Insulin-Mediated Vasorelaxation in a Genetic and Diet-Induced Model of Insulin Resistance

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Arterial dysfunction that exists in individuals with type 2 diabetes could result from impaired insulin-mediated signal transduction in the vasculature and/or from systemic metabolic abnormalities that exist in patients with this condition. We investigated this issue in two models of insulin resistance: a genetic model that lacks insulin receptors in the vasculature and most metabolic disturbances associated with type 2 diabetes (e.g., TIKO mice); and a diet-induced model of type 2 diabetes that does possess systemic metabolic disturbances. After verifying that TIKO mice lack insulin receptor mRNA in the vasculature and most metabolic abnormalities, femoral artery vasorelaxation in response to insulin (50-500 U/ml), acetylcholine (Ach, 10-8 M - 3 x 10-6 M; to evaluate endothelium-dependent responses), and sodium nitroprusside (SNP, 10-8 M - 3 x 10-6 M to evaluate endothelium-independent responses), was evaluated. While maximal-percent vasorelaxation in response to insulin was predictably blunted in femoral arteries from TIKO (4±2%) vs. Control mice (12±2%), Ach-mediated responses (91±3% vs. 91±1%) and SNP-evoked responses (96±1% vs. 98±1%) were similar between groups. Thus, insulin-mediated vasorelaxation is impaired in TIKO vs. Control mice, whereas endothelium-dependent and -independent responses are similar between groups. Because TIKO mice represent an extreme model of insulin "resistance" that does not occur clinically, we assessed vascular reactivity in mice that consumed high fat (45% fat; HF) or standard chow (10% fat; same controls as above) for 10 weeks. At ~20 weeks of age, metabolic disturbances (e.g., glucose intolerance, hyperglycemia, hyperinsulinemia, hypertension, increased free fatty acids, and obesity) were present in HF vs. Control mice. Furthermore, maximal-percent relaxation in response to insulin (7±2%) and Ach (80±3%) was lower relative to the respective control responses shown earlier e.g., 12±2% and 91±1%, respectively. Maximal SNP-evoked responses were similar in vessels from HF (95±1%) and control animals (98±1%). Taken together, our data indicates that endothelium-dependent dysfunction is evoked by systemic metabolic abnormalities rather than by impaired insulin-mediated signal transduction in the vasculature.