Mechanisms and Cardiovascular Damage in Hypertension

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Abstract—Angiotensin (Ang) II is considered a regulatory hormone stimulating vascular smooth muscle cell constrictions, aldosterone release from the adrenal gland, and sodium reabsorption in the renal tubule. Furthermore, Ang II may be formed and act locally as a chemokine, inducing tyrosine phosphorylation, cell growth, hypertrophy, and differentiation. In addition, evidence has recently accrued showing that Ang II is important in stimulating the production of reactive oxygen species and the activation of ancient inflammatory mechanisms. The transcription factor nuclear factor κ-B is pivotal to these processes. Nuclear factor κ-B activation stimulates the expression of a gene menagerie important to chemoattraction, surface adhesion molecule expression, coagulation, and inflammation. Anti-inflammatory interventions may have therapeutic utility. (Hypertension. 2001;37[part 2]:594-598.)

Key Words: angiotensin ■ hypertension, experimental ■ animals, transgenic ■ aldosterone

As the growing role of “oxidative stress” in the pathogenesis of hypertension becomes more appreciated, our impression of hypertension as a rather indolent, solely hemodynamic process is being revised. Reactive oxygen species are the end result of univalent reductions in oxygen, resulting in the production of superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and water (H$_2$O). Reactive oxygen species influence both normal and abnormal cellular processes, including cellular growth, hypertrophy, remodeling, lipid oxidation, modulation of vascular tone, and inflammation. Reactive oxygen species can also act as intracellular signaling molecules in vascular cells controlling growth, survival, and apoptosis. The potential targets of reactive oxygen species in endothelial and vascular smooth muscle cells are extracellular signal–related kinases, stress-activated protein kinases, caspases, and nuclear factor-κ-B (NF-κB). NF-κB activation has been associated with vascular inflammation and cell survival.

An important source of reactive-oxygen species are the NADH/NADPH oxidases, which are regulated in part by angiotensin (Ang) II and certain cytokines. Touyz and Schiffrin recently showed that in vascular smooth muscle cells from human peripheral resistance arteries, Ang II increased H$_2$O$_2$ generation through phospholipase D–dependent, NADH/NADPH oxidase–sensitive pathways. A role for reactive oxygen species in Ang II–mediated transcription factor activation has been established. Mitogen activated protein (MAP) kinase activation and the stimulation of the transcription factor activator protein-1 (AP-1) have recently been delineated. Furthermore, activation of NF-κB by Ang II is also well described, and the hypothesis that Ang II is involved in inflammatory cell recruitment has been tested. NF-κB is a pivotal transcription factor in chronic immune responses and inflammatory diseases. NF-κB is activated by numerous stimuli including cytokines, protein kinase C activators, viruses, immune stimuli, and above all, reactive oxygen species. The activation of NF-κB involves the phosphorylation and subsequent proteolytic degradation of the inhibitory protein 1-κB by specific I-κB kinases. The free NF-κB, a heterodimer consisting of 2 proteins, p50 and p65, passes into the nucleus, where it binds to κB sites in the promoter region of numerous genes involved in inflammation. Many of these genes code for cytokines, chemokines, enzymes, proteins involved in coagulation, receptors, proteinases, and adhesion molecules. These molecules contribute to the alterations in structure and mechanical properties responsible for the remodeling of resistance arteries in hypertension.

Ang II and Inflammation

A schematic view of how Ang II operates to initiate inflammation is shown in Figure 1. NF-κB and AP-1, when activated, can initiate the transcription of various inflammation–relevant genes coding for surface adhesion molecules, chemokines, cytokines, coagulation factors, and matrix proteins. The first report associating NF-κB and the renin-angiotensin system demonstrated an activation of the angiotensinogen gene by NF-κB rather than the other way around. Brasier et al showed that the angiotensinogen gene was transcriptionally activated in hepatocytes during the acute-phase response; the mechanism involved the activation of NF-κB. This body of evidence suggests that the NF-κB transcription factor complex exerts influences on angiotensin gene regulation and thereby the renin-angiotensin system. Additional evidence for this hypothesis stems from the study of Jamaluddin et al. These investigators found that...
Figure 1. Schematic view of our current hypotheses regarding Ang II–induced inflammatory and vascular injury responses. NF-κB is a pleiotropic transcription factor. Ang II and reactive oxygen species trigger signal transduction pathways leading to NF-κB activation. Also involved are small G proteins of Ras family and others (Rho-A, cdc42, and Rac1 not shown). I-κ kinase complex consists of several enzymes capable of phosphorylating NF-κB, thereby releasing p50 and p65 from inhibitory I-κB complex. I-κB is subsequently degraded by ubiquitinization, p50 and p65 form heterodimer, which translocates to nucleus. AP-1 transcription factor consists of fos, jun heterodimer. Activation of both transcription factors involves NF-κB–inducing kinase and MAP kinase, ERK pathway, including upstream MAP/ERK kinase, and MEK kinase.

protein kinase C is important in the Ang II–induced NF-κB activation.

Hernandez-Presa et al showed that Ang II is responsible for directing neointimal monocyte infiltration by promoting NF-κB activation and monocyte chemoattractant protein (MCP)-1 expression in a model of accelerated atherosclerosis in rabbits. Their data provided direct evidence that Ang II can initiate an inflammatory response in the vessel wall through activation of NF-κB. The response was ameliorated by ACE inhibitors, supporting a therapeutic benefit of such drugs in patients with atherosclerosis. The authors then observed that ACE inhibitor treatment reduced NF-κB and dependent proinflammatory factor activation but not collagen I expression.

The results of the recent Heart Outcomes Prevention Evaluation (HOPE) study, in which patients with cardiovascular risk factors but without heart failure were treated by ACE inhibitors, support the notion that Ang II induces NF-κB activation, implying an anti-inflammatory effect of the drugs. The expression of Ang II and interleukin (IL)-6 in human coronary artery plaques suggests potential implications for inflammation and plaque instability. NF-κB is involved in these processes. Han et al observed that Ang II induced IL-6 transcription in vascular smooth muscle cells through activation of NF-κB. This effect could be blocked completely by inhibiting the proteolysis of I-κBa. Further evidence for the notion that Ang II induces NF-κB in vascular smooth muscle cells was presented by Kranzhofer et al. These investigators found that human vascular smooth muscle cells stimulated with Ang II released IL-6 dose dependently. The effect was eliminated by ACE inhibitor administration. NF-κB was activated by Ang II stimulation and inhibited by ACE inhibition and by a relatively specific inhibitor pyrroline dithiocarbamate. Puyo et al showed that Ang II stimulates endothelial cells to express vascular cell adhesion molecule (VCAM)-1 through NF-κB activation induced by oxidative stress. Thus, endothelial cells, vascular smooth muscle cells, and infiltrating mononuclear cells can all be stimulated by Ang II activation of NF-κB and genes related to this transcription factor.
Recently, Kitamoto et al. have described increased NF-κB activity in the vascular wall as a consequence of NO inhibition with L-NAME. They found that NF-κB participates in early vascular inflammation and subsequent medial thickening in the coronary arteries of the rat. They used a novel decoy technique to block NF-κB. NF-B, on the other hand, had no effect. Decorin, an inhibitor of transforming growth factor (TGF)-β, canceled the Ang II–induced effect on the collagen I gene. These studies nicely separated the NF-κB, MAPK/ERK–AP-1, and TGF-β signaling pathways.

Double-Transgenic Rat Model

Our group has studied a double-transgenic rat model outlined in Figure 2. The rats harbor both the human renin and human angiotensinogen genes. The rat and human renin-angiotensin systems do not interact, so the hypertension and vascu-
test whether or not we could ameliorate Ang II–induced end-organ damage in our model. We found that HMG-CoA reductase inhibition with cerivastatin improved survival, decreased blood pressure, reduced proteinuria, improved renal function, reduced cardiac hypertrophy, and reduced myocardial fibrosis. To obtain insight into cellular mechanisms, we observed that the activation of NF-kB and AP-1 was attenuated. As a result, surface adhesion molecule expression, inflammatory infiltration, tissue factor production, matrix protein production, and cellular proliferation were all attenuated. We briefly studied some possible signal transduction pathways that might be important to the process. We presented evidence that cerivastatin interfered with the ERK and MAP kinase signaling pathway as well as PKC signaling. Both pathways could have a bearing on NF-kB–related and AP-1–related effects.

The mechanisms are unknown but may involve G proteins involved in receptor-coupled signal transduction, particularly Rho. The Rho proteins belong to the Ras superfamily. The Ras proteins alternate between an inactivated GDP-bound form and activated GTP-bound form, allowing them to act as molecular switches for growth and differentiation signals. Prenylation is a process involving the binding of hydrophobic isoprenoid groups consisting of farnesyl or geranylgeranyl residues to the carboxy-terminal region of Ras protein superfamily. Farnesyl pyrophosphate and geranylgeranyl pyrophosphate are metabolic products of mevalonate that are able to supply prenyl groups. The prenylation is conducted by prenyl transferases. The hydrophobic prenyl groups are necessary to anchor the Ras superfamily proteins to intracellular membranes so that they can be translocated to the plasma membrane. The final cell-membrane fixation is necessary for Ras proteins to participate in their specific interactions. Statins decrease the production of mevalonate, geranyl pyrophosphate, and farnesylpyrophosphate and subsequent products on the way to construction of the cholesterol molecule. Thus, statins could act, independent of circulating LDL, by decreasing the formation of reactive oxygen species.

References


Acknowledgments

This work was supported by grants-in-aid from the Klinisch-Pharmakologischer Verbund Berlin-Brandenburg and by Hoffmann-LaRoche Corp.


Workshop: Mechanisms and Cardiovascular Damage in Hypertension
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Hypertension. 2001;37:594-598
doi: 10.1161/01.HYP.37.2.594

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/37/2/594

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