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

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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[(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[(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-α (ACC-α), GLUT-1 and the insulin receptor (IR)[(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-α, 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-α 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-α 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.

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