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Nutrition restriction in late-gestation and postnatal overfeeding change metabolic preferences in skeletal muscles of sheep

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Maternal dietary restriction during pregnancy is related to development of metabolic disorders in the offspring. In addition, postnatal exposure to overfeeding leads to metabolic adaptations. The aim of the experiment was to demonstrate if foetal programming leads to changes in catabolic preferences in skeletal muscle. Twenty twin-pregnant multiparous Shropshire ewes were divided into two groups, receiving either a NORM (semi-ad libitum) or a LOW (global feed restriction, 50% of NORM) diet during the last 6 weeks of gestation. From 3-day until 6-month of age, the twin-lambs (n=39) were assigned to each their postnatal diet: CONV (moderate hay feeding) or HCHF (high-carbohydrate, high-fat) diet. From 6-month to 24-month of age, sheep were raised on the same moderate grass based diet. Biopsies of Biceps femoris were obtained post-mortem at either 6-month or 24-month of age. mRNA levels of genes relating to glucose and lipid metabolism were measured by qPCR. Genes were grouped into four categories: 1) glucose metabolism: INSRbeta, IRS1, and GLUT4, 2) regulators of oxidation: PPARa, and PPARd, 3) coordinators: PGC1a and PGC1, and 4) mitochondrial FA oxidation regulators: CPT1b, UCP2, and UCP3. Preliminary results: UCP2 were down-regulated by LOW treatment at both 6- and 24-month of age ($P<0.05$). PGC1a was down-regulated by LOW treatment ($P<0.05$), and 6-month HCHF feeding ($P<0.05$). CPT1b tended to be up-regulated by overfeeding at 6-month of age. Conclusions: nutritional restriction during late pregnancy has substantial influence on adult body composition and fat accumulation possibly by influencing key gene functions involved in energy, fat and glucose metabolism.

Induction of muscle thermogenesis by high-fat diet in postweaning mice: association with obesity-resistance

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Adaptation to extrauterine environment depends on a switch from glucose utilization to catabolism of lipids from milk. Results of Palou and colleagues suggest that the postnatal switch is controlled, at least in part, by leptin absorbed from milk trough stomach to the circulation of the neonate, since leptin is known to enhance lipid oxidation in muscle via the stimulation of AMP-activated protein kinase (AMPK). These studies also demonstrated that (i) oral administration of leptin to suckling rats could imprint a lean phenotype, and (ii) in humans, leptin milk concentrations at 1 month of lactation correlated negatively with infant BMI until 2 years of age (for review, see Sanches et al, Endocrinology, 2008). The lasting effects of leptin could reflect modulation of signalling mechanisms of energy balance in central nervous system, as well as metabolic effects in muscle and other tissues of the offsprings. Our studies (Kus et al, AJP, 2008) on inbred strains of mice differing in propensity to dietary obesity, namely the obesity-resistant A/J as compared with obesity-prone C57BL/6J (B/6J) mice, showed large differences between the strains with respect to the effect of weaning to high-fat (HF) diet on thermogenesis and skeletal muscle metabolism. Measurements at 2 weeks after weaning suggest a role of muscle nonshivering thermogenesis and lipid oxidation in the obesity-resistant phenotype of A/J mice and indicate that HF diet could induce thermogenesis in oxidative muscle, possibly via the leptin-AMPK axis. The interactions between leptin and genetic background during lactation may be critical for the observed phenotypes.

Genetic markers of adult obesity risk are associated with protection from infant failure to thrive

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Background There is uncertainty whether early postnatal underweight or rapid weight gain has more relevance to future obesity risk. We employed genetic variants robustly associated with adult obesity in order to explore the timing of childhood weight change that lead to adult obesity. Methods Children from the ALSPAC birth cohort were genotyped for 10 variants robustly associated with adult BMI. Eight variants which showed individual associations with childhood BMI (in/near: FTO, MC4R, TMEM18, GNPDA2, KCTD15, NEGR1, BDNF and ETV5) were used to derive an 'obesity-risk-allele score' comprising the total number of risk-alleles' (range: 2 to 15 alleles) in each child with complete genotype data (n=7,146). Repeated measurements of weight and length/height from birth to age 11 years were expressed as SD scores (SDS). Early infancy failure to thrive was defined as conditional weight ga between birth to age 6 weeks below the 5th centile. Results The obesity-risk-allele score showed little association with birth weigh (regression coefficient: 0.01 SDS per allele; 95% CI: 0.00-0.02), and showed a much larger association with the rate of weight gair during early infancy (0.119 SDS/allele/year; 0.023-0.216) than during subsequent childhood (0.004 SDS/allele/year; 0.004-0.005). The obesity-risk-allele score was positively associated with early infancy length gain (0.158 SDS/allele/year; 0.032-0.284) and with reduced risk of early infancy failure to thrive (OR=0.92 per allele, 0.86-0.98). Conclusions The use of robust genetic markers in a contemporary birth cohort identified very early infancy gains in weight and length SDS as the start of the pathway to adult obesity.