

**Joey P. Granger**

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## An emerging role for inflammatory cytokines in hypertension

Joey P. Granger

Department of Physiology and Biophysics, Center for Excellence in Cardiovascular-Renal  
Research, University of Mississippi Medical Center, Jackson, Mississippi

EPIDEMIOLOGICAL and experimental studies have revealed an association between biochemical markers of systemic inflammation and cardiovascular disease such as atherosclerosis, heart failure, and hypertension (2–4, 15, 16). Although significant progress has been made in our understanding of the role of inflammatory cytokines in pathogenesis of atherosclerotic disease, the quantitative importance of cytokines in the regulation of arterial pressure and in the pathogenesis hypertension has yet to be fully elucidated.

Important blood pressure-regulatory systems, such as the renin-angiotensin system and sympathetic nervous system, interact with the proinflammatory cytokines, such as IL-6 and TNF- $\alpha$ . The sympathetic nervous system stimulates the release of proinflammatory cytokines, and sympathetic nerves may also serve as a source of cytokines (17). There is also experimental evidence that proinflammatory cytokines may activate the sympathetic nervous system (17). ANG II enhances the synthesis of TNF- $\alpha$  and IL-6 and stimulates chemokine monocyte chemoattractant protein-1 and nuclear factor- $\kappa$ B (5, 8, 13, 14). ANG II also increases the production of reactive oxygen species, including hydrogen peroxide, that participate in the process of inflammation (13, 14).

Proinflammatory cytokines also affect vascular function and endothelium-derived factors involved in blood pressure regulation. TNF- $\alpha$  and IL-6 have both been shown to induce structural as well as functional alterations in endothelial cells (3, 6, 7). These cytokines enhance the formation of a number of endothelial cell substances, such as endothelin; reduce acetylcholine-induced vasodilatation; and destabilize the mRNA of endothelial nitric oxide synthase (3, 6, 7, 10). Thus endothelial dysfunction associated with many forms of hypertension may, in part, be mediated by proinflammatory cytokines.

Also supporting a potential role for cytokines in the regulation of arterial pressure are findings that plasma levels of proinflammatory cytokines correlate with increased blood pressure in certain forms of human hypertension and experimental animal models of hypertension (2, 9). Moreover, several recent studies have demonstrated that chronic increases in plasma levels of cytokines, comparable to concentrations observed in the hypertension associated with preeclampsia, result in significant and sustained increases in arterial pressure. For example, Alexander et al. (1) and Lamarca et al. (9) reported that a twofold elevation in the plasma levels of TNF- $\alpha$  significantly increased arterial pressure and renal vascular resistance in pregnant rats, and Orshal and Khalil (12) reported similar findings, infusing IL-6 for 5 days in pregnant rats. Although these studies demonstrate that increasing plasma levels of

cytokines comparable to concentrations observed in certain forms of hypertension can lead to significant elevations in blood pressure, the quantitative role of endogenous cytokines in mediating increases in arterial pressure in various forms of hypertension associated with enhanced formation of proinflammatory cytokines remains unclear.

In this issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Lee et al. (11) tested the role of endogenous IL-6 in mediating the hypertension caused by ANG II. Male C57BL6 and IL-6 knockout mice were implanted with biotelemetry devices and placed in metabolic cages for chronic hemodynamic and metabolic monitoring during chronic ANG II-induced hypertension. Plasma levels of IL-6 were significantly elevated in the wild-type mice during chronic ANG II hypertension. The major finding from this study is that the hypertension caused by chronic ANG II excess depends significantly on the presence of IL-6. The mice with knockout of IL-6 had significantly lower mean arterial pressure (~30 mmHg) than wild-type mice during 2 wk of ANG II infusion. These findings clearly demonstrate a quantitatively significant role for IL-6 in mediating the chronic hypertensive response to ANG II. Moreover, the fact that there was no post-ANG II hypertension and that the between-group differences in blood pressure preceded group differences in urinary albumin excretion suggests that IL-6 contributes to ANG II-induced hypertension via mechanisms independent of ANG II-induced renal injury.

Although the findings of Lee et al. (11) suggest an important direct role for endogenous IL-6 in mediating some of the chronic hypertensive response to exogenous ANG II, the results also raise a number of important unanswered questions. For example, what are the source(s) of increased circulating IL-6 in ANG II hypertension? What role do elevations in blood pressure have in causing enhanced IL-6 production? Does IL-6 contribute to the increase in blood pressure in forms of hypertension caused by increases in endogenous ANG II formation (renovascular hypertension)? Because ANG II is believed to cause chronic hypertension by decreasing renal pressure natriuresis, by which mechanisms do proinflammatory cytokines reduce renal excretory function? Because inflammatory cytokines are known to stimulate the production of endothelin and reactive oxygen species and both play a role in chronic ANG II-induced hypertension, what role(s) do endothelin and reactive oxygen species have in mediating IL-6-induced hypertension? These are only a few questions that quickly come to mind. I could have listed many more intriguing questions, and I am sure that many of the readers of this interesting and provocative article will have other important unanswered questions. Thus it is quite obvious that the article of Lee and colleagues (11) will stimulate interest and further investigation into this exciting and emerging field of hypertension research.

Address for reprint requests and other correspondence: J. P. Granger, Dept. of Physiology and Biophysics, Univ. of Mississippi Medical Center, 2500 North State St., Jackson, MS 39216-4505 (e-mail: jgranger@physiology.umsmed.edu).

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