COMMENTARY

Pre(peri)-natal ω -3 PUFA deficiency-induced hypertension and its broader implications

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Essential hypertension is common and is an important risk factor for coronary heart disease (CHD), stroke, atherosclerosis and peripheral vascular disease. Blood pressure progression is a strong and independent predictor of the occurrence of type 2 diabetes mellitus in hypertensive patients,¹ suggesting a close link between diabetes and hypertension. It is estimated that hypertension affects approximately 20–25% of all adults above the age of 45–50 years, and it is common in overweight and obese subjects. Hence, a better understanding of the pathobiology of hypertension may help to develop effective strategies for the prevention and management of not only hypertension, but also of its associated conditions, such as obesity, type 2 diabetes mellitus and CHD. This is especially true in the light of the fact that increases in peripheral vascular resistance, insulin resistance and endothelial dysfunction and enhanced activity of the sympathetic nervous system are observed in obesity, type 2 diabetes mellitus and hypertension.^{2–11}

Hypertension is characterized by an increase in peripheral vascular resistance that could be attributed to the loss or decrease in endothelium-dependent vasodilation. The endothelium produces vasoactive factors such as prostacyclin (PGI₂), nitric oxide (NO), endothelium-derived hyperpolarizing factor, endothelin and prostaglandin E₁ (PGE₁).^{12–17} Under normal physiological conditions, a balance is maintained between vasoconstrictors and vasodilators to maintain

normal blood pressure. When this balance is tilted more in favor of vasoconstrictors, and/or when the concentrations of vasodilators are reduced, hypertension will set in. There is evidence to suggest that free radicals, such as superoxide anion (O₂[−]) and hydrogen peroxide (H₂O₂), also have a significant role in the pathobiology of hypertension, partly by modulating the formation, half-life and action of NO, lipid peroxides and arachidonic acid (AA). Free radicals also modulate the formation, half-life and action of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) metabolites formed by the action of the cytochrome p450 enzyme system; these molecules include epoxyeicosatrienoic acids from AA, 20-hydroxypentaenoic acid (20-HEPE) and 17,18-epoxyeicosatetraenoic acid (17,18-EETeTr) from EPA, and 22-hydroxydocosahexaenoic acid (22-HDHE) and 19,20-epoxydocosapentaenoic acid (19,20-EDP) from DHA^{18–21} (see Figure 1, see Figure 2 for the metabolisms of AA, EPA and DHA).

In light of this evidence, it is interesting that Begg *et al.*²² reported in this issue that the expression of angiotensin-II_{1A} receptors and dopamine D3 receptors was significantly increased in the hypothalamic tissue of ω -3-deficient animals at age 10 weeks, and the α 2a and β 1 adrenergic receptor expression was significantly reduced at 36 weeks in animals that developed hypertension in adult life as a result of having received an ω -3-deficient diet during the prenatal period. This model of hypertension, developed by Weisinger *et al.*, formed the basis of many studies by the same group.^{23–27} This seems to be a good model in which to study the interaction between dietary fatty acids and hypertension, especially the role of ω -3 fatty acids. The concept that prenatal deficiency of ω -3 fatty acids leads to the development of adult-onset hypertension

gains support from the observations that supplementation of ω -3 fatty acids (especially EPA and DHA) reduces blood pressure in spontaneously hypertensive rats,²⁸ and infants supplemented with ω -3 fatty acids have lower blood pressures.²⁹ Furthermore, breast milk consumption has been associated with lower blood pressure in later life,^{30–32} and this beneficial action could be due to the presence of significant amounts of PUFAs (polyunsaturated fatty acids) in human milk (AA > DHA > EPA; see Table 1 for the fatty acid composition of human breast milk). Breast-fed infants have a significantly higher percentage of PUFAs in their tissues compared with those who are fed formula, lending support to this assumption.³³ In addition, both EPA and DHA suppress the development of hypertension in stroke-prone SHR, inhibit the activity of angiotensin-converting enzyme (ACE), and enhance the production of endothelial NO (eNO) generation, which may aid in their ability to lower blood pressure (reviewed in 34). Despite this evidence of the relationship between PUFAs (especially ω -3 EPA and DHA) and blood pressure, several questions still remain.

The concept of prenatal ω -3 deficiency leading to the development of adult-onset hypertension is not a true replica of the essential hypertension observed in adults, as these animals showed marginal increases in systolic pressure (although significant compared with the control group), but no significant increases in diastolic pressure at 36 weeks of age (10 weeks of age: systolic: ω -3 DEF (w-3 PUFA deficient): 123.5 ± 1.9 mm Hg, SUF-S (diet sufficient in short-chain omega-3 fatty acids (7% safflower oil + 3% flaxseed oil)): 120.1 ± 1.9 mm Hg, SUF-SL (diet sufficient in short- and long-chain omega-3 fatty acids (7% safflower oil + 2.9% flaxseed

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Figure 1 Scheme showing the formation of various products from AA, EPA and DHA due to the action of cytochrome p450.

oil + 0.1% tuna oil)): 124.2 ± 2.2 mm Hg; diastolic: ω-3 DEF: 82.5 ± 1.6 mm Hg, SUF-S: 81.3 ± 1.2 mm Hg, SUF-SL: 82.1 ± 1.5 mm Hg; 36 weeks of age: systolic: ω-3 DEF: 149.4 ± 3.7 mm Hg, SUF-S: 133.1 ± 3.6 mm Hg, SUF-SL: 132.2 ± 2.0 mm Hg; diastolic ω-3 DEF: 87.9 ± 2.7 mm Hg, SUF-S: 83.3 ± 2.1 mm Hg, SUF-SL: 84.5 ± 1.6 mm Hg).²² It is not known whether these ω-3 DEF animals develop the complications observed in humans with essential hypertension, such as malignant hypertension, hypertensive retinopathy, atherosclerosis, stroke, CHD, cardiac failure, cardiac arrhythmias and renal failure. A study in this direction is needed.

Despite the fact that pre(peri-)natal ω-3 deficiency could lead to adult onset of hypertension, at least in experimental animals, the exact mechanism of this action is not clear. Begg *et al.*²² noted that at 10 weeks, the expression of angiotensin-II_{1A} receptors and dopamine D3 receptors significantly increased in the hypothalamic tissue, whereas at 36 weeks the α_{2a} and β₁ adrenergic receptor expression was significantly reduced in the ω-3 DEF group. These alterations in the expression of angiotensin-II_{1A}, dopamine D3, α_{2a} and β₁ adrenergic receptors suggest

that they may have a role in the pathobiology of hypertension, or they may simply be bystander changes. One way of establishing their role in ω-3-deficient hypertension is by studying the effect of angiotensin-II_{1A}, dopamine D3, α_{2a} and β₁ adrenergic receptor agonists and antagonists on blood pressure. It is not clear how this animal hypertension model responds to various antihypertensive drugs (that is, whether centrally acting antihypertensive drugs will be more effective than peripherally acting drugs, and if so, why and how). The possibility that lipid profile abnormalities in the form of high plasma cholesterol, triglycerides, low-density lipoprotein and very low-density lipoprotein, with low-high-density lipoprotein, (as observed in obesity, type 2 diabetes mellitus and some hypertensive subjects) could occur in this animal model needs to be studied with special emphasis on the functional capacity of high-density lipoprotein, as dysfunctional high-density lipoprotein is believed to be an important risk factor for atherosclerosis. It is important to know whether these animals have insulin resistance, which is observed in humans with hypertension.

Patients with uncontrolled essential hypertension have enhanced levels of O₂⁻, H₂O₂, lipid peroxides, NADPH oxidase, ACE activity, and myeloperoxidase activity, and decreased half-life and/or concentrations of PGI₂ and endothelial nitric oxide.^{2,12} It is worthwhile to investigate whether these abnormalities are present in the ω-3-deficient hypertension model of Begg *et al.*²²

Low-grade systemic inflammation, as evidenced by enhanced plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and high-sensitive CRP (hs-CRP), occurs in patients with hypertension.³⁴⁻³⁸ Begg *et al.*²² have not measured plasma cytokines and hs-CRP levels in the ω-3-deficient hypertensive animal model to know whether low-grade systemic inflammation is present. In all probability, inflammation would be present, as ω-3 PUFAs are known to suppress the production of IL-6, TNF-α and myeloperoxidase activity. If this is true, and as plasma levels of hs-CRP, TNF-α and IL-6 are also elevated in subjects with obesity, insulin resistance and type 2 diabetes,^{39,40} it remains to be seen whether ω-3-deficient hypertensive animal models have some, if not all, of the features of the

Figure 2 Metabolism of AA. Products similar to those formed from AA are also formed from EPA and DHA. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 1 Polyunsaturated fatty acids composition of mature human breast milk

Fatty Acid		%, wt/wt
Linoleic acid (LA)	18:2 n-6	10.76
Gamma-linolenic acid (GLA)	18:3 n-6	0.16
Dihomo-GLA (DGLA)	20:3 n-6	0.26
Arachidonic acid (AA)	20:4 n-6	0.36
Alpha-linolenic acid (ALA)	18:3 n-3	0.81
Eicosapentaenoic acid (EPA)	20:5 n-3	0.04
Docosapentaenoic acid (DPA)	22:5 n-3	0.17
Docosapentaenoic acid (DHA)	22:6 n-3	0.22

metabolic syndrome, and whether they have or would eventually develop peripheral insulin resistance, secondary hyperinsulinemia and type 2 diabetes mellitus.

Previously, Begg *et al.*²⁵ reported that 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. The latter group developed an ω -3 fatty acid deficiency. In addition, safflower oil + flaxseed oil-fed animals consumed more food and water. These results can be reinterpreted to mean that the consumption of a balance of ω -3 and ω -6 fatty acids (safflower oil + flaxseed oil fed animals in this study) lowered body weight and plasma leptin and maintained normal blood pressure. These results also suggested that ω -3 and ω -6 fatty

acids interact with each other to influence body weight, plasma leptin and, possibly, fatty acid composition and its metabolism in various tissues. It would have been interesting if the authors had studied hypothalamic Neuropeptide Y, serotonin, dopamine, pro-opiomelanocortin, melanocortins and acetylcholine levels in these studies,^{22,25} to determine the cause for the changes in the consumption of food and water, lower body weight, less adiposity and lower plasma leptin levels. Unfortunately, in both studies,^{22,25} the authors did not measure the fatty acid composition of the plasma, vascular tissue, kidneys, heart or liver to determine whether an ω -3 PUFA deficiency was present in these tissues and in the brain. Such a study, along with the measurement of plasma NO, cytokines, NADPH oxidase (in the leukocytes and macrophages) and myeloperoxidase, would have provided a clue about the contribution of and interaction(s) among the various bioactive molecules involved in the pathobiology of hypertension in this animal model.

Figure 3 Scheme showing what studies can be performed in the ω -3-deficient hypertensive animal model to elucidate the pathophysiological mechanisms of development of hypertension. It is necessary to study the incidence of non-alcoholic fatty liver disease in this animal model.

It is probably worthwhile to study the metabolism of PUFAs in the ω -3-deficient hypertensive animal model, as shown in Figures 1 and 2. For instance, the pro-inflammatory products formed from AA, EPA and DHA (such as prostaglandins, leukotrienes and thromboxanes) and their anti-inflammatory products (lipoxins, resolvins and protectins in the plasma and kidney, vascular tissue, liver, myocardium and hypothalamus) need to be estimated in an ω -3-deficient hypertensive animal model. As lipoxins, resolvins and protectins appear to be responsible for some, if not all, of the beneficial actions of AA/EPA/DHA, a close look at their synthesis and action^{41–43} needs special attention. Thus, studies that could be performed to answer some of the questions mentioned above in this ω -3-deficient hypertensive animal model are depicted in Figure 3.

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