Selective Insulin Resistance in the Vasculature Leads to Hypertension

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There is a connection between insulin resistance in the vasculature and systemic hypertension. Activation of phosphatidylinositol 3-kinase (PI3K) and Protein Kinase B (AKT) by insulin increases endothelial nitric oxide synthase (eNOS) activity, leading to vasodilatation. In contrast, activation of mitogen-activated protein kinase (ERK 1 and 2, ERK 1/2) by insulin stimulates endothelin-1 and promotes vasoconstriction. Total insulin receptor knockout mice (TTR-IR-/-) are null for the insulin receptor (IR), but have transgenic re-expression of Irs1 in the brain, liver and beta-cells. These mice do not possess many of the metabolic disturbances associated with diet-induced insulin resistance. In blood vessels from TTR-IR-/- vs. wild type (WT) mice, insulin mediated downstream signaling of Akt and ERK 1/2 is absent and eNOS expression and bioavailability is reduced. Furthermore, six days after implanting telemetry units, 48-hour averages of mean arterial pressure (MAP; mmHg) were similar between TTR-IR-/- (104±1) and WT mice (108±1; n=8-10 per group). Because complete absence of insulin-signaling is not observed clinically, we compared the same variables between mice that consumed a high-fat diet (45% fat; HF) to those that consumed standard rodent chow (10% fat; CON; n=10 per group) for 10 weeks. Glucose intolerance, hyperglycemia, hyperinsulinemia, and obesity (all p<0.05) were present in HF vs. CON mice. Furthermore, insulin-stimulated phospho (p-Akt was reduced and p-ERK/total-ERK was increased, in the vasculature of HF vs. Con mice. eNOS bioavailability was also reduced in blood vessels from HF vs. CON mice. 48-hour telemetry results indicated that hypertension existed (p<0.05) in HF (123±1) vs. Con (104±1) mice. Thus, hypertension does not develop in mice with non-selective impairment of insulin-mediated signal transduction (i.e., TTR-IR-/- mice). However, selective resistance to insulin mediated Akt signaling in the vasculature of mice with diet-induced obesity (i.e., HF mice) leads to hypertension.