Possible Role of Oxidative Stress in the Pathogenesis of Hypertension

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Recently oxidative stress has been proposed as the cause of hypertension. An imbalance in superoxide and nitric oxide production may account for reduced vasodilation, which in turn can favor the development of hypertension. In vitro and in human studies support this hypothesis. The supplementation of antioxidants, particularly in the form of fresh fruit and vegetables, reduces blood pressure, supporting a role for free radicals in hypertension.

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It is estimated that 30% of the adult population may have arterial hypertension (1) and that 30–60% of diabetic patients have associated hypertension (2).

Hypertension is often associated with metabolic abnormalities such as dyslipidemia, impaired glucose tolerance, insulin resistance, and obesity. This is known as the "metabolic syndrome." A series of observations has provoked much speculation and interest in the phenomenon of insulin resistance as a common factor underlying the link between obesity, diabetes, and hypertension (3). Epidemiological data linking hyperinsulinemia, obesity, and hypertension seem to be associative rather than causal, but this is inconsistent (4). It has become increasingly evident that the relationship between insulin, insulin resistance, and blood pressure varies according to racial group (5). On the other hand, chronic and marked hyperinsulinism in patients with insulinomas is not associated with elevated blood pressure values (6). Although the causal relationship between insulin and blood pressure is still inconclusive, evidence suggests that a reduced hepatic insulin clearance may contribute to increased insulin levels in hypertension (7,8). To summarize, current experimental findings linking hyperinsulinemia or insulin resistance to hypertension have been provocative: many inconsistencies remain and causal relationships have not been established. A recent hypothesis pointed out the possible role of oxidative stress as a key player in the pathogenesis of insulin resistance, β-cell dysfunction, and hypertension (9).

OXIDATIVE STRESS AS CAUSE OF HYPERTENSION

— Regarding hypertension, endothelial cells play a major role in arterial relaxation. Nitric oxide is the factor released by the endothelium that causes vascular relaxation (10). The half-life of nitric oxide is only a few seconds, since it is rapidly degraded by the oxygen-derived free radical superoxide anion. Superoxide anion is a major determinant of nitric oxide (NO) biosynthesis and bioavailability and can thus modify endothelial function. It can also act as a vasoconstrictor. In addition, nitric oxide synthase (NOS), and in particular the endothelial isoform of NOS (eNOS), is now recognized as an important source of superoxide (11,12). The finding that eNOS can generate superoxide rather than NO in response to atherogenic stimuli has led to the concept of "NOS uncoupling," where the activity of the enzyme for NO production is decreased, in association with an increase in NOS-dependent superoxide production (13). As a result, eNOS may become a peroxynitrite generator, leading to a dramatic increase in oxidative stress, since peroxynitrite formed by the NO-superoxide reaction has additional detrimental effects on vascular function by oxidation of cellular proteins and lipids (14).

A decrease in NO bioavailability and an increase in oxidative stress are present in human hypertension (15). These findings are based, in general, on increased levels of biomarkers of lipid peroxidation and oxidative stress (16–18). Decreased antioxidant activity (superoxide dismutase and catalase) and reduced levels of reactive oxygen species (ROS) scavengers (vitamins E and C and glutathione) may also contribute to oxidative stress (16,17,19). Furthermore, L-arginine, a NO precursor that augments endothelium-dependent vasodilation, acutely improves endothelium-dependent flow-mediated dilation of the brachial artery in patients with essential hypertension (20).

Growing evidence indicates that NADPH-driven generation of ROS and activation of reduction-oxidation (redox)-dependent signaling cascades are critically and centrally involved in the role of Ang II-induced hypertension (21). Ang II elicits its actions via two distinct receptors: the AT1 and Ang II type 2 receptors (AT2) (22). Although the AT2 receptor is usually expressed at low density in adults, it is upregulated in pathological states such as vascular injury, salt depletion, heart failure, or cardiac hypertrophy (23). Pharmacological studies indicate that there is crosstalk between AT1 and AT2 receptors and stimulation of the AT2 receptor opposes the effect of the AT1. Whereas stimulation of the AT1 receptor leads to cellular growth, angiogenesis, and vasoconstriction, AT2 receptor stimulation causes opposite effects, antiproliferation, anti-angiogenesis, and vasodilation (23). Thus, AT1 and AT2 receptors are ideal candidates for maintaining a proper balance between the vasodilator agent NO and ROS. Recent data demonstrate that Ang II, acting through the AT1 receptor, stimulates nonphagocytic NADPH oxidase, causing the accumulation of superoxide, hydrogen peroxide, and peroxynitrite (24).

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Abbreviations: DASH, Dietary Approaches to Stop Hypertension; ROS, reactive oxygen species; RVD, renovascular disease.

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Thus, in pathological states, the stimulation of the AT1 receptor by increased circulating or tissue levels of Ang II will produce an inflammatory response. In contrast, blockade of the AT1 receptor, which is accompanied by increased circulating Ang II levels, will stimulate the AT2 receptor and oppose the effect of AT1 receptor activation, a mechanism that appears to be involved in the beneficial effects of the angiotensin receptor blockers (24). These beneficial effects may be exerted at various levels, as Cipollone et al. (25) demonstrated that the AT1 receptor antagonist irbesartan decreases inflammation and inhibits cyclooxygenase (COX) and prostaglandin (PG)E_2-dependent synthase (COX-2/mPGES-1) expression in plaque macrophages, and this effect may in turn contribute to plaque stabilization by inhibition of metalloproteinase-induced plaque rupture (25).

Human studies seem to support a role of oxidative stress in the development of hypertension. In diabetes and obesity, which are commonly associated with hypertension, chronic oxidative stress is present (26). Conversely, caloric restriction in the obese and fasting in normal subjects leads to a marked reduction in ROS generation and other indexes of oxidative stress (26,27). Studies using nonspecific markers of oxidative damage have observed higher superoxide and hydrogen peroxide production in hypertensive subjects, which returned to levels observed for control subjects after blood pressure reduction (28). A reduction in superoxide dismutase and glutathione peroxidase activity have been observed in newly diagnosed and untreated hypertensive subjects, compared with control subjects, with superoxide dismutase activity being inversely correlated with blood pressure within the hypertensive group, but not the control group (29). Higher production of hydrogen peroxide has also been observed in treated and untreated hypertensive subjects compared with normotensive subjects, with a significant correlation between hydrogen peroxide levels and systolic blood pressure (30). In addition, both malignant and nonmalignant hypertensive subjects had higher lipid hydroperoxide production, as measured by the ferrous oxidation–xylenol (FOX) assay, compared with control subjects (31).

Accordingly, Minuz et al. (32) recently demonstrated that oxidant stress is markedly increased in hypertensive patients with renovascular disease (RVD) compared with either patients with essential hypertension and comparable levels of blood pressure or healthy normotensive subjects and suggested that increased oxidative stress might be related to renal artery stenosis and activation of Ras. These authors found a significant positive correlation between the urinary excretion of 8-*iso*-prostaglandin $F_{2\alpha}$ (a reliable marker of in vivo lipid peroxidation) and renal vein renin ratio (a highly specific functional test for the detection of renal artery stenosis, renal hypoperfusion, and activation of Ras) (33). Moreover, Minuz et al. (32) found a significant correlation between the reduction in 8-*iso*-prostaglandin $F_{2\alpha}$ excretion after successful angioplasty in RVD hypertensive patients with baseline Ang II ratio and renal vein renin ratio. All these findings provide additional evidence for a causal link between renin activation and enhanced oxidative stress and may suggest that Ang II is a stimulus for oxidant stress in RVD (33).

ANTIOXIDANTS AND THEIR EFFECTS ON OXIDATIVE STRESS IN HYPERTENSION

— If oxidative stress is indeed a cause or consequence of hypertension, then reductions in oxidative damage may result in a reduction in blood pressure. Antioxidants are compounds that are able to trap ROS and thus may be capable of reducing oxidative damage and possibly blood pressure.

The Dietary Approaches to Stop Hypertension (DASH) study has examined the effect of a diet rich in fruit and vegetables and a combination diet rich in fruits and vegetables, low-fat dairy, reduced fat, and increased protein and fiber intake (34). The fruit and vegetable diet and the combination diet both reduced clinical and ambulatory blood pressure in hypertensive and normotensive subjects more so than a control diet. The combination diet was most effective and hypertensive subjects showed the greatest benefit. The reductions in blood pressure were not due to reduced sodium, BMI, or alcohol, which did not change during the study for any group. In addition, blood pressure reductions began in the second week of intervention and continued for the 6-week duration of the study, reaching targets observed after drug therapy (34). A substudy using the DASH diet demonstrated that this modification in diet resulted in an increase in serum antioxidant capacity and a decrease in malondialdehyde, an in vitro marker of lipid peroxidation, suggestive of a reduction in oxidative stress (35). The DASH 2 study has further highlighted the benefit of following the combination DASH diet as well as reducing sodium intake. This combination effect reduced blood pressure in both hypertensive and normotensive patients greater than either dietary change alone and, as with the DASH diet, was most effective in the hypertensive subjects (36). A 6-month primary care intervention, aiming to increase fruit and vegetable intake to five servings a day in hypertensive subjects, revealed increases in α- and β-carotene, lutein, β-crytoxanthin, and vitamin C and decreases in systolic and diastolic blood pressure (37). A recent diet and lifestyle modification program that incorporated the DASH diet in addition to increased fish intake, increased physical activity, and moderated alcohol intake has also shown a benefit on blood pressure. In this study, treated hypertensive subjects on the 4-month diet and lifestyle program had significant reductions in blood pressure compared with the control group. However, at the 1-year follow-up, the difference in blood pressure was no longer significant and effects on markers of oxidative damage were not assessed (38).

A number of trials have investigated the use of a combination antioxidant supplement rather than dietary incorporation. However, most of the studies investigating combination antioxidant therapy have looked at all-cause or cardiovascular mortality, rarely focusing on blood pressure as a primary end point. One of the largest studies, undertaken by the Heart Protection Collaborative Group (39), saw no improvement in blood pressure after treatment with an ascorbic acid, synthetic vitamin E, and β-carotene combination versus placebo after 5 years in subjects thought to be at high risk of cardiovascular disease. Furthermore, a meta-analysis has revealed no clear benefit after antioxidant supplementation in either all-cause or cardiovascular mortality (40).

The use of a combination supplement (zinc, ascorbic acid, α-tocopherol, and β-carotene) versus placebo has been investigated in both treated hypertensive and normotensive subjects. The combination supplement resulted in a significant reduction in systolic blood pressure in both hypertensive and normotensive groups versus placebo and a nonsignificant reduction in diastolic blood pres-

sure. Markers of oxidative damage were not measured, although levels of circulating vitamins increased (41).

These data are consistent with the evidence that several antioxidants, particularly glutathione and vitamin C, have shown a blood pressure–lowering effect in both normal and hypertensive subjects, with or without diabetes (42,43).

While dietary antioxidants seem to have beneficial effects on hypertension and more in general on the cardiovascular risk, antioxidant supplementation has been shown to be ineffective or even dangerous (44). One of the possible explanations is that, in the diet, there is a mix of antioxidants and it is well recognized that they work as a continuous chain, while supplementation is usually given using one or two substances. Therefore, the antioxidant chain is not completely available. Moreover, it is well known that after scavenging free radicals, if an antioxidant is not restored by the following antioxidant in the chain, it begins to be a prooxidant. Not surprising, therefore, the final effect of such supplementations would be no effect or a damaging effect. Caution should also be exercised in micronutrient supplementation, which can induce oxidative stress (45).

ANTIHYPERTENSIVE TREATMENT

— Antihypertensive drug therapy, in addition to its blood pressure–lowering properties, may also have beneficial effects on oxidative stress (46). Treatment with a β-blocker or angiotensin receptor blockers has been shown to reduce both blood pressure and markers of oxidative damage, despite no significant relationship between the two variables (47). Similarly, other studies have reported beneficial effects on blood pressure, oxidative stress, and endothelial function after treatment with ACE inhibitors (48), AT1 blockers (49), or calcium antagonists (50).

CONCLUSIONS

— A unifying hypothesis has been proposed for pathogenesis of cardiovascular disease through the enhanced oxidative stress of arterial wall between hypertension and atherosclerosis (9). At present, great interest is focused on antioxidant properties of currently available antihypertensive drugs and supplementation with antioxidant principles. Nevertheless, specifically designed clinical trials are currently needed to document the effective pathogenetic role of oxidative stress in hypertension and the possibility that its reversal can add effective advantages in antihypertensive treatment.

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