Estrogen and Asymmetric Dimethylarginine in Postmenopausal Women

To the Editor:

We read with great interest the recent article by Holden et al dealing with the relationship between estrogen and asymmetric dimethylarginine (ADMA) metabolism in postmenopausal women. The results of their study demonstrated that hormone replacement therapy significantly decreased plasma ADMA levels in postmenopausal women. In an in vitro study, Holden et al observed that estrogen increased the activity of dimethylarginine dimethylaminohydrolase activity in endothelial cells. They proposed that estrogen can alter the catabolism and release of ADMA, which might partially contribute to the positive effect of estrogen on NO synthesis.

Several studies have already reported that ADMA might have a crucial role in cardiovascular regulations. It was demonstrated that inhibition of NO bioavailability by ADMA and a subsequent reduction in endothelial function might contribute to the increase in blood pressure during salt intake in normotensive postmenopausal women not receiving estrogen. Similarly, it was reported that there was a significant inverse correlation between plasma ADMA and flow-mediated dilatation of brachial artery, indicating that ADMA might be related to a decline in endothelial vasodilator function. In a previous study, we showed that estrogen-induced improvement of membrane fluidity of erythrocytes was mediated by NO production, which was counteracted by ADMA in postmenopausal women. The finding suggests that ADMA might actively participate in the regulation of cell membrane function in postmenopausal women. Because the deformability and microviscosity of erythrocyte membranes may be highly dependent on the membrane fluidity, the reduction in membrane fluidity could cause a disturbance in the blood rheological behavior and in the microcirculation, which might contribute to the pathophysiology of hypertension.

Recently, Achan et al demonstrated that intravenous infusion of ADMA increased blood pressure and systemic vascular resistance and decreased heart rate and cardiac output in humans. Therefore, we would like to know whether the hormone replacement therapy–induced decrease in plasma ADMA level might be accompanied by the changes in blood pressure and cardiac function. It would be important to assess more precisely whether ADMA may be involved in the cardiovascular disorders in postmenopausal women.

Kazushi Tsuda, MD
Ichiro Nishio, MD
Division of Cardiology
Department of Medicine
Wakayama Medical University
Wakayama, Japan
tsudak@mail.wakayama-med.ac.jp

Response

We thank Drs Tsuda and Nishio for their interest in our paper on estradiol effects on dimethylarginine dimethylaminohydrolase (DDAH) activity and the metabolism of asymmetric dimethylarginine (ADMA). We previously showed a correlation between serum ADMA concentrations and blood pressure in pregnancy, a state associated with high concentrations of circulating estrogens. In the present study, we examined whether estrogen had a direct role in the regulation of ADMA metabolism. Our results both from cell culture and from women using estrogen replacement therapy demonstrated the effect of estradiol on ADMA physiology. Some of these results have been independently confirmed.

We were intrigued by the finding that estradiol affects erythrocyte membrane fluidity in an NO-dependent manner, attenuated by ADMA. There is, to our knowledge, a single report in the literature that erythrocytes contain DDAH. In our clinical study, we did not examine changes in blood pressure or cardiovascular function during estrogen therapy, whereas unfortunately Tsuda and co-workers did not measure erythrocyte DDAH activity in their study. Therefore, it is clear that only when these parameters are measured in the same study will we be in a position to comment fully on the various contributions of estrogen to ADMA/DDAH regulation and physiology in the cardiovascular system.

Desmond P. Holden, MRCOG, PhD
Departments of Obstetric and Gynaecology
Royal Sussex County Hospital
Brighton, UK

Judith E. Cartwright, PhD
Guy St.J. Whiteley, PhD
Departments of Biochemistry and Immunology
St George’s Hospital Medical School
London, UK

Stephen S. Nussey, FRCP, DPhil
Oncology, Gastroenterology, Endocrinology, and Medicine
St George’s Hospital Medical School
London, UK

Estrogen and Asymmetric Dimethylarginine in Postmenopausal Women
Kazushi Tsuda and Ichiro Nishio

_Circulation_. 2004;109:e174
doi: 10.1161/01.CIR.0000121686.53780.84

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/12/e174

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/