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Alleviations in fuel homeostasis in adult male rats by periatal 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 20:5n-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.

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 p27Kip1 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.