Fit mum, fat dad: Can mum exercising during pregnancy overcome the detrimental effects on insulin sensitivity in offspring of a high fat eating dad?

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The developmental origins of health and disease paradigm investigates how environmental cues early in life impacts on long-term disease susceptibility, such as type 2 diabetes. Epidemiological studies, clinical trials and different animal models have demonstrated that a wide range of stimuli (*e.g.* smoking, stress, poor diet) during development compromise offspring's phenotype, and both parents appear to play an important role in this process. In fact, offspring sired by fathers fed a high-fat diet demonstrate impaired insulin secretion which is linked to epigenetic changes. Whether insulin sensitivity is affected in this case needs further exploration. On the other hand, we and others have demonstrated that maternal exercise before and during pregnancy benefits offspring metabolic outcomes, including glucose tolerance. However, whether maternal exercise can protect paternal high-fat diet induced metabolic dysfunction in the offspring has not been examined. Therefore, we investigated 1) if offspring sired from fathers fed a high fat diet prior to conception have impaired insulin sensitivity; and 2) if maternal exercise before and during pregnancy can improve the offspring's phenotype and overcome these detrimental metabolic effects.

Female Sprague-Dawley rat offspring were divided into 4 groups (n=8-10 per group, from different litters) according to their parents' treatment: pups of normal (N) chow fed fathers and sedentary (S) mothers (N-S); pups of high-fat (HF) fed fathers and sedentary mothers (HF-S); pups of normal chow fed fathers and trained (T) mothers (N-T); and, pups of high-fat fed fathers and trained mothers (HF-T). Fathers consumed a high-fat diet (23% fat) for 8 weeks before mating. Meanwhile, mothers exercised for 4 weeks before and during gestation on a motorised treadmill, gradually reducing the duration and intensity during pregnancy (5 days/week, 60-20 min/day and 20-10m/min). Offspring remained sedentary and fed normal rat chow (4.80% fat) throughout the experiments.

At 12 and 24 weeks of age, an intraperitoneal glucose tolerance test (IpGTT; 1g/kg) was performed, and blood glucose and plasma insulin were analysed. On the following week, animals were anaesthetized intraperitoneally (90mg/kg pentobarbitone sodium) after an overnight fast. Epitrochlearis and *soleus* muscles were dissected to evaluate insulin-stimulated 2-deoxyglucose (2DG) uptake under blinded conditions. Statistical differences were determined by ANOVA and time-courses experiments by repeated-measures ANOVA. Significance was set at $P<0.05$. At 12 and 24 weeks of age the IpGTT response was similar among the four groups of offspring. However, young pups from trained mothers tended to have lower glucose area under the curve during the IpGTT compared with N-S pups ($P=0.07$). At 25 weeks of age, 2DG uptake in the *soleus* muscle was similar in the four groups of offspring. In the epitrochlearis muscle, offspring of HF-S had lower basal and insulin-stimulated 2DG uptake compared with N-S ($P<0.05$) and this was normalized in HF-T pups. Maternal exercise in chow fed dads did not affect 2DG uptake profile in the offspring.

In conclusion, paternal high-fat feeding does not disturb offspring's whole body glucose tolerance although it impairs basal and insulin-stimulated glucose uptake in the epitrochlearis muscle. Maternal exercise improves glucose tolerance early in life, and ameliorates the negative effects of paternal high-fat diet on skeletal muscle glucose uptake in adult female rats indicating protective effects and a healthier phenotype.