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Influence of birth weight, sex, age and adiposity on central leptin and insulin sensitivity in young growing sheep, as indicated by changes in voluntary food intake

C. L. Adam, P. A. Findlay, R. P. Aitken, J. S. Milne and J. M. Wallace

Obesity and Metabolic Health, Rowett Institute of Nutrition and Health, University of Aberdeen, Bucksburn, Aberdeen AB21 9SB, UK

Since prenatal growth influences postnatal predisposition to obesity, and obesity is associated with leptin and insulin resistance, we examined developmental changes in central leptin and insulin sensitivity in normal birth weight and intra-uterine growth restricted (IUGR) lambs. Singleton lambs derived from single sire embryo transfer, gestated and suckled by adequately-nourished adolescent dams (CONTrol; *n* 6 male, *n* 6 female) or by over-nourished adolescent dams[1] (IUGR; *n* 5 male, *n* 7 female), were weaned onto good quality diet ad libitum from 3 months of age. Indwelling intracerebroventricular (ICV) cannulae were surgically implanted and voluntary food intake (VFI) responses to single ICV injections of leptin and insulin were measured at 6, 9, 12 and 18 months of age. Mean birth weight was greater in CONT than IUGR lambs (males, 4.9 *v.* 3.4 kg, $P<0.05$; females, 4.5 *v.* 2.5 kg, $P<0.01$). At 3 months, body weight was similar between groups and sexes and there were no significant differences in body composition measured by dual energy X-ray absorptiometry (DEXA). At 6 months, body weight started to diverge with males heavier than females from this point onwards, and all groups had >30% total body fat from 9 months onwards. At 18 months, males were heavier than females (135 *v.* 108 kg, $P<0.01$) but females were fatter than males (49 *v.* 36%, $P<0.01$), with no effect of birth weight.

ICV leptin (0.5 mg) decreased VFI over 6h post-injection by 33% in all groups at 6 months, and by 45, 47, 62 and 71%, respectively, in male and female CONT and male and female IUGR groups at 9 months, thus showing an influence of birth weight in both genders (IUGR>CONT; $P<0.05$). At 12 and 18 months, ICV leptin had no effect on VFI. There was no correlation at any stage between ICV leptin response and total body fat for either sex.

ICV insulin (5 IU) had no effect on VFI at 6 months, and decreased VFI by 5, 27, 42, and 28%, respectively, in male and female CONT and male and female IUGR sheep at 9 months, when responses correlated inversely with birth weight ($r=-0.60$, $P<0.05$) and total body fat% ($r=-0.75$, $P<0.01$) in males but not females. At 12 months ICV insulin decreased VFI by 0, 23, 16 and 34% in male and female CONT and male and female IUGR lambs, respectively, indicating an influence of birth weight in both sexes (IUGR>CONT; $P<0.05$), and responses correlated inversely with total body fat% in females ($r=-0.65$, $P<0.05$) but not males. At 18 months, ICV insulin had no effect on VFI in any group.

Therefore, all animals initially showed central sensitivity to leptin and central resistance to insulin as young lambs, but they all became obese and centrally resistant to both leptin and insulin as adults at the end. During the intervening period of juvenile growth and development, low birth weight was unexpectedly transiently associated with increased central sensitivity to both leptin and insulin in both sexes. However, apparently this effect was ultimately overridden by the continuous access to high quality diet and the development of obesity, the extent of which was not influenced by birth weight in this study.

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1. Wallace JM, Luther JS, Milne JS, *et al*. (2006) *Placenta* **27**, S61–S68.