Inflammatory cytokines, vascular function, and hypertension

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THERE IS GROWING INTEREST in the potential role of inflammatory cytokines in the pathogenesis of cardiovascular diseases such as atherosclerosis, heart failure, and hypertension (7, 14–16). Although the role of cytokines in atherosclerosis is well established, the importance of cytokines in cardiovascular diseases such as hypertension has yet to be fully elucidated. One form of hypertension that is associated with increases in tissue and circulating levels of inflammatory cytokines is the hypertension observed in women with preeclampsia (4, 5, 10).

Preeclampsia is estimated to affect 5–10% of all pregnancies in the United States (9, 10). Preeclampsia in women is typically characterized by hypertension, proteinuria, and edema. Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are unknown. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease (9, 10). An initiating event in preeclampsia has been postulated to be reduced placental perfusion that leads to widespread dysfunction of the maternal vascular endothelium by mechanisms that remain to be defined (1, 2, 9–11). Although several factors have been proposed to link reduced placental perfusion with maternal endothelial dysfunction, a key role for plasma cytokines in the pathogenesis of hypertension during preeclampsia has been hypothesized (5, 9, 10).

Several lines of evidence support the cytokine hypothesis of preeclampsia. Plasma levels of cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 have been reported to be elevated in women with preeclampsia (5, 9, 10). Furthermore, more recent studies have shown that a two- to threefold elevation in plasma IL-6 or TNF in late pregnant rats results in significant increases in vascular resistance and arterial pressure (3, 12). Moreover, endothelium-dependent vascular relaxation is reduced and vascular contraction is enhanced in vessels of pregnant rats chronically infused with TNF or IL-6 to mimic plasma levels observed in women with preeclampsia (6, 7).

Although the recent findings that physiological elevations in plasma levels of proinflammatory cytokines result in altered vascular function and hypertension during pregnancy are important and support the cytokine hypothesis of preeclampsia, these findings also raise a number of important unanswered questions. Is the alteration in vascular function caused by cytokines a consequence of the hypertension developed during chronic infusion of cytokines during pregnancy? Do cytokines have a direct effect on vascular function? Do cytokines directly activate contracting factors such as endothelin and/or inhibit vasodilator systems such as the L-arginine-nitric oxide (NO) pathway? Does the hormonal environment of pregnancy influence the vascular effects of cytokines?

In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Orshal and Khalil (13) provide answers to some of these important questions. To address the issue of direct actions of IL-6 on vascular function, the authors examined the acute effects of IL-6 (1-h exposure) on the active stress in aortic strips isolated from virgin and late pregnant Sprague-Dawley rats. IL-6 caused enhancement of the contraction that was greater in pregnant than virgin rats. They also found that IL-6 inhibits endothelium-dependent NO-cGMP-mediated relaxation in systemic vessels of virgin and pregnant rats. Although these acute effects of IL-6 on NO production are most likely related to alterations in endothelial NO synthase activity, IL-6 may also act at a point downstream to decrease the bioactivity/bioavailability of NO, possibly via the generation of reactive oxygen species.

The study by Orshal and Khalil gives renewed importance to determining the mechanism whereby cytokines influence vascular function in cardiovascular diseases associated with elevations in proinflammatory cytokines such as IL-6 and TNF-α. Their findings that IL-6 induced greater inhibition of vascular relaxation and enhancement of contraction in systemic vessels of pregnant rats also provides additional support for IL-6 as one of the potential mediators of increased vascular resistance associated with hypertension during preeclampsia.

REFERENCES


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