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COMMENTARY

Essential fatty acids and their metabolites in the context of hypertension

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Hypertension is associated with an increase in peripheral vascular resistance, insulin resistance, endothelial dysfunction and enhanced activity of the sympathetic nervous system.[1] The condition causes morbidity and mortality. Hence, understanding its pathobiology is necessary to develop effective strategies for both prevention and management.

There is increasing evidence that nutritional factors and type and level of fat in the diet are critical in the pathogenesis of essential hypertension.[2] Earlier, Weisinger *et al.*[3] showed that perinatal deficiency of the essential dietary ω-3 fatty acid α-linolenic acid (ALA) resulted in a reduction in hypothalamic docosahexaenoic acid (DHA, 22:6 ω-3). This caused hypertension in Sprague–Dawley rats, although hypothalamic DHA levels eventually returned to normal in the adults. This suggests that restoring hypothalamic DHA to normal is not sufficient to prevent the development of hypertension. Li *et al.*[4] reported that in animals fed a diet rich in ω-6 with very little ALA and then re-fed the control diet rich in ALA for 24 weeks, DHA levels were still significantly less than the control values in phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol fractions (by 9, 18 and 34%, respectively). The results led to the suggestion that ω-6/ω-3 PUFA imbalance early in life leads to irreversible changes in hypothalamic composition. The increased ALA and reduced DHA proportions in the animals re-fed ALA in later life are consistent with dysfunction or down-regulation of the conversion of ALA to DHA. In this issue of the journal, Begg *et al.*[5] report that different sources of ALA (canola or flaxseed oil) are effective in preventing hypertension related to ω-3 fatty acid deficiency. However, animals that received canola oil had lower body weight, less adiposity, lower plasma leptin levels and consumed less food, whereas animals fed safflower oil + flaxseed oil also had lower but less marked reductions in adiposity and plasma leptin levels compared with animals that were given safflower oil only. This latter group developed an ω-fatty acid deficiency. In addition, safflower oil + flaxseed oil-fed animals consumed more food and water. These results suggest that body weight, plasma leptin and brain DHA are the main determinants of blood pressure. This study also implies that there exists an interaction between ω-3 and ω-6 fatty acids that influences body weight, plasma leptin and, possibly, fatty acid composition and its metabolism in various tissues. This potential mechanism was not investigated by Begg *et al.*[5] and may have a function in the pathophysiology of hypertension and metabolic syndrome.[6]

Earlier, we observed that in patients with uncontrolled essential hypertension, $O_2^{-\cdot}$, hydrogen peroxide and lipid peroxides were produced in significantly large amounts by both unstimulated and stimulated polymorphonuclear leukocytes that reverted to normal after the control of hypertension by anti-hypertensive medicines such as calcium antagonists, β blockers and ACE inhibitors.[7,8] As free radicals themselves are known to modulate the tone of vascular smooth muscles directly and also indirectly by altering the half-life of prostacyclin (PGI_2) and nitric oxide (NO), enhanced free radical generation may lead to an increase in peripheral vascular resistance and hypertension.[7] It was suggested that $O_2^{-\cdot}$ itself could be an endothelial-derived vasoconstrictor[9] and participate in the pathogenesis of hypertension.[10,11] Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the most important source of $O_2^{-\cdot}$ in vascular and other cells. Angiotensin II stimulates free radical generation[7] by up-regulating several subunits of membrane-bound NADPH oxidase.[12,13] These results are supported by the recent reports that reduction of extracellular superoxide dismutase in the central nervous system promotes T-cell activation and vascular inflammation, modulates sympathetic outflow and induces hypertension.[14] It has also been found that active oxygen species and thromboxane A_2 reduced angiotensin-II type 2 receptor-induced vasorelaxation in diabetic rats.[15] Tumor necrosis factor-α has a function in activation of polymorphonuclear leukocyte NADPH oxidase, leading to systemic oxidative stress, inflammation and the development of hypertension.[16] In healthy middle aged and older adults, impaired endothelium-dependent dilation is decreased by a higher polymorphonuclear leukocyte count, which is mediated by reduced responsiveness to NO and increased myeloperoxidase-associated reductions in tetrahydrobiopterin and NO bioavailability.[17] How can these data explain the results reported by Begg *et al.*[5] that DHA deficiency in the brain contributes to the development of hypertension?

Patients with hypertension have low plasma concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA) and DHA. Supplementation of EPA and DHA could lower blood pressure in these patients and an inverse association between plasma PUFA content and blood pressure has been described.[18–21] Dihomo-GLA, AA, EPA and DHA not only form precursors to vasodilator and platelet anti-aggregator factors PGE_1, PGI_2 and PGI_3, but also inhibit ACE activity and augment the synthesis of endothelial

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NO.[22–25] Therefore, PUFA deficiency leads to increased ACE activity, which causes an increase in the levels of angiotensin II that, in turn, augment superoxide anion generation by activating NADPH oxidase, events that lead to a decrease in NO levels.[26] As the brain contains all components of the renin–angiotensin system, it is likely that low brain levels of DHA and EPA could enhance the level of angiotensin II, increasing the generation of free radicals and thereby accelerating the development of hypertension.[9–16]

AA, EPA and DHA can also form precursors to anti-inflammatory compounds such as lipoxins, resolvins, protectins, maresins and nitrolipids (see Figure 1 for the metabolism of essential fatty acids) that suppress leukocyte activation, inhibit free radical generation and pro-inflammatory cytokine production, enhance NO generation and exhibit potent anti-inflammatory effects.[26,27] Hence, whenever DHA (and probably other fatty acids such as AA and EPA) levels are low in the brain (especially in the hypothalamus), the production of lipoxins, resolvins, protectins, maresins and nitrolipids will be low as well, resulting in inflammation (as a result of increased production of tumor necrosis factor-α) and the induction of hypertension.[14,16] EPA and possibly DHA suppress the production of leptin,[28] which has pro-inflammatory effects[29] similar to those of angiotensin II. This may explain the increased plasma leptin levels noted by Begg *et al.*[5] and the function of leptin in hypertension because hypertension is a low-grade systemic-inflammatory condition.[30] It is important to note that DHA is formed from EPA and that DHA can be retroconverted to EPA. This relationship might indicate a dynamic balance between EPA and DHA. AA is also present in the brain, but at relatively lower concentrations compared with EPA and DHA. AA forms the precursor to pro-inflammatory eicosanoids and anti-inflammatory lipoxins, resolvins and nitrolipids. Therefore, its function in hypertension needs to be studied.

On the basis of the results of Begg *et al.*[5] and other evidence discussed above, it is important to delve more deeply into the function of perinatal deficiency of PUFAs in the context of hypertension. It is likely that animals on an ALA-deficient diet have low levels of DHA not only in the brain, but also in other tissues such as endothelial cells, peripheral leukocytes and the kidney. This may explain the enhanced leukocyte-free radical generation in hypertension.[7] High levels of myeloperoxidase generation by

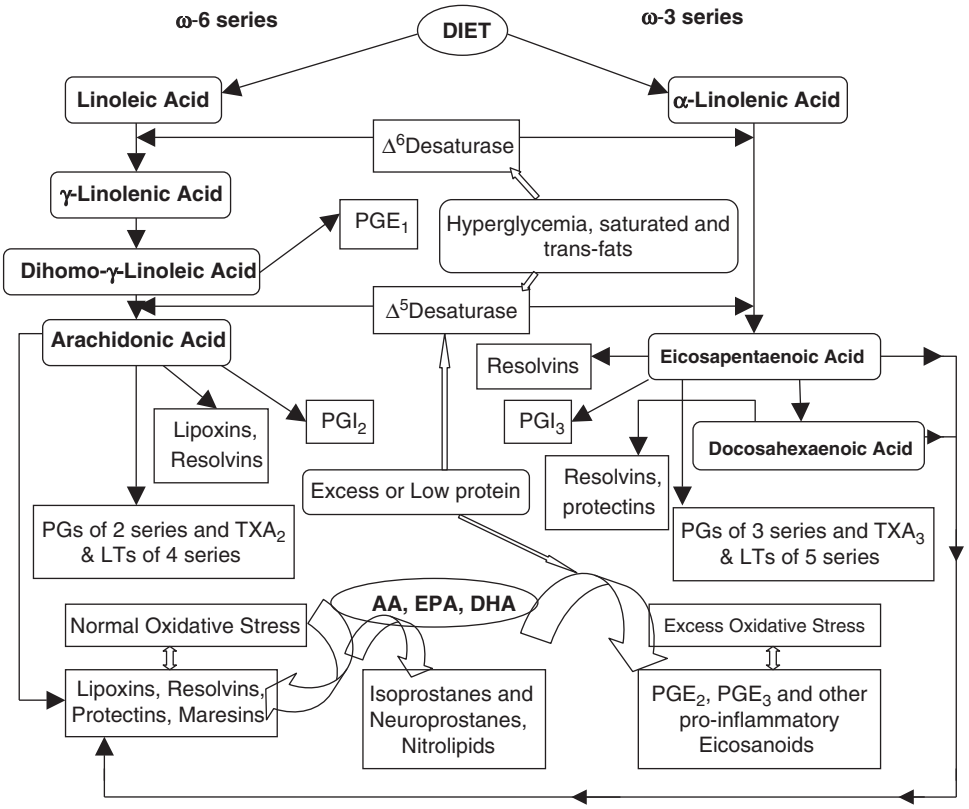

Figure 1 Scheme showing metabolism of essential fatty acids (EFAs). Dietary EFAs linoleic acid (LA, 18:2 ω-6) and α-linolenic acid (ALA, 18:3 ω-3) are converted to γ-linolenic acid (GLA, 18:3 ω-6), dihomo-GLA (DGLA, 20:3 ω-6) and arachidonic acid (AA, 20:4 ω-6) and eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3), respectively, by Δ^6 and Δ^5 desaturases and elongases. DGLA forms precursor to 1 series of prostaglandins (PGs), AA is the precursor of 2 series of PGs and thromboxanes (TXs) and 4 series leukotrienes (LTs), whereas EPA is the precursor of 3 series PGs, TXs and 5 series LTs. In general, most of the PGs, TXs and LTs have pro-inflammatory actions. But, some such as PGE_1, PGI_2 and PGI_3 show anti-inflammatory properties and have vasodilator and platelet anti-aggregatory actions. EPA is converted to DHA and DHA can be retroconverted to EPA. Thus, the levels of EPA and DHA in tissues and plasma may depend on the rate of conversion of EPA to DHA and retroconversion of DHA to EPA. In addition, AA, EPA and DHA give rise to anti-inflammatory compounds lipoxins, resolvins, protectins and maresins. Isoprostanes are prostaglandin-like compounds produced from esterified AA, EPA and DHA in tissues by non-enzymatic reactions catalyzed by free radicals *in vivo*. Isoprostanes have a short half-life and have potent biological activities in the lungs and kidney. They are useful markers for oxidative stress, and can be assayed by non-invasive means. Autoxidation of DHA generates isoprostane-like compounds called as neuroprostanes. NO reacts with PUFAs to yield their respective nitroalkene derivatives that can be detected in plasma. These nitroalkene derivatives, termed as nitrolipids, produce vascular relaxation, inhibit neutrophil degranulation and superoxide formation, inhibit platelet activation and show anti-atherosclerotic properties.

activated leukocytes[17] could be secondary to reduced formation of lipoxins, resolvins, protectins, maresins and nitrolipids.[31] It is predicted (see Figure 2) that ALA-deficient animals that develop hypertension have (a) increased levels of plasma pro-inflammatory cytokines; (b) reduced levels of EPA/DHA, lipoxins, resolvins, protectins, maresins and nitrolipids in various tissues including vascular endothelial cells, hypothalamus and kidney; (c) high levels of angiotensin II as a result of enhanced ACE activity in the brain, leukocytes and kidney; (d) augmented production of free radicals because of enhanced NADPH oxidase activity and high levels of myeloperoxidase (released by leukocytes and endothelial cells); (e) reduced levels of endothelial NO; (f) decreased plasma levels

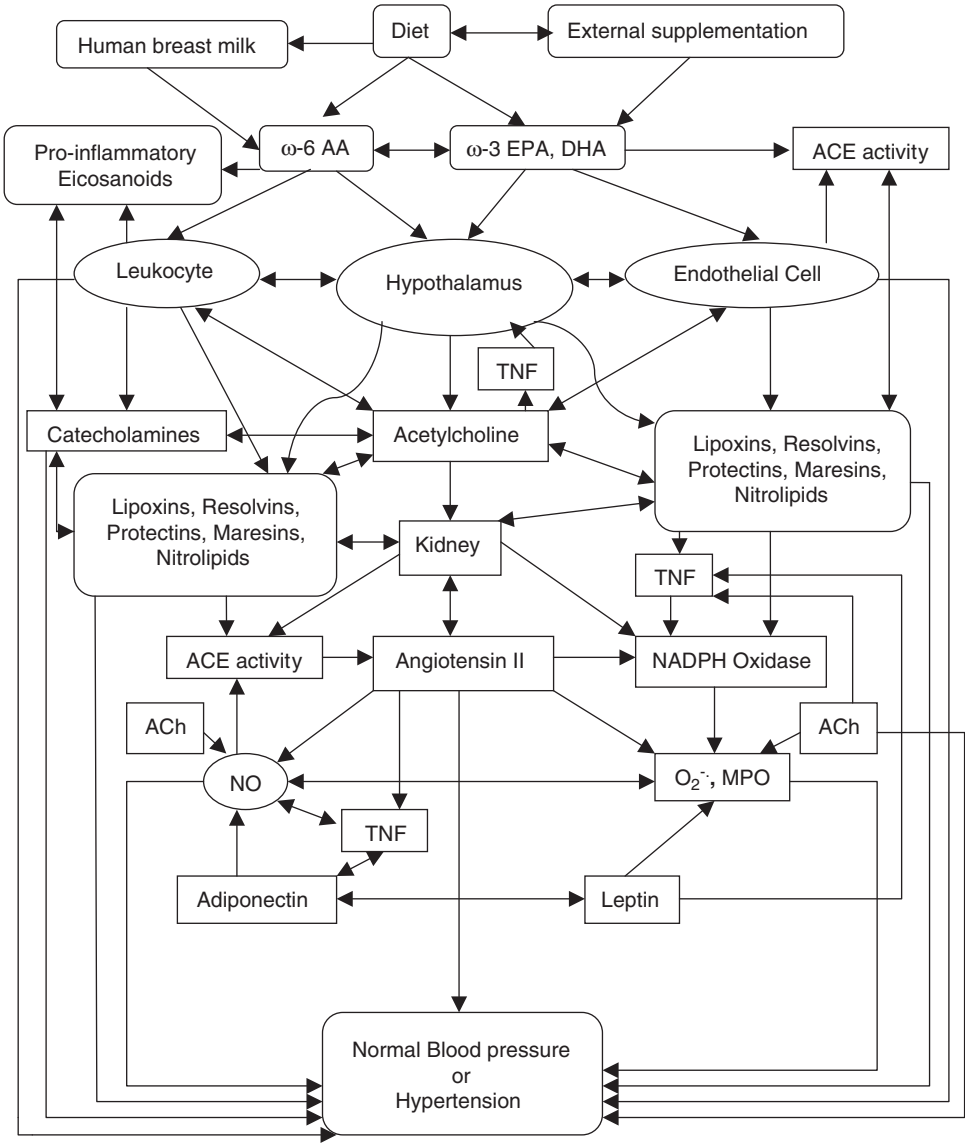

Figure 2 Scheme showing possible relationship between PUFAs and their metabolites and their function in hypertension. AA, EPA and DHA can be obtained from human breast milk, as an external supplement or formed in the body from the dietary LA and ALA. AA gives rise to both pro-inflammatory eicosanoids and anti-inflammatory lipoxins, resolvins and nitrolipids, whereas EPA and DHA form precursors to resolvins, protectins, maresins and nitrolipids. These biologically active lipid molecules could be formed in the brain, leukocytes, endothelial cells, kidney and other tissues. Lipoxins, resolvins, protectins, maresins and nitrolipids, and AA, EPA and DHA inhibit the activity of ACE and thus, suppress angiotensin II formation, inhibit pro-inflammatory cytokine (TNF) production, reactive oxygen species, myeloperoxidase and leptin; and enhance the production of adiponectin, acetylcholine and nitric oxide and thus, suppress the development of hypertension. Nitric oxide is a potent inhibitor of ACE. Deficiency of EPA/DHA will lead to reduced formation of lipoxins, resolvins, protectins, maresins, nitrolipids and nitric oxide that will lead to increase in the production of angiotensin II, enhanced oxidative stress and enhanced sympathetic activity that results in the development of hypertension. The exact function of AA in the pathogenesis of hypertension is not clear but hypertensives have low levels of this lipid. AA, EPA and DHA increase the levels of acetylcholine in the brain and thus, may enhance parasympathetic tone. Acetylcholine has anti-inflammatory actions and enhances nitric oxide generation, whereas catecholamines have pro-inflammatory actions. There could be a close cross-talk among brain, endothelial cells, leukocytes and kidney. AA, EPA and DHA both directly and indirectly by influencing the levels of acetylcholine could modulate the concentrations of serotonin, dopamine, catecholamines and other neurotransmitters in the brain. It is possible that under conditions of normal oxidative stress lipoxins, resolvins, protectins, maresins and nitrolipids are favored to form, whereas under increased oxidative stress pro-inflammatory eicosanoids are formed in large amounts (see Figure 1). This scheme should not be considered as comprehensive and more work is needed to confirm or refute some of the proposals made here. For more details see the text.

of adiponectin (because hypertensives have peripheral insulin resistance and are more prone to develop type 2 diabetes mellitus and metabolic syndrome[32]); (g) depressed anti-oxidant capacity; (h) enhanced sympathetic tone (catecholamines have pro-inflammatory actions[33]) and (i) low acetylcholine levels in the brain and leukocytes (because acetylcholine is an anti-inflammatory molecule, it enhances NO generation and its levels are enhanced by AA/EPA/DHA supplementation[34,35]). Some of the suggested studies could be performed in human beings using peripheral leukocytes and macrophages because they contain the complete intracellular machinery for the generation, release and metabolism of dietary essential fatty acids, lipoxins, resolvins, protectins, maresins, nitrolipids, catecholamines, acetylcholine and serotonin, as well as the renin–angiotensin system and anti-oxidants. Such a study may prove to be extremely informative.

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