Leptin, C-Reactive Protein, and Nitric Oxide Production in Healthy Humans

To the Editor:

We read with great interest the article by Dr Shamsuzzaman and colleagues1 dealing with the possible relationship between plasma leptin and C-reactive protein (CRP) in healthy humans. The results of their study demonstrated that hyperleptinemia is associated with increased CRP independently of age, body mass index (BMI), waist-to-hip ratio, smoking, and alcohol consumption in both men and women. The authors also indicated that, when only subjects with BMI <25 kg/m² were considered, a significant correlation between plasma leptin and CRP was still evident. The authors proposed that both leptin and CRP might be involved in inflammatory and cardiovascular disease processes in normal humans.

Evidence indicates that leptin has an important role in the regulation of nitric oxide (NO) production. It was shown that leptin attenuated cardiac contraction in rat ventricular myocytes, possibly through an increased NO production.2 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 rheological behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of circulatory disorders. 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.3 One hypothesis is that leptin may actively participate in the improvement of the rheological behavior of erythrocytes and the microcirculation by increasing NO production. This might be an important defense mechanism against vascular complications in the metabolic syndrome and cardiovascular diseases. In the separate series of the study, we showed that the relaxing effect of leptin on blood vessels was partially mediated by the NO-dependent pathway.4 In this context, we speculate that, because CRP may inhibit NO synthase,5 endothelial dysfunction with increased CRP levels might be partially counteracted by the leptin-induced NO, which could modulate cardiovascular disease processes. Therefore, we would like to know whether plasma NO metabolite levels might be linked to leptin and CRP in healthy humans in the present study by Dr Shamsuzzaman and colleagues. It would be necessary to assess more precisely the functional interactions among leptin, CRP, and NO and their contribution to the metabolic and inflammatory cardiovascular disease mechanisms.

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

Response

We very much appreciate the interest of Drs Tsuda and Nishio in our work.1 They raise the interesting possibility that leptin contributes importantly to the regulation of nitric oxide production. Evidence about the breadth of actions of leptin is evolving, particularly with regard to the cardiovascular system. Leptin has been found to be relevant to many aspects of cardiac and vascular regulation, including angiogenesis,2 thrombosis,3 hemodynamics,4 and cardiac hypertrophy, among others. Leptin also contributes to the modulation of metabolism, breathing control,5 and inflammation, all of which may further influence cardiovascular health and disease. It is interesting that leptin’s spectrum of actions includes effects that are potentially both beneficial and harmful. Evidence suggests that higher leptin levels are independently related to poorer cardiovascular outcomes.6 How the range of leptin’s actions relates to its prognostic implications remains unclear. Further delineation is needed of the specific actions of leptin, as well its differential effects—for example, in men compared with women, in obese compared with lean individuals, and in health compared with disease. The observations of Tsuda and Nishio about leptin and nitric oxide address, in part, these important questions. We have not analyzed plasma nitric oxide metabolite levels and therefore have no information about these measurements in our study population.

Abu S.M. Shamsuzzaman, MBBS, PhD
Mikolaj Winnicki, MD, PhD
Robert Wolk, MD, PhD
Anna Svatikova, BA
Diane E. Davison, RN, MA
Virend K. Somers, MD, PhD
Division of Cardiovascular Disease
Mayo Clinic
Rochester, Minn

Bradley G. Phillips, BSc, PharmD
Division of Clinical and Administrative Pharmacy
University of Iowa
Iowa City

Peter B. Berger, MD
Duke University Medical Center
Duke Clinical Research Institute
Durham, NC


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Kazushi Tsuda and Ichiro Nishio

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