Abstract

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Insulin as a vascular hormone: implications for the pathophysiology of cardiovascular disease.

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BACKGROUND: Metabolic disorders, such as obesity and non-insulin-dependent diabetes mellitus, and cardiovascular disorders, such as essential hypertension, congestive cardiac failure and atherosclerosis, have two features in common, namely relative resistance to insulin-mediated glucose uptake and vascular endothelial dysfunction. Significant increases in limb blood flow occur in response to systemic hyperinsulinaemia, although there is marked variation in the results due to a number of confounding factors, including activation of the sympathetic nervous system. Local hyperinsulinaemia has a less marked vasodilator action despite similar plasma concentrations, but this can be augmented by co-infusing D-glucose. Insulin may stimulate endothelial nitric oxide production or may act directly on vascular smooth muscle via stimulation of the Na+-H+ exchanger and Na+/K+-ATPase, leading to hyperpolarization of the cell membrane and consequent closure of voltage-gated Ca2+ channels.

DISCUSSION: There is evidence both for and against the existence of a functional relationship between insulin-mediated glucose uptake (insulin sensitivity) and insulin-mediated vasodilation (which can be regarded as a surrogate measure for endothelial function). If substrate delivery is the rate-limiting step for insulin-mediated glucose uptake (in other words, if skeletal muscle blood flow is a determinant of glucose uptake), then endothelial dysfunction, resulting in a relative inability of mediators, including insulin, to stimulate muscle blood flow, may be the underlying mechanism accounting for the association of atherosclerosis and other cardiovascular disorders with insulin resistance. Glucose uptake may determine peripheral blood flow via stimulation of ATP-dependent ion pumps with consequent vasorelaxation. A 'third factor' may cause both insulin resistance and endothelial dysfunction in cardiovascular disease. Candidates include skeletal muscle fibre type and capillary density, distribution of adiposity and endogenous corticosteroid production.

SUMMARY: A complex interaction between endothelial dysfunction, abnormal skeletal muscle blood flow and reduced insulin-mediated glucose uptake may be central to the link between insulin resistance, blood pressure, impaired glucose tolerance and the risk of cardiovascular disease. An understanding of the primary mechanisms resulting in these phenotypes may reveal new therapeutic targets in metabolic and cardiovascular disease.

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