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Review

Arachidonic acid in health and disease with focus on hypertension and diabetes mellitus: A review

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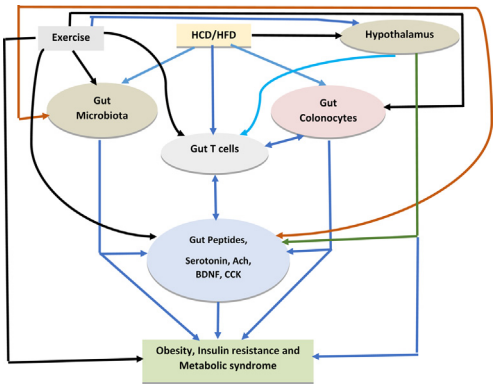
GRAPHICAL ABSTRACT



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ABSTRACT

Arachidonic acid (AA 20:4n-6) is an essential component of cell membranes and modulates cell membrane fluidity. AA is metabolized by cyclo-oxygenase (COX), lipoxygenase (LOX) and cytochrome P450 enzymes to form several metabolites that have important biological actions. Of all the actions, role of AA in the regulation of blood pressure and its ability to prevent both type 1 and type 2 diabetes mellitus seems to be interesting. Studies showed that AA and its metabolites especially, lipoxin A4 (LXA4) and epoxyeicosatrienoic acids (EETs), potent anti-inflammatory metabolites, have a crucial role in the pathobiology of hypertension and diabetes mellitus. AA, LXA4 and EETs regulate smooth muscle function and proliferation, voltage gated ion channels, cell membrane fluidity, membrane receptors, G-coupled receptors, PPARs, free radical generation, nitric oxide formation, inflammation, and immune responses that, in turn, participate in the regulation blood pressure and pathogenesis of diabetes mellitus. In this review, role of AA and its metabolites LXA4 and EETs in the pathobiology of hypertension, pre-eclampsia and diabetes mellitus are discussed. Based on several lines of evidences, it is proposed that a combination of aspirin and AA could be of benefit in the prevention and management of hypertension, pre-eclampsia and diabetes mellitus.

Introduction

Arachidonic acid (AA, 20:4n-6) is one of the important polyunsaturated fatty acids (PUFAs) that forms an important constituent

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of cell membranes. It is available in very small amounts in human diet. Human milk contains significant amounts and cow's milk small amounts of AA. Meat, egg yolks, some seaweeds, and some shrimps also contain AA. Average daily intake of AA is in the region of 50–300 mg/day that accounts for the total daily production of various prostaglandins (PGs), which is estimated to be about 1 mg/day [1]. Even though AA is present in human diet, it is likely that it is insufficient for our body needs since most, if not all, of it may be destroyed or degraded during storing, cooking and other processes. It is estimated that more than 90% of AA may be inactivated in these processes though, precise estimation is not available. In view of this our tissues depend on endogenous formation of AA from its precursor linoleic acid (LA 18:2n-6), an essential fatty acid (EFA). It should be noted here that there are two EFAs, LA and alpha-linolenic acid (ALA, 18; 3n-3). Both LA and ALA are widely distributed in our diet and hence, their deficiency is unlikely. Even though LA and ALA are essential for life, some, if not all, of their actions are brought about by their metabolites namely long-chain metabolites such as gamma-linolenic acid (GLA, 18:3n-6), di-homo-GLA (DGLA, 20:3n-6) and AA from LA and eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) from ALA. The formation of GLA, DGLA and AA from LA and EPA and DHA from ALA are regulated by the actions of enzymes desaturases and elongases as shown in Fig. 1. It is noteworthy that DGLA, AA and EPA and DHA are further metabolized to form a variety of metabolites by the actions of COX-1, COX-2 and LOX enzymes as described below.

Metabolism of EFAs

EFAs are polyunsaturated fatty acids (PUFAs) since they contain two or more double bonds. There are at least four independent families of PUFAs. They include:

The "ω-3" series derived from α-linolenic acid (ALA, 18:3, ω-3).
The "ω-6" series derived from *cis*-linoleic acid (LA, 18:2, ω-6).
The "ω-9" series derived from oleic acid (OA, 18:1, ω-9).
The "ω-7" series derived from palmitoleic acid (PA, 16:1, ω-7).

Both LA and ALA are converted to their respective long-chain fatty acids by the action of enzymes: Δ^6 and Δ^5 desaturases (d-5-d). Thus, LA is converted to gamma-linolenic acid (GLA, 18:3), dihomo-GLA (DGLA, 20:3) and AA (20:4) whereas ALA is converted to form eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6) respectively. DGLA forms precursor to 1 series prostaglandins whereas AA forms the precursor of 2 series of PGs, thromboxanes (TXs) and the 4 series of leukotrienes (LTs) and anti-inflammatory compounds: lipoxins. EPA derived from

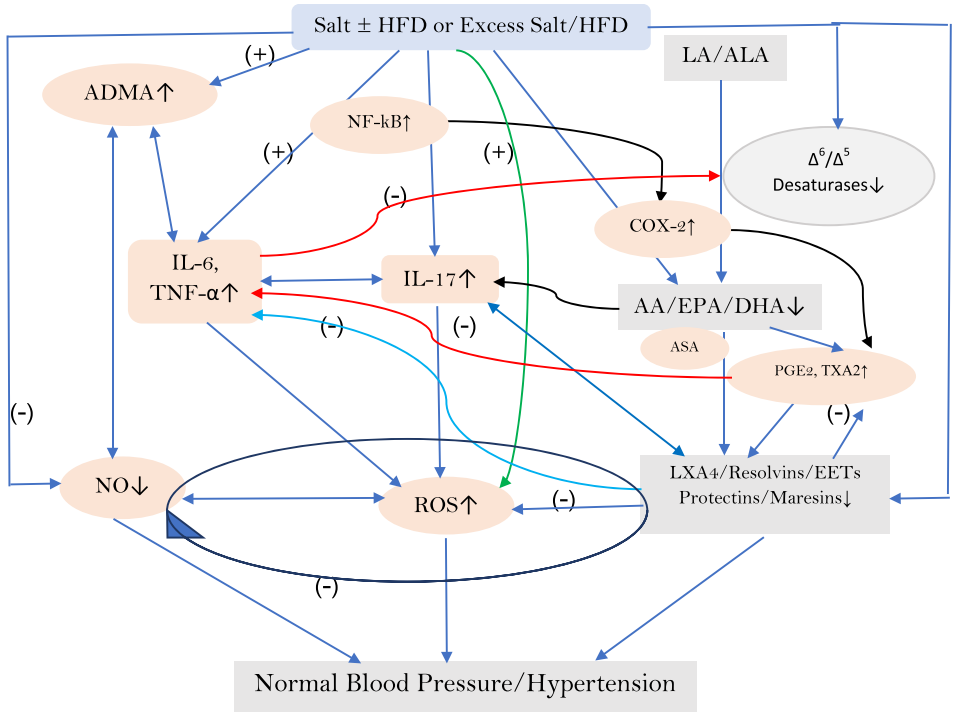

Fig. 1. Scheme showing possible interaction(s) among various factors involved in the pathobiology of blood pressure maintenance and development of hypertension. (+) indicates enhancement of action/synthesis; (−) indicates decrease in synthesis/action. ASA = Aspirin. Aspirin is known to enhance the formation of LXA4, resolvins, protectins and maresins from their respective precursors. Legend to Fig. 1: High fat diet (HFD)/excess salt intake enhances pro-inflammatory cytokines IL-17, IL-6 and TNF-α production (by enhancing NF-kB expression) that may enhance ROS (reactive oxygen species) generation. ROS inactivates eNO production. HFD/excess salt intake also enhances ADMA formation that interferes with eNO production. IL-6 and TNF-α decrease activity of desaturases resulting in decreased conversion of dietary LA/ALA to AA/EPA/DHA, the precursors of LXA4/resolvins/protectins/maresins that enhance NO and decrease ROS generation and block IL-6, TNF-α and IL-17 formation and action. Thus, patients with HTN have low plasma NO, AA/EPA/DHA and LXA4/resolvins/protectins/maresins and higher concentrations of ADMA, ROS/lipid peroxides, IL-17/IL-6/TNF-α and decrease in the activity of Δ^6 and Δ^5 desaturases. Paradoxically, whenever there is deficiency of AA, production of PGE2 is increased (HFD/excess salt enhance COX-2 expression either directly or as a result of NF-kB activation), a pro-inflammatory molecule that can decrease IL-6 and TNF-α production as a feed-back regulatory evet but seldom is able to suppress inflammation [2–5]. Some studies suggested that under some very specific conditions, PGE2 may have anti-inflammatory actions and enhances tissue repair by augmenting the formation of LXA4 and 15-PGDH–deficient mice display a twofold increase in PGE2 levels across multiple tissues—including bone marrow, colon, and liver—and that they show increased fitness of these tissues in response to damage. Thus, PGE2 has many actions and may have both pro- and anti-inflammatory actions. Genetic polymorphisms of desaturases, COX-1 and COX-2 and 5-, 12-, 15-lipoxygenases (LOX) may also lead to decreased formation of AA/EPA/DHA/LXA4/resolvins/protectins/maresins and modulate development of HTN. Co-factors needed for optimal activity of desaturases and elongases are important for adequate formation of AA/EPA/DHA and hence, their deficiency may also have a role in the pathogenesis of HTN. Salt intake may also reduce the production of EETs that have vasodilator and anti-hypertensive function. EETs are derived from AA by the action of cytochrome P450 enzymes (soluble epoxide hydrolase). It is possible that EETs may interact with lipoxins. Resolvins, protectins, maresins.

ALA forms the precursor to 3 series of PGs, TXs and the 5 series of LTs and anti-inflammatory compounds: resolvins. EPA can be elongated to form DHA, the precursor of anti-inflammatory compounds: resolvins, protectins and maresins. LA, GLA, DGLA, AA, ALA, EPA, and DHA are all PUFAs, but only LA and ALA are EFAs. In general, PGs, TXs, and LTs formed from AA and EPA have pro-inflammatory actions (though eicosanoids derived from EPA are much less pro-inflammatory in nature compared to those formed from AA) and play a significant role in atherosclerosis, asthma, inflammatory bowel disease, rheumatoid arthritis, lupus, sepsis, cancer, etc. Although the terms EFAs and PUFAs are used interchangeably, all EFAs are PUFAs but all PUFAs are not EFAs. Many actions of EFAs can also be brought about by PUFAs. Thus, EFA-deficiency can be corrected by PUFAs, and hence, PUFAs can also be termed as "functional EFAs" [6,7].

The exact mechanism(s) involved in the preferential release of AA, EPA, and/or DHA from the cell membrane lipid pool and their subsequent conversion to their respective specific products is not known. For instance, it is not clear how a cell decides to convert AA to PGs, LTs or TXs and/or LXA4 is not well understood. Since, AA, EPA, and DHA give rise to both pro-inflammatory (PGs, LTs and TXs) and anti-inflammatory compounds (lipoxins, resolvins, protectins, maresins, and nitrolipids) it is reasonable to propose that the balance between these mutually antagonistic compounds plays a significant role in the initiation, progression and/or reversal of a disease process. Biologically active nitrolipids such as nitrolinoleate (formed due to the nitration of linoleate by nitric oxide) are known to stimulate smooth muscle relaxation, inhibit platelet aggregation, and suppress human neutrophil pro-inflammatory functions [8–12]. Thus, PUFAs and their metabolites play a significant role in several diseases.

Since LA, ALA, and OA are metabolized by the same set of desaturases and elongases, these 3 series compete with one another for the same set of enzymes. It is generally believed that enzymes (desaturases and elongases) prefer ω-3 to ω-6 and ω-6 over ω-9 (ω-3 > ω-6 > ω-9). Presence of significant amounts of 20:3 ω-9 indicates that there is deficiency of ω-3 and ω-6 fatty acids and so its presence can be used as an indication of EFA deficiency. The activities of Δ^6 and Δ^5 desaturases are low in humans ($\Delta^5 > \Delta^6$) and hence, the conversion of LA and ALA to their respective metabolites may be inadequate in conditions such as atherosclerosis. It is recommended that the intake of ω-6 to ω-3 fatty acids need to be maintained ~1:1 while the Western diet is believed to be around 10:1 (ω-6 to ω-3 ratio is 10:1).

PLA2 can be activated by various hormones and growth factors via G-protein coupled receptors (GPCRs). The released free AA, EPA and DHA, are acted upon by cyclo-oxygenases, lipoxygenases and cytochrome P450 enzymes to form their respective metabolites. P450 enzymes function as hydroxylases or epoxygenases. Cytochrome P450 enzymes are inhibited by nitric oxide (NO), carbon monoxide (CO) and reactive oxygen species (ROS), which are produced in variable amounts during inflammation and other diseases by leukocytes, monocytes, macrophages and other cells. Products formed from AA, EPA and DHA by the action of cytochrome P450 function as second messengers in various signalling pathways and regulate vascular, renal and cardiac function.

It is highly likely that there exists a balance between pro-inflammatory and anti-inflammatory products formed from AA. For instance, many prostaglandins leukotrienes and thromboxanes have pro-inflammatory actions whereas LXA4, PGI2 (prostacyclin) and PGJ eicosanoids are anti-inflammatory in nature. Thus, it is anticipated that under normal physiological conditions a balance is maintained among these pro- and anti-inflammatory products to maintain homeostasis and prevent inappropriate inflammation. This implies that when this balance is tilted more towards pro-inflammatory products, initiation and perpetuation of inflammation may occur. It is highly likely that inflammation may be initiated and perpetuated not simply because pro-inflammatory metabolites are synthesized and released in excess amounts but also because adequate amounts of anti-inflammatory metabolites that suppress inflammation and induce resolution of inflammation from AA, EPA and DHA are not formed in adequate amounts. Thus, ultimately it is the balance between pro- and anti-inflammatory metabolites that determines the persistence of inflammation or its resolution. This is supported by the observation that in obesity, type 2 diabetes mellitus, hypertension, coronary heart disease, non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease, depression, schizophrenia, and ageing the plasma and specific tissue AA content of phospholipid fraction is low. Because of this, formation of anti-inflammatory LXA4 (lipoxin A4) is not formed in sufficient amounts and hence, inflammation persists. It is noteworthy that anti-inflammatory products such as LXA4, resolvins, protectins and maresins inhibit formation of pro-inflammatory prostaglandins (PGs), leukotrienes (LTs) and thromboxanes (TXs). This feed-back regulation between pro and anti-inflammatory products is crucial to regulate inflammation and inflammation-associated diseases. In general, it is assumed that prostaglandins, leukotrienes and thromboxanes formed from EPA are considered as anti-inflammatory, But, it is emphasized here that this is not true and it needs to be understood that 3 series of PGs, TXs and 4 series of LTs formed from EPA are, in fact, pro-inflammatory in nature except that they are relatively weak pro-inflammatory compounds compared to 2 series of PGs, TXs and 4 series LTs derived from AA.

Modulators of desaturases and elongases

Several factors are known to modulate the activities of desaturases and elongases that may result either in normal or decrease in their action. As a result of this, the formation of metabolites of dietary LA and ALA may vary. Some of the factors that can influence the activities of desaturases and elongases are saturated fats, cholesterol, trans-fatty acids, alcohol, adrenaline, and glucocorticoids that are known to inhibit the activities of Δ^6 and Δ^5 desaturases [1,6]. On the other hand, pyridoxine, zinc, nicotinic acid, and magnesium are regarded as co-factors that are essential for normal Δ^6 desaturase activity. Another important factor that activates Δ^6 desaturase is insulin. Hence, in condition wherein insulin levels are low or insulin resistance is present could result in decreased activity of Δ^6 desaturase. This could be one of the reasons as to why diabetics have low activity of Δ^6 desaturase and this results in decrease plasma and tissue levels of GLA, DGLA, AA, EPA and DHA. Of all the metabolites, AA is an important fatty acid that has anti-diabetic action and hence, normal activity of Δ^6 desaturase is needed to maintain normal plasma and tissue levels of AA. Furthermore, AA is the precursor of LXA4, a potent anti-inflammatory molecule. Our recent studies revealed that both AA and LXA4 have anti-diabetic actions as discussed below. It is known that the activity of Δ^6 desaturase falls with age that may explain decreased levels of plasma and tissue AA content. Other factors that inhibit Δ^6 desaturase activity are oncogenic viruses and radiation. The suppressive action of oncogenic viruses on Δ^6 desaturase activity may explain as to why cancer cells have low content of GLA, AA, EPA and DHA. In addition, total fasting, protein deficiency, and a glucose-rich diet reduce, whereas fat-free diet and partial caloric restriction enhance Δ^6 desaturase activity. It is known that Δ^6 and Δ^5 desaturases are regulated by sterol regulatory element binding protein-1 (SREBP-1) and peroxisome proliferator-activated receptor-α (PPAR-α), which may explain the ability of various PUFAs to reduce plasma cholesterol, triglycerides and their lipogenic actions [13]. Alternatively, the lipogenic

functions of SREBP-1 and PPAR-α may be ascribed to their interaction with PUFAs.

Both type 1 and type 2 diabetes mellitus, essential hypertension, dyslipidemia and metabolic syndrome are associated with decreased activities of Δ^6 and Δ^5 desaturases that may explain low circulating and tissue levels of GLA, DGLA, AA, EPA and DHA. Trans-fatty acids are known to interfere with the metabolism of EFAs, promote pro-inflammatory status, atherosclerosis and coronary heart disease [6,7,14]. EPA and DHA of n-3 series and GLA, DGLA and AA of n-6 series have been shown to suppress the production of pro-inflammatory interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-1, IL-2 and HMGB1 (high mobility group box 1) [15]. In a similar fashion, saturated fatty acids and cholesterol have the ability to interfere with EFA metabolism and thus, promote production of IL-6 and TNF-α that may account for their involvement in atherosclerosis and coronary heart disease (CHD). Since saturated fatty acids, cholesterol and trans-fatty acids interfere with the activities of desaturases, this could lead to reduced formation of GLA, DGLA, AA, EPA, and DHA. As a result of this action, formation of prostacyclin (PGI2) from AA; PGI3 from EPA; lipoxins from AA; resolvins, protectins and maresins from EPA and DHA and nitrolipids from various PUFAs are likely to be low that may initiate and accelerate the progression of atherosclerosis. Reduced formation of PGI2, PGI3, lipoxins, resolvins, protectins, maresins and nitrolipids results in persistence of low-grade systemic inflammation, CHD and reduced healing of wounds [7,15].

NO, ADMA, PGI2, and oxidative stress in hypertension

Hypertension (HTN) is common. It is estimated that ~20–25% of the subjects above the age of 45 have detected or undetected HTN [16,17]. It is estimated that worldwide, approximately 1 billion people have hypertension that accounts for more than 7.1 million deaths per year. In view of this high prevalence, it is important to understand its pathophysiology and develop effective methods of prevention and management of HTN.

HTN is associated with an increase in peripheral vascular resistance, insulin resistance, endothelial dysfunction and enhanced activity of the sympathetic nervous system [18]. Endothelial cells produce prostacyclin (PGI2), nitric oxide (NO), and endothelins [19] that have a role in the regulation of vascular diameter and tone [20]. Dysfunction of endothelial cells has a role in the pathogenesis of atherosclerosis, hypertension and coronary and/or cerebral vasospasm or thrombosis [18–21]. Superoxide anion inactivates nitric oxide (NO) [22], whereas superoxide dismutase (SOD) enhances the half-life of NO by quenching the superoxide anion [23]. Hence, it is likely that superoxide anion can enhance vascular resistance by inactivating NO. In fact, it has been suggested that superoxide anion itself can cause vasoconstriction and increase peripheral vascular resistance [21]. Previously, we observed that patients with essential hypertension have high levels of superoxide anion and hydrogen peroxide whereas those of NO are low [21]. In addition, the concentrations of antioxidants such as vitamin E and SOD were found to be low and those of lipid peroxides are increased in these patients [24]. All these biochemical abnormalities reverted to normalcy after the control of hypertension with various anti-hypertensive drugs [21]. These results imply that HTN is associated with an imbalance between pro- and anti-oxidants and predominantly a state of heightened oxidative stress. In this context, it is noteworthy that patients with essential HTN have increased circulating levels of IL-1ra (IL-1 receptor antagonist) and increased IL-1 and IL-6 production capacity suggesting that HTN is associated with an altered profile of pro- and anti-inflammatory cytokines with the balance tilted more towards inflammation [25]. It is likely that this increased pro-inflammatory cytokine profile could induce excess production of free radicals seen in those with uncontrolled HTN [21–24]. These and other evidences suggest that HTN is an inflammatory disorder wherein both systemic inflammation and inflammation in the hypothalamus could be seen [24–32]. Furthermore, increased sympathetic nervous system activity is seen in uncontrolled HTN that also contributes to inflammation since both epinephrine and nor-epinephrine have pro-inflammatory actions whereas acetylcholine, the principal neurotransmitter of the parasympathetic vagal nerve, is a potent anti-inflammatory molecule [33,34]. Acetylcholine is a potent enhancer of endothelial NO generation implying that NO has anti-inflammatory actions. Thus, autonomic nervous system, inflammation and HTN are interrelated [35,36].

It is likely that acetylcholine is a stimulator of formation of lipoxin A4, a potent anti-inflammatory molecule that may also account for the anti-inflammatory action of acetylcholine [37]. Patients with HTN have reduced plasma concentrations of AA, the precursor of LXA4 (see Table 4) [38]. Based on these observations, it is suggested that patients with essential HTN may have low plasma levels of LXA4 [39]. It is likely that circulating plasma LXA4 levels may be low not only in HTN but also in diabetes mellitus, CHD and heart failure [39,40] that may explain the close association seen among HTN, diabetes mellitus, CHD and heart failure.

In addition, patients with HTN have significantly increased plasma levels of asymmetrical dimethyl arginine (ADMA), an inhibitor of NO generation [41,42]. Furthermore, angiotensin-II is a potent pro-inflammatory molecule that can enhance the generation of free radicals and thus decrease eNO and produce vasoconstriction and induce development of HTN [43]. It is relevant to note that exercise that is of significant benefit in HTN is known to have anti-inflammatory actions, enhance NO and LXA4 generation [44–46]. LXA4 is a potent inducer of eNO generation [47]. Previously, we showed that AA can enhance the formation of LXA4 [46,47] and inhibits the action of angiotensin-converting enzyme (ACE) activity that leads to reduced formation of angiotensin-II [48]. This could be one mechanism by which AA is able to suppress inflammation since angiotensin-II is a pro-inflammatory molecule. Because of these actions of AA (increasing LXA4 formation, inhibition of ACE activity) could be considered as an anti-inflammatory molecule. Furthermore, AA can augment eNO generation [49,50]. Similar NO synthesis enhancing action is also evident with other PUFAs such as DHA and EPA [51]. Thus, it is likely that AA, EPA and DHA enhance the production of NO, LXA4 and possibly, resolvins (from EPA and DHA), protectins and maresins (from DHA), inhibit ACE activity and thus, function as anti-inflammatory and anti-hypertensive molecules.

Salt, eicosanoids, and LXA4 in HTN

Excess salt intake is known to cause development of hypertension, though its exact mechanism of action is not clear. High salt intake (>20 g/day) suppresses NO production and thus, may increase blood pressure [52]. Salt enhances plasma ADMA levels, an inhibitor of NO synthesis, whereas high dietary potassium intake reduces blood pressure and ADMA levels while increasing NO bioactivity in normotensive salt-sensitive but not salt-resistant Asian subjects after salt loading [53]. Salt loading enhances the expression of COX-2 by activating NF-kB that, ultimately leads to increased production of PGE2 and thromboxane A2 (TXA2), a pro-inflammatory and platelet aggregator substances but PGE2 is a vasodilator whereas TXA2 is a vasoconstrictor molecule [54]. Paradoxically PGE2 suppresses the production of IL-6 and TNF-α. AA (the precursor of PGE2), EPA and DHA also suppress IL-6 and TNF-α production and thus, serve as anti-inflammatory

molecules. In addition, AA, EPA and DHA, the precursors of LXA4 (from AA), resolvins (from AA and EPA) and protectins and maresins (from DHA) that are potent anti-inflammatory metabolites and suppress IL-6 and TNF-α production as well. It is interesting that PGE2 exacerbates pro-inflammatory actions of IL-17 [55,56].

Recent studies revealed that salt enhances the production of pro-inflammatory cytokine IL-17 [57–59] whose elaboration could be suppressed by AA, EPA and DHA, LXA4, resolvins, protectins and maresins [60–62]. In addition, salt can suppress the activities of desaturases and thus, reduce plasma and tissue content of AA, EPA and DHA. Thus, ultimately, excess salt intake leads to an increase in the generation of ROS. Based on these evidences, it can be proposed that salt is pro-inflammatory in nature though salt is essential for life and excess salt is harmful.

This close interaction and negative and positive feed-back regulation among PUFAs, NO, ACE, cytokines, eicosanoids, LXA4, resolvins, protectins and maresins may account for their regulatory role in the pathobiology of hypertension and its associated conditions: atherosclerosis, CHD, heart failure and diabetes mellitus [[63–70] Fig. 1].

Pufas in diabetes mellitus

Apart from the fact that essential hypertension is a risk factor for the development of coronary heart disease, stroke, atherosclerosis, and peripheral vascular disease, its presence also need to be suspected for the presence of diabetes mellitus. In majority of the instances, essential hypertension is associated with insulin resistance if not for the presence of established diabetes mellitus. As discussed above, free radicals, nitric oxide (NO), eicosanoids, pro- and antiinflammatory cytokines, PUFAs, folic acid, tetrahydrobiopterin (BH4), and vitamin C (folic acid and vitamin C are co-factors in the metabolism of EFAs especially for the activity of desaturases, whereas BH4 is a co-factor for the synthesis of NO) not only play a role in the pathobiology of hypertension but may also have a role in the pathogenesis of diabetes mellitus. This is since, insulin resistance is common both in hypertension and diabetes mellitus (especially type 2 DM). Vascular endothelium is the source of vasodilators: prostacyclin (PGI2), NO, and endothelium-derived hyperpolarizing factor, and other vasoactive factors such as endothelins and prostaglandin E1 (PGE1) [71]. Since under normal conditions a balance is maintained between endothelial vasoconstrictors and vasodilators, it is likely that when this balance is tilted more towards vasoconstrictors and/or when the concentrations of vasodilators are reduced, hypertension develops. Endothelium dependent vasodilatation is likely to be impaired as a result of an increase in the oxidative stress that inactivates NO and PGI2. This is supported by our observation that polymorphonuclear leucocytes of patients with uncontrolled essential hypertension produce significantly higher amounts of superoxide anion, hydrogen peroxide (H2O2), and lipid peroxides, indicating an increase in oxidative stress in hypertension [21]. These abnormalities revert to normal after the control of hypertension by conventional antihypertensive drugs. It is likely that an increase in free radical generation could be responsible for the heightened peripheral vascular resistance seen in hypertension. This could be due to a decrease in NO bioavailability and an increase in superoxide anion generation possibly, due to enhanced NAD(P)H oxidase activity [72]. Low-grade systemic inflammation occurs in hypertension as evidenced by elevated plasma levels of CRP, TNF-α, and IL-6. These pro-inflammatory molecules are elevated in subjects with type 2 diabetes as well [73]. Subjects with elevated CRP levels are known to have higher risk of developing diabetes mellitus [72,74]. Dietary glycemic load significantly and positively enhances plasma CRP [72,75], indicating that hyperglycemia is a potent inducer of inflammation.

Acute elevation of plasma glucose levels in normal and impaired glucose tolerance (IGT) subjects increased plasma IL-6, TNF-a, and IL-18 levels, and these increases were much larger and lasted longer in IGT subjects compared with control [76]. In addition, hyperglycemia induced production of acute phase reactants from adipose tissue [77]. These data indicate that the increased incidence of type 2 diabetes seen in the elderly is as a result of alterations in the homeostatic mechanisms that control TNF-α, IL-6, and CRP levels, and that low-grade systemic inflammation occurs in type 2 diabetes. Low-grade systemic inflammation occurs both in hypertension and type 2 diabetes mellitus that may explain as to why blood pressure progression is a strong and independent predictor of occurrence of type 2 diabetes in hypertensives. In view of the overlap of several biochemical abnormalities among obesity, type 2 diabetes, hypertension, and insulin resistance (such as cytokines, adipokines, reactive oxygen species, anti-oxidants, and NO), it is reasonable to propose that a more generalized pathophysiological process underlies in them (hypertension and DM) [72]. One such underlying abnormality in both hypertension and diabetes mellitus could be an alteration in the metabolism of PUFAs.

Cytokines and PUFAs in DM

Excess production of interleukin-1 (IL-1), IL-2, IL-6, TNF-α and macrophage migration inhibitory factor (MIF), nitric oxide (NO), superoxide anion, and other free radicals occurs in type 1 DM and may have a role in its pathophysiology. These cytotoxic molecules are released by macrophages, lymphocytes, and monocytes infiltrating pancreatic β cells [78,79]. Both streptozotocin (STZ) and alloxan also induce production of excess of ROS, NO and other nitroso compounds possibly, by enhancing production of IL-2, interferon-γ (IFN-γ), and TNF-α by TH1 lymphocytes, which activate macrophages that, in turn, cause apoptosis of β cells [80–82]. TNF-α upregulates MIF production [83,84] and both TNF-α and MIF act in concert with each other to induce type 1 DM.

MIF, TNF-α, and ILs augment the synthesis and release of pro-inflammatory prostaglandins (PGs) but, suppress prostacyclin PGI2 production. On the other hand, PGE2 suppresses TNF-α and IL-1 production suggesting that TNF-α, IL-1-induced enhancement of PGE2 has a negative regulatory control on these cytokines. Thus, an interaction exists between cytokines and PGs [82,85–88]. Peroxisome proliferator-activated receptor-γ (PPAR-γ) activators suppress free radical generation and TNF-α and IL-2 and, thus, ameliorate the occurrence of diabetes in the Zucker diabetic fatty fa/fa rat [89,90]. PUFAs function as endogenous ligands of PPARs and we noted that oral supplementation of PUFAs-rich oils and pure individual PUFAs: GLA, AA, EPA, and DHA prevented the development of both alloxan and STZ-induced type 1 DM in experimental animals [82,91–94]. These results are interesting since, free radical-induced DNA damage activates poly (ADP-ribose) polymerase (PARP) synthase that leads to enhanced NAD+ utilization because of which NAD+ depletion occurs. This leads to a significant alteration in protein metabolism resulting in pancreatic β cell death [95,96]. This is supported by the observation that nicotinamide supplementation suppresses free radical generation and, thus, ameliorates DM implying a role for PARP and free radicals in the pathogenesis of type 1 DM. Based on these evidences, I propose that the protective actin of PUFAs against alloxan and STZ-induced type 1 DM [82,91–94] is as a result of their (PUFAs) ability to restore anti-oxidant defenses to normal [82]. Our recent studies revealed that STZ-induced type 1 and type 2 DM and high-fat diet-induced type 2 DM can be prevented by AA (unpublished data). In an extension of this study, it was noted that this anti-diabetic action of AA is due to increased formation of LXA4, an anti-inflammatory metabolite of AA. In addition, LXA4 also protected

Wistar rats from the development of chemical-induced type 1 and type 2 DM by restoring the altered antioxidant defenses, and expressions of Pdx1, NF-kB, and IKB genes in the pancreas and plasma TNF-α levels in type 1 and type 2 DM; Nrf2, Glut2; COX-2 and inducible nitric oxide (iNOS) proteins in pancreatic tissue of type 1 DM and LPCLN2 (lipocalin 2), NF-kB, IKB I in adipose tissue of type 2 DM to normal [82,97,98]. It is noteworthy that GLA, EPA, and DHA also showed similar beneficial action but were much less effective compared to AA that could be ascribed to their limited capacity to enhance LXA4 formation. . It is likely that decreased formation of LXA4 in the presence of GLA, EPA and DHA could be due to their limited capacity to displace AA from the cell membrane lipid pool, whereas AA is the direct precursor of LXA4. In this context, it is interesting to note that oral administration of cod liver oil, a source of EPA and DHA, during pregnancy can decrease the incidence of type 1 DM [99,100]. No such studies have been performed in type 2 DM. In view of the evidences ([82,91–94,97,98], it will be interesting to know whether supplementation of PUFAs during pregnancy and early childhood can prevent adult onset of type 2 DM [101,102].

Low and high dose IL-2/TNF-α in type 1 DM and its relationship to PUFAs metabolism

Chronic and low dose and systemic administration of TNF-α and IL-2 inhibit the development of type 1 DM in BB rats and NOD mice and other autoimmune/inflammatory diseases suggesting that a defect in TNF-α and IL-2-mediated immunoregulation has a significant role in the pathogenesis of these diseases [103–107]. It is relevant to note the high levels/doses of IL-2/TNF-α are cytotoxic to pancreatic β cells whereas low-doses of IL-2/TNF-α prevent β cell damage and protect from the development of type 1 DM. These paradoxical actions of IL-2/TNF-α suggest that high concentrations of IL-2 enhance free radical generation and reduce antioxidant content of β cells, whereas low concentrations of IL-2/TNF-α have opposite action. It is unclear how different concentrations of IL-2/TNF-α can produce such opposite actions. This led me to propose that low and high concentrations of IL-2/TNF-α may have diametrically opposite actions on COX (cyclo-oxygenase) and LOX (lipoxygenase) enzymes and metabolism of PUFAs (see Fig. 2). It is possible that these molecules (IL-1, IL-2, TNF-α, PUFAs and their metabolites) interact with the gut microbiota, gut hormones, and hypothalamic neurotransmitters. In addition, IL-4 and IL-10 that are anti-inflammatory cytokines enhance the conversion of AA, EPA, and DHA to their respective LXs (from AA), resolvins (from EPA and DHA), protectins (from DHA), and maresins (from DHA) that suppress inflammation [108–113]. It is relevant to note that IL-4 upregulates 15-LO gene expression leading to increased production of LXs, especially LXA4 to initiate from inflammation/suppress inflammation and autoimmune disease process.

In this complex interaction among cytokines, COX, LOX enzymes and PUFAs, there seems to be a very significant role for phospholipases as shown in Fig. 2. From the initiation of inflammation till its resolution, there is a sequential activation of various types of PLA2s. During the first 24 h of initiation of inflammation type VI iPLA2 protein expression is increased, while in the next 48–72 h type IIa and V sPLA2 expressions are increased, whereas the expression of type IV cPLA2 expression is gradually increased during resolution phase of inflammation and peaking at 72 h. Increase in type IV cPLA2 expression occurs in parallel with enhanced expression of COX-2 [114], suggesting that these enzymes are coupled to each other to regulate inflammation. Thus, different types of PLA2 have distinct and specific yet different roles in the inflammatory process. A decrease in the production/secretion of PGE2, LTB4, IL-1β, and platelet-activating factor (PAF) occurs when cPLA2 is inhibited. By contrast, inhibition of types IIa and V sPLA2 blocked PAF and LXA4 formation with a simultaneous reduction in the activities of cPLA2 and COX-2. Thus, sPLA2-derived PAF and LXA4 enhance COX-2 and type IV cPLA2 expression and IL-1β induces the expression of cPLA2. These results suggest that IL-1 has dual action: not only initiates and participates in the progression of inflammation but also plays a role in the resolution of inflammation [109,110,114–116]. LXA4 suppresses the production of ILs and TNF-α; enhances TNF-α-mRNA decay, inhibits TNF-α secretion, and leukocyte trafficking and, thus, suppresses inflammation [6,117,108,109,115–123] (see Fig. 2). This close interaction between cytokines and bioactive lipids in the induction and resolution of inflammation is crucial to regulate inflammatory process. In this complex set of interactions among cytokines, PUFAs and their metabolites there appears to be a role for gut microbiota and hypothalamic neurotransmitters as well (see Fig. 2).

Gut microbiota and PUFAs and their metabolites in type 1 DM

It is now believed that gut microbiota have a role in the pathobiology of type 1 DM. It has been suggested that increased incidence of type 1 DM in recent years could be attributed to changes in the human microbial environment [82,124] secondary to changes in the diet. Both promotion and inhibition of autoimmunity can be ascribed to gut microbes that signal their influence through TLRs [82,125]. In general, *Bacteroidetes* protection from type 1 DM, whereas *Firmicutes* promote type 1 DM [126].

Gut microbiota can regulate immune response, alter efficacy of cancer therapy, influence neuronal function by altering the concentrations of various neurotransmitters, etc. [127–132]. It is known that microbiota produce metabolites that act on the gut, gut-associated immunocytes, alter production and action of neurotransmitters, such as serotonin, both in the gut and hypothalamus. Gut microbiota induce and expand specialized Treg cells and thus, prevent aberrant inflammatory responses to β cells and maintain homeostasis [133,134] partly, by controlling differentiation of TH17 cells [135–138]. Butyrate, a short chain fatty acid, produced by gut microbiota selectively expands intestinal Treg cells [139] and enhances Treg cells abundance to induce increased production of anti-inflammatory cytokine IL-10 that can prevent type 1 DM.

Since the proliferation and type of gut microbiota depends on the presence of specific nutrients present in the food consumed by the individual, it is imperative to suggest that generation of unique metabolites by gut microbiota depends on the food we consume. Thus, indirectly it can be suggested that the ability of gut microbiota to produce specific metabolites that play a vital role in the regulation of immune response is dependent on the food that is ingested. In other words, gut microenvironment influences the composition of the microbiota. Some of the dietary components, such as sugar, fat, or fiber influence and determine which microbial species thrive in the gut. Gut microbiota has a critical role in the regulation of host serotonin production since they (gut microbiota) can augment serotonin biosynthesis from colonic enterochromaffin cells (ECs), which supply serotonin to the mucosa, lumen, and circulating platelets [130,131]. Both acetate and butyrate, the short chain fatty acids produced by the gut microbiota, determine enteric serotonin production, and, thus, regulate beta cell proliferation and function since, serotonin stimulates β cell proliferation [140,141]. Both exogenous and endogenous stimuli (toxins) that reduce β cells mass in type 1 DM may do so by interfering with β cells mass enhancing ability of serotonin. Recently, we observed that serotonin enhances the viability of rat insulinoma pancreatic β cells *in vitro*. Based on these results, it can be suggested that gut microbiota metabolites: acetate and butyrate, enhance serotonin production from ECs that, in

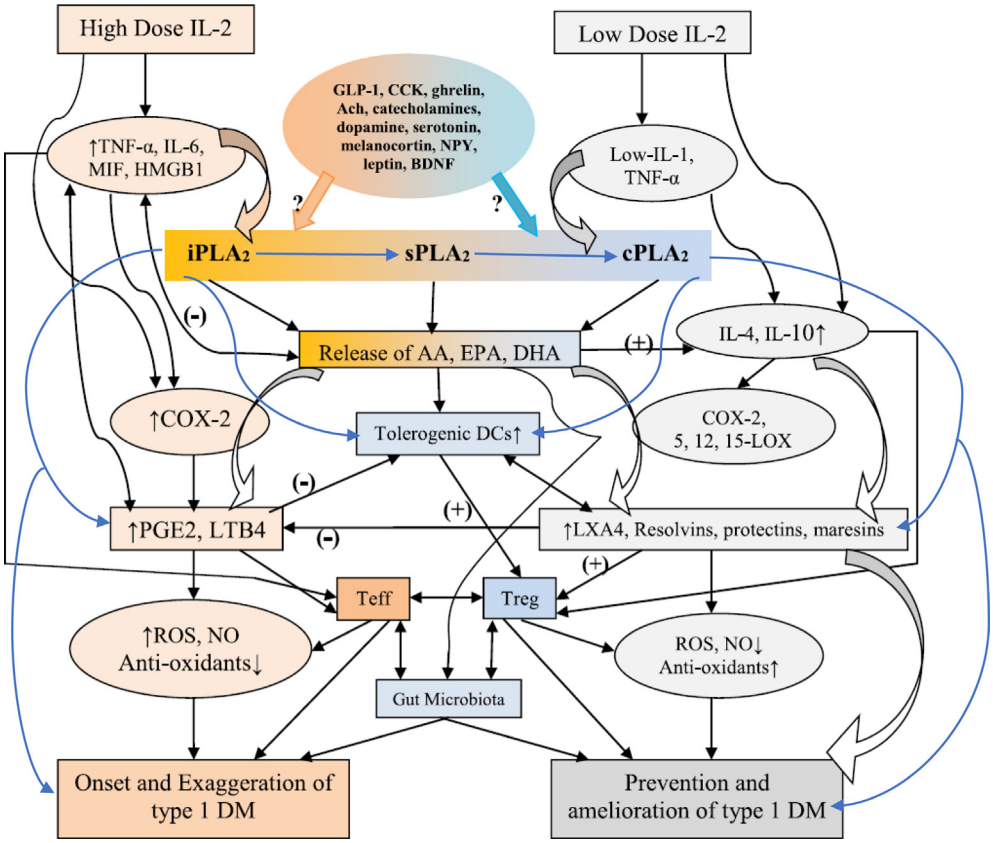

Fig. 2. Scheme showing interaction among high and low doses of IL-2/TNF-α in the induction and prevention of type 1 DM. It is likely that high doses of IL-2/TNF-α induce the activation of iPLA2 and COX-2 leading to the synthesis and release of excess of PGE2 and LTB4 and other pro-inflammatory molecules that, in turn, enhance ROS generation leading to apoptosis of pancreatic β cells and onset of type 1 DM. In contrast, low doses of IL-2/TNF-α activate sPLA2 and cPLA2 (cPLA2 > sPLA2) that leads to the synthesis and release of lipoxins, reoslvins, protectins and maresins which suppress the formation of ROS and enhance antioxidant Dasstatus of pancreatic β cells and prevention of type 1 DM. Same set of events are likely to occur in type 2 DM as well except that in this instance, IL-2/IL-6 and TNF-α produce sysemic insulin resistance. Production of adeuate amounts of lipoxins, resolvins, protectins and maresins suppress IL2/IL-6/TNF-α production and amelioration from systemic insulin resistance and type 2 DM. It is likely that activation of iPLA2 inhibit the formation of tolerogenic Dcs and enhance the occurrence of type 1 DM, whereas activation of cPLA2 enhances the formation of tolerogenic DCs and suppresses the occurrence of type 1 DM. It is alsopossible that activation of iPLA2 enhances the formation of pro-inflammmatory eicosanoids such as PGE2 and LTs, whereas activation of cPLA2 augments the formation of anti-inflammmatory lipoxins, resolvins, protectins and maresins. *This figure is modified from Das UN. Frontiers Endocrinology 2017; 8:182* (Ref. [82]).

turn, enhance β cell proliferation. Thus, one mechanism by which gut microbiota prevent type 1 DM is by enhancing serotonin production. Tryptophan present in the diet is utilized by gut microbiota to form indole derivatives: indole-3-acetic acid, indoxyl-3-sulfate, indole-3-propionic acid, and indole-3-aldehyde that are ligands for the aryl hydrocarbon receptor (AHR). These indole metabolites activate AHR of gut-resident T cells and innate lymphoid cells to augment production of IL-22, which protects β cells. Tryptophan also regulates the formation of neurotransmitter serotonin. Thus, gut microbiota and their metabolites, tryptophan, serotonin, and β cell survival and proliferation and inflammatory events, especially secretion of IL-22, are interrelated to each other in a complex fashion. It is possible that gut microbiota enhances the formation of branched fatty acid esters of hydroxy fatty acids, such as palmitic-acid-9-hydroxy-stearic acid, which is known to increase insulin sensitivity and lower plasma glucose levels by stimulating glucagon-like peptide-1 (GLP-1) and insulin secretion and reduce adipose tissue inflammation [142]. Gut microbiota may also alter endocannabinoids and thus, influence development of type 1 DM.

It is not yet known but entirely possible that gut microbiota convert dietary LA and ALA to their long chain metabolites: AA, EPA and DHA that, in turn, enhance the formation of anti-inflammatory and antidiabetic molecules: LXA4 (from AA), resolvins (from EPA and DHA), and protectins and maresins (from DHA), which results in the prevention of type 1 DM as discussed above and elsewhere [91–94,97,98].

Cytokines, gut microbiota, PUFAs and type 2 DM

In contrast to the aetiopathogenesis of type 1 DM wherein the inflammatory events occur close to pancreatic β cells, in type 2 DM there is low grade systemic inflammation as evidenced by increased circulating concentrations of IL-6, TNF-α, CRP (C-reactive protein) and decreased NO and adiponectin [143–154]. Thus, efforts made to suppress IL-6 and TNF-α levels and enhance NO and adiponectin concentrations are of benefit in the prevention and management of type 2 DM. This may explain as to why AA, EPA and DHA and lipoxins, resolvins, protectins and maresins are of benefit in type 2 DM since they are able to suppress inflammation [15,66,82,91–94,97,98,102]. PUFAs augment adiponectin production by their ability to function as endogenous ligands of PPARs [102]. Furthermore, patients with type 2 DM have low plasma phospholipid content of AA and LXA4 that may increase the plasma and tissue levels of TNF-α and IL-6 due to lack of negative feed-back control exerted by PUFAs and LXA4 on pro-inflammatory cytokines. Low plasma and tissue concentrations of PUFAs can result in low secretion of adiponectin [82,155,156] that

can aggravate insulin resistance and enhance the occurrence of type 2 DM.

Like the involvement of gut microbiota in type 1 DM, there is a strong relationship between gut microbiota and type 2 DM. Some of the mechanisms that relate gut microbiota to the onset of insulin resistance and type 2 DM include: changes in bowel permeability, endotoxemia, interaction with bile acids, changes in the proportion of brown adipose tissue, and effects associated to use of drugs like metformin [82,157–162]. The role of gut microbiota in type 2 DM can, in part, be attributed to their ability to produce acetate, propionate and butyrate that have anti-inflammatory actions. It has been shown that commensal microbes of gut microbiota can induce colonic regulatory T (Treg) cells that have a role in the suppression of inflammatory responses by producing butyrate. A positive correlation has been found between luminal concentrations of butyrate and the number of Treg cells in the colon. Butyrate can induce differentiation of Treg cells *in vitro* and *in vivo*, and ameliorated the development of colitis. These observations suggest that butyrate may have a role in host–microbe interactions establish immunological homeostasis in the gut and thus, influence pathobiology of type 2 DM [82,157–165]. In addition, obesity and type 2 DM are associated with hypothalamic inflammation due to enhanced production of TNF-α that explains the involvement of brain in these conditions including changes in the concentrations of various neurotransmitters [82,102]. It is possible that the high content of AA and DHA in the brain may function as anti-inflammatory molecules to prevent HFD-induced hypothalamic inflammation and thus, prevent obesity and type 2 DM. Furthermore, PUFAs have the ability to alter gut microbiota [82,166,167], neurotransmitter release, and action [82,168–171], enhance BDNF synthesis and secretion [171], and LXA4 enhances BDNF secretion and vice versa, modulate immune response and suppress IL-6 and TNF-α synthesis (reviewed in 78], gut hormone release (including that of GLP-1) [172–174], and finally alter gene expressions as well [82,175–179]. These and other evidences (reviewed in [82,180–182] support the contention that PUFAs (especially AA) and their metabolites (such as LXA4) play a major role in the pathogenesis of both type 1 and type 2 DM.

P-450 enzyme actions on AA and their role in hypertension and diabetes mellitus

AA is not only acted upon by COX and LOX enzymes but also by the cytochrome P-450 (CYP) pathway (see Fig. 3 for metabolism of AA). CYP hydroxylase enzymes generate HETEs, such as 20-HETE, that have cardiovascular and proinflammatory activities [183,184], whereas epoxyeicosatrienoic acids (EETs) are derived from CYP epoxygenase enzymes that have cardiovascular actions and are anti-inflammatory in nature. Hormonal and paracrine factors as well as environmental factors and diseases can alter CYP expression and activity [185–189]. These CYP epoxygenase enzymes are located in the endoplasmic reticulum and add an epoxide across one of the four double bonds in AA to produce four EET regioisomers: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET [186,190]. EETs generated by epoxygenase enzymes can then be further metabolized. EETs can be catabolized to their corresponding diols by the soluble epoxide hydrolase (sEH) enzyme. 14,15-EET is the preferred substrate for sEH with 11,12-EET and 8,9-EET also being converted to their corresponding dihydroxyeicosatrieonic acids (DHETs).

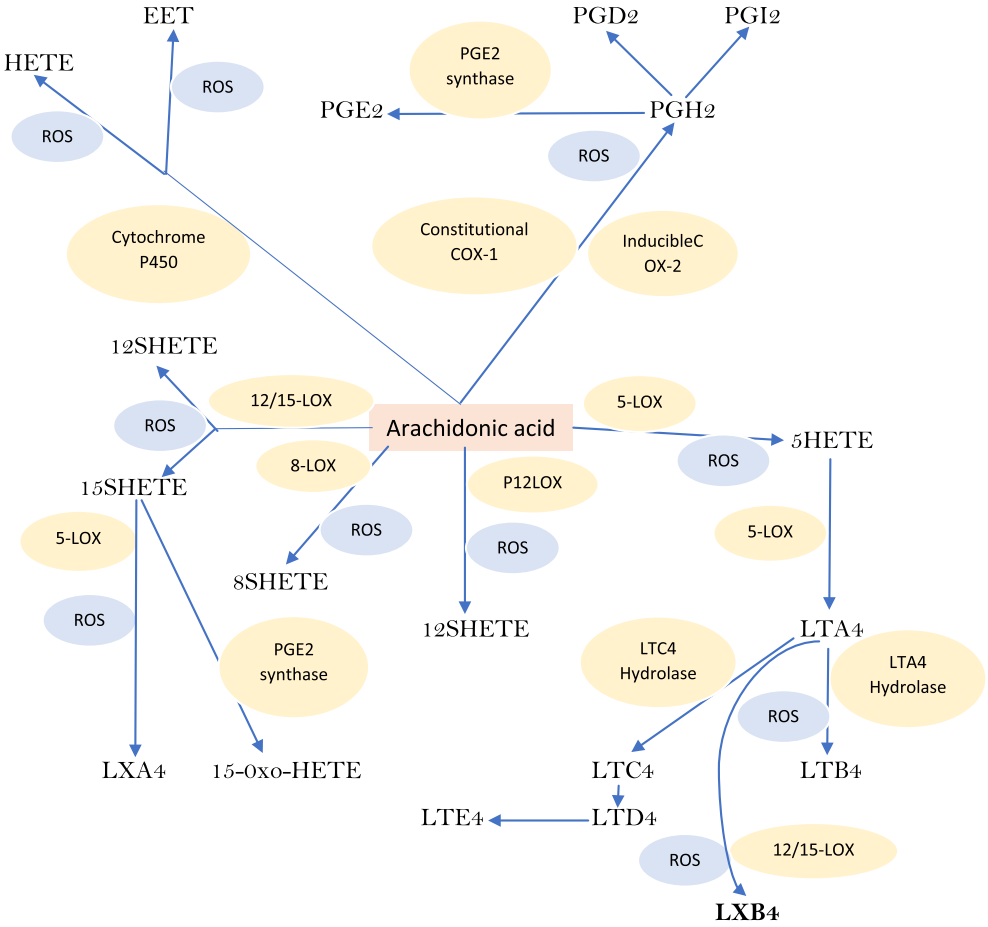

Fig. 3. Scheme showing metabolism of arachidonic acid.

EETs modulate cardiac and vascular physiology to maintain cardiovascular homeostasis. EETs have angiogenic actions that contribute to their action on cancer. For instance, increased epoxygenase enzyme expression and increasing EETs appear to be associated with increased tumor size [191,192]. One of the cell-signaling mechanisms by which EETs act is by their ability to activate PPAR-α. EETs may bring about some of their actions via receptor-dependent and receptor-independent mechanisms and function in a paracrine or autocrine manner.

Increased salt intake causes oxidant stress, reduces NO generation and endothelial dysfunction despite reduced production of angiotensin-II. This suggests that angiotensin-II does not participate in salt-induced hypertension and it could be due to decreased NO generation and inflammatory events that occur as a result of enhanced IL-17 production as already discussed above. Angiotensin-II has pro-inflammatory actions and augments free radical generation [193]. NO quenches superoxide anion. PUFAs and NO have been shown to inhibit the activity of angiotensin converting enzyme (ACE) activity and thus, lower angiotensin-II levels. This feed-back regulation among ACE activity, PUFAs, NO and free radicals is disturbed in hypertension resulting in lower NO generation, reduced PUFAs content, increased free radical generation and possibly, lower levels of LXA4 and EETs (possibly, secondary to lower AA levels [21,24,38]). These results imply that methods designed to enhance the production of EETs (by inhibiting the activity of sHE, soluble epoxide hydrolase) may be of benefit in the prevention and management of hypertension. It is likely that AA (and other PUFAs), LXA4 and EETs enhance NO generation to produce their vasodilatory action, whereas 20-hydroxyeicosatetraenoic acid (20-HETE), a major vasoconstrictor eicosanoid in the microcirculation inhibited NO formation [194].

There is preliminary evidence to suggest that EETs may have a role in insulin resistance and diabetes mellitus. CYP2J3 activation reversed insulin resistance via upregulated AMPK signaling and is associated with decreased endoplasmic reticulum stress response in adipose tissue [195]. CYP2J3-derived EETs alleviate insulin resistance, in part, through upregulated endothelial nitric oxide synthase expression [196,197]. Inhibition of sEH has been shown to enhance insulin signaling and sensitivity, increased islet size and vasculature, and decreased plasma glucose [198]. Similarly, sEH knockout attenuated insulin resistance and enhanced glucose-stimulated insulin secretion from islet cells and decreased islet cell apoptosis [199–202]. These results suggest that EETs and sFE has a significant role in the pathobiology of diabetes mellitus.

Conclusions and future perspectives

It is evident from the preceding discussion that AA and its metabolite LXA4 and EETs play a critical role in the pathobiology of hypertension and type 1 and type 2 DM. It is likely that a deficiency of AA, LXA4 and EETs may lead to the development of hypertension and diabetes mellitus. This deficiency could be due to a defect in the activities of desaturases, COX, LOX and sEH enzymes and/or the much-needed co-factors that are vital for their normal activities. Based on these evidences, it is proposed that a rational combination of AA (and possibly other PUFAs) and low dose aspirin (to enhance the formation of LXA4) and other co-factors such as vitamin C, folic acid, niacinamide, B12 and magnesium could be employed to prevent hypertension and diabetes mellitus. It is suggested that supplementation of AA, aspirin and other co-factors during pregnancy may prevent the development of pre-eclampsia (that is characterized by hypertension and insulin resistance and growth retardation of the fetus) and during lactation and early childhood may help in proper growth and development of the newborn and prevent occurrence of hypertension and diabetes in the adulthood.

Conflict of interest

The author has declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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