RESISTIN INDUCES VASCULAR INSULIN RESISTANCE THROUGH AN IMPAIRMENT OF AKT/ENOS PHOSPHORYLATIONS

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Since vascular dysfunction is a main trait of obese subjects, in the present study we evaluated the vascular impact of resistin, a recently discovered adipocyte hormone markedly increased in obesity.
In aortic and mesenteric segments from young and old C57BL6 mice, recombinant murine resistin did not induce changes in either basal vascular tone or phenylephrine-induced vascular contraction. In contrast, both in vivo and in vitro administration of resistin significantly impaired dose-dependent insulin-evoked vasodilation by reducing endothelial nitric oxide synthase (eNOS) enzymatic activity. This effect of resistin was selective for insulin vascular action, since vasodilatation induced by increasing doses of acetylcholine or nitroglycerine was not influenced by the adipocyte hormone. Molecular analysis on endothelial cells further detailed resistin-induced vascular resistance by showing impairment of insulin-evoked AKT and eNOS phosphorylations after exposure to resistin. Even this latter abnormality is selective of insulin signaling since AKT/eNOS phosphorylations are normally activated during acetylcholine stimulation. More important, the resistin induced endothelial dysfunction depends on resistin ability to alter IRS-1 Tyrosine/Serine phosphorylation and its consequent interaction with PI3K.
Our results demonstrate that resistin is able to induce a selective vascular insulin resistance impairing endothelial IRS-1 signaling pathway that leads to eNOS activation and vasodilation, thus suggesting that part of the vascular abnormalities present in obesity could be ascribed to the increased resistin levels of obese subjects.