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Maternal nutrient restriction between early-to-mid gestation amplifies the insulin response to obesity in conjunction with increased mRNA abundance for GLUT4 but not the insulin receptor in skeletal muscle

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Maternal nutrient restriction during late gestation results in young adult offspring with increased fat mass in which GLUT4 abundance is reduced, indicating impaired glucose uptake by adipose tissue. In contrast, the muscle does not appear to be similarly affected[(1)]. The aim of the present study was to determine whether nutrient restriction targeted during the period of early muscle and pancreatic development impacts on plasma insulin concentration and the expression of genes involved in glucose metabolism following juvenile obesity.

Pregnant sheep (*n* 26) were randomly assigned to a normal diet (7 MJ/d) or nutrient-restricted diet (NR; 3.5 MJ/d) from 30 d to 80 d gestation (term 147 d) and fed to requirements at all other times. Following weaning at 10 weeks postnatal age offspring were reared in an environment of restricted activity and increased availability of energy-dense food to promote fat deposition and thus juvenile obesity. Two groups of offspring were exposed to this postnatal intervention, those born to prenatal NR mothers (NR-O, *n* 11) and control (normal-fed) mothers (O; *n* 7). A further group of control normal-fed offspring (*n* 8) remained on pasture and were therefore designated as lean (L). At 1 year of age plasma samples were taken from all animals before feeding for the measurement of plasma insulin and glucose concentrations. All sheep were humanely killed and the longissimus dorsi (LD) muscle sampled, from which total RNA was extracted and mRNA abundance determined for the insulin receptor (IR), GLUT1 and GLUT4 by real-time PCR analysis. All results were calculated using the $2^{-\Delta CT}$ method[(2)] and expressed in arbitrary units (au) as a percentage of an L reference. Data were analysed by ANOVA using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA). Animal procedures had local Animal Ethics Committee approval and were performed in accordance with UK legislation.

Obesity had no effect on plasma glucose concentrations; however, plasma insulin was raised in O animals, a response that was amplified in NR-O animals. In contrast, gene expression for the IR was only increased in the O group, whilst GLUT4 was raised in both groups of obese offspring, while GLUT1 mRNA was unaffected (Table).

Table. Effects of obesity and maternal nutrient restriction on plasma insulin, mRNA abundance of IR, GLUT1 and GLUT4 in longissimus dorsi muscle

	L		O		NRO		*P*	
	Mean	SE	Mean	SE	Mean	SE	L *v.* O	O *v.* NRO
Insulin (mM)	0.6	0.2	1.0	0.1	1.7	0.3	<0.05	<0.05
mRNA abundance (au)								
IR	1.0	0.2	3.3	0.7	1.9	0.5	<0.05	<0.05
GLUT1	1.0	0.2	1.4	0.2	0.9	0.1	NS	NS
GLUT4	1.0	0.2	3.8	0.7	4.3	0.7	<0.05	NS

In conclusion, despite maternal nutrient restriction targeted to the period of early muscle and pancreatic development, which resulted in an exacerbated insulin response to obesity, there appears to be no inhibitory effect on the potential ability for muscle to take up glucose. Surprisingly, gene expression for the IR in muscle was not increased in offspring born to NR mothers. Nutrient sensing and signalling pathways within the muscle are currently being investigated to determine whether these factors may be differentially reset by obesity in the NR offspring.

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