Estrogen protection, oxidized LDL, endothelial dysfunction and vasorelaxation in cardiovascular disease: New insights into a complex issue

C. Subah Packer *

Indiana University School of Medicine, Department of Cellular and Integrative Physiology, 635 Barnhill Drive, Indianapolis, Indiana 46202-5120, United States

Received 5 November 2006; accepted 9 November 2006
Available online 16 November 2006

See article by Monsalve et al. [14] (pages 66–72) in this issue.

Pre-menopausal women have a lower risk of developing hypertension than men or post-menopausal women [1]. Estrogens may prevent or delay the onset of hypertension in pre-menopausal women. Similarly, animal models such as the spontaneously hypertensive rat (SHR) exhibit sexual dichotomy in development of essential hypertension, and estrogen reduces blood pressure in hypertensive female rats [2,3]. Such animal models are useful in the study of the protective effects of estrogen in the development of human essential hypertension [4–6].

Peripheral resistance is abnormally elevated at any given level of cardiac output in all forms of hypertension [7]. Resistance arteries are normally maintained in a state of partial constriction (vascular tone). Increased resistance may be due to altered contractility or relaxation of arterial smooth muscle. Diminished relaxation of blood vessels in SHR has been suggested to play a role in the mechanism of hypertension [8–11]. Impaired arterial muscle relaxation has been well documented in male SHR [9] and has more recently been reported to occur in female SHR of the same age as well, although females manifest less severe hypertension than their male counterparts [2,3]. Endothelium-dependent and endothelium-independent as well as β-adrenergic receptor-mediated relaxations are impaired in arterial muscle from SHR compared with WKY rats [12]. These findings suggest that the underlying defect is in the ability of the arterial smooth muscle to relax regardless of the stimulus initiating the relaxation. Alternatively, several regulatory mechanisms of relaxation may be simultaneously impaired.

The need to understand the role of impaired vasorelaxation and the impact of estrogens on cardiovascular disease have become increasingly important as metabolic syndrome has become epidemic. Metabolic syndrome is typified by high cholesterol, dyslipidemia, hyperglycemia, and hyperinsulinemia. Eventually, hypertension and coronary heart disease develop. But what is the etiology of the hypertension that is associated with metabolic syndrome and/or type II diabetes? Interestingly, oxidized low-density lipoprotein cholesterol (oxLDL) has been identified as a vasoconstrictor [13]. Patients with metabolic syndrome who have high LDL levels would also have higher than normal oxLDL levels especially since their hyperglycemia provides a high oxidizing environment. But the cellular mechanism of the oxLDL-induced vasoconstriction is unknown.

While some studies report that oxLDL directly stimulates arterial smooth muscle contraction [13], experiments using a human endothelial cell culture model have produced evidence that oxLDL may impair endothelium-dependent arterial muscle relaxation as reported by Monsalve et al. in the current issue of the Journal [14]. The work by Monsalve et al. also provides insight into the effects of estradiol on the etiology of the endothelial dysfunction that occurs in some cardiovascular diseases, especially those associated with elevated oxLDL. Endothelial cells produce both nitric oxide synthase (NOS) and asymmetric dimethylarginine (ADMA), an inhibitor of NOS. The balance between NOS and ADMA production and activity determines the level of NO. Interestingly, ADMA levels increase when oxLDL levels...
increase, and the balance shifts towards a net decrease in NO release. While it has been thought for some time that estradiol stimulates NO production through both increased NOS expression and activity, the current work by Monsalve et al. suggests that estradiol might increase NO by reducing or reversing the effects of oxLDL on increased ADMA production. Estrogens have long been known to have anti-oxidant effects [15], which could also play a role in preventing or reducing both the endothelial dysfunction and the direct vasoconstriction that would occur in conditions such as metabolic syndrome in which LDL and oxLDL levels would be high. In addition, estrogens are associated with lowering cholesterol and, in particular, reducing the LDL such that the HDL/LDL ratio improves. Estrogens are known to prevent or reduce the severity of endothelial dysfunction by increasing NO synthesis via increased NOS synthesis and/or activity and by reducing the oxLDL-induced increase in ADMA production, as shown in the current work of Monsalve et al. [14]. While estrogens clearly have many mechanisms of action that are beneficial to cardiovascular health, there are many additional actions of estrogens that must be considered in determining the therapeutic role of estrogens. Furthermore, the concentration-dependent effects must be fully understood. For example, the concentration at which estrogen is an anti-oxidant is very different from the concentration at which it is an NOS inducer, as pointed out by Monsalve et al. Clearly, much more work is needed to tease out the physiological effects of estrogens before hormone replacement therapy can be provided based on safe and exact science. The specific effects of various estrogen analogues and concentrations as well as the effects of estrogens as a function of the aging process must be understood. Estrogen is unlikely to have the same effects in older women as it has in younger women. In addition to changes in ovarian hormone production, there will be changes in receptor number and, possibly, receptor type and in cellular responses to receptor activation in post-menopausal compared with pre-menopausal women. Nevertheless, work such as that by Monsalve et al. is promising. Eventually, the complex effects of estrogens on cardiovascular function and health will be understood and new efficacious therapeutic agents will be developed.

References