Hypertension as a Low-grade Systemic Inflammatory Condition That has its Origins in The Perinatal Period

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Abstract

Genetics, oxidative stress: superoxide anion (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), endothelial nitric oxide (eNO), lipid peroxides, anti-oxidants, endothelin, angiotensin converting enzyme (ACE) activity, angiotensin-II, transforming growth factor-β (TGF-β), insulin, homocysteine, asymmetrical dimethyl arginine, pro-inflammatory cytokines: interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (hs-CRP), and long-chain polyunsaturated fatty acids (LCPUFAs), and activity of NAD(P)H oxidase have a role in human essential hypertension. There is a close interaction between endogenous molecules: eNO, endothelin, cytokines, and nutrients: folic acid, L-arginine, tetrahydrobiopterin (H$_4$B), vitamin B$_6$, vitamin B$_12$, vitamin C, and LCPUFAs. Statins mediate some, if not all, of their actions through LCPUFAs, whereas these fatty acids (especially ω-3 fatty acids) suppress cyclo-oxygenase activity and the synthesis of pro-inflammatory cytokines, and activate parasympathetic nervous system, actions that reduce the risk of major vascular events. Some LCPUFAs form precursors to lipoxins and resolvins that have anti-inflammatory actions. Low-grade systemic inflammation seen in hypertension seems to have its origins in the perinatal period and availability of adequate amounts of LCPUFAs during the critical periods of brain growth prevents the development of hypertension. This indicates that preventive strategies aimed at decreasing the incidence of hypertension and its associated conditions such as atherosclerosis, type 2 diabetes, coronary heart disease (CHD), and cardiac failure in adulthood need to be instituted during the perinatal period if they are to be effective. ©

INTRODUCTION

Although hypertension is common, the exact cause for increase in both systolic and diastolic blood pressure is not clear. In subjects with secondary hypertension, either atherosclerosis or fibromuscular dysplasia of one or both renal arteries is responsible for renovascular hypertension. The other forms of secondary hypertension such as those due to endocrine causes are rare, but nevertheless should be kept in mind whenever hypertension presents itself in an unusual form. Hence, discussion about the role of various factors in the pathophysiology of hypertension is centered on primary hypertension. But, wherever it is relevant other forms of hypertension is also included.

Although hypertension is easily amenable to treatment with the currently available drugs, a better understanding of its cause(s) is expected to lead to newer modes of treatment and development of newer drugs that are less expensive, with fewer side effects. The importance of hypertension lies in the fact that it forms one of the risk factors for coronary heart disease (CHD), stroke, atherosclerosis, and peripheral vascular disease (PVD). With the increasing incidence of overweight and obesity both in children and adults, it is likely that the incidence of hypertension will also increase. Many pediatricians do not to measure blood pressure in their patients, partly with the assumption that hypertension is uncommon in children. But with the increasing incidence of obesity in children, it is probably necessary to measure blood pressure as frequently as possible, at least, in obese children.

Recent studies revealed that free radicals, nitric oxide (NO), eicosanoids, pro- and anti-inflammatory cytokines, long-chain polyunsaturated fatty acids (LCPUFAs), folic acid, tetrahydrobiopterin (BH$_4$), and vitamin C play a significant role in the pathobiology of hypertension. These factors/molecules interact with angiotensin converting enzyme (ACE), endothelins, and anti-hypertensive drugs such as calcium antagonists, and β blockers that may have relevance to the prevention and treatment of hypertension.

INCREASED OXIDANT STRESS OCCURS IN HYPERTENSION

Vascular endothelium produces vasodilators: prostacyclin (PGL$_2$), nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EHF) and other
vasoactive factors such as endothelins, and prostaglandin E₁ (PGE₁). Under physiological conditions a balance is maintained between endothelial vasoconstrictors and vasodilators such that normal blood pressure is maintained. When this balance is altered more in favor of vasoconstrictors such as endothelins, when the concentrations of vasodilators are reduced, or both, hypertension develops. One mechanism by which endothelium-dependent vasodilatation is impaired is due to an increase in the oxidative stress that inactivates NO and PG₁₂.

Previously, I showed that in patients with uncontrolled essential hypertension O₂⁻; hydrogen peroxide (H₂O₂), and lipid peroxides were produced in significantly large amounts both by unstimulated and stimulated polymorphonuclear leukocytes (PMNs) indicating that there is indeed an increase in oxidative stress in hypertension. The enhanced levels of free radicals and lipid peroxides reverted to normalcy after the control of hypertension by anti-hypertensive medicines such as calcium antagonists, β blockers and ACE inhibitors. O₂⁻; itself could be an endothelial-derived vasoconstrictor, implying that increase in free radical generation observed in untreated hypertensives could be one of the factors responsible for the heightened peripheral vascular resistance. A decrease in the levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase, and vitamin E in the RBC membranes of uncontrolled hypertensives was noted. The concentrations of SOD also reverted to normalcy following control of hypertension with various medicines. It is interesting to note that a fusion protein (HB-SOD) consisting of human Cu-Zn type SOD (superoxide dismutase) and a C-terminal basic peptide with a high affinity for heparan sulfate on endothelial cells not only can localize to the vascular walls but also can effectively prevent the development of hypertension in the spontaneously hypertensive rats (SHR). These results suggest that the impaired endothelium-dependent vasodilatation in human essential hypertension is closely related to increase in the generation of free radicals. This is supported by the observation that SOD deficiency is seen in hypertension and that SOD activity decreased with advancing age. Decreased NO bioavailability and increased O₂⁻; generation with increasing age could be related to enhanced NAD(P)H oxidase activity that is known to increase O₂⁻; generation. These results indicate that there is a close interaction and delicate balance maintained between SOD, O₂⁻; eNO, and NAD(P)H oxidase activity.

Simvastatin, a hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that is used in the management of hyperlipidemias behaves like an antioxidant and improves endothelial function and increased SOD and glutathione peroxidase activities. This implies that SOD by quenching O₂⁻; restores endothelial function. Since, simvastatin does not reduce the increased blood pressure this suggests that O₂⁻; alone is not responsible for the development of hypertension. Further, anti-oxidants such as vitamin E are not useful to lower elevated blood pressure both in experimental animals and humans.

Hypertension induced in experimental animals by giving 10% glucose drinking solution showed elevation in the aortic basal O₂⁻; production, plasma levels of insulin and glucose, as well as insulin resistance index events that reverted to normal following aspirin administration. An increase in plasma SOD activity was observed in glucose-fed rats but not in aspirin fed rats, suggesting that aspirin prevented the development of hypertension and reduced insulin resistance in glucose-fed rats. Aspirin preferentially block the synthesis of thromboxane A₂ (TXA₂) from its precursor arachidonic acid without interfering with the synthesis of PG₁₂, a potent vasodilator and platelet anti-aggregator, and enhance the synthesis of anti-inflammatory compounds such as lipoxins and resolvins from arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). It is likely that aspirin increases eNO, lipoxins and resolvins production and/or their half-life by decreasing oxidative stress and restoring SOD levels to normalcy. These studies indicate that the balance between O₂⁻; and eNO and PG₁₂ is critical in the prevention of hypertension.

Why and how superoxide anion production is increased in hypertension

NAD(P)H oxidase is present in vascular cells and enhanced O₂⁻; generation is as a result of its activation in hypertension. NAD(P)H oxidase responds to stimuli such as vasoactive factors, growth factors, and cytokines. Kidneys of adult SHR (spontaneously hypertensive rats) had a significantly greater mRNA for p47phox (a major component of NAD(P)H oxidase). A 10-fold up regulation of vascular NAD(P)H oxidase was associated with a 3-fold increased production of O₂⁻; and a concomitant impairment of the eNO signal transduction pathway in hypertension. Chronic inhibition of eNO synthesis increased aortic O₂⁻; production, and redox sensitive transcription factors NF-κB and AP-1 in experimental animals. Angiotensin II type 1 receptor antagonists prevented these changes, suggesting that inhibition of eNO synthesis increases vascular oxidative stress and oxidative stress-sensitive signals via the action of angiotensin II mediated type 1 receptors. Further, angiotensin II stimulates free radical generation by up regulating NAD(P)H oxidase, lending support to this view. Thus angiotensin II-induced free radicals seem to play an important role in hypertension, endothelial dysfunction, nitrate tolerance, atherosclerosis, and cellular remodeling. This offers an explanation for the beneficial actions of angiotensin receptors antagonists.
and ACE inhibitors in cardiovascular diseases.

**Superoxide anion and hypertension**

Under normal conditions, a balance is maintained between the steady state level of eNO and the $O_2^-$, NO reacts with $O_2^-$, producing peroxynitrite. It was reported that endothelial NO synthase inhibition increased mean $O_2^-$ release, with a corresponding reduction in peroxynitrite formation. Conversely, NO donors and $O_2^-$ scavengers reduced $O_2^-$ release, whereas only NO donors enhanced peroxynitrite formation. These changes in the concentrations of NO, peroxynitrite, and $O_2^-$ were much larger in arteries compared to those seen in veins. A significant correlation was seen between NO bioavailability, peroxynitrite formed and $O_2^-$ production. Both NO and PGI2 are inactivated by $O_2^-$. Thus, $O_2^-$ by decreasing the half-life of NO and PGI2, and lowering their circulating concentrations could initiate the development of hypertension.

Endothelial cells also produce endothelin, a potent vasoconstrictor and a physiological antagonist of NO. Human endothelial cells and coronary artery smooth muscle cells showed increased endothelin-1 production when exposed to oxidative stress, whereas NO reduced the production of endothelin-1. Thus, NO and $O_2^-$ have opposite actions on the production of endothelin-1 by endothelial cells.

**NO in hypertension**

NO is synthesized from the semi-essential amino acid, L-arginine. NO is not stored and is formed and released as needed. Three NOS iso-enzymes have been characterized: neuronal or type 1, nNOS; inducible NOS or iNOS; and endothelial NOS or eNOS, each the product of a unique gene, have been identified and well characterized. Type 1 or nNOS is a Ca$^{2+}$-dependent enzyme found in neuronal tissue and skeletal muscle. Type 2 or iNOS is inducible in a variety of cells and tissues in response to cytokine or endothoxin action, and this enzyme (iNOS) binds Ca$^{2+}$/calmodulin so tightly that at normal physiologic levels its activity is functionally Ca$^{2+}$-independent. Type 3 or eNOS is also Ca$^{2+}$ dependent and is myristoylated and palmitoylated at the N-terminus, modifications, which are needed for localization to the plasmolemmal caveolae of endothelial cells. Though both nNOS and eNOS are constitutive enzymes, all three enzymes can be induced, albeit to different levels and by different stimuli.

Vasodilator response to acetylcholine (which stimulates eNO release from endothelial cells) was significantly reduced in hypertensives. However, the vasodilator response to sodium nitroprusside, a NO donor, was similar in normotensives and hypertensives, suggesting that endothelial dysfunction in essential hypertension are due to selective abnormality of NO synthesis. An inverse correlation was found between platelet cytosolic Ca$^{2+}$ and eNO levels indicating that there is a link between hypertension and altered platelet function and suggest a role for NO in cardiovascular events, suggesting that NO abnormality is not localized to the vascular endothelium but may occur in several other tissues as well.

Oral administration of L-NG-nitro-L-arginine, a NO synthase inhibitor, to rats with elevated blood pressure, decreased plasma level and urinary excretion of nitrate ions, and increased peripheral vascular resistance. Infusion of NG-monomethyl 1-L-arginine (L-NMMA), an inhibitor of NOS, elevated mean arterial pressure, decreased heart rate and cardiac index, increased total peripheral resistance, urinary sodium and fractional sodium excretions were increased but creatinine clearance remained unchanged. These results suggest that basal generation of eNO regulates peripheral vascular resistance and normal blood pressure.

**SALT, CYCLOSPORINE, CALCIUM, NO, AND HYPERTENSION**

Inhibition of basal eNO synthesis decreases renal blood flow and sodium excretion. Intrarenal inhibition of eNO synthesis reduces sodium excretion in response to changes in renal arterial pressure without any effect on renal autoregulation, suggesting that eNO has a role in pressure natriuresis. NO released from macula densa can affect afferent arteriolar constriction. NO can influence the effects of angiotensin on tubular reabsorption, alter solute transport, and play an active role in the glomerulus. In contrast, in conditions such as glomerulonephritis, enhanced NO generation is from the infiltrating macrophages suggesting a role for iNO in proteinuria, mesangial proliferation and other features seen in this condition.

In hypertensive patients, increase in blood pressure by high salt diet correlated with decreased plasma nitrate plus nitrite, and increased asymmetrical dimethylarginine (ADMA) concentrations that were reversed to normalcy following salt restriction, suggesting that salt intake modulates eNO synthesis and this could be a mechanism for salt sensitivity in human hypertension via change in ADMA levels.

Subcutaneous injections of cyclosporine to experimental animals resulted in impaired vascular response to acetylcholine that was normalized by pretreatment with SOD, implying that cyclosporine-induced endothelial dysfunction and hypertension are due to increased $O_2^-$ generation and concomitant decreased production of eNO. Cyclosporine also increased endothelin-1 and decreased endothelial NOS both in the aorta and the renal cortex lending support to the concept that an increase in $O_2^-$ generation, decreased eNO synthesis and enhanced endothelin occurs in hypertension.

Dietary calcium reduces blood pressure, possibly by
stabilizing the arterial membranes, blocking its own entry into the cell, rendering the arterial smooth muscles less likely to contract,26 and by enhancing eNO synthesis.26,27 Although there is some controversy with regard to the role of NO in salt-induced hypertension,28 it is likely that high salt intake initially stimulates eNO production to maintain blood flow and when the salt intake continues for a prolonged period eNO synthesis falls leading to the development of hypertension. This so explanation is supported by the observation that supplementation of L-arginine reduces high salt intake-induced hypertension.29,31 Decrease in blood pressure in hypertensives following potassium chloride intake32 suggests that potassium enhances eNO synthesis and release and thus reduces blood pressure. It is likely that at optimum physiologic concentrations of sodium, potassium, calcium, and magnesium the synthesis and release of eNO and other vasodilators such as PGE1 and PGI2 remain adequate to maintain normal blood pressure.26,33

Asymmetrical dimethylarginine and hypertension

One endogenous factor that interferes with NO synthesis is asymmetrical dimethylarginine (ADMA). Endothelial dysfunction in hypercholesterolemic individuals could be related to plasma concentrations of ADMA,34 is a strong and independent predictor of overall mortality and cardiovascular outcome in hemodialysis patients,35 and increased plasma concentrations of ADMA have been reported in hypertension and pre-eclampsia.36,37 High serum concentrations of ADMA were associated with increased risk of acute coronary events suggesting that endothelial dysfunction as a cause of coronary heart disease (CHD).38 This suggests that displacing ADMA with excess L-arginine could be useful in hypertension, pre-eclampsia, and CHD. In offspring of patients with essential hypertension in whom endothelial dysfunction is present could be reverted to normal by intra-brachial L-arginine.39,40 These results suggest that impairment in eNO production precedes the onset of hypertension that could be due to increase in the levels of ADMA.

Anti-hypertensive drugs possess anti-oxidant actions and enhance eNO synthesis

ACE inhibitors and calcium antagonists not only reduced blood pressure but increased plasma 6-keto-PGF₁α, a metabolite of PGI₂, eNO, and normalized cGMP levels as well.41,42 These results suggest that anti-hypertensive drugs bring about their actions by increasing eNO, PGI₂, and bradykinin formation. Previously, I showed that NO is a potent inhibitor of ACE activity in vitro,43 and both calcium antagonists and β-blockers inhibit free radical generation and lipid peroxidation process.1 Thus, anti-hypertensive drugs inhibit O₂⁻ generation, increase the half-life of eNO, and enhance eNO production (see Fig. 1).

Transforming growth factor-β (TGF-β) in hypertension

Circulating levels of TGF-β were significantly higher in hypertensives compared with normotensives.44,45 Studies suggested that TGF-β1 gene at chromosome 19q13.1 could be a candidate susceptibility locus for hypertension.46 Patients with albuminuria in hypertension and diabetic nephropathy showed elevated plasma TGF-β concentration whereas angiotensin receptor blockade and ACE inhibitors decreased its excretion.47-49 Angiotensin II in association with endothelin and TGF-β activates collagen type I gene resulting in increased formation of extracellular matrix protein in the renal cortex and aorta that leads to renal scarring and end-stage renal disease in patients with hypertension and diabetes mellitus. In contrast, chronic anti-TGF-β antibody significantly reduced blood pressure, proteinuria, and the degree of glomerulosclerosis and renal medullary fibrosis in experimental animals.50 Increased synthesis of collagen was reported in vitro in the presence of high glucose, and this was reduced by the neutralization of TGF-β indicating that TGF-β enhances collagen synthesis.51 In this context, it is important to note that angiotensin II, high salt diet, and cyclosporine stimulated TGF-β expression in the kidney and endothelium.52 High salt intake and high glucose stimulated eNO synthesis reported,53,54 thus could be considered as a compensatory phenomenon. This is so since, NO blocks TGF-β synthesis and thus, suppresses matrix protein synthesis.
by mesangial cells\textsuperscript{55,56} and TGF-\(\beta\) in turn inhibits eNO synthesis.\textsuperscript{37} This indicates that there is a close interaction and feed back regulation between TGF-\(\beta\) and NO. Thus, NO seems to play an important role in the pathogenesis of hypertension irrespective of the underlying cause.

**Long-chain polyunsaturated fatty acids and hypertension**

Dietary linoleic acid (LA, 18:2 \(\omega-6\)) is converted to gamma-linolenic acid (GLA, 18:3 \(\omega-6\)) and dihomo-GLA (DGLA, 20:3 \(\omega-6\)) by specific enzymes, which are controlled by genetic, hormonal, and nutritional factors.\textsuperscript{58-62} Saturated fatty acids reduce the formation of PGE\(_1\) and PGI\(_2\), elevate blood pressure, and exacerbate spontaneous hypertension,\textsuperscript{61} whereas supplementation of LA and DGLA augment the synthesis of PGE\(_1\) and PGI\(_2\) and prevent the increase in blood pressure induced by saturated fats. Fish oil, a rich source of \(\omega-3\) fatty acids: eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), reduced blood viscosity and lowered blood pressure.\textsuperscript{61} EPA and DHA inhibit the formation of thromboxane \(\alpha\) (TXA\(_\alpha\)), a potent vasoconstrictor and platelet aggregator; enhance that of PGI\(_2\), a vasodilator and platelet anti-aggregator; and lower the tissue levels of AA and enhances those of DGLA, the precursor of PGE\(_1\). Thus, it is expected that provision of adequate amounts of \(\omega-3\) and \(\omega-6\) fatty acids in the right proportion may help to prevent the development of hypertension (see Fig. 2 for the metabolism of essential fatty acids).

LCPUFAs, especially DGLA, AA, EPA and DHA, not only form precursors to PGE\(_1\), PGI\(_2\), and PGI\(_3\) but also inhibit ACE activity\textsuperscript{63,64} and augment the synthesis of eNO. L-arginine and eNO, in turn, are known to up-regulate the metabolism of LCPUFAs.\textsuperscript{65-67} This suggests that in the presence of low tissue concentrations of LCPUFAs the synthesis and release of eNO will be decreased and vice versa. Since endothelial cells are the major source of NO, it is possible that LCPUFA content of endothelial cells would have a major impact on the synthesis and release of NO. This is supported by the observation that in patients with hypertension the plasma concentrations of LA, AA, and DHA and eNO are low.\textsuperscript{66} Normal Asian Indians, who are at high risk of developing insulin resistance and hypertension, have significantly lower concentrations of AA, EPA, and DHA than do normal, healthy Canadians and Americans in their plasma phospholipids.\textsuperscript{68} Further, LCPUFAs inhibit the synthesis of tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and other pro-inflammatory cytokines,\textsuperscript{69} that are known to have a significant role in insulin resistance and metabolic syndrome X. Hence, low plasma concentrations of LCPUFAs seen in Indian Asians could lead to an increase the production of TNF-\(\alpha\), IL-6 that, in turn, may cause insulin resistance, hypertension, and metabolic syndrome X.\textsuperscript{69,70} Despite these evidences, it is not clear how, when and why these molecules render an individual to develop hypertension. In this context, it is interesting to note that hypertension could be a low-grade systemic inflammatory condition and seeds of its occurrence in adult life are sown during the perinatal period.

**Essential hypertension and low-grade systemic inflammation**

Elevated plasma IL-6 levels in women with hypertension and insulin resistance in men has been described.\textsuperscript{71} A direct correlation between blood pressure and levels of ICAM-1 (intercellular adhesion molecule-1) and IL-6 was noted.\textsuperscript{72} A direct relationship between plasma CRP (C-reactive protein) levels and advancing age, BMI (body mass index), systolic blood pressure, HDL, smoking, and hormone replacement therapy was reported in the Women’s Health Study.\textsuperscript{73} These observations suggest that low-grade systemic inflammation occurs in hypertension. Our earlier observation that in uncontrolled essential hypertension, elevated plasma lipid peroxides and significantly higher levels of leukocyte O\(_2^-\), low eNO, decreased vitamin E and superoxide dismutase (SOD) in RBC membranes occurred lends support to this view.\textsuperscript{1}

Angiotensin II activates leukocyte NADPH oxidase and enhanced O\(_2^-\) generation.\textsuperscript{15} Plasma adiponectin concentrations were enhanced and insulin resistance was decreased after the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers.\textsuperscript{74} \(\beta\)-blockers and calcium antagonists suppressed O\(_2^-\) generation.\textsuperscript{14,15} This suggests that that \(\beta\)-blockers and calcium antagonists could augment plasma

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Fig. 2 : Metabolism of essential fatty acids.
adiponectin levels similar to ACE inhibitors and angiotensin II receptor blockers. These results suggest that anti-hypertensive drugs (except β-blockers) reduce peripheral vascular resistance and enhance insulin action by augmenting adiponectin secretion.

**Homocysteine In Cardiovascular Diseases**

Increased plasma levels of homocysteine are known to be associated with CHD. Homocysteine undergoes auto-oxidation leading to the formation of homocystine, homocysteine-mixed disulfides, and homocysteine thiolactone, during which O\(_2^−\) and hydrogen peroxide (H\(_2\)O\(_2\)) are generated that could cause endothelial cytotoxicity and dysfunction.\(^{75}\) These free radicals induce lipid peroxidation that, in turn, oxidizes low-density lipoprotein leading to the formation of oxidized LDL (Ox-LDL) that could initiate and perpetuate atherosclerosis. Homocysteine increases Factor V and Factor XII activity, decreases protein C activation, inhibits thrombomodulin expression, induces tissue factor expression, suppresses heparan sulfate expression, and reduces the binding of tissue-type plasminogen activator to its endothelial cell receptor: annexin II, reducing the production of eNO and PG\(_{1\alpha}\), events that increase the generation of thrombin and enhances thrombotic tendency.\(^{75,77}\) Normal endothelial cells release NO or a related S-nitrosothiol that induces the formation of S-nitroso-homocysteine,\(^{79}\) a potent vasodilator and platelet anti-aggregator. Thus, S-nitroso-homocysteine attenuates sulfhydryl-dependent generation of H\(_2\)O\(_2\), and nullifies the prothrombotic actions of homocysteine. However, continued exposure of endothelium to homocysteine reduces the production of eNO and this leads to homocysteine-mediated injury to the endothelium and initiation of atherosclerosis and/or thrombus formation or acceleration of existing atherosclerosis. Hence, methods designed to enhance eNO production could restore the antithrombotic properties of endothelium and prevent atherosclerosis.

Furthermore, homocysteine inhibits glutathione peroxidase (GP) activity in vitro and reduces its synthesis in endothelial cells. GP catalyzes the reduction of both H\(_2\)O\(_2\) and lipid peroxides to their corresponding alcohols, and thus, prevents inactivation of eNO. Inhibition of GP activity by homocysteine is responsible for its (homocysteine) vascular toxicity.\(^{79}\) Homocysteine induces smooth muscle cell migration and proliferation,\(^{80}\) upregulated vascular cell adhesion molecule-1 expression, and enhanced monocyte adhesion. Folic acid not only reduced plasma homocysteine levels, but also reduced oxidized LDL-stimulated release of GRO\(_{α}\), ENA-78, and interleukin-8 (IL-8), and CC chemokines: monocyte chemoattractant peptide-1 and RANTES in peripheral blood mononuclear cells. Oxidized-LDL-induced release of ENA-78 by peripheral blood mononuclear cells was reduced when cells were incubated with folic acid.\(^{81}\)

Low circulating vitamin B\(_{12}\) is associated with higher C-reactive protein (CRP), a marker of inflammation, levels independent of plasma homocysteine levels.\(^{82}\) Vitamin B\(_{12}\) enhances the production of PGE\(_{1}\), a potent vasodilator, platelet anti-aggregator, and anti-inflammatory eicosanoid.\(^{83,84}\) Thus, vitamin B\(_{12}\) has anti-inflammatory actions.

Homocysteine enhanced the activity of HMG-CoA reductase in human umbilical vein endothelial cells (HUVECs), and enhanced cellular cholesterol content, whereas simvastatin, an HMG-CoA reductase inhibitor, reduced HUVECs cholesterol content and prevented homocysteine-induced suppression of eNO production in a dose dependent manner.\(^{85}\) Thus, homocysteine facilitates atherosclerosis by enhancing cholesterol synthesis.

**Nutritional factors, oxidant stress and cardiovascular diseases**

Folic acid, H\(_{4}\)B (tetrahydrobiopterin), and insulin suppress O\(_2^−\) production and prolong the half-life of NO\(^{26,75,86}\) and thus, preserve endothelium-dependent vasodilation, which also accounts for their anti-inflammatory property.\(^{26,75,86,87}\) Folic acid and H\(_{4}\)B attenuate cholesterol-induced endothelial dysfunction\(^{86}\) and coronary hyperreactivity to endothelin.\(^{88}\) Folic acid restores tissue stores of H\(_{4}\)B, whereas H\(_{4}\)B stimulated endothelial cell proliferation. H\(_{4}\)B augments NO generation. Vitamin C stabilizes H\(_{4}\)B and increases its intracellular levels and thus, enhances eNOS activity.\(^{89,90}\) and vitamin C also enhances NO release by suppressing the formation of total S-nitrosothiols and S-nitrosoalbumin.\(^{92}\) These results suggest that when L-arginine, folic acid or 5-methyltetrahydrofolic acid, the active form of folic acid, and H\(_{4}\)B when provided together could stimulate eNO synthesis.

Does adult hypertension have its origins in the perinatal period?

One of the issues that need to be established is when events that trigger the development of hypertension are initiated? There is reasonable evidence to suggest that adult hypertension has its origins in the perinatal period. For instance, it was reported that breast milk consumption lowered blood pressure in later life. Previously, I attributed this beneficial action to the presence of significant amounts of LCPUFAs in human milk.\(^{93}\) This is supported by the observation that breast-fed infants had a significantly higher percentage of LCPUFAs in their tissues compared with those of the formula-fed group. It was reported that DHA deficiency in the perinatal period can raise blood pressure later in life, even when animals were subsequently repleted with this fatty acid. Animals raised on an LCPUFA-deficient diet underdrank water and overingested sodium,
features that are somewhat similar to high salt intake-induced hypertension. But it is not known whether these LCPUFA-deficient animals had any abnormalities in the NO-O$_2^-$ generation and pro-inflammatory cytokine profile. But, based on the current evidence it is reasonable to predict that there would be a decrease in eNO synthesis/half-life and an increase in O$_2^-$ generation and IL-6 and TNF-α levels. This implies that availability of adequate amounts of DHA and other LCPUFAs during the perinatal period i.e. during the critical periods of growth prevents the development of hypertension in adulthood. Both EPA and DHA have been reported to inhibit the development of proteinuria and suppressed hypertension in stroke-prone spontaneously hypertensive rats, and prevented the exaggerated growth of vascular smooth muscle cells from these animals through suppression of TGF-β (see discussion above). Since, LCPUFAs interact with other nutrients and L-arginine-NO-O$_2^-$system, modulate ACE enzyme activity, and lower blood pressure (as discussed above), this suggests that there is a close interaction between L-arginine-NO-O$_2^-$system, other nutritional factors including saturated fats, salt, magnesium, calcium, various pro-inflammatory cytokines including TNF-α, and TGF-β, sympathetic and parasympathetic system.

Saturated fats, trans-fats and cholesterol inhibit Δα and Δδ desaturases, enzymes that are essential to convert dietary LA and ALA to their respective LCPUFAs (GLA, DGLA and AA and EPA and DHA respectively) this may explain their ability to cause hypertension and initiate and perpetuate atherosclerosis. This inhibitory action of saturated and trans fats and cholesterol on LCPUFAs formation could also be responsible for low-grade systemic inflammation seen in hypertension due to an increase in IL-6 and TNF-α levels since normally LCPUFAs have a negative feed back control on the formation of these cytokines. Thus, as depicted in Figure 1, a delicate balance is normally maintained between various vasoactive factors, nutrients, and cytokines and this interaction between these factors has its origins during the perinatal period.

**CONCLUSION**

Blood pressure is controlled by genetic, hormonal, and nutritional factors and genetic predisposition to develop hypertension is precipitated by either hormonal and/or nutritional factors. Epidemiological evidences suggest that dietary factors play a critical role in the development and progression of hypertension. Both obesity and hypertension are associated with high intake of saturated fats, high-energy food intake, high salt intake, reduced intakes of calcium and potassium and vitamins A and C. It is evident from the preceding discussion that dietary high salt intake, calcium, various anti-hypertensive drugs, angiotensin II, and cyclosporine interact with the NO-O$_2^-$ system and thus, modulate blood pressure. LCPUFAs enhance eNO synthesis and suppress O$_2^-$ generation and thus, lower blood pressure. In addition, LCPUFAs suppress the production of TGF-β, a cytokine that is closely associated with increase in blood pressure and target organ damage both in hypertension and diabetes mellitus. In contrast, eNO not only has anti-hypertensive action but also suppresses TGF-β production and thus, protects the kidney and lowers albuminuria in patients with hypertension and diabetes mellitus. Thus, both eNO and LCPUFAs modulate the synthesis and actions of TGF-β in addition to interacting with each other. This interaction between various factors/molecules play a crucial role in the pathobiology of hypertension is not only interesting but also suggests that the pathobiology of hypertension is complex (see Figure 1). But, it is not yet clear which is the initial trigger for the development of hypertension. Is it the perinatal deficiency of LCPUFAs as proposed earlier or is there an impaired basal eNO production as demonstrated in the offspring of patients with essential hypertension? High dietary intake of saturated and trans fats present in the Western diet could reduce the formation of vasodilator PGs, eNO, and increase TNF-α, IL-6, and O$_2^-$ that ultimately results in elevation of blood pressure. These saturated fats interfere with the metabolism and formation of LCPUFAs and induce their deficiency (which could be sub-clinical). Reduced endothelial cell deficiency of LCPUFAs would lead to eNO deficiency that initiates the development of hypertension. If so, this implies that perinatal supplementation of LCPUFAs will prevent and/or postpone the development of hypertension in adult life. LCPUFAs are essential for both somatic and brain growth and development of the fetus and newborn, and have several other important physiological actions in various tissues, organs and systems. It is evident from the preceding discussion that perinatal supplementation of LCPUFAs could be of benefit in the prevention of adult hypertension. Such a study is of major public-health importance.

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