The Effect of Nutritional Early-life Programming on Adult Body Composition and Appetite Regulation

J. Anastasovska1, N. A. Nadkarni1, P-W. So2, N. Modi3, E. L. Thomas1, G. Frost1, and J. D. Bell1

1Metabolic and Molecular Imaging Group, Imaging Sciences Department, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, London, United Kingdom; 2Biological Imaging Centre, Imaging Sciences Department, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, London, United Kingdom; 3Section of Neonatal Medicine, Chelsea and Westminster Campus, Imperial College London, London, United Kingdom; 4Nutrition and Dietetics Research Group, Metabolic Medicine, Hammersmith Hospital, Imperial College London, London, United Kingdom

Introduction

There is evidence linking fetal nutrition and obesity in later life [1-3]. Therefore it is important to investigate the effect of nutrition at specific stages of development. This has been done using combinations of different diets during fetal and neonatal development. Fetal undernutrition (low protein 8%) followed by adequate nutrition (20% protein) during the early post-natal period, results in accelerated ‘catch-up growth’. This phenotype has been shown to lead to reduced life-expectancy [4], and higher susceptibility to weight gain during exposure to a high fat diet in later life [1-3]. In addition, it has been shown that normal fetal nutrition followed by undernutrition during the early post-natal period, increases life-expectancy in mice and does not cause a detrimental phenotype when animals are maintained on a high fat diet [4]. In this study, the effects on adipose tissue content and distribution as well as on appetite regulation of the two diet induced phenotypes mentioned above, are investigated in adult offspring using a combination of magnetic resonance imaging (MRI) and spectroscopy (MRS).

Methods

Animals and Treatment: Pregnant C57Bl/6 mice were maintained on a low 8% protein diet (LP) or a control 20% protein diet (C), from the day mating was confirmed, for the duration of the gestation period (19 days). At birth, the offspring of mothers on the low protein diet were cross-fostered to mothers on the control diet and the offspring from mothers on the control diet were cross-fostered to those on the low protein diet for the duration of the lactation period (21 days). The two resulting groups of offspring were under nourished either in utero (LP/C) or in the post-natal period (C/LP). A third group of pregnant mice were given the control (C) diet during both the gestation and lactation period. These offspring were the control group (C/C). At 21 days of age, the offspring from all three diet groups were weaned to either a normal (NF) 3% fat diet (LP/C/NF, C/LP/NF, C/C/NF; n=26) or a high (HF) 12% fat diet (LP/C/HF, C/LP/HF, C/C/HF; n=24), for a period of 12 weeks. Body weights and food intake were measured.

MR experiments: Whole body MRI and localised 1H MRS of the liver were performed on offspring (age 15 weeks) at 4.7T using a VRMIS scanner and data were analysed, as previously described (5). Manganese-enhanced MRI (MEMRI) was performed on a 9.4T VMRIS scanner and a transmit-receive quadrature birdcage coil. 66 consecutive timepoints were acquired using a 2D FSE sequence: TR 1.8s, TEeff 5.6ms (6 echoes, spacing 5.6ms, k-space centre=1), FOV 25x25mm, matrix 192x192, 46 axial 0.4mm slices, 2 averages. After the third acquisition, 100mM MnCl2+ was infused at 0.2ml/hr, total dose 0.5μmol/g body weight. 4D images were spatially normalized before signal intensity (SI) timecourse measurement in ROIs. SIs were then baseline corrected and Mn2+ dose normalized (to SI in Pituitary gland). Z statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05. Offspring from both LP/C and C/LP groups showed significantly higher body weight gains when given the higher fat diet at weaning (P<0.001, in both, data not shown). More rapid weight gain is only observed in the C/C offspring after 10 weeks on the weaning diets. The LP/C offspring caught up to the C/C mice in the first week of weaning and had an increasingly higher weight throughout, and to a greater extent in the HF groups (LP/C/NF vs. C/C/NF 14.3% increase, LP/C/HF vs. C/C/HF 22.5% increase, at week 12, data not shown). The C/LP offspring showed a similar effect compared to the C/C group but to a lesser extent than the LP/C mice. This increase in body weight appears to stop around week 7. As expected increased % body adiposity was observed in mice fed HF compared to NF throughout the offspring groups (Fig. a). However, the C/LP/NF mice showed significantly lower % adiposity compared to C/C/NF mice (10.2±0.8% and 15.1±1.6%, respectively, P<0.05, Fig. a). The LP/C/HF mice appeared to have a higher % adiposity than the C/C/HF offspring, although this effect was not significant. The percentage of internal AT, measured by MR image segmentation, was lower in the C/LP/HF offspring compared to the C/C/HF mice (6.1±0.5% and 9.0±0.7%, respectively, P=0.05, Fig. b). No significant difference was apparent in % internal AT between the LP/C and C/C offspring. A significant decrease in IHCL content in C/LP mice was observed compared to C/C mice (6.5±2.0; C/LP/NF, 18.3±2.9; C/C/NF, P=0.01, 12.0±3.3; C/LP/HF, 24.2±4.5; C/C/HF, P<0.05, arbitrary units, Fig. c). There appeared to be a trend of higher lipid content in the HF compared to the NF groups, though this was not significant.

Neuronal activity in specific hypothalamic nuclei associated with appetite was assessed by MEMRI. NPE in SI at steady state in 1), FOV 25x25mm, matrix 192x192, 46 axial 0.4mm slices, 2 averages. After the third acquisition, 100mM MnCl2+ was infused at 0.2ml/hr, total dose 0.5μmol/g body weight. 4D images were spatially normalized before signal intensity (SI) timecourse measurement in ROIs. SIs were then baseline corrected and Mn2+ dose normalized (to SI in Pituitary gland). Z statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05. Both the C/LP and LP/C offspring show greater weight gain and caloric intake than C/C mice possibly as a result of increased appetite.

Conclusion

Maternal nutrition during gestation and lactation significantly influences growth and adipose tissue distribution in their offspring. The stage of early life at which undernutrition occurs appears to be important and can cause very different adult phenotypes, such that low protein in the early post-natal period leads to an improvement in adiposity and lipol metabolism, despite an increase in appetite.

References