Estrogen Regulation of Tumor Necrosis Factor-α
A Missing Link Between Menopause and Cardiovascular Risk in Women?

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Over the past decade, inflammation has been gaining widespread attention among scientists because of accumulating evidence implicating inflammation as an important mediator in the progression of cardiovascular disease (CVD). Clinical and experimental studies have shown strong associations between the risk for CVD and several inflammatory markers. In the majority of conditions that are high risk factors for CVD (eg, hypercholesterolemia, hypertension, and diabetes), the vascular system or, more specifically, the vascular endothelium, elicits an inflammatory response that could lead to increased oxidative stress as well as to other processes that contribute to vascular damage. This theory has also been supported by the fact that the most common drugs used for the treatment of CVD—statins, aspirin, angiotensin II inhibitors, and PPARγ agonists—all have anti-inflammatory effects. Among the proinflammatory molecules, tumor necrosis factor-α (TNF-α) has been identified as an important mediator of vascular dysfunction through its ability to decrease the expression of endothelial nitric oxide synthase (eNOS) and, concomitantly, to induce NADPH oxidase activity. Moreover, high levels of TNF-α in the systemic circulation have been detected in conditions that present significant risk for CVD such as hypertension and diabetes. In this issue, Arenas et al demonstrate a new role of TNF-α in the development of vascular dysfunction in what can be considered another risk factor for CVD, ie, estrogen deficiency.

Although heated controversy exists over the value of estrogen replacement therapy in protecting against cardiovascular disease, many animal and clinical studies have shown that estrogen has direct beneficial effects on the cardiovascular system. Estrogen exhibits favorable effects on endothelial function. Estrogen deficiency, as a consequence of menopause or ovariectomy, decreases endothelium-dependent relaxation in women and in animal models, thereby potentially contributing to increased vasoconstrictor mechanisms that lead to increased blood pressure. This negative effect of estrogen deficiency is reversed by estrogen replacement. The positive vascular effects of estrogen have been attributed primarily to estrogen upregulation of endothelium-derived nitric oxide (NO). Probable mechanisms involved in estradiol-induced increases in NO production include: (1) transcriptional stimulation of eNOS gene expression; (2) nongenomic activation of eNOS enzyme activity via a PI3-kinase/Akt-mediated signaling pathway; and (3) a decrease in NO catabolism via reduced superoxide anion (O2•−)-mediated conversion of NO to peroxynitrite. Induction of eNOS transcription by estrogen has been demonstrated in a variety of tissues, which is consistent with the presence of estrogen response elements in the eNOS promoter. In addition to the increase in eNOS expression, estrogen causes rapid amplification of eNOS activity by directly activating the PI3-kinase/Akt pathway resulting from the interactions between the estrogen receptor and the regulatory subunit of PI3-kinase. Furthermore, the protective effects of estrogen have also been attributed to an increase in the NO/O2•− ratio in the vessel wall, thereby resulting in increased bioavailability of NO. A recent study has shown that estrogen reduces O2•− bioavailability in rat microvessels in vivo and in human umbilical vein cultured endothelial cells, 17β-estradiol decreases expression of the NAD(P)H oxidase subunit, gp91phox, and upregulates eNOS expression, thereby improving the NO/O2•− balance.

Estrogen-mediated anti-inflammatory effects have also been proposed to contribute to cardiovascular protection. The onset of menopause has been associated with spontaneous increases in cytokine production, specifically, TNF-α and the interleukins, IL-1 and IL-6. Moreover, cytokine levels are reportedly lower in postmenopausal women on hormone replacement therapy and in estrogen-treated ovariectomized mice compared with untreated controls. Estrogen treatment in vitro inhibits the release of proinflammatory cytokines in a variety of cell types, such as monocytes, osteoblasts, and endothelial cells. Estrogen deficiency has also been shown to enhance the sensitivity of those cells to these cytokines by upregulating cytokine receptor expression. Despite the increasing evidence demonstrating the anti-inflammatory effects of estrogen, before now there has been no evidence clearly linking cardiovascular damage to the upregulation of pro-inflammatory cytokines that occurs during estrogen deficiency.

In this issue of Hypertension, Arenas et al report a novel mechanism for estrogen action in the vasculature and provide data demonstrating an important link between inflammation and cardiovascular risk in the menopausal female. Circulating levels of the proinflammatory cytokine TNF-α were found to be 7-fold greater in ovariectomized rats compared with estrogen-replaced ovariectomized animals or intact cycling animals. The elevated levels of TNF-α after estrogen defi-
ciency were associated with impairment in vascular function; this effect was mediated by concomitant decreases in eNOS and increases in NAD(P)H oxidase expression. Although most studies have proposed that estrogen directly modulates the expression of these enzymes, Arenas et al demonstrate an indirect mechanism whereby estrogen deficiency can regulate NO and O$_2^-$ production and thereby affect vascular function. The mechanism underlying elevated TNF-α and consequent vascular dysfunction was not determined in this study but may involve direct modulation of estrogen on TNF-α expression. In addition, because estrogen deficiency is frequently associated with weight gain, increased production of TNF-α by fat may also be implicated. This latter hypothesis raises an interesting question: Would increased levels of TNF-α persist if the commonly observed weight gain in postmenopausal women were prevented?

Although much data suggest that estrogen has protective effects in the vasculature, recent clinical trials have questioned the value of estrogen replacement therapy in protecting against vascular disease. Large clinical trials, such as the Women’s Health Initiative (WHI), have reported that hormone replacement therapy not only showed no cardiovascular benefit but also showed increased risk to the cardiovascular system. However, the WHI has been heavily criticized because the average age of women beginning the trial was 62.7, which is approximately 10 years past the average age of menopause onset, and because the study was underpowered by 10-fold to assess cardiovascular benefit in hormone-replaced women entering the menopause transition. Currently, the value of estrogen replacement therapy remains one of the major unanswered questions in this field. Hopefully, the recently begun Kronos Early Estrogen Prevention Study (KEEPS), a 5-year study of hormone replacement therapy aimed at providing prospective data on the risks and benefits of early menopausal hormonal intervention, particularly as it relates to the progression of atherosclerosis, will shed much needed light on this question.

Among the theories extensively discussed in the literature to explain why so much data suggest estrogen replacement therapy should be cardioprotective yet, based on the results of recent clinical trials, is apparently not, is the theory that different estrogens can regulate inflammatory pathways in distinctly different ways. For example, the conjugated equine estrogens (the most used estrogenic therapy in clinical trials) distinctly different ways. For example, the conjugated equine estrogens (the most used estrogenic therapy in clinical trials) consistently increase the proinflammatory molecule, matrix metalloproteinase-9, whereas 17β-estradiol is known to decrease this molecule. Another explanation is that estrogen modulates different types of proinflammatory molecules in distinct ways. For example, estrogen consistently exerts anti-inflammatory effects by inhibiting cellular adhesion molecules and cytokines such as TNF-α (as proposed by Arenas et al); however, estrogen is also known to increase C-reactive protein, which is an inflammatory marker. The fact that estrogen downregulates one (or more) of the inflammatory markers does not necessarily mean that estrogen significantly inhibits the inflammatory process and therein reduces cardiovascular risk. Another possible explanation is that estrogen may be less effective in exerting anti-inflammatory actions in a system with established inflammation, such as hypertension or aging. This possibility raises the following questions. Would the anti-inflammatory effects of estrogen observed in young normotensive females also be observed in elderly hypertensive females with preexisting progressive vascular inflammatory processes? Would the anti-inflammatory potential of estrogen be effective enough to improve vascular function and prevent CVD in postmenopausal women?

In summary, the study of Arenas et al opens a new window into our understanding of how estrogen modulates inflammatory processes and how the hormone protects against the progression of CVD. Whether estrogen-modulated anti-inflammatory effects will have therapeutic potential remains unknown at this time; however, determining the exact mechanisms involved in this newly revealed action of estrogen and the precise role of this mechanism in the regulation of cardiovascular function could lead to the development of novel pharmacological therapies for CVD not only in postmenopausal women but also in men.

References

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