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ENDOTHELIAL SHIP2 CONFERS AGE-DEPENDENT CONTRASTING AFFECTS ON WHOLE BODY GLUCOSE HOMEOSTASIS AND VASCULAR FUNCTION

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Introduction Aging is an important risk factor for diabetes and cardiovascular disease and integrity of the endothelium plays a critical role in cardiovascular pathophysiology. Although the vascular implications of endothelial insulin resistance are well understood, the effect of *enhanced* endothelial insulin signaling on whole body glucose regulation and vascular function remains poorly characterized. We therefore generated mice with endothelial-specific downregulation of the lipid phosphatase SHIP2 (a negative regulator of insulin signaling) to investigate whether enhanced insulin signaling in the endothelium modulates vascular function and whole body glucose regulation.

Methods Exons 18–19 of the ship 2 gene were deleted using Cre-Lox technology under control of the Tie2 promoter generating a catalytically inactivate protein. Male heterozygotes for the inactive protein (EC-SHIP2$^{+/-}$) were compared to sex-matched littermate controls.

Results EC-SHIP$^{+/-}$ mice were morphologically indistinguishable from controls, exhibiting normal development. At 8 weeks of age EC-SHIP2$^{+/-}$ mice displayed increased glucose tolerance after glucose challenge (P=0.03) and improved insulin sensitivity (P=0.02) after insulin challenge compared to controls. Surprisingly however, by 40 weeks of age this phenotype was reversed; EC-SHIP2$^{+/-}$ mice revealed significant insulin resistance 60 min after insulin challenge (P=<0.05). This phenotype was confirmed by euglycemic hyperinsulinemic clamping showing whole body insulin resistance in EC-SHIP$^{+/-}$ mice (decreased glucose infusion rate of 26% P<0.05). In young mice *ex vivo* aortic vasomotor studies in both controls and EC-SHIP$^{+/-}$ revealed similar contractile responses to phenylephrine and displayed decreased contraction after insulin incubation (Emax 0.88±0.05g vs 0.62±0.05g P=0.002 and 0.83±0.05g vs 0.69±0.05g P=0.025 respectively). Both groups displayed increased contraction after NO synthase inhibitor LNMMA incubation (Emax 0.88±0.05g vs 1.31±0.11g P=0.01 and 0.83±0.05g vs 1.28±0.02g P=<0.0001 respectively). However, at 40 weeks old in EC-SHIP2$^{+/-}$ mice the vasodilatory aortic ring response to insulin was abolished (Emax controls 0.59±0.04g vs 0.47±0.03g P=0.04, EC-SHIP2$^{+/-}$ 0.64±0.04g vs 0.63±0.06g P=0.9) and EC-SHIP2$^{+/-}$ displayed no increase in contraction to LNMMA incubation (Emax controls 0.59±0.04g vs 0.82±0.08g P=0.02, EC-SHIP2$^{+/-}$ 0.64±0.04g vs 0.69±0.07g P=0.5) indicating insulin resistance and lower basal NO production, suggesting the change in glucose homeostasis may be mediated by changes in NO bioavailability.

Conclusion Endothelial functional downregulation of SHIP2 augments whole body glucose disposal in young mice but attenuates whole body glucose disposal in older mice. Although further studies are required to elucidate the molecular mechanisms our data suggest a previously unrecognised age dependent role for the vascular endothelium in whole body glucose regulation.