Methodology Blood pressure (pressure-volume analysis or tail cuff plethysmography) was measured in wild type (WT) and Brn-3b knockout (KO) mice. Immunostaining and histological analysis were performed in the aorta of these animals. Gene expression analysis was performed using RNAseq and the expression pattern of Brn-3b was evaluated in primary VSMC cultures by immunofluorescence and qRT-PCR.
Results Brn-3b KO mice (2–6 months) developed spontaneous hypertension and vascular dysfunction such as neointimal hyperplasia, increased extracellular matrix (ECM) deposition and calcification. RNAseq analysis revealed that loss of Brn-3b in the aorta increased ECM gene expression, including collagens. Immunostaining of aortic sections from WT mice showed that Brn-3b was principally expressed in the tunica media, mostly composed of VSMC. Additionally, Brn-3b protein and mRNA were detectable in human and rodent primary VSMC cultures.
Conclusions Brn-3b loss *in vivo* is associated with vascular dysfunction and hypertension. Future studies will aim to investigate the role of Brn-3b in VSMC phenotypical changes.

P30 EFFECTS OF CARNITINE SUPPLEMENTATION IN THE TYPE 1 DIABETIC HEART: AN IN VIVO HYPERPOLARIZED MRS STUDY

Dragana Savic, Kerstin Timm, Vicky Ball, Lisa Heather, Damian Tyler. *Department of Physiology, Anatomy and Genetics, University of Oxford*

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Carnitine transports long-chain fatty acids across the mitochondrial membrane for subsequent β-oxidation. It is known that carnitine levels are decreased in cardiac diseases, such as diabetes, and that carnitine supplementation can have cardioprotective effects.

The purpose of this study was to investigate the effects of l-carnitine supplementation on cardiac metabolism in the diabetic rat heart.

Type 1 diabetic rats were generated by streptozotocin injection, control rats were injected with citrate buffer and all were treated for 3 weeks with daily injections of either l-carnitine or saline, where after they were subjected to CINE-MRI and hyperpolarized MRS.

Blood glucose levels were elevated in both diabetic groups, with the saline treated diabetic group showing a progressive increase in hyperglycaemia. Hyperpolarized MRS demonstrated reduction of pyruvate dehydrogenase (PDH) flux in the diabetic groups, but PDH flux was significantly higher in the l-carnitine treated diabetic group. Both lactate and alanine were significantly elevated in the animals treated with l-carnitine.

l-carnitine supplementation stabilises hyperglycaemia and increases the metabolism of pyruvate in the diabetic heart. l-carnitine provides a means to improve pyruvate metabolism in the diabetic heart.

P31 EFFECT OF GLYCOGEN CONTENT ON KETONE BODY OXIDATION AND GLYCOLYSIS IN THE ISOLATED RAT HEART

Azrul Abdul Kadir, Cher-Rin Chong, Henry Lee, Brianna Stubbs, Pete Cox, Kieran Clarke, Rhys Evans. *Department of Physiology, Anatomy and Genetics – University of Oxford*

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Apart from acting as an alternative energy source in oxidative tissues, including muscle, ketone bodies regulate the metabolism of other substrates, but are cataplerotic. Glycogen can be mobilised for anaplerosis, regenerating Krebs cycle intermediates, thus glycogen availability may affect the hearts' ability to oxidise ketone bodies. We hypothesise that glycogen acts as an anaplerotic substrate for myocardial ketone body oxidation, and thereby affects cardiac exogenous glucose utilisation. We aimed to determine the effects of cardiac glycogen content and ketone body metabolism on glucose utilisation.
Methods Isolated rat hearts were pre-perfused with buffer containing either no substrate (to deplete glycogen) or pyruvate, lactate, glucose and insulin (to augment glycogen content), before switching to 14C–hydroxybutyrate (βHB) or 5–3 hour-glucose, plus 11 mM glucose. Timed buffer samples were analysed for 14CO2 or $3H_2O$ to measure βHB oxidation or glycolysis, respectively. Hearts were freeze-clamped for glycogen content.
Results Removal of substrate in the perfusion period significantly decreased myocardial glycogen content (5.4±1.6 vs 43.5 ±5.1 μmol glycosyl units/gww). βHB oxidation rate in high glycogen hearts was twice that of low glycogen hearts. Presence of βHB in both high and low glycogen hearts significantly decreased glycolysis from perfusate glucose by 60% and 38% respectively (both to 0.29 μmol/gww/min).
Conclusion βHB oxidation was increased, and glycolysis from exogenous glucose was decreased, in high glycogen hearts.

P32 MITOCHONDRIA MUST CHOOSE BETWEEN RESISTANCE TO FATTY ACYL CoA REGULATION OR RAPID RESPIRATION IN THE TYPE 2 DIABETIC HEART

Matthew Kerr, Sara Rohling, Maria Sousa Fialho, Colleen Lopez, Damian Tyler, Lisa C Heather. *Department of Physiology, Anatomy and Genetics – University of Oxford*

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Introduction Cardiac metabolism in type 2 diabetes is abnormal, with increased fatty-acid oxidation, and decreased glucose oxidation. We have previously shown a reduction in energetics in the type 2 diabetic heart (20% decrease in ATP). The control of respiratory rate is mediated primarily (70%) by one protein, the adenine nucleotide translocator (ANT). The ANT is inhibited by fatty acyl CoA groups which may relate the reduced energetics in the type 2 diabetic heart to its high fatty acid environment.
Results Palmitoyl-CoA (P-CoA) decreased respiration in control mitochondria by 50%, but in diabetic mitochondria by just 20%. We showed unchanged Vmax, but increased Km in the presence of P-CoA, demonstrating competitive inhibition by the fatty acyl CoA group.

Diabetic mitochondria had decreased ADP stimulated, and maximal respiration compared to controls when respired on glutamate, pyruvate and malate. The addition of fatty acids rescued only the ADP stimulated respiratory defect.

Finally, we showed a very strong correlation between decreased respiration, and decreased sensitivity to fatty acyl CoA regulation.
Conclusion We have shown that type 2 diabetic mitochondria are resistant to fatty acyl CoA regulation, indicating that this is unlikely to be the cause of energetic dysfunction. We have shown a strong correlation between fatty acid sensitivity and the rate of respiration, two phenomena that are intrinsically linked by the ANT. We propose that changes to ANT kinetics