Oxidative stress may explain how hypertension is maintained by normal levels of angiotensin II

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Abstract

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It is well known that essential hypertension evolves in most patients with "near normal" levels of plasma renin activity. However, these levels appear to be responsible for the high levels of arterial pressure because they are normalized by the administration of angiotensin II converting inhibitors or angiotensin receptor antagonist. In experimental animals, hypertension can be induced by the continuous intravenous infusion of small doses of angiotensin II that are not sufficient to evoke an immediate pressor response. However, this condition resembles the characteristics of essential hypertension because the high levels of blood pressure exist with normal plasma levels of angiotensin II. It is suggested that small amounts of angiotensin whose plasma levels are inappropriate for the existing size of extracellular volume stimulate oxidative stress which binds nitric oxide forming peroxynitrite. The latter compound oxidizes arachidonic acid producing isoprostaglandin F2α (an isoprostane) which is characterized by a strong antinatriuretic vasoconstrictor renal effect. In this chain of reactions the vasoconstrictor effects derived from oxygen quenching of nitric oxide and increased isoprostane synthesis could explain how hypertension is maintained with normal plasma levels of renin.

Introduction

Essential hypertension is one of the most prevalent diseases in western societies (1). Although the pathogenesis of this disease has remained so far elusive (1), there is general agreement that the disease is related to renal dysfunction and that such a dysfunction is mainly characterized by inappropriate circulating levels of renin. This assumption is based first on the efficacy of converting enzyme inhibitors or angiotensin receptor antagonists in reducing blood pressure in essential hypertension (2,3), and second, hypertension can be induced in normotensive humans or animals by transplantation of the kidney from hypertensive subjects (2). Alternatively, hypertension can also be cured by transplanting the kidney from normotensive donors into a previously hypertensive individual (2). One of the major stumbling blocks explaining the role played by these two elements, the kidney and renin, in the pathogenesis of essential hypertension is that the levels of circulating plasma renin are within the normal range in most essential hypertensives (3).

The vasoconstrictor effects of normal levels of angiotensin

To a large extent, one can suggest that the "normal" levels of plasma renin activity observed in most patients with essential hypertension are not normal but inappropriate with respect to the levels of blood pressure (3-5). In fact, if systemic pressure is elevated and renal perfusion pressure increases, the release of renin is immediately suppressed (3). This observation leads to the question on the extent to which hypertension can be induced by "inappropriate" levels of renin. Such a postulate was first supported by the observation of Dickinson et al. (6) who demonstrated in 1963 in rabbits that the infusion of a very small amount of angiotensin II (ang II) that was not sufficient to elicit an immediate elevation of blood pressure produced nonetheless chronic hypertension. This led to the proposal of a new modality of a vasoconstrictor effect produced by angiotensin called slow responses to ang II (7,8). It should be clarified that the fast pressor responses are produced by relatively high concentrations of angiotensin II which induce rapid smooth muscle contraction when administered as a bolus (9,10). The response reaches the maximal pressor response in seconds and returns to normal levels in 2-3 min. The slow pressor response needs 5-10 h to develop, reaching a maximum peak 3-5 days after the onset of the infusion (8). The important characteristic of the slow pressor response is that it is not specific for any particular animal species since it has been demonstrated in man (11), rats (12), rabbits (6), and dogs (7). In our laboratory we have demonstrated similar responses in the swine model (13). Also, it appears that the slow pressor response evolves at doses of angiotensin that are insufficient not only to produce an immediate elevation of blood pressure but also to stimulate steroidogenic and dipsogenic actions typical of blood-borne angiotensin (12,14). The consistent delayed action of small subpressor doses of angiotensin in producing an increase in blood pressure suggests that there is a time requirement for the activation of additional vasoconstrictor processes which can then trigger an autocatalytic action accelerating or potentiating the vasoconstrictor effect of ang II. For example, Brown et al. (12) demonstrated in rats that the administration of 20 ng kg^{-1} min^{-1} of ang II did not alter blood pressure during the first hour of infusion but on the morning of the following day there was a significant increase by 14 mmHg. On day 7 blood pressure had reached 153 ± 6 mmHg. In a study conducted in a separate group of animals, this investigator showed that the amount of angiotensin to be infused for one hour to achieve a comparable level of blood pressure was 279 ng kg^{-1} min^{-1}. In these studies, the circulating levels of ang II on day 7 of infusion of 20 ng kg^{-1} min^{-1} were 230 pg/ml, which is not much different from the 150 pg found in animals during the infusion of 20 ng kg^{-1} min^{-1} for one hour when blood pressure was still normal. In contrast, the level of ang II found in acute animals (146 ± 3 mmHg) infused with 270 ng kg^{-1} min^{-1} for one hour was approximately 2500 pg/ml. This study showed that a small amount of angiotensin could trigger a delayed mechanism that produced vasoconstriction or alternatively potentiated ang II leading to hypertension. In an extensive review on this subject, Lever (8) ruled out the participation of other mechanisms such as the central nervous system, vascular hypertrophy, etc. In this survey, we will examine the possibility that the slow responses to ang II may be due to a vasoconstrictor effect of oxidative stress.

Role of ang II, oxidative stress, nitric oxide, and isoprostanes in the slow responses to ang II

Ang II has been shown to stimulate the production of superoxide that quenches nitric oxide (NO) (15,16). It is known, on the

other hand, that the chemical combination of superoxide with NO yields peroxynitrite (16) which is a potent oxidant that could oxidize arachidonic acid, releasing a potent renal vasoconstrictor, antinatriuretic substance, 8-isoprostaglandin $F_{2\alpha}$ (an isoprostane). This sequence of events is illustrated in Figure 1 (16). Additionally, ang II may also stimulate endothelin (ET) synthesis (17-19) which can be further increased by the oxidative stress cascade mentioned above (20-23). Therefore, the reduced levels of NO, increased isoprostane and increased ET represent potent vasoconstrictor effects which can enhance the vasopressor action of ang II and may explain how hypertension is maintained in pathological situations (such as two kidney, one clip Goldblatt hypertension or essential hypertension) where the levels of angiotensin are frequently found to be normal (24). The importance of these pathogenic events is that in the future the clinician may have a better index of the damage produced by hypertension with inappropriate levels of renin by measuring products of oxidative stress rather than the level of plasma renin activity. Oxidative stress has been shown to produce hypertension and renal damage (25,26).

Oxidative stress

Pryor et al. (16) have shown that oxygen free radicals (superoxide) are constantly being combined with NO, forming peroxynitrite, which is in equilibrium with peroxynitrous acid (superoxide$^-$ + NO → peroxynitrite ⇒ OONO) (16). Peroxynitrite has a higher oxidative capacity than any other compound (16) (Figure 1). An important observation that links superoxide production to an increased level of ang II was obtained by Rajagopalan et al. (15). This study showed that arteries isolated from rats rendered hypertensive by the administration of a large amount of ang II (270 µg/kg) exhibited an impaired relaxation in response to acetyl-

choline associated with an increased level of superoxidation. These alterations were corrected by pretreating the rats with Losartan (an ang II antagonist) or by treatment of vessels with liposome-encapsulated superoxide dismutase. In this study, hypertension was not felt to be responsible for stimulating superoxide production because norepinephrine infusion which raised blood pressure to similar levels as ang II was not accompanied by activation of superoxide. Additional studies of Rajagopalan et al. (15) showed that the stimulation of superoxide production in intact vascular segments was not related to the participation of xanthine oxidase, mitochondrial electron transport, cyclooxygenases, NO synthase and/or lipoxygenases because the response was unaffected by the administration of oxypurinol, rotenone, indomethacin, nitro-L-arginine-methyl ester (L-NAME) or nordihydroguayaretic acid (15). We have recently shown that superoxide can be stimulated by very low doses of ang II in swine because it increases plasma free isoprostanes. This effect was not seen in age-matched control animals that were not treated with ang II.
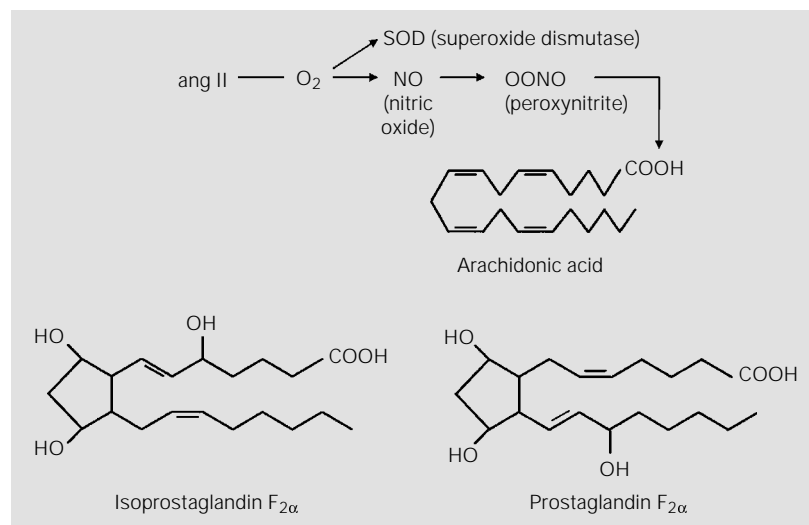

Figure 1 - Ang II induces superoxidation that can be neutralized by superoxide dismutase or could be bound to nitric oxide (NO) forming peroxynitrite. This compound oxidizes arachidonic acid forming isoprostaglandin $F_{2\alpha}$ which has a molecular constitution similar to that of prostaglandin $F_{2\alpha}$.

Endothelin

Whether ET plays a role in mediating oxidative stress or is impacted upon by oxidative stress is not clear. Both ET production and NO synthesis can be stimulated by ang II (17-19,27). In cultured endothelial cells inhibition of NO synthesis can stimulate the release of ET whose effects can be inhibited by Bosentan, a nonspecific ET antagonist (28,29). NO can also regulate the vasoconstrictor effects of ET in vascular smooth muscle (30,31). Supporting the hypothesis that both NO reduction and ET stimulation play a role in mediating the oxidative stress induced as a consequence of slow pressor responses to ang II are data showing that the acute hypertension induced by NO synthase inhibition can be attenuated by acute nonselective ETA/ETB antagonism (32,33), whereas chronic NO synthesis inhibition (4 weeks) cannot be attenuated by acute ETA specific receptor antagonism (34). The role that ET plays in two kidney, one clip Goldblatt hypertension is not clear since oxidative stress, measured by production of isoprostanes, can induce the release of ET from smooth muscle cells (20-22). More directly we have recently observed that stimulation of oxidative stress by hypercholesterolemia in pigs evolves with a reduction in circulating NO and a significant increase in isoprostane and these changes can be obliterated by ET antagonism (35). This indicates the need to evaluate whether ET stimulates oxidative stress or whether oxidative stress stimulates production of ET. Caution should be taken in ascribing to ET a definitive role in experimental hypertension models because ET has been shown to have a potent diuretic and natriuretic effect at doses that do not lower glomerular filtration rate and this would antagonize any hypertensive effect (36,37).

Isoprostanes

Isoprostanes are prostaglandin-like compounds produced by free radical-catalyzed peroxidation of arachidonic acid (38). Although there are 64 compounds that can be theoretically formed by peroxidation of polyunsaturated fatty acids, there are four classes of regioisomers currently found in mammals of which the most abundant is isoprostane (39,40) (Figure 1). This compound is detected in plasma from healthy volunteers at levels of 35 ± 6 pg/ml while urine contained 1.6 ± 0.6 ng/mg of creatinine (41,42). The levels of isoprostanes in plasma exceed by 10-20 times the levels of circulating prostaglandins (41). Isoprostane is increased about 200 times after oxidant injury inflicted by carbon tetrachloride (CCl_4) or the herbicide diquat (41,42). It is also increased by smoking (43). There is evidence showing that, unlike prostaglandins, isoprostanes can be formed while the molecule of arachidonic acid is still esterified to phospholipids from where it can subsequently be released by phospholipases (44). This effect is clearly shown during the administration of CCl_4 which increases the amount of isoprostane bound to liver phospholipids (by 40 times at 2 h) which are then released into the circulation. Free isoprostane peaks in the circulation 8 h after the administration of CCl_4 (45).

Arachidonic acid oxidation can also form iso-D_2/E_2 along with isothromboxane and isoleukotrienes. Although some of these compounds can be detected in tissue, they are not detected in the circulation under normal conditions (40). Another important issue is that isoprostane, the most abundant compound form *in vivo*, has been shown to be the most reliable index of lipid peroxidation (46). This provides an important tool to evaluate oxidative stress *in vivo*. A good review on this issue has been recently published by Morrow and Roberts (40).

Isoprostane can be locally produced in the kidney (20,41). Administration of isoprostanes to the rat (low nanomole range) produces a potent renal vasoconstriction, reducing glomerular filtration rate and renal

blood flow by 40-45% (20,41). These effects appear to be predominantly exerted on the afferent arteriole (20,21). Reckelhoff et al. (47) have shown that aging rats (22 months) exhibit a 50% reduction in glomerular filtration rate and 3-fold increases in renal isoprostane when compared to young rats aged 3-4 months. Chronic treatment (9 months) with the antioxidant vitamin E normalizes renal isoprostane levels and improves glomerular filtration rate significantly (47). In rabbits and rats, isoprostane is also a potent pulmonary artery vasoconstrictor and causes bronchoconstriction in the rat lung (48,49). In addition, isoprostane has been shown to induce a significant release of ET from bovine aortic endothelial cells (23).

An important characteristic concerning the biological activity of isoprostane is that the vasoconstrictor effects are blocked by the thromboxane receptor antagonist SQ29548 (20). However, several lines of indirect evidence (50) show that isoprostane interacts with a receptor in vascular smooth muscle that is distinct from the thromboxane receptor. Studies using molecular cloning strategies will be required to provide unequivocal proof of the existence of a unique isoprostane receptor.

The relationship between sodium intake, plasma renin activity, extracellular fluid volume, and the development of oxidative stress

The proposition that small increments in plasma concentrations of ang II are ultimately responsible for hypertension through the development of oxidative stress appears to be difficult to reconcile with the fact that during dietary sodium restriction the levels of plasma ang II are approximately 10-fold higher than those observed in subjects on a normal sodium diet (3). These conditions are illustrated in Figure 2 which also shows that a progressive increase in sodium intake produces a proportional volume expansion which

exhibits a tight inverse correlation with the circulating levels of plasma renin activity. As shown in the figure, when the levels of extracellular fluid volume have achieved a maximal expansion with high sodium intake, plasma renin activity has virtually disappeared from the circulation. Guyton et al. (51) have suggested that this inverse relationship between fluid volume and plasma renin is extremely critical to maintain blood pressure within normal limits (see Figure 2). If this relationship is altered, for example, when the levels of plasma ang II are driven above those that correspond to a given level of either sodium intake or extracellular fluid volume, then the organism becomes susceptible to the development of hypertension through slow responses to ang II. This is shown in the figure where the levels of ang II have been "inappropriately" increased in animal models to levels A, B, C, and D, which induce proportional increments in mean arterial pressure (at the bottom of the
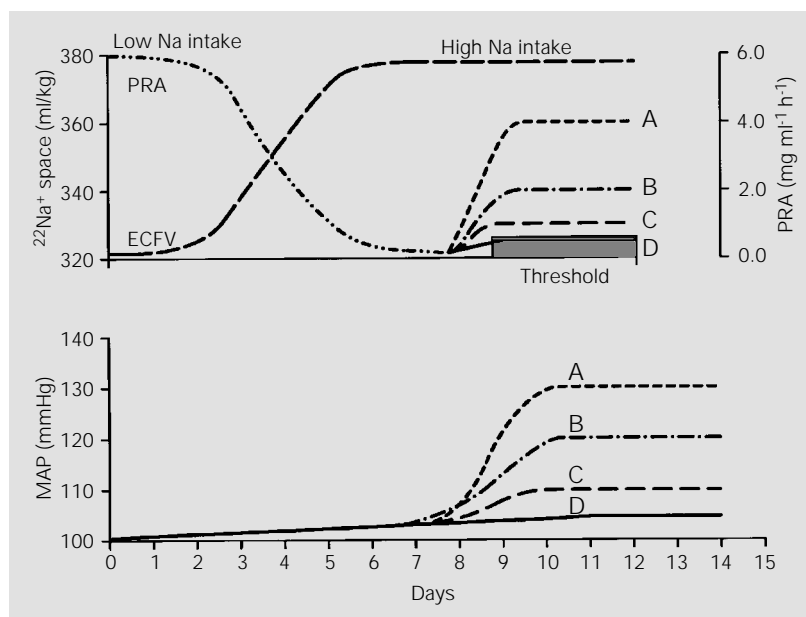

Figure 2 - Reciprocal changes in plasma renin activity (PRA) and extracellular fluid volume (ECFV) that occur when a low sodium diet is shifted to a high sodium diet (upper figure). This change contributes to the maintenance of mean arterial pressure (MAP) (lower figure). Infusion of different doses of ang II (A, B, and C) which maintain the plasma levels of this peptide inappropriately high with respect to ECFV produces hypertension. D, Smaller doses of ang II than (C) do not appear to alter MAP.

figure). This assumption has led us to suggest that the circulating levels of angiotensin are "inappropriate" or "in excess" when compared with the level of extracellular fluid volume. This hypothesis is largely supported by the studies of DeClue et al. (52) who showed that when sodium intake is increased without allowing the circulating levels of angiotensin to be decreased because of continuous intravenous infusion, then the levels of blood pressure become strictly determined by the level of sodium intake. The observations of DeClue et al. (52) have many physiological and clinical implications. From the physiological standpoint, they demonstrate that hypertension through slow pressor responses can be induced by small elevations of circulating angiotensin that are inappropriate for the existing levels of extracellular fluid volume and, reciprocally, they show that hypertension can also be produced if the intake of sodium is inappropriate with respect to the existing levels of circulating ang II. The corollary of this conclusion is that the disruption of the reciprocal interaction between extracellular fluid volume and plasma renin activity (which serves to maintain blood pressure) appears to activate a permissive mechanism that renders oxidative stress susceptible to stimulation by ang II.

An alternative to this interpretation is the suggestion of the group of investigators directed by C. Wilcox that long-term effects of ang II are characterized by stimulation of aldosterone and sympathetic activity (53) and produce a simultaneous uncoupling of NO release and shear stress (54). These investigators have also found that the administration of a superoxide dismutase mimetic to spontaneous hypertensive rats normalizes mean arterial pressure (55).

As it is apparent, more studies are needed to unravel the specific pathways of oxidative stress that could affect blood pressure regulation.

The evidence examined in this review strongly favored the idea that metabolic products related to oxidative stress could play an important role in the development of hypertension with near normal levels of plasma renin activity.

Acknowledgments

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