Editorial Comment

Mechanical Stress and Humoral Factors Linked to the Induction of Oxidative Stress

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The earth formed about 4.5 billion years ago and the very first living cells appeared approximately 1 billion years later. It has been estimated that the earth was anoxic for at least 2 billion years. Around 2.3 billion years ago, there was a sudden increase in oxygen in the oceans and atmosphere. It is believed that the first photosynthetic organisms, cyanobacteria, were responsible for this oxidation event as well as depletion of other gases, such as methane, that permitted oxygen to accumulate (*1*). The newly appearing oxygen became available as an energy source for complex multicellular organisms. Because both plants and animals came to depend on oxygen, a very complex biology arose. Cells were forced to adapt small molecules as antioxidants and developed enzymes that produce, scavenge and utilize reactive oxygen species (ROS) and other enzymes that can repair oxidative damage. Some of these enzymes are highly preserved from bacteria to humans, suggesting that their co-existence with oxygen metabolites has been essential for millions of years. Among damages by oxidative stress, recent studies have revealed the importance of hypertensive organ damages (*2*, *3*). ROS, which include hydroxyl radical, superoxide anion, hydrogen peroxide, and singlet oxygen, are generated by a variety of cells, particularly vascular cells, renal cells and cells of the central nervous system. While there are numerous enzyme systems that produce ROS, five enzyme systems seem to predominate in such production. These are xanthine oxidase, NADPH oxidase, uncoupled NO synthase, mitochondrial sources, and myeloperoxidase, and the production of ROS from these enzymes is stimulated by radiation, chemical substances, ageing, smoking, and so on. Several humoral factors are known to stimulate NADPH oxidase in vascular smooth muscle cells: platelet-derived growth factor (PDGF), endothelin-1, transforming growth factor-β (TGF-β), tumor necrosis factor (TNF)-α thrombin and angiotensin II (AII) (*4*). AII is of particular significance with respect to hypertension. The precise mechanisms that link these humoral factors, especially AII, to the enzyme and upstream-signaling molecules have not been fully elucidated, but phospholipase D (PLD), protein kinase C (PKC), c-Src, phosphoinositol 3-phosphate kinase (PI3K) and Rac may be important (*5*).

In vivo experiments have revealed the importance of ROS in blood pressure regulation using genetic models such as spontaneously hypertensive rats (SHR), stroke-prone SHR (SHRSP), Dahl salt-sensitive rats, Ren-2 transgenic rats, or p47phox (an NADPH oxidase component) knockout mice (*6*). Also, AII, aldosterone and adrenomedullin have been reported to be closely related with ROS regulation, and to thereby cause high blood pressure and organ damages (*7*). In the present issue of *Hypertension Research*, Kai *et al*. reveal new aspects of the relation between ROS and organ damages (*8*). Their report demonstrates that pressure overload by aortic constriction increases ROS production in the heart by stimulating the local renin-angiotensin system. The levels of renin, angiotensin converting enzyme (ACE) activity, serum AII and aldosterone were unchanged by aortic constriction, but increased ROS production was successfully reduced by AII type 1 (AT1) receptor blockade at a dose that did not reduce blood pressure. It is assumed that local AII stimulates AT1 receptors, but another possible mechanism may be that AT1 receptors are stimulated by the mechanical stretch of cardiac myocytes. The AT1 receptor blocker behaved as an inverse agonist to inhibit AT1 receptor signaling and thus inhibited

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ROS production. These new insights lead us to hypothesize that not only high renin hypertensives but all hypertensives have higher ROS production, and it is feasible that this production leads to organ damage.

So far, although the clinical trials of antioxidants such as vitamin C, E and β-carotene have not been successful, we can target constitutively active AII signaling to reduce oxidative stress and thereby aim at organ protection in hypertensive patients.

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