Sustained consumption of dietary fats induces endothelial dysfunction and insulin resistance in experimental models and humans. Endothelial dysfunction, manifested by reduced endothelium-dependent dilation, is a hallmark of several cardiovascular diseases and obesity. Indeed, exercise training and caloric restriction attenuate endothelial dysfunction and delay the onset or reduce the magnitude of vascular diseases and insulin resistance.

A major pathway controlling endothelium-dependent vasodilation is via endothelial NO synthase (eNOS) generation of the vasodilatory, anti-inflammatory, antioxidant autacoid, NO. NO can serve as a paracrine mediator promoting various beneficial functions through several mechanisms including activation of soluble guanylyl cyclase and nitrosation of cellular proteins and lipids that promote vascular relaxation and attenuate proinflammatory pathways.

In this issue of Circulation Research, Sansbury et al provide striking evidence that eNOS-derived NO actively participates in regulating the extent of adiposity. Previous work has shown that feeding mice a high-fat diet (HFD) induces insulin resistance, obesity, hypertension, and eNOS dysfunction in conduit and resistance vessels. In Sansbury et al, feeding wild-type mice an HFD results in increased adiposity and reduced eNOS protein levels in adipocyte fractions but not aortic lysates, suggesting specific downregulation of eNOS in adipose tissue and presumably dysfunctional eNOS in the aorta. The reduction of eNOS in obese, adipose tissue has been previously reported in humans and mice. To examine whether the loss of eNOS is causal in regulating adiposity, the authors used well-characterized eNOS transgenic mice (eNOS-TG). These mice were generated by expressing eNOS transgenically in the endothelium using a preproendothelin promoter, and they are protected from tissue and vascular injury, yet exhibit increased atherosclerosis. In eNOS-TG mice, eNOS is expressed in the endothelium of adipocyte tissue. In contrast to normal mice, HFD feeding of eNOS-TG mice did not reduce total eNOS levels in adipose tissue and remarkably protected against HFD-induced weight gain, suggesting that maintaining or augmenting eNOS levels in adipose tissue regulates adipose tissue metabolism. This occurs despite eNOS-TG mice consuming similar amounts of food with equal levels of activity compared with normal mice. In addition to reduced adiposity, eNOS-TG mice did not exhibit HFD-induced hyperinsulinemia or elevations in plasma triglycerides, and free fatty acids, however, did manifest insulin resistance (via glucose and insulin tolerance tests) comparable to control mice. Mechanistically, the authors demonstrate that overexpression of eNOS changes the metabolome, increases both branched chain amino acids and fatty acid metabolism, and promotes mitochondrial biogenesis, effects that would enhance oxygen consumption and resistance to obesity. Previous work has shown that eNOS-derived NO promotes mitochondrial biogenesis because eNOS-deficient mice have reduced numbers of mitochondria in skeletal muscle and adipose tissue. The work of Sansbury et al provides additional support for the concept that vascular-derived NO provides a direct influence on mitochondrial metabolism.

The findings in Sansbury et al also raise interesting questions. For example, how does diet regulate eNOS levels in adipose tissue relative to eNOS in conduit or resistance vessels? The selective reduction of eNOS in adipose vasculature implies unique mechanisms of transcriptional or posttranscriptional control perhaps intrinsic to endothelium in fat or regulation of eNOS by adipose-derived signals or factors. An additional question: Would agents that augment eNOS function reduce diet-induced obesity? There is evidence that a small molecule transcriptional activator of eNOS and a cell-permeable peptide that antagonizes the inhibitory actions of caveolin-1 on eNOS can improve eNOS-dependent functions in vivo. The effect of these pharmacological approaches in reducing HFD-induced endothelial dysfunction and obesity should be considered. Finally, can the effects of eNOS in endothelium of adipose tissue be entirely explained based on regulating mitochondrial biogenesis? Although eNOS-TG mice have similar numbers of capillaries in adipose tissue, it is possible that augmented eNOS function and blood flow would also improve oxygen consumption. Regardless of the precise cellular mechanism, the gain-of-function studies provided in this article provide another piece of evidence supporting the concept that eNOS regulation of mitochondrial biogenesis may be a powerful way to stay lean when we are reluctant to count calories!

Sources of Funding

W.C.S. is supported by grants R01 HL64793, R01 HL61371, R01 HL081190, R01 HL096670, and P01 HL1070205.

Disclosures

None.

DOI: 10.1161/CIRCRESAHA.112.279794

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Circulation Research is available at http://circres.ahajournals.org

(Circ Res, 2012;111:1111-1112.)

Editorial

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Just Activate Endothelial NO Synthase!

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References


Key Words: metabolism ◼ mitochondria ◼ NO ◼ obesity
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Circ Res. 2012;111:1111-1112
doi: 10.1161/CIRCRESAHA.112.279794

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