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VASCULAR ENDOTHELIAL INSULIN SENSITISATION REDUCES BLOOD PRESSURE AND PROMOTES ENDOTHELIAL REPAIR IN THE CONTEXT OF GLOBAL INSULIN RESISTANCE

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doi:10.1136/heartjnl-2013-304019.163

Introduction Insulin resistant syndromes are associated with an increased risk of sustaining major cardiovascular events; diminished endogenous vascular endothelial repair may contribute to this phenomenon. It remains unclear whether insulin sensitisation is a valid target to reduce cardiovascular events.

Methods Global insulin receptor haploinsufficient mice (IRKO; n=8) were crossed with mice overexpressing the human insulin receptor under the transcriptional regulation of the Tie2 promoter-enhancer (IRKOxHIRECO; n=8) in order to augment vascular endothelial insulin sensitivity. Metabolic assessment was performed by assay of fasting glucose and insulin, followed by glucose- and insulin-tolerance tests. Blood pressure was assessed with tail cuff plethysmography. Femoral artery denuding injury was induced with an angioplasty guidewire and sham surgery performed contralaterally; 4 days later vessels were explanted after Evans blue dye perfusion in order to assess persistent endothelial denudation.

Results IRKOxHIRECO exhibited weight gain (28.3 [1.2] versus 27.4 [0.4] g at 4 months of age; p=NS), basal plasma glucose (6.9 [0.5] versus 7.0 [0.4] mmol/L; p=NS) and basal serum insulin (0.74 [0.13] versus 0.66 [0.16] ng/ml; p=NS) concentrations comparable to IRKO; glucose tolerance testing and insulin tolerance testing also suggested comparable metabolic insulin sensitivity. However, IRKOxHIRECO mice demonstrated reduced systolic blood pressure when compared with IRKO (mean 101.0 [SEM 0.6] versus 110.1 [0.6] mmHg; p<0.05). Moreover, IRKOxHIRECO mice exhibited enhanced re-endothelialisation of the injured femoral artery (56.9 [4.2] versus 46.0 [2.3] % vessel area re-endothelialised; p<0.05).

Conclusions Restoration of vascular endothelial insulin signalling in the context of global insulin resistance reduces blood pressure and augments vascular endothelial regeneration after denuding injury. These data support the pursuit of vascular insulin sensitising strategies as a means of promoting vascular repair.