Long-term effect of prenatal nutrient restriction on hypothalamic energy sensing and energy balance control: importance to juvenile obesity development?

Sylvain Sebert\textsuperscript{1}, Laureen Chan\textsuperscript{1}, Melanie Hyatt\textsuperscript{1}, Helen Budge\textsuperscript{1}, Terence Stephenson\textsuperscript{1}, Michael Symonds\textsuperscript{1} and David Gardner\textsuperscript{2}

\textsuperscript{1}Centre for Reproduction and Early Life, School of Human Development, Academic Division of Child Health, University of Nottingham, Nottingham, UK and \textsuperscript{2}School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, UK

Both obesity and prenatal nutrient restriction modify energy balance. Part of this alteration in appetite control takes place in the hypothalamus through changes in the leptin signalling pathway\textsuperscript{(1)}. It has previously been observed that despite differences in food intake and feeding behaviour, neither obesity nor maternal nutrient restriction influence leptin signalling within the hypothalamus\textsuperscript{(2)}. However, in order to be fully effective, the leptin stimulus on appetite-control neurons requires a complementary signal from energy-sensing pathways, which includes AMP kinase (AMPK), acetyl-CoA carboxylase-\(\alpha\) (ACC-\(\alpha\)), GLUT-1 and the insulin receptor (IR)\textsuperscript{(3)}.

In order to analyse the influence of obesity and nutrient restriction in early gestation to mid-gestation (a period of early brain development) on hypothalamic energy sensing, pregnant sheep were used. Twenty-two twin-bearing mothers were fed either a 50\% nutrient-restricted diet (NR, \(n = 8\)) from 28 d of gestation to 80 d of gestation or a control diet (C, \(n = 14\)) throughout pregnancy. Mothers gave birth naturally to twins at term (145 d of gestation). Half the offspring from each group were killed at 1 week of age. The remaining fourteen C and eight NR offspring were then followed up to 1 year of age. After weaning offspring were either allocated to an obesogenic sedentary lifestyle environment (O) or a free-living active environment (L) up to 12 months of age. Food intake (per kg lean body mass) and physical activity were determined at 1 year of age. At 1 week and 1 year of age hypothalamic mRNA abundance of AMPK, ACC-\(\alpha\), GLUT-1 and IR were determined by real-time PCR standardised by 18 S rRNA.

Birth weight, early postnatal growth and hypothalamic mRNA abundance were unaffected by maternal nutrient restriction as measured at 7 d of age. At 1 year of age the O offspring had a greater positive energy balance than the L group (\(P < 0.001\)); the result of a very low diurnal physical activity. Nevertheless, the NRO offspring had a similar energy balance to L animals. The NRO group had a lower daily energy intake than the L and O groups (\(P < 0.01\)). This adaptation in the NRO group was associated with significant up-regulation of AMPK and ACC-\(\alpha\) mRNA abundance (\(P < 0.05\)). GLUT-1 mRNA remained unaltered by obesity whereas the IR mRNA abundance was elevated in both groups of O offspring compared with the L offspring.

The difference in regulation of energy balance observed in NRO offspring could have been triggered by the up-regulation of the energy-sensing system. ACC-\(\alpha\) and AMPK can modify food intake. Thus, if changes in mRNA are translated into protein, this greater level of energy-sensory products provoked by the maternal nutrient restriction may have corrected the level of leptin resistance induced by juvenile obesity. These results suggested an indirect long-term adaptation induced during the gestational period that has yet to be determined.