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.
Endothelial insulin resistance and promotion of atherosclerosis. A, Under normal conditions, insulin binds to the insulin receptor (IR) on endothelial cells, and this initiates phosphorylation of IR substrate 1 and 2 (IRS) and downstream activation of phosphoinositide 3-kinase (PI3K), Akt, and endothelial nitric oxide (NO) synthase (eNOS). Activation of eNOS causes increased production of NO and vasodilatation and is believed to inhibit atherosclerosis. This pathway also results in suppression of vascular cell adhesion molecule-1 (VCAM-1) expression, a monocyte adhesion receptor known to promote atherosclerosis; inhibition of forkhead box O (FoxO) nuclear translocation; and activation of proatherogenic target genes. B, Endothelial insulin resistance is characterized by a reduced ability of insulin to activate the antiatherosclerotic PI3K-Akt-eNOS pathway, mediated by increased expression of protein kinase C \( \beta_2 \) isoform (PKC\( \beta_2 \)) and Nox2 and perhaps an increased activation of insulin-insulin-like growth factor-1 (IGF-1) hybrid receptors. 

Figure.
Disclosures

None.

References


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