Role of endothelin in vascular dysfunction in human obesity and diabetes
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Obesity and related disorders, including hypertension and type 2 diabetes, are associated with heightened risk of cardiovascular disease. Endothelin (ET)-1, the most potent vasoconstrictor peptide, also possesses important properties to stimulate the development and progression of the atherosclerotic process. It is therefore conceivable that increased ET-1 activity might participate in the derangement of adiposity-related vascular homeostasis. This concept is supported by the results of studies using receptor antagonists to show that the activity of endogenous ET-1 is indeed enhanced in overweight and obese, as well as in type 2 diabetes. Also, increased ET-1 contributes to endothelial dysfunction related to obesity and type 2 diabetes, whereas decreasing ET-1 vasoconstrictor tone corrects the defect of endothelium-dependent vasodilation in these patients. Furthermore, ET-1-dependent forearm vasoconstriction is increased in overweight and obese, but not in lean hypertensive patients. In addition, in patients with central adiposity and the metabolic syndrome, enhanced intravascular ET-1 activity coexists with decreased nitric oxide (NO)-dependent vasodilator capacity, suggesting a prevalence of vasoconstrictor mediators in obese vessels. One of the mechanisms evoked to explain the development of vascular abnormalities in obesity deals with the physiological endothelial effects of insulin and their derangement in insulin-resistant states. Thus, in addition to NO-dependent vasodilator properties, insulin also stimulates ET-1 production. This action has been demonstrated by use of antagonists of ET-1 receptors in the forearm circulation of healthy subjects, where ET-1-dependent vasoconstriction is increased following local infusion of insulin and accompanies a concurrent rise in NO-mediated vasodilation. In the healthy state, therefore, there is a balance between insulin-stimulated release of ET-1 and NO, with a resulting neutral hemodynamic response to the hormone. In conditions of caloric excess and adiposity, by contrast, insulin resistance implies defective insulin-mediated vasodilation, leading in turn to impaired ability of the hormone to enhance its delivery and that of substrates to peripheral tissues. An important role of ET-1 in this abnormality is supported by studies showing that upregulation of the ET-1 system impairs NO-mediated vasodilation in the vessels of insulin-resistant patients with obesity or type 2 diabetes, whereas NO bioactivity is restored following blockade of ET-1 receptors. This notion is further strengthened by the observation that ET-1 receptor antagonism improves insulin sensitivity in obese patients with insulin resistance. In conclusion, considerable evidence supports a mechanistic role of ET-1 in the pathophysiology of adiposity-related vascular dysfunction. Given the link between higher ET-1 activity and obesity, targeting the ET-1 system has hence the potential for effective cardiovascular prevention in this condition.


Molecular mechanism for suppression of insulin signaling by endothelin-1 in skeletal muscle cells
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Background: Endothelin-1 (ET-1) attenuates insulin-stimulated glucose uptake in human skeletal muscle, leading to the development of insulin resistance. However, the molecular mechanism underlying negative regulation of insulin receptor signaling by ET-1 remains unclear. The purpose of this study was to determine the inhibitory effects of ET-1 on insulin-induced Akt phosphorylation in rat skeletal muscle (L6) cells. Methods: Western blot experiments were used to analyze changes in the phosphorylation levels of Akt at threonine 308 (Thr308) and serine 473 (Ser473), mRNA expression for two ET receptors (ETAR and ETBR) and the C-terminus region of G protein-coupled receptor kinase 2 (GRK2-ct) were detected by reverse transcription polymerase chain reaction. GRK2-ct was overexpressed in L6 cells using adenovirus-mediated gene transfer. Results: mRNAs for ETAR and ETBR were detected on L6 cells as well as on human skeletal muscle. Insulin induced sustained Akt phosphorylation at Thr308 and Ser473, which was completely abolished by a phosphatidylinositol 3-kinase (PI3K) inhibitor, LY294002. The insulin-induced phosphorylation of Akt was suppressed by addition of ET-1 after insulin stimulation. The inhibitory effect of ET-1 was counteracted by a Gqq/11 protein inhibitor, YM-254890, and by a selective ETAR antagonist, BQ-123. Overexpression of GRK2-ct to interfere with the function of endogenously expressed GRK2 canceled the ET-1-induced suppression of insulin-stimulated Akt phosphorylation. Conclusions: ETAR activation with ET-1 suppresses insulin-induced, PI3K-mediated phosphorylation of Akt at Thr308 and Ser473 in a GRK2-dependent manner in skeletal muscle. These results indicate that both ETAR and GRK2 are therapeutic targets for insulin resistance and type 2 diabetes.