Evidence Stacks Up That Endothelial Insulin Resistance Is a Culprit in Atherosclerosis

Jenny E. Kanter, Karin E. Bornfeldt

Type 2 diabetes mellitus and the metabolic syndrome greatly increase the risk of cardiovascular disease, manifested as myocardial infarction and stroke. Although it is well known that this risk is largely the result of increased atherosclerosis, the cellular and molecular events within the artery wall responsible for the worsening of atherosclerosis associated with type 2 diabetes mellitus and the metabolic syndrome are less clear. These states are frequently associated with several cardiovascular risk factors, including dyslipidemia, hypertension, obesity, hyperglycemia, and systemic insulin resistance, each of which may contribute to atherosclerosis.

Insulin resistance in now known to affect the vascular wall itself, in addition to the better-studied insulin target tissues liver, skeletal muscle, and adipose tissue. Vascular endothelial cells, which play critical roles in atherosclerosis by allowing monocytes and other immune cells to enter the atherosclerotic lesion and by producing proatherogenic and antiatherogenic molecules, develop insulin resistance in both humans and mice concomitant with dyslipidemia and systemic insulin resistance. Endothelial cells can also contribute to systemic insulin resistance.

Insulin has important biological effects in endothelial cells that affect atherosclerosis. Activation of the insulin receptor results in tyrosine phosphorylation of insulin receptor substrate 1 and 2 and subsequent activation of phosphoinositide 3-kinase (PI3K) and the serine/threonine protein kinase Akt. Akt has several targets in endothelial cells, one of which is endothelial nitric oxide (NO) synthase (eNOS). Insulin-induced activation of the PI3K-Akt-eNOS pathway causes increased production of NO, vasorelaxation, and suppressed expression of vascular cell adhesion molecule-1, an important adhesion molecule used by monocytes to invade the vessel wall. These actions of insulin are likely to be antiatherosclerotic (Figure) because both vascular cell adhesion molecule-1–deficient mice and eNOS-deficient mice exhibit reduced atherosclerosis (although eNOS can exert proatherogenic effects if uncoupled to produce superoxide).

Furthermore, the effect of complete loss of insulin signaling in the endothelium was revealed by the development of endothelium-specific insulin receptor–deficient mice. These mice demonstrate impaired vasorelaxation, increased endothelium-leukocyte adhesion, and accelerated atherosclerosis, consistent with the notion that the overall effect of insulin in the endothelium is antiatherogenic, at least in mice. However, human studies and studies primarily on bovine endothelial cells have demonstrated that insulin also stimulates production of endothelin 1, which mediates proatherosclerotic effects. Insulin-induced endothelin 1 production is mediated by the serine/threonine kinase extra-cellular signal-regulated kinase (ERK) independently of the PI3K-Akt-eNOS pathway.

How does the endothelium become insulin resistant? Previous studies have implicated the protein kinase C β2 isoform (PKCβ2), the transcription factor FoxO (another Akt target), and the NADPH oxidase Nox2 isoform as mediators of endothelial insulin resistance. Other studies suggest that formation of hybrid receptors consisting of 1 insulin hemireceptor and 1 insulin-like growth factor-1 hemireceptor reduces endothelial insulin sensitivity. All of these molecules inhibit the PI3K-Akt-eNOS pathway.

In this issue of Circulation Research, Li et al nicely illustrate the role of endothelium-specific overexpression of PKCβ2 in inducing endothelial insulin resistance and promoting atherosclerosis. This group has previously shown that PKCβ2 is activated in aortas of insulin-resistant rats. Using fat-fed ApoE−/− mice that overexpress PKCβ2 under control of the endothelial cell–specific vascular endothelial (VE)-cadherin promoter, they now demonstrate that PKCβ2 mediates insulin resistance in part by stimulating threonine phosphorylation of the PI3K p85α subunit, which in turn blunts insulin-stimulated Akt-eNOS activation (Figure). Another recent study demonstrated that PKCβ2 increases serine phosphorylation of insulin receptor substrate 2, suggesting that PKCβ2 has multiple targets in the endothelial insulin signaling pathway. The authors also show that PKCβ2 overexpression results in increased endothelium-leukocyte adhesion via increased expression of vascular cell adhesion molecule-1, as well as loss of insulin-mediated inhibition of vascular cell adhesion molecule-1 expression. Accordingly, endothelial overexpression of PKCβ2 increased atherosclerosis, predominantly in the abdominal aorta, without affecting plasma lipids or blood pressure. The abdominal lesions in PKCβ2-overexpressing mice were larger and more advanced at the 12-week time point studied, indicating that a more rapid initiation of lesions might have been responsible for the phenotype. The finding that lesions in the aortic root and arch, which often develop earlier than those of the abdominal aorta, were no different in size after 12 weeks of fat feeding.
might indicate that PKCβ2 overexpression primarily promotes lesion initiation. However, it is possible that progression of lesions is also exacerbated by PKCβ2 overexpression.

The studies by Li et al. show that endothelial insulin resistance induced by PKCβ2 is likely to promote atherosclerosis, similar to findings on mice with endothelium-targeted deletion of FoxO. However, like FoxO, PKCβ2 clearly has proatherosclerotic effects in endothelial cells beyond inhibition of insulin signaling, in part by regulating basal levels of eNOS and ERK. The proatherosclerotic effects of endothelial PKCβ2 are consistent with recent studies on whole-body PKCβ2-deficient mice, which exhibit reduced atherosclerosis. It is not known to what extent endothelial deletion of PKCβ2 contributes to atherosclerosis in these whole-body knockout mice, but it is likely that non–insulin-dependent mechanisms are at play both in endothelial cells and in myeloid cells.

It has been shown that hepatic insulin resistance does not affect all downstream arms of insulin signaling equally. Thus, whereas insulin-mediated suppression of gluconeogenesis is susceptible to insulin resistance, insulin-stimulated lipogenesis is not. This phenomenon, called selective insulin resistance, diverges downstream of Akt in hepatocytes. In the arterial wall and in endothelial cells in particular, a similar phenomenon has been proposed in which the PI3K arm of insulin signaling becomes insulin resistant, whereas the ERK arm is spared. Furthermore, this divergence in signaling has been hypothesized to explain the dual effect of insulin on endothelin-1 and NO release: NO release is downstream of PI3K-Akt-eNOS, whereas endothelin-1 release is downstream of ERK (Figure). Selective endothelial insulin resistance has been proposed to contribute to endothelial dysfunction and augmented atherosclerosis in states of insulin resistance. In the studies by Li et al., insulin does not activate ERK unless PKCβ2 is overexpressed. It is therefore possible that ERK is preferentially active in insulin-resistant endothelial cells. Furthermore, the ERK pathway is basally activated in states of endothelial insulin resistance, which could contribute to atherosclerosis. Thus, in insulin-resistant states, there might be a shift from the antiatherosclerotic PI3K-Akt-eNOS pathway to a proatherosclerotic ERK pathway, which governs the biological effects not only of insulin but also of other molecules that activate these signaling pathways. The role of endothelial ERK in atherosclerosis needs further investigation.

In aggregate, recent research shows that several molecules act to inhibit the insulin PI3K-Akt-eNOS pathway in insulin-resistant endothelial cells and that endothelial insulin resistance is likely to promote atherosclerosis. The studies by Li et al. convincingly add endothelial PKCβ2 as a mediator of endothelial insulin resistance and atherosclerosis.

### Sources of Funding

The authors are supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) under award numbers R01HL062887, P01HL092969, and R01HL097365 (K.E. Bornfeldt). J.E. Kanter is supported in part by The Dick and Julia McAbee Endowed Fellowship in Diabetes Research Fellowship from the Diabetes Research Center (P30DK017047). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Disclosures

None.

References


Key Words: Editorial ■ atherosclerosis ■ endothelial cell ■ insulin resistance ■ protein kinase Cβ
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doi: 10.1161/CIRCRESAHA.113.301998

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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