

Over- and undernutrition: challenges and approaches. 29 June–2 July 2009

## Effect of maternal dietary restriction during pregnancy in rats on PPAR $\alpha$ -regulated genes in the heart of the male offspring

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The demands of the heart for energy are met by a variety of substrates. In the fasting state fatty acids are the main substrate for ATP synthesis, while in the fed state glucose is the preferred substrate<sup>(1)</sup>. An investigation was conducted into whether prenatal undernutrition constrained future flexibility in the use of substrates for energy production in the heart by measuring the mRNA expression of PPAR $\alpha$  and of specific target genes involved in fatty acid metabolism.

Rats were fed a control (C; 180 g/kg feed protein) or protein-restricted (PR; 90 g/kg feed protein) diet throughout pregnancy and AIN76G<sup>(2)</sup> during lactation. Offspring (twelve to seventeen per dietary group) were fed the C diet containing 4 or 10 g fat/100 g from weaning until postnatal day 105 when hearts were collected and frozen in liquid N<sub>2</sub>. Total RNA was prepared using the AllPrep DNA/RNA Mini kit (Qiagen Ltd, Crawley, West Sussex, UK). RNA pools were prepared from each dietary group. Total RNA was analysed by an Agilent rat whole-genome oligo microarray (>41 000 genes; Oxford Gene Technology, Oxford, UK). Feature-extracted files were imported into GeneSpring GX (version 7.3.1; Agilent Technologies UK Ltd, Stockport, Ches., UK) and normalised using the Lowess signal-intensity-dependent normalisation method. mRNA expression of PPAR $\alpha$ , carnitine palmitoyl transferase (CPT)-1, acyl-CoA oxidase (ACO), diacylglycerol acyltransferase 2 (DGAT2) and lipoprotein lipase (LPL) was measured by real-time RT-PCR<sup>(3)</sup>. There was no significant effect of post-weaning fat intake and no interaction effect of maternal and post-weaning diet on any of the outcome measures, and so the results from offspring fed the different post-weaning diets were combined.

Based on marginal means, RT-PCR analysis showed that the mRNA expression of PPAR $\alpha$  and CPT-1 was 12% and 8% lower respectively ( $P > 0.001$ ) in the offspring of the PR dams than C offspring. ACO, DGAT2 and LPL expression was not significantly different between groups. Microarray analysis of pooled samples showed thirty-eight of sixty-two genes associated with the PPAR $\alpha$  signaling pathway were altered in the offspring of the PR dams compared with C offspring. Eight genes exhibited up-regulation (40–60% increase), including ACO synthetase long-chain family member 4 and 5, and thirty genes were down regulated (50–280% increase), including ACO synthetase long-chain family member 1.

Since PPAR $\alpha$  regulates the use of fatty acids for energy production, these findings suggest that prenatal undernutrition may increase capacity for fatty acid uptake, but limits energy production by mitochondrial fatty acid  $\beta$ -oxidation. Since cardiomyopathy involves dysregulation of fatty acid metabolism<sup>(4)</sup>, one implication of these findings is that nutritional constraint in early life may contribute to risk of heart failure.

This study was funded by the British Heart Foundation, who also provided salary support for J. S.-J., G. B. and M. H.

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