Role of Oxidative Stress in the Pathogenesis of Hypertension

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During the past decade, increasing evidence has emerged pointing to the causal interaction between elevated arterial pressure, oxidative stress and inflammation in different models of hereditary and acquired hypertension (HTN). This review is intended to briefly describe the nature, the mechanism and the potential approach to management of oxidative stress in hypertension.

Evidence for Link Between Oxidative Stress and Hypertension

Compelling evidence has emerged pointing to a causal link between oxidative stress, HTN and inflammation[1]. This proposition is based on the following observations :

I. A consistent association has been found between oxidative stress and HTN in nearly all forms of acquired and hereditary HTN in experimental animals. For instance, oxidative stress has been shown to be present in animals with lead-induced HTN, uremic HTN, salt-DOCA-induced HTN, aorta coarctation, diabetes mellitus, syndrome X, NOS inhibitor-induced HTN and angiotensin II induced HTN[2-30].

II. Alleviation of oxidative stress with various antioxidant regiments has been shown to reduce blood pressure in hypertensive animals, but not in the normotensive animals[2, 3, 5-10, 14-23].

III. Induction of oxidative stress has been shown to cause HTN in genetically normal, otherwise, intact animals[31, 32].

IV. HTN, per se, has been shown to cause oxidative stress. This conclusion is based on investigations that revealed oxidative stress in the vascular tree residing proximal to (hypertensive zone), but not the distal to abdominal aorta coarctation site in rats with abdominal aorta banding[33]. Since both arterial segments are supplied by the same blood in this model, these findings have clearly isolated the effect of blood pressure and shear stress from possible effects of circulating humoral factors as a cause of oxidative stress.

Taken together, these observations suggest that oxidative stress can cause HTN and HTN can cause oxidative stress, hence, the two conditions are involved in a vicious cycle.

Cellular and Molecular Sources of Oxidative Stress in HTN

Oxidative stress is a condition in which generation of reactive oxygen species (ROS) exceeds the capacity of the antioxidant defense system. Thus, oxidative stress can occur as a consequence of excess generation of ROS, depressed antioxidant capacity or a combination thereof.

NAD(P)H oxidase family of enzymes has been identified as the main source of ROS in the kidney and vascular tissues in various models of HTN[34]. This enzyme was originally found in phagocytes serving as a source of ROS to destroy invading microbes.

More recently, NAD(P)H oxidase and its closely related isotypes have been found in numerous other cell types including endothelial cells, renal tubular epithelial cells (Renox) and vascular smooth muscle cells (Nox-I and Nox-4). Shear stress, angiotensin II and proinflammatory cytokines which are intimately related to HTN, can activate and/or upregulate NAD(P)H oxidases. In fact, upregulation of NAD(P)H oxidase and its isotypes has been demonstrated in various models of HTN[11, 18, 24].

Several studies have demonstrated renal tubulointerstitial infiltration of activated macrophages and T-lymphocytes in various animal models of HTN[22, 23, 35-38]. These findings point to association of HTN with inflammation. These infiltrating immune cells, as well as, cells of renal origin, have been shown to produce superoxide and angiotensin II, events that can contribute to oxidative stress and HTN[22, 23]. This assumption is supported by the observations that interventions aimed at reducing the inflammatory infiltrate result in amelioration of HTN[35-39]. It is of note that the activated immune cells release large quantities of ROS which promote regional oxidative stress.

Conversely, oxidative stress can promote inflammation by activating the redox-sensitive transcription factor, NFKB which can, in turn, trigger generation of proinflammatory cytokines and hence, inflammation. This supposition is supported by recent studies that clearly demonstrated NFKB activation in conjunction with the tubulointerstitial inflammation and their amelioration with antioxidant therapy in hypertensive animals[22, 23].

Taken together, the available data point to increased ROS generation by the renal parenchymal cells, as well as, the infiltrating inflammatory cells as sources of ROS in the kidney of hypertensive animals and humans. In addition, excess generation of ROS by endothelial cells, vascular smooth muscle cells and possibly circulating leukocytes can cause oxidative stress in the vascular tissue.

Insufficient Antioxidant System

Normally, ROS are contained by the natural antioxidant defense system, which consists of a large number of antioxidant enzymes, as well as, endogenous and dietary ROS scavengers. Persistent oxidative stress can result in exhaustion of the ROS scavenger molecules and as such, weaken the antioxidant defense system. Several recent studies have demonstrated significant impairment of antioxidant enzymes in various models of HTN including spontaneously hypertensive rats and rats with chronic renal failure, lead-induced HTN and diabetes[5, 11, 15].

Mechanisms by Which Oxidative Stress Raises Blood Pressure

Oxidative stress can raise blood pressure by several mechanisms :

1. ROS inactivate nitric oxide (NO) and reduce its bioavailability in key tissues and organs involved in blood pressure regulation. For instance, inactivation of NO by ROS in the vascular tissue can raise systemic vascular resistance and, hence, blood pressure. In addition, ROS mediated inactivation of NO in the kidney can augment renal tubular sodium and water reabsorption and inhibit pressure natriuresis, events that can raise blood pressure via extracellular volume expansion. Moreover, inactivation of NO in the brain can increase central sympathetic outflow which can contribute to the rise in blood pressure. Finally, oxidative stress can directly and indirectly (via inactivation of NO) promote endothelial dysfunction, vascular remodeling (matrix protein accumulation, vascular smooth muscle and fibroblast proliferation) and leukocyte/platelet adhesion, events that are critical for the maintenance and long term complications

of HTN.

2. Nonenzymatic oxidation of arachidonic acid in lipoproteins and cell membrane phospholipids leads to generation of vasoconstrictive, proinflammatory product, such as, isoprostanes which can contribute to the rise in blood pressure and renal and cardiovascular complications.

3. Oxidative stress can promote endothelial injury and dysfunction which can support development of HTN and cardiovascular disease.

Treatment of HTN-Associated Oxidative Stress

Successful management of oxidative stress in a given condition is predicated upon the in-depth understanding of its cellular and biochemical mechanisms. Consequently, a mere administration of an antioxidant vitamin cannot cure oxidative stress associated with HTN, renal disease, diabetes, etc. Instead, specific interventions directed at the specific underlying factor would be most effective. For instance, since HTN can cause oxidative stress, therapeutic interventions that can reduce blood pressure represent an ideal antioxidant therapy for the HTN-associated oxidative stress. In addition, since stimulation of AT-1 receptors by angiotensin-II promotes oxidative stress and HTN via activation and upregulation of NAD(P)H oxidases, drugs that interrupt renin angiotensin system can be considered as specific therapies for management of oxidative stress in certain types of HTN especially chronic kidney disease. Similarly, adequate glycemia control in diabetes and lipid-lowering strategies in hyperlipidemia are most effective in reversing oxidative stress associated with these conditions. Finally, consumption of a diet rich in natural antioxidants and other essential micronutrients, as well as, regular exercise and weight control would be desirable in combating oxidative stress and promoting good health.

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