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T1:OS2.4

Alterations in fuel homeostasis in adult male rats by perinatal polyunsaturated fatty acid supplementation are insulin-dependent

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Maternal factors can have major imprinting effects on homeostatic mechanisms in the developing fetus and newborn. Here we studied whether supplemented perinatal polyunsaturated fatty acids (PUFAs) influence energy balance and fuel homeostasis later in life. Between day 10 after conception and day 10 after delivery, female rats were subjected to chow enriched with 10% fish-oil (FO-rich). Fish oil contains high concentration of n-3 biosynthesis endpoint products, which caused increased membrane phospholipid incorporation (particularly derived from the long-chain 20:5α-3 PUFAs) in pup brains. Adult male offspring of FO-rich fed rats had reduced body weight (~20%) at 3 months, and had lower levels of plasma leptin (~54%), insulin (~41%), triglycerides (~65%), and lactate (~46%) than controls. All differences between groups were lost 48 hr after streptozotocin treatment, indicating that differences between control and FO-rich offspring depend on insulin action. At 4.5 months of age increased insulin sensitivity (following intraperitoneal injection) to lower blood glucose was found in FO-rich as compared to controls. We concluded that perinatal FO supplementation has lasting effects on body weight homeostasis and fuel metabolism in male offspring.

T1:OS2.5

Impact on Weight Dynamics and General Growth of the Common FTO rs9939609

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Background: The A-allele of FTO rs9939609 is associated with fatness. We aimed to investigate the impact of this variant on cross-sectional and longitudinal measures of BMI, height, and lean body mass.

Methods: At up to eight points in time from birth to adulthood, anthropometric measures were available on 753 obese (BMI≥31.0 kg/m²) and 879 random selected non-obese men, originally identified at the Danish draft boards. Logistic regression was used to assess the odds for being a carrier of FTO rs9939609 according to 1) z-scores for BMI, height and lean body mass (assessed by bioimpedance and DXA-scans) at given time-points and 2) longitudinal changes in growth.

Results: Except at birth, the AA genotype was associated with increased BMI z-scores at any point during the monitored life span, starting at age 7. This effect remained stable until early adulthood (age 20), where homzygous individuals were predisposed for further weight gain. The AA genotype was further associated with accelerated linear growth in childhood (age 7; OR, 1.36; 95% CI, 1.06 – 1.74), whereas final height was unaffected. Finally, individuals homozygous for the A allele had increased lean body mass (OR, 1.24; 95% CI, 1.02 – 1.32). These associations where only partly explained by the FTO-related obesity.

Conclusion: The fatness induced by FTO rs9939609 in early childhood remains stable until early adulthood, where further weight gain may occur. Moreover, this obesity-promoting gene variant is associated with features of general growth (linear growth and lean body mass).

T1:OS3.1

The anti-diabetic drug metformin exerts an anti-tumoral effect in vitro and in vivo through a decrease in cyclin D1 level

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As a widely used anti-diabetic drug Metformin regulates glucose homeostasis and improves metabolic disorders associated with obesity. Recent studies suggest that metformin may reduce the risk of cancer, but its mode of action remains not elucidated. We investigated the effect of metformin on human prostate cancer cell proliferation in vitro and in vivo. Metformin inhibited the proliferation of DU145, PC-3 and LNCaP cancer cells with a 50% decrease of cell viability and had a modest effect on normal prostate epithelial cell line P69. Metformin did not induce apoptosis but blocked cell cycle in G0/G1. This blockade was accompanied by a strong decrease in cyclin D1 protein level, pRb phosphorylation and an increase in p27kip protein expression. Although, metformin activated the AMP kinase pathway, a fuel sensor signalling pathway, this effect does not appear to be involved in its anti proliferative effect. Indeed, inhibition of the AMPK pathway using siRNA against the two catalytic units of AMPK did not prevent the effect of metformin in prostate cancer cells. Importantly, oral and intraperitoneal treatment of mice bearing xenografts of LNCaP with metformin led to a 50% and 35% reduction of tumor growth, respectively. Similarly, to the in vitro study, metformin led to a strong reduction of cyclin D1 protein level in tumors providing evidence for a mechanism that may contribute to the antineoplastic effects of metformin suggested by recent epidemiological studies.

T1:OS3.2

Cooperation of adipocytes with breast cancer cells promotes an invasive phenotype

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Accumulating recent evidences propose that metastatic traits of breast cancer cells are acquired through exposure of tumour cells to paracrine signals that they receive from the tumour-associated stroma. Most of the studies on epithelial-stroma interactions during breast cancer cell invasion have focused on fibroblasts, endothelial and inflammatory cells. Very little attention has been given to adipocytes when tumour cells were grown in the presence of adipocytes-conditioned medium, suggesting a cross talk between the two cell population. In fact, culture of adipocytes with breast tumour cells increases the levels of pro-inflammatory cytokines that in turn stimulate the level of CXCR-4 expression. We are currently investigating the expression of these cytokines either in normal (isolated from mammoplasty) or peritumoral (isolated from tumorectomy) breast adipocytes. In conclusion, our results strongly suggest that peri-tumoral adipocytes cooperate with breast tumour cells to provide an invasive phenotype. In addition, these results might contribute to explain the poor prognosis of breast cancer in obese women.

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