PlGF, and TGF-β also interact with ROS, NO, and PUFAs metabolism. For further details see the text. AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; HMGB1, high-mobility group box 1; IL, interleukin; LA, Linoleic acid; LT, leukotrienes; LXs, lipoxins; NL, nitrolipid; NO, nitric oxide; PG, prostaglandins; PlGF, placental growth factor; PT, protectin; PUFA, polyunsaturated fatty acid; RAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; RSV, resolvin; sFlt1; soluble Fms-like tyrosine kinase-1; TGF, transforming growth factor; TNF, tumor necrosis factor; TX, thromboxanes; VEGF, vascular endothelial growth factor.

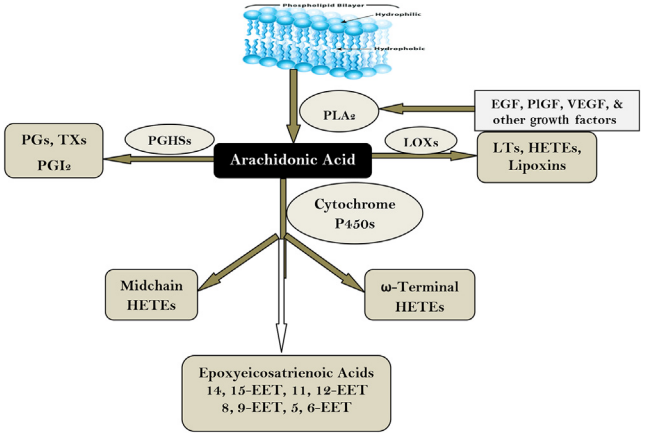

Fig. 2. Metabolism of AA. In response to hormonal stimulation and growth factors (EGF, VEGF, PlGF), phospholipases are activated that induce the release of AA form the cell membrane lipid pool (mainly form phospholipids, PLs). Free AA is then metabolized along three pathways. The PGHS metabolize AA to PGs, TXs, and prostacyclin. The lipoxygenases (LOXs) metabolize AA to leukotrienes, HETEs and lipoxins. The P450 monooxygenases AA to midchain HETEs, ω-terminal HETEs and EETs. Similar products may also be formed form EPA and DHA (see Fig. 4). AA, arachidonic acid; DHA, docosahexaenoic acid; EET, epoxy eicosatrienoic acid; EGF, epidermal growth factor; EPA, eicosapentaenoic acid; HETE, hydroxyeicosatrienoic acid; LOX, lipoxygenase; PG, prostaglandins; PGHS, prostaglandin G/H synthase; PL, phospholipase; PlGF, placental growth factor; P450, cytochrome P450; TX, thromboxane; VEGF, vascular endothelial growth factor.

other hand, in women with chronic hypertension in whom preeclampsia developed, BP decreased and the RAS was stimulated in the first trimester, but as BP began to rise in the second trimester, RAS was stimulated. In the early third trimester, when preeclampsia was diagnosed, plasma renin activity and urine aldosterone excretion decreased. These results have since been confirmed by others [87,88]. Although the exact reason for the low aldosterone levels in preeclampsia is not clear, there is evidence to suggest that part of it could be due to diminished Aldo synthase (CYP11 B2) and methyl-oxidase activities. This compromised methyl-oxidase step of aldosterone synthesis favors extracellular volume depletion that leads to placental hypoperfusion and consecutive development of preeclampsia [89].

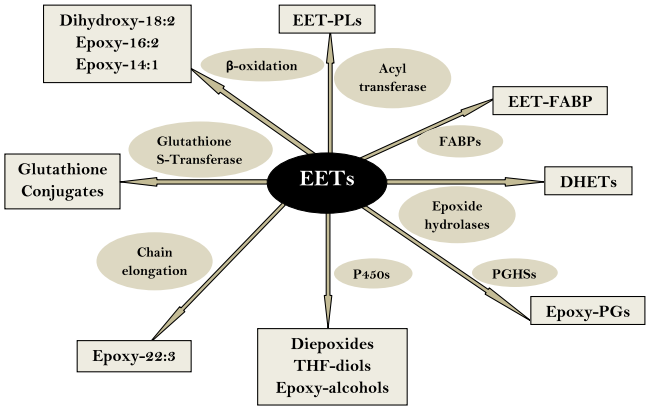

Fig. 3. Scheme showing fate of EETs. Intracellular FABP may bind to EETs and thus, may modulate their metabolism, activities, and/or targeting. FABPs are carriers of PUFAs. DHET, dihydroxyeicosatrienoic acids; EET, epoxy eicosatrienoic acid; FABP, fatty acid binding protein; PG, prostaglandins; PGHS, prostaglandin G/H synthase; PL, phospholipase; PUFA, polyunsaturated fatty acid; P450, cytochrome P450; THF, tetrahydrofurandiols.

In this context, it is interesting to note that reduced circulating aldosterone levels in preeclamptic women [14] were found to be due to the presence of angiotensin II type 1 receptor agonistic autoantibody (AT1-AA) and elevated sFlt1 [90]. In an adoptive transfer animal model of preeclampsia, injection of IgG from women with preeclampsia, but not IgG from normotensive individuals, resulted in hypertension, proteinuria, and a reduction in aldosterone production in pregnant mice that were prevented by coinjection with an epitope peptide that blocks antibody-mediated angiotensin type 1 receptor activation [90]. Thus, maternal circulating autoantibody in preeclamptic women is responsible for decreased aldosterone production via angiotensin type 1 receptor activation in a pregnancy-dependent manner. Furthermore, circulating sFlt1 was induced in autoantibody-injected pregnant mice but not nonpregnant mice and produced vascular impairment in adrenal glands of pregnant mice. Infusion of VEGF attenuated AT1-AA-induced adrenal gland vascular impairment and restored circulating aldosterone to normal. These results suggest that AT1-AA-induced sFlt1 elevation is responsible for decreased aldosterone production in preeclampsia [14,90]. This study also highlights the relationship among VEGF, aldosterone, and AT1-AA and implies that VEGF is crucial to maintain vascular health and regulate aldosterone production. Endothelial cells grown in the presence of VEGF enhanced aldosterone synthase activity in human adrenocortical cells. VEGF either alone or combined with angiotensin II increased aldosterone production in adrenal cells, suggesting that endothelial cell-dependent and independent activation of aldosterone is regulated by VEGF. Furthermore, angiotensin II stimulated both aldosterone and cortisol synthesis, whereas VEGF enhanced only aldosterone production. Overexpression of sFlt1, an endogenous VEGF inhibitor, induced adrenocortical vascular impairment and inhibited aldosterone production that correlated inversely with sFlt1 levels. These findings indicate that enhanced VEGF production, which is essential to augment vascular capacity during gestation, increases aldosterone production during normal pregnancy. This may explain why inappropriately low aldosterone levels occur in preeclampsia despite relatively lower plasma volumes that could be due to high sFlt1 [91–93].

VEGF, RAS, and NO interaction

In this context, it is relevant to note that VEGF stimulates endothelial NO generation and prostacyclin (PGI_2) and, in turn, NO enhances VEGF production [94–100]. Because NO is the ultimate vasodilator that is essential to prevent hypertension [101], and NO deficiency occurs both in hypertension [102] and preeclampsia [103,104], it is important to know the interaction between RAS and NO, which may have relevance to preeclampsia.

It was reported that intravenous administration of L-arginine, the precursor of NO, to healthy men (at the rate of 500 mg/kg over 30 min) decreased mean BP (from 81.2 ± 2.7 to 74.0 ± 2.5 mm Hg; $P < 0.001$) and renal vascular resistance (from 0.085 ± 0.007 to 0.074 ± 0.006 mm Hg·mL·min; $P < 0.01$), increased renal plasma flow (from 616.6 ± 37.8 to 701.0 ± 49.2 mL/min; $P < 0.05$) and reduced serum angiotensin-converting enzyme (ACE) activity (from 10.4 ± 0.6 to 8.9 ± 0.5 nmol·mL·min; $P < 0.05$) and plasma angiotensin-II (from 19.3 ± 3.3 to 12.7 ± 2.8 pg/mL; $P < 0.001$) [105]. One mechanism by which L-arginine decreases BP may be, at least in part, by inhibiting RAS. This is supported by the observation that adenovirus-mediated gene transfer of eNOS in adrenal zona glomerulosa cells decreased the aldosterone synthesis associated with the expression of active eNOS enzyme

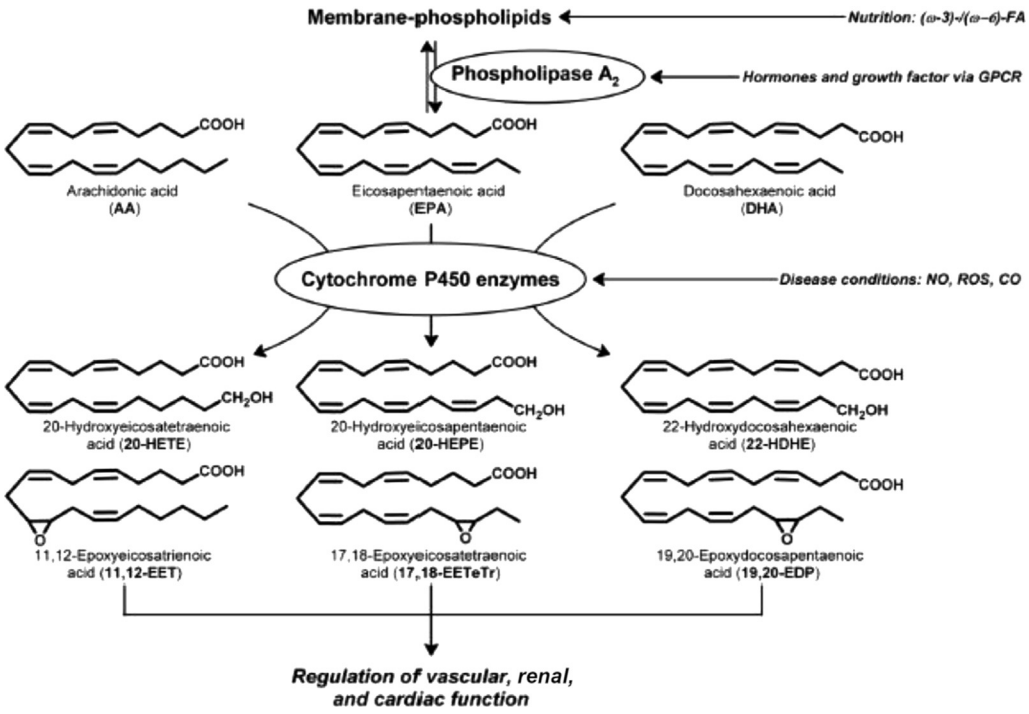

Fig. 4. Generation and function of cytochrome P450-dependent eicosanoids. Once AA, EPA, and DHA are released by phospholipase A2 from the cell membrane lipid pool due to the action of various growth factors (EGF, VEGF, etc.) via GPCRs, they are acted upon by P450 enzymes to form respective epoxy and hydroxy metabolites that have significant actions in the regulation of vascular, renal and cardiac function. P450 enzymes are inhibited by NO, carbon monoxide and ROS. EGF, epidermal growth factor; GPCR, G-protein coupled receptor; NO, nitric oxide; P450, cytochrome P450; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

[106]. These results coupled with the observation that Wistar-Kyoto rats that received continuous intracerebroventricular infusion of aldosterone (5 ng/h) from an implanted osmotic minipump for 4 wk showed significant increase in BP with a significant decrease in the amount of nNOS mRNA in the hypothalamus and rostral and caudal ventrolateral medulla. This indicates that reduced nNOS activity contributes to the increase in BP in rats with central mineralocorticoid-induced hypertension [107]. These results imply that RAS inhibited NO generation and NO, in turn, suppressed ACE activity [108] and reduced the formation of angiotensin II and aldosterone and thus reduced BP. Thus, there exists a feedback regulation between NO and RAS. Hence, to maintain normal BP, a delicate balance between RAS and NO needs to be maintained. In preeclampsia, inappropriately low aldosterone levels occur despite relatively lower plasma volumes [91–93]. This could be an attempt to enhance NO synthesis (since aldosterone inhibits NO synthesis) that fails to occur. This failure on the part of the NO system to respond to low aldosterone levels suggests that there could exist a mediator among VEGF, sFlt1, Eng, COMT, and 2-ME, AT1-AA, RAS, NO, eicosanoids, cytokines, and various other angiogenic factors that play important roles in normal pregnancy and consequently are relevant to preeclampsia. In this context, it is noteworthy that endothelial cell membrane dynamics need consideration.

RAS and endothelial cell dynamics

Aldosterone is a known regulator of cell mechanics and is capable of promoting the expression of epithelial sodium channels (ENaC) and modifies the morphology of endothelial cells in terms of mechanical stiffness, surface area, and volume. Aldosterone can render endothelial cells highly sensitive to changes in extracellular sodium and potassium. Within seconds to minutes of the addition of aldosterone, endothelial cells showed transient swelling, softening, and insertion of ENaC in the apical plasma membrane and in parallel, NO was released from the cells. On the other hand, aldosterone produced opposite effects on long-term (h) exposure to endothelial cells in the form of an increase in the mechanical stiffness, decrease in the volume of the cells, and NO production. This implies that aldosterone, at physiologically relevant concentrations and for a short period of time stabilizes BP and regulates tissue perfusion, whereas chronically high concentrations over extended time periods may impair sodium homeostasis and promote endothelial dysfunction [109]—a set of events that could occur in preeclampsia. It is likely that low aldosterone levels seen in preeclampsia could be yet another futile attempt to enhance NO synthesis. Furthermore, it was reported that nanomechanic properties of vascular endothelial cells determine NO release, indicating that even minor changes in cell membrane fluidity could alter NOS activity [110]. C-reactive protein renders endothelial cells stiff and in the presence of aldosterone this stiffness is further enhanced leading to significant reduction in NO generation [111]. Thus, when endothelial cells are more fluid, NOS activity will be high, whereas stiff cell membranes suppressed NOS. PUFAs are important constituents of cell membrane and determine their fluidity. Hence, it is conceivable that cell membrane PUFA content determines NOS activity and response of endothelial cells to RAS. It is important to note that both angiotensin II and aldosterone have proinflammatory actions [112–115], and angiotensin II induces vascular expression of VEGF [116] that also has proinflammatory actions [117–119], whereas PUFAs and some of their metabolites have potent anti-inflammatory action [38,39,120–123]. This indicates that PUFAs and their altered metabolism and metabolites can modulate the action/role of VEGF, sFlt1, Eng, COMT and 2-ME, AT1-AA, RAS, NO, cytokines,

and various other angiogenic and antiangiogenic factors in preeclampsia.

PUFAs and their metabolites in preeclampsia

It is evident from the preceding discussion that patients with preeclampsia have the following:

- elevated plasma levels of proinflammatory cytokines IL-6 and TNF-α [73–78,124–126];
- diminished immunostaining of IL-10, an anti-inflammatory cytokine, in villous trophoblast compared with normal pregnant villous trophoblast [21];
- IR [73,74];
- decreased amounts of vasodilator PGI_2, and relatively enhanced TXA_2, a physiological antagonist of PGI_2 [31–36, 127–129];
- decreased NO generation [22,79–84]; sometimes produced increased amounts of NO but is not adequate to induce much needed vasodilation;
- enhanced oxidative stress [17–19,28];
- inappropriate activation of leukocytes, platelets, and macrophages [18,19] and deficiency of antioxidants [22];
- decreased angiogenic VEGF, PlGF, and enhanced antiangiogenic sFlt-1 and Eng factors [7,8]; and decreased heme-oxygenase [15,16];
- deficiency of COMT activity, which results in absence or decrease of 2-ME, a natural metabolite of estradiol [12,13];
- enhanced levels of autoantibodies AT1-AAs that bind and activate the angiotensin II receptor type 1 a (AT1 receptor) [14]; and
- decreased levels of AA, EPA, and/or DHA in the plasma phospholipid fraction, red blood cell (RBC) membrane, placental tissue, and umbilical vessels [23–30].

indicating that several complex biochemical events occur in this important clinical condition.

How can the role of these apparently disparate factors in preeclampsia be reconciled to form a uniform and logical hypothesis that could form the basis of newer diagnostic, therapeutic, and prognostic platform?

Hypothesis: A deficiency of lipoxins, resolvins, protectins, maresins, and nitrolipids may be responsible for the initiation and progression of preeclampsia

I propose that a deficiency of LXA_4 and its congeners resolvins, protectins, maresins, and nitrolipids that have potent anti-inflammatory, vasodilator, and insulin-sensitizing actions [130–132] may initiate and perpetuate pathobiology of preeclampsia. Lipoxins (including LXA_4), resolvins, protectins, maresins, and nitrolipids are potent antioxidants [39,133–135]; regulate the formation of VEGF [136]; prevent platelet aggregation; have vasodilator actions; and suppress production of IL-6 and TNF-α and thus, suppress inflammation [39,121–123,136–138]. Placenta, endometrium, decidua tissue to glandular epithelial cells, and cells within the stromal compartment, including cells lining the blood vessels and immune cells, and human extravillous trophoblast cells are capable of producing lipoxins and other products [139]. Hence, it is proposed that a deficiency of PUFAs, especially that of AA, EPA, and DHA, may lead to reduced formation of lipoxins, resolvins, protectins, maresins, and nitrolipids, which leads to endothelial dysfunction, inflammation, hypertension, and intrauterine growth retardation (IUGR) of the fetus seen in preeclampsia.

Placenta-derived soluble TGF-β co-receptor, sEng, which is elevated in the sera of preeclamptic individuals, correlated with disease severity, has the ability to induce vascular permeability and hypertension and plays a significant role in preeclampsia [7,8]. Eng interferes with the binding of TGF-β1 to its receptors and reduces the formation of NO, which may explain peripheral vasoconstriction and hypertension seen in preeclampsia [7,8]. TGF-β interacts with LXA_4 [140,141] and is both an inducer and inhibitor of NO generation [142–146], depending on the cell type and the stimulus used and, in turn, NO modulates TGF-α production [147] indicating feedback regulation among TGF-α, NO, and LXA_4 (LXA_4 enhances NO generation) molecules. Similar to the interaction between TGF-β and NO, VEGF enhances NO generation [99,100] and NO, in turn regulates VEGF production [95,96,98], suggesting that both TGF-β and VEGF bring about their actions by modulating NO synthesis and action. Both LXA_4 and resolvin D_1 are not only anti-inflammatory molecules but also suppress the production and action of TGF-β [140,141] and VEGF [148–151], yet they enhance the formation of NO (unlike sEng, which inhibits NO formation). This implies that a close interaction exists among TGF-β, VEGF, NO, and LXA_4, resolvins, protectins, and nitrolipids. TGF-β and VEGF also play a role in inflammation—TGF-β is an anti-inflammatory molecule [152], whereas VEGF has proinflammatory actions [153] and NO has both pro- and anti-inflammatory actions (excess may augment inflammation as it happens during the activation of iNOS, whereas physiological concentrations produced by eNOS has anti-inflammatory properties) [154,155]. These results suggest that interaction(s) among these molecules is aimed at suppressing inappropriate inflammation and restore homeostasis. Hence, it is suggested that when production of lipoxins, resolvins, protectins, and nitrolipids are adequate, especially in response to demands of pregnancy when blood volume expansion occurs, vasodilator response tends to be optimal so that hypertension will not occur. Additionally, inflammatory and immunologic events that are triggered by the invasion of extravillous trophoblast cell types into maternal uterine tissues that is essential for successful human placental development and progression of pregnancy; migration of endovascular trophoblasts into the maternal spiral arteries, invasion of interstitial trophoblasts into the decidual stroma; and colonization of the vessels that communicate with diverse uterine cell types such as decidual stromal cells, macrophages, and uterine natural killer cells [155] will be optimally regulated if the production of lipoxins, resolvins, protectins, maresins, and nitrolipids are adequate. In the event the synthesis and release of these bioactive lipids is inadequate, it would lead to hypoxic conditions due to suboptimal vasodilation of placental vessels that are likely to initiate preeclampsia.

Testing the hypothesis

This proposal can be verified by measuring plasma levels of various PUFAs (especially AA, EPA, and DHA), lipoxins, resolvins, protectins, nitrolipids, cytokines, VEGF, Eng, and TGF-β and correlating them to the initiation and progression of preeclampsia and fetal growth and development. It is predicted that plasma levels of lipoxins, resolvins, protectins, maresins, and nitrolipids will be low in patients with preeclampsia and could be correlated with the degree and severity of the disease. Serial measurement of plasma levels of lipoxins, resolvins, protectins, maresins, and nitrolipids from the initial stages of pregnancy

until parturition in both normal and those who are at high-risk of preeclampsia will give an indication as to when preeclampsia is initiated. For instance, the first dip in the plasma concentrations of lipoxins, resolvins, protectins, maresins, and nitrolipids (all may be altered or only LXA_4 may show a decrease) in comparison to those who have normal pregnancy will give an indication as to when preeclampsia is initiated. It is possible to measure lipoxins, resolvins, protectins, maresins, and nitrolipids in urine [156–158]. It will be interesting to study plasma and urinary levels of lipoxins, resolvins, protectins, maresins, and nitrolipids in patients with preeclampsia who responded to the conventional therapy (such as magnesium sulfate infusion) to know whether their recovery is due to enhancement in the production of these bioactive lipids.

In cell culture studies, the ability of normal and preeclamptic trophoblasts, decidual cells, vascular endothelial cells, macrophages, natural killer cells, uterine, and placental tissue to produce lipoxins, resolvins, protectins, maresins, and nitrolipids need to be studied to note any differences in their synthesis. It is possible that their lower levels in preeclampsia could be due to altered activities of Δ^6 and Δ^5 desaturases (that are needed for the formation of GLA, DGLA, AA, EPA, and DHA from their respective precursors; see Figure 1 for metabolism of essential fatty acids) cyclooxygenase 1 and 2 and 5-, 12- and 15-lipoxygenases and phospholipases [159–163] and specific genetic polymorphism(s) in these enzymes that predisposes some women to preeclampsia. It is relevant to know whether VEGF, TGF-β, Eng, sFlt1, and AT1-AAs alter the synthesis and action of lipoxins, resolvins, protectins, maresins, and nitrolipids, PGI_2, PGI_3, thromboxanes, leukotrienes, and vice versa. It is possible that some patients with preeclampsia may have normal plasma and tissue concentrations of AA, EPA, and DHA yet are unable to form adequate amounts of lipoxins, resolvins, protectins, maresins, nitrolipids, PGI_2, and PGI_3 due to defects in the expression and activity of cyclooxygenases and lipoxygenases. On the other hand, low plasma and tissue concentrations of AA, EPA, and DHA could be due to a defect in the activities of Δ^6 and Δ^5 desaturases. Based on the preceding discussion, it is predicted that Eng, sFlt1, and AT1-AAs inhibit, whereas VEGF and TGF-β enhance the formation of lipoxins, resolvins, protectins, maresins, PGI_2, and PGI_3.

Conclusions

It is evident from the preceding discussion that preeclampsia is not only a low-grade systemic inflammatory condition but also characterized by peripheral IR, hypertension, and a prediabetic-like state (Fig. 5). Patients with preeclampsia have increased plasma levels of proinflammatory cytokines (especially IL-6 and TNF-α), reactive oxygen species, Eng, sFlt-1, thromboxanes, and other proinflammatory eicosanoids and AT1-AAs and decreased PUFAs (especially AA, EPA, and DHA), VEGF, PlGF, 2-ME, NO (or its activity), PGI_2, PGI_3, and possibly of lipoxins, resolvins, protectins, maresins, and nitrolipids.

It is noteworthy that magnesium, one of the sheet anchors in the treatment of preeclampsia [164–168], enhances activity of delta desaturases [169–171] that are essential for the formation of AA, EPA, and DHA from dietary essential fatty acids: linoleic acid and α-linolenic acid (see Fig. 1); estrogen [139] is an inducer of the formation of LXA_4; PUFAs [172,173] and LXA_4 enhance the formation of NO [174–176], whose deficiency and/or decreased action is known to occur in preeclampsia [103]. Both Eng and sFlt-1 augment NO deficiency [104,177]. Furthermore, lipoxins inhibited proliferation of macrophages and secretion of TNF-α in preeclampsia in a dose-dependent manner [178]; lipoxin A_4 suppressed IL-1β production of monocytes from severe preeclampsia women by inhibiting extracellular calcium influx [179]; aspirin-triggered lipoxin A_4 (ATL) reduced human polymorphonuclear (PMN)–endothelial cell adhesion when human PMN were incubated with ATL before addition to endothelial monolayers [180]; and BML-111 (synthetic analogue of LXA_4) effectively alleviated experimental preeclampsia induced by low-dose endotoxin (LPS) in rats and inhibited LPS-triggered apoptosis, activation of NF-κB, TNF-α, and IL-8 mRNA, and protein expression in human extravillous trophoblast (TEV-1) cells [181]. These evidences suggest that PUFAs, lipoxins, and resolvins (and also for protectins, maresins, and nitrolipids, which have actions similar to lipoxins and resolvins) have an important role in preeclampsia in view of their vasodilator, anti-inflammatory, and immunosuppressive actions (Figs. 1–5).

One possibility that needs to be considered is the metabolites of AA, EPA, and DHA that are formed due to the action of cytochrome P450 enzymes to form epoxy- and hydroxy-metabolites that have potent vascular actions [182]. These metabolites (epoxyeicosatrienoic acids [EETs] and dihydroxyeicosatrienoic acids [DHETs], see Figs. 2–4) formed from AA, EPA, and DHA can be detected in human urine using negative ion and chemical ionization gas chromatography–mass spectrometry methods. It was reported that urinary excretion of 8,9- and 11,12-DHET increased in healthy pregnant women compared with nonpregnant females. On the other hand, excretion of 11,12-DHET and 14,15-DHET, but not the 8,9-DHET regioisomer, was increased in patients with pregnancy-induced hypertension compared with normal pregnant women. These evidences suggest that P450 metabolites of AA, EPA, and DHA are formed in humans and may contribute to the physiological response to normal pregnancy and the pathophysiology of pregnancy-induced hypertension and preeclampsia (Figs. 2–4) [183].

Because PUFAs, lipoxins, resolvins, protectins, maresins, nitrolipids, EETs, DHETs, PGs, LTs, and TXs have a regulatory role in inflammation, immune response, vascular diameter, and the modulation of oxidative stress, it is likely that these bioactive lipid molecules could be exploited both as biomarkers of preeclampsia and as a pharmaceutical target for drug development. PUFAs, lipoxins, resolvins, protectins, maresins, and nitrolipids are also capable of protecting normal cells and tissues from various pathologic insults as noted in our recent studies [184–186; and Das UN. unpublished data] and thus, are capable of maintaining the histologic cellular organization of placenta, endothelial cells and may prevent IUGR [39,170].

Further support of the concept proposed here is derived from previous work [184] that showed that plasma EET is higher in normotensive and preeclamptic women than in nonpregnant controls and correlate with RBC EETs, C-reactive protein, and arterial stiffness. Renal production of EETs, measured as urinary DHETs, was reduced in preeclamptic compared with normotensive pregnancies. EETs are three-to fivefold greater in fetoplacental than in maternal circulation. These results suggest that EETs may modulate systemic and fetoplacental hemodynamics in normal and preeclamptic pregnancies. Decreased renal EET generation may be associated with the development of maternal renal dysfunction and hypertension in preeclampsia. Additionally, a significant increase in IL-6, IL-8, TNF-α, IFN-γ, endothelin-1, malondialdehyde, and 8-iso-protaglandin F2α occurred on hypoxic treatment of the dual placental perfusion system as a model for preeclampsia [185]. These results support the contention that preeclampsia is an inflammatory condition and

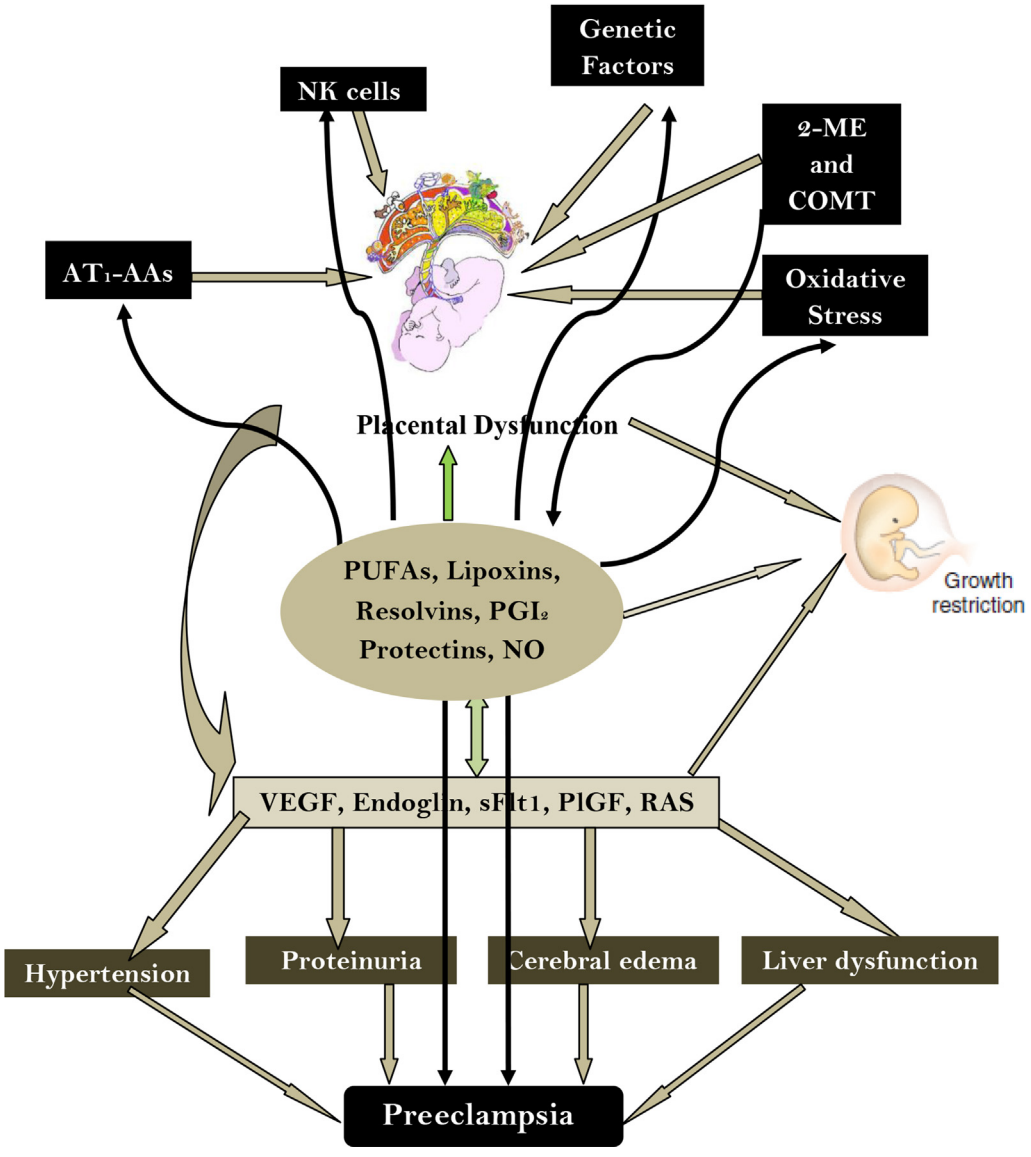

Fig. 5. Scheme showing the role of various factors in the pathophysiology of preeclampsia and their relationship to PUFAs, lipoxins, resolvins, and protectins. AA, arachidonic acid; AT_1, angiotensin II receptor type 1; COMT, catechol-*O*-methyltransferase; NK, natural killer; NO, nitric oxide; PUFAs, polyunsaturated fatty acid; PGI, prostaglandin I; PlGF, placental growth factor; RAS, renin–angiotensin–aldosterone system; 2-ME, 2-methoxyoestradiol.

oxidative stress occurs in these patients. On the other hand, it has been noted that formyl peptide receptor-2/ALX (FPR2 also known as ALX that serves as a receptor for LXA_4) and LXA_4 and its biosynthetic enzymes were decreased in women with pre-eclampsia, while replenishing LXA_4 improved the symptoms of lipopolysaccharide-induced preeclampsia in rats, while blocking LXA_4 signaling resulted in features of preeclampsia [187]. It was also noted that LXA_4 significantly reduced IL-6, TNF-α, and IFN-γ but increased IL-10, an anti-inflammatory cytokine and LXA_4 upregulated 11 β-hydroxysteroid dehydrogenase (HSD)-2 enzyme activity. Placental 11 β-HSD2 is reduced in pregnancies complicated with IUGR such as preeclampsia. Placental 11 β-HSD2 serves as a functional barrier to protect the fetus from excessive exposure to high levels of maternal cortisol [186]. Thus, LXA_4 by enhancing the activity of 11 β-HSD2 is able to reduce the exposure of fetus to maternal cortisol and prevent IUGR, one of the complications of preeclampsia. These evidences [184–187] strongly support the concept proposed here that an altered metabolism of PUFAs and a deficiency of lipoxins, resolvins, protectins, maresins, and nitrolipids may have a role in the pathogenesis of preeclampsia and implies that administration of PUFAs, lipoxins, resolvins, protectins, maresins, and nitrolipids by themselves or their more stable synthetic analogs may prevent, ameliorate and reverse preeclampsia.

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