Role of Leptin in Regulating Nitric Oxide Production and Membrane Microviscosity

To the Editor:

We read with interest the article by Ardilouze et al1 dealing with the possible roles of nitric oxide (NO) and adrenergic stimulation in the regulation of subcutaneous adipose tissue blood flow in humans. The results of their study demonstrated that NO seems to determine the absolute level of adipose tissue blood flow, whereas the postprandial enhancement of adipose tissue blood flow is highly dependent on β-adrenergic stimulation. The authors proposed that NO and β-adrenergic receptors may be major regulators of subcutaneous adipose tissue blood flow in humans.

There is evidence that leptin, which is secreted from adipose tissue, might actively participate in the regulation of NO production. Nickola et al2 showed that leptin attenuated cardiac contraction in rat ventricular myocytes, possibly through an increased NO production. In a study we presented previously, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and leptin was investigated by means of an electron paramagnetic resonance method.3 The decreased membrane fluidity of erythrocytes might cause a disturbance in the blood rheologic behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of circulatory disorders.4 We demonstrated that leptin increased the membrane fluidity of erythrocytes and improved the rigidity of cell membranes in humans via the NO-and cGMP-dependent mechanism.5 One hypothesis is that leptin may actively participate in the improvement of the rheologic behavior of erythrocytes and the microcirculation in humans by increasing NO production. In a separate series of the experiment, we showed that the relaxing effect of leptin on blood vessels was partially mediated by the NO-dependent pathway.5 In this context, we speculate that leptin-induced NO production with a concomitant improvement of erythrocyte membrane microviscosity could partially modulate the adipose tissue blood flow in humans. Therefore, we would like to know whether the adipose tissue blood flow might be correlated with the plasma leptin level in the current study of Dr Ardilouze and colleagues.1 It would be necessary to assess more precisely the functional interactions between leptin and NO in the regulation of membrane microviscosity and their contribution to the mechanism underlying increased adipose tissue blood flow in humans.

Kazushi Tsuda, MD
Ichiro Nishio, MD
Division of Cardiology
Department of Medicine
Wakayama Medical University
Wakayama, Japan


Response

We thank Drs Tsuda and Nishio for indicating a potential link between leptin produced in adipocytes and the role of NO for adipose tissue vascular function. In 2 separate in vitro studies, they have found that phenylephrine-contracted arterial rings were relaxed by leptin (an effect mediated through endothelial NO production1) and that leptin appears to have a direct effect on red blood cell membrane fluidity.2 Theoretically, both mechanisms could work in concert to increase blood flow. In tissues with a high local concentration of leptin, such as adipose tissue, this mechanism could be of particular importance. Unfortunately, we have not determined tissue concentrations of leptin in our experiments. Therefore, we cannot test this hypothesis. However, the factors determining tissue blood flow arise from an integrated physiological response.3 This is well demonstrated in our study of adipose tissue.4 On the one hand, we found that local production of NO is a major regulator of blood flow; on the other hand, we showed that blockade of β-adrenoreceptor function abolishes the augmented blood flow seen after a meal. The latter is likely to depend on sympathetic activation originating from the central nervous system. We are only aware of one study in which adipose tissue generation of leptin, observed within a wide range of obesity, has been quantified along with tissue blood flow.5 It clearly shows that obese women produce more leptin per unit of adipose tissue, yet their blood flow is substantially lower than in lean women. In order to reconcile this observation with the apparent contradictory in vitro effects suggested by Tsuda et al, we can think of 3 different explanations. First, the observation may reflect leptin resistance, which has been demonstrated in other systems involving this hormone. Second, there might be an as-yet-unidentified counterbalancing effect in adipose tissue. Third, the in vitro effects have limited relevance in vivo.

Jean-Luc Ardilouze, MD
Barbara A. Fielding, PhD
Jenny M. Curry, BSc
Keith N. Frayn, PhD, ScD
Fredrik Karpe, MD, PhD
Oxford Centre for Diabetes, Endocrinology, and Metabolism
Nuffield Department of Clinical Medicine
University of Oxford
Oxford, UK


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Kazushi Tsuda and Ichiro Nishio

Circulation. 2004;109:e316
doi: 10.1161/01.CIR.0000129326.31606.B1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/109/22/e316

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