CORONARY VASCULAR FUNCTION IN INSULIN RECEPTOR-DEFICIENT MICE.

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Type 2 diabetics often have a clustering of coronary risk factors including insulin resistance, hypertension, obesity, dyslipidemia, and hyperglycemia. To test the hypothesis that insulin resistance per se contributes to coronary microvascular dysfunction, we used mice wherein insulin receptors (IRs) were genetically deleted everywhere but the brain, pancreatic β-cells, and liver. These mice have normal blood glucose that results from a compensatory rise in insulin due to "insensitivity" of the deleted IRs. This is similar to the pre-diabetic human condition. Forty-two week old mice homozygous for knockout of the IR (KO, n=8) were compared with their wild-type littermates (WT, n=8). Body weight (g) and blood glucose (mg/dl) were similar between KO (27±1, 119±1) and WT mice (26±1, 121±4), respectively. Two coronary artery segments (~70 μm, internal diameter) from each heart were mounted on arteriographs that were immersed in a chamber filled with physiological saline solution (pH 7.4; 37°C). First, each artery was precontracted with the thromboxane A2 receptor mimetic U-46619. Once stable, cumulative doses of acetylcholine (ACh) were administered to the vessel bathing medium. ACh causes nitric oxide (NO) release from the innermost layer of the blood vessel called the endothelium. NO then diffuses to the smooth muscle cell layer, activates cyclic GMP, and causes vasorelaxation of the blood vessel. This is called endothelium-dependent vasorelaxation. Percent relaxation from precontraction tension in response to 10⁻⁶, 10⁻⁵, and 10⁻⁴ M ACh was similar in vessels from KO (11±6, 34±7; 33±2%) and WT (8±5, 35±6; 34±5%) mice, respectively. Second, cumulative doses of sodium nitroprusside (SNP) were administered to precontracted vessels. SNP directly stimulates cGMP in vascular smooth muscle to cause endothelium-independent vasorelaxation. Responses to SNP were similar in vessels from both groups. Third, ACh dose response curves were repeated in the presence of a pharmacological agent that inhibits NO production by endothelial cells. Under these conditions, percent relaxation to 10⁻⁶, 10⁻⁵, and 10⁻⁴ M ACh was greater (p<0.05) in vessels from KO (9±9, 22±11, 26±12%) versus WT (4±5, 1±6, 9±8%) mice. These data suggest that a signaling mechanism other than NO can produce vasorelaxation to a greater degree in KO versus WT mice. This pathway may be compensating for a lack of insulin-mediated NO production due to deletion of IRs in KO mice.