

MSc DEFENCE Monday, April 10th, 2017

Student: Amanda Henderson

Title: MATERNAL B-VITAMIN STATUS DURING DEVELOPMENT AND PROGRAMMING OF ADULT OFFSPRING ADIPOSITY

Time and location: 1:00pm PDT; Room 3113, BC Children's Hospital Research Institute (formerly CFRI)

Supervisor: Angela Devlin

ABSTRACT

Background: Developmental programming suggests that prenatal and early postnatal environmental factors, such as maternal nutrition, can impact risk for chronic diseases later in life. Population studies have reported greater insulin resistance and adiposity in offspring from mothers with adequate folate but low vitamin B12 (B12) status during pregnancy. Rodent studies further characterizing the physiological effects of maternal folate/B12 imbalance during pregnancy have shown that these effects on offspring adiposity and glucose homeostasis are sex-specific. Folate, a methyl nutrient, is metabolically linked to B12. Low B12 status, even when folate is adequate, can trap folate in a metabolically inactive form. Folate deficiency is rare in Canada due to mandatory folic acid fortification of grain products, yet 1 in 20 Canadians are estimated to be B12-deficient. The objective of this thesis is to determine the mechanisms underlying the relationship between maternal B-vitamin status during pregnancy and offspring adiposity and glucose homeostasis.

Methodology/Results: Female mice (C57BL/6J) were fed one of 3 maternal diets six weeks prior to conception and through breeding, pregnancy and lactation: control (M-CON), supplemental folic acid with adequate vitamin B12 (SFA+B12), or SFA without B12 (SFA-B12). Tissue was harvested from dams at 13 weeks of age (one week after weaning of offspring). Dams that were supplemented with folic acid (SFA-B12) had larger ($p \leq 0.05$) total body weight and subcutaneous adipose tissue depots than dams fed the M-CON diet. In vitro experiments assessed direct effects of folic acid on adipocyte energy metabolism. In 3T3-L1 adipocytes, cells treated with $1.6 \mu\text{M}$ folic acid had lower ($p \leq 0.05$) mitochondrial respiration rates than cells treated with $0.16 \mu\text{M}$ folic acid. Adipocytes treated with $1.6 \mu\text{M}$ 5-methyltetrahydrofolate (5-MTHF), the circulating form of folate, had higher ($p \leq 0.01$) mitochondrial respiration rates than cells treated with $0.16 \mu\text{M}$ 5-MTHF.

At weaning of the offspring, one male and one female from each dam were weaned onto either a control diet or a western diet (45% energy from fat) and fed for 20 weeks (males) or 30 weeks (females). Sex-specific differences in the effects of maternal diet on adult offspring health were observed. Female control-fed SFA-B12 offspring had lower ($p \leq 0.05$) serum IGF-1 (insulin-like growth factor-1) concentrations than M-CON and SFA+B12 offspring. This was accompanied by higher ($p \leq 0.05$) hepatic Cpt1a mRNA in SFA-B12 and SFA+B12 offspring than M-CON offspring. Female western-fed SFA+B12 offspring had higher ($p \leq 0.05$) hepatic FADS2 and ELOVL2 protein than M-CON offspring. Conversely, male control-fed SFA-B12 offspring had higher ($p \leq 0.05$) hepatic linoleic acid (C18:2n-6) and lower ($p \leq 0.05$) eicosapentaenoic acid (C20:5n-3) concentrations, and lower ($p = 0.08$) hepatic ELOVL2 protein than M-CON offspring.

Conclusion: These findings suggest programming of offspring adiposity and glucose homeostasis by maternal B-vitamin status occurs through sex-specific alterations in IGF-1, and adipose tissue and hepatic lipid metabolism. It is vital that we understand the implications of B-vitamin status, particularly during pregnancy, to better optimize the health of future generations.