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MUTATING THE IGF-1 ON THE VASCULAR ENDOTHELIUM: DIVERGENT EFFECTS ON WHOLE BODY AND ENDOTHELIAL INSULIN RESISTANCE

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Introduction Endothelial dysfunction is associated with the onset of atherosclerosis and cardiovascular disease. Whole body and endothelial cell insulin resistance can result in reduced nitric oxide (NO) bioavailability; this is a prominent feature of endothelial dysfunction. Recent work published by our group has shown that expression of insulin like growth factor-1 receptors (IGF-1R) in the endothelium may play a role in determining both endothelial cell insulin sensitivity and NO bioavailability.

Methods To further examine this relationship we have generated a transgenic mouse which expresses a non-functional mutation of the IGF-1R solely on the vascular endothelium (MIGFREO), under control of the Tie2 promoter. In order to assess metabolic and vascular phenotypes we have performed *in vivo* insulin, glucose and IGF-1 tolerance tests and have assessed vasomotor function *ex-vivo* using an organ bath.

Results MIGFREO mice display normal growth and development, have weight and blood pressure comparable with wild type litter mates. Extraction of pulmonary endothelial cells and subsequent quantitative PCR has demonstrated that the mutant IGF-1R is expressed solely on endothelial cells from transgenic mice. MIGFREO mice have preserved glucose tolerance but enhanced insulin sensitivity (mean [SEM] % of baseline blood glucose 30 minutes following insulin injection MIGFREO 55.99% [2.31], wild type 68.04% [2.43] $p<0.001$).

Assessment of vasomotor function shows that MIGFREO mice are resistant to the endothelial dependent vasodilatory effect of insulin as measured by maximum constriction in response to phenylephrine in the presence of insulin (Figure 1) (mean [SEM] maximum constriction in grams (g), wild type 0.54g [0.06], MIGFREO 0.75g [0.06] $p<0.05$). Endothelial function as assessed by vasorelaxation in the presence of acetylcholine in the MIGFREO mice is comparable with wild type mice. Exposure to catalase in the organ bath significantly reduces vasorelaxation to acetylcholine in MIGFREO mice (Figure 2) (mean [SEM} maximal relaxation with and without catalase respectively, wild type 89.29% [3.27} vs. 86.02% [8.56] MIGFREO 86.85% [3.02] vs. 73.36% [5.97] $p=0.05$) a finding not demonstrated in wild type litter mates. This suggests that MIGFREO mice may have elevated levels of H_2O_2 in comparison with wild type controls.

Conclusion Mutation of the IGF-1R specific to the vascular endothelium appears to have divergent effects on whole body and endothelial insulin sensitivity, measured by assessment of vasomotor response to insulin. Preliminary data suggests that MIGFREO mice have a higher basal level of H_2O_2 than the wild type controls. This is interesting in view of recent evidence which suggests that reactive oxygen species may play a role in enhancing insulin sensitivity. Further work will focus on examining insulin sensitivity in

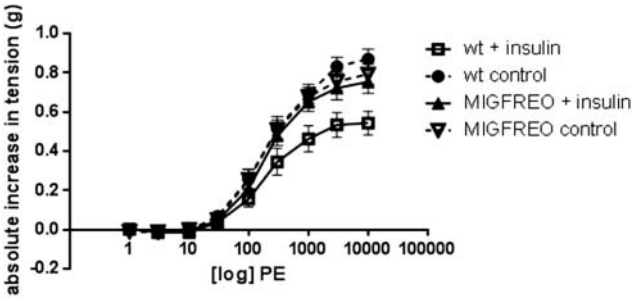

Figure 1 Vasomotor response to phenylepherine in presence of insulin or control.

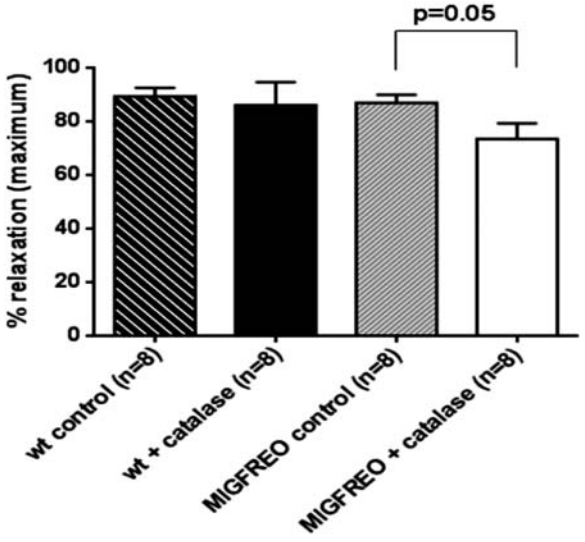

Figure 2 Percentage of relaxation achieved in response to autylcholine with presence of catacase or control.

endothelial cells and attempting to elucidate a cause for the observed findings to date.