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Double insults: phenotypic consequences of folate depletion during development and high fat intake from weaning

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The developmental origins of health and disease hypothesis propose that exposures during early life may contribute to increased risk of disease in adulthood. Growing evidence from animal models suggests that nutritional insults *in utero* result in altered programming of offspring, causing increased disease risk in later life. In a previous study, we observed that maternal folate depletion during pregnancy resulted in adult offspring which were heavier ($P = 0.016$) and had heavier organs (liver, $P = 0.024$; small intestine, $P = 0.036$) (unpublished data). The present study aimed to test the hypothesis that offspring born to folate-depleted mothers are more susceptible to increased adiposity and associated health consequences, particularly when fed a high-fat diet from weaning.

Pairs of female C57BL/J6 mice were assigned randomly to folate-adequate (2 mg folic acid/kg) or folate-deplete (0.4 mg folic acid/kg) diets 4 weeks prior to mating. Dams remained on the allocated diets during pregnancy and lactation. At weaning (mean 23 d), offspring were allocated at random to a low (LF; 5 %) or high fat (HF; 20 %) diet, resulting in four treatment groups. Offspring were weighed weekly from weaning and food intake was assessed at 9 and 18 weeks of age. Total adiposity and liver fat deposition were assessed in a subset of mice (n 9 per treatment group) by MRI scanning at 12 and 24 weeks of age. Data were analysed using univariate ANOVA.

At 9 weeks, food intake was not statistically different between treatment groups for female mice, but males given the HF diet post-weaning ate 21.1 % less per week ($P<0.001$) than those on the LF diet. Folate depletion during pregnancy and lactation did not significantly affect body weight, total adiposity or liver fat deposition in offspring at 12 weeks. At 12 weeks, female offspring fed the HF diet were 13.2 % heavier ($P<0.001$) than those on the LF diet. Although HF-fed male offspring were 6.9 % heavier than those fed the LF diet, this difference was not statistically significant ($P>0.05$). Total adiposity was increased ($P<0.001$) in both male (23.0 %) and female (30.2 %) mice fed the HF diet from weaning. Liver fat tended to be higher in HF-fed female (23.2 %, $P = 0.059$) and male (17 %, $P = 0.284$) mice.

Folate depletion during development did not appear to influence appetite, body weight or adiposity at 12 weeks of age. However, HF feeding from weaning resulted in sex-specific phenotypes with the male mice appearing to have greater ability than the females to regulate food intake when exposed to the HF diet. This difference was reflected in the greater divergence in body weight and liver adiposity between females fed the LF and HF diets. Similar gender dimorphic responses have been observed in rats fed HF diets[1,2]. These preliminary data provide evidence for sex-specific responses to high-fat intake but no apparent effect (up to 12 weeks of age) of the maternal low-folate insult.

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2. Priego T *et al*. (2009) Sex-associated differences in the leptin and ghrelin systems related with the induction of hyperphagia under high-fat diet exposure in rats. *Horm Behav* **55**, 33–40.