Late gestation undernutrition (LG-UN) affects overall development and thyroid function in sheep

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III-36 Altered nutrition during the F0 pregnancy changes the phenotype of F1 and F2 pregnant rats

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There is evidence for the transmission of altered phenotypes between generations in several taxa. The mechanism underlying such transmission between generations is not known. We investigated in rats the effect of feeding an altered diet during F0 pregnancy on physiological outcomes and hepatic gene expression in F1 and F2 dams. Wistar rats were fed diets with 25% more energy with either sufficient (PS) (18% (w/w)) or restricted (PR) (9% (w/w)) protein contents during pregnancy. Dietary energy content was maintained throughout the life course in F1 and F2 generations. Dams were killed on post-conceptional (PC) day 8.5 or allowed to deliver naturally. Pregnancy weight gain was lower (40g) in F1 and F2 dams (PC age*generation $P<0.0001$) irrespective of F0 protein intake. There was no difference in energy intake, litter size, length of gestation or litter weight. Plasma glucose was significantly lower and -hydroxybutyrate higher in F2 compared to F0 dams (generation both $P<0.0001$). Corticosterone concentration was increased in F1 and F2 dams contingent on F0 protein intake (generation* F0 diet $P=0.023$). On PC day 8.5, F0 diet and generation altered hepatic glucocorticoid receptor, phosphoenolpyruvate carboxykinase and phosphofrutokinase-2 mRNA expression (interaction all $P<0.0001$). The results suggest that altered nutrition during pregnancy induced changes in maternal physiology and gene transcription in subsequent generations. This suggests that an altered intra-uterine environment represents one mechanism for the transmission of induced phenotypes between generations. Furthermore, sustained environmental change may induce adaptation over the course of several generations.

III-37 Late gestation undernutrition (LG-UN) affects overall development and thyroid function in sheep

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Objective: To assess 1) whether LG-UN have long-term implications for development of different organ systems, and 2) whether the postnatal diet affects the phenotypical expression of foetal programming. Methods: Twenty twinpregnant ewes were fed a NORM (energy and protein) or LOW (50% of NORM) diet the last 6 wks of gestation (term=147d). Twin lambs were from age 3d-6mo assigned to each their feeding: CONV (moderate) or HCHF (High-Fat-High-Carbohydrate). Male lambs were slaughtered at 6mo (~puberty). Female off-spring were raised on pasture from 6mo-2yrs (young adulthood) and then slaughtered. Results: Growth until 6 mo of age was determined exclusively by the postnatal diet. LG-UN resulted in smaller adult body size with most tissues/organs being proportionately smaller, but thyroid and adrenals were increased in LOW animals. HCHF lambs at 6mo had massive fat infiltration in adipose tissue; functional hepatocyte mass and kidney weight was reduced. By 2yrs (after 1 yrs on a moderate diet), postnatal diet effects disappeared, except for redistribution towards higher abdominal:renal fat in HCHF compared to CONV animals. Postnatal nutrition determined serum T3 and T4 in young lambs being highest in HCHF lambs, but in adult animals prenatal nutrition effects became manifested (highest in LOW). Conclusions: We have demonstrated implications of LG-UN for thyroid development and regulatory function, possibly involved in earlier termination of growth and smaller adult body size in LG-UN individuals. LG-UN effects were rarely detectable in adolescent lambs, where the actual postnatal diet was the main determinant. LG-UN effects, however, became consistently manifested in early adulthood.

III-38 A maternal low protein diet programs glucose and fatty acid metabolism differentially in adult male and female mouse offspring

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Nutritional conditions during human fetal life can influence the risk to develop the metabolic syndrome in adult life (metabolic programming'). Dysregulated fatty acid metabolism and impaired glucose tolerance are hallmarks of the metabolic syndrome. We aimed to establish a mouse model of metabolic programming focusing on the effects of a maternal low protein diet during gestation on glucose and lipid metabolism in the adult offspring. Methods: Pregnant C57BL/6J mice received a control or a low protein diet throughout gestation. Offspring received a low fat diet or a high fat diet from 6-22 weeks of age. Glucose metabolism was studied with a whole-body-glucose test using [6,6-2H]-glucose. Hepatic gene expression was characterized by microarray. Results: Maternal low-protein-diet did not affect glucose metabolism in male offspring. Male offspring showed lower insulin sensitivity after receiving a high fat diet than female offspring, regardless of the diet of the dam. Female offspring from normal-protein fed dams was relatively resistant to diet-induced metabolic dysregulation. Maternal low-protein-diet during gestation led to deteriorated insulin sensitivity upon high-fat feeding in female offspring. Conclusions: We conclude that, in mice, maternal protein restriction during gestation does not change the glucose response to a high fat diet in male offspring. However, gestational protein restriction changes fatty acid and glucose metabolism in female offspring in such a way that it resembles male metabolism. Our study shows limited effects of fetal malnutrition in male mouse offspring. On the contrary, females presented a masculinized reaction to a high-fat challenge when derived from a protein-restricted dam.

III-39 Early origins of disease: mild maternal zinc deficiency during pregnancy causes obesity and insulin resistance in the offspring

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Zinc is critical for insulin function; however, interactions between Zn, insulin, and glucose metabolism are complex. Mild maternal Zn deficiency affects maternal carbohydrate metabolism and fetal growth, but mechanisms behind changes in offspring glucose homeostasis are not understood. Rats were fed Zn deficient (ZnD, 7g/g) or control diet (CON, 25 g/g) for 3 weeks, bred and kept on ZnD during pregnancy and lactation. Litters were culled to 7pups/dam. After weaning, pups were fed regular chow. Insulin and glucose tolerance tests were performed at 5 and 10 weeks of age. Rats were killed at 3 and 15 weeks of age. mRNA expression of adipokines