Circadian rhythms meet in utero metabolic programming

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Circadian rhythms meet *in utero* metabolic programming

Faria et al (in this issue) investigated the effects on offspring glucose metabolism from rat dams having day-restricted feeding during gestation and lactation. Day-restricted feeding was maintained throughout gestation and in the lactating period. Feeding at day is in contrast to the normal circadian rhythm of rats and cause decreased food intake of the dams, decreased birth weight of pups, impaired glucose tolerance of male offspring and decreased islet glucose stimulated insulin secretion (GSIS). Further experiments using pair-feeding of a control group to the day-restricted dams during gestation and lactation showed a similar phenotype of male offspring: Impaired glucose tolerance during an intraperitoneal glucose tolerance test and decreased GSIS. This shows that out-of-phase feeding and a related alteration of the circadian rhythm during gestation and lactation by itself results in fetal metabolic programming of male offspring.

In adult rodents, switching the circadian rhythm by forced day-light feeding results in an impaired metabolic phenotype with weight gain and impaired glucose tolerance (Salgado-Delgado et al., 2010, Shamsi et al., 2014). Studies of genetically modified mouse models have shown that chronic switch of day-night circadian patterns promote development of weight gain and insulin resistance (Lamia et al., 2011). There is ample evidence from epidemiological studies that night shift work is associated with development of the metabolic syndrome as well as increases the risk of depression (Gonnissen et al., 2013).

Changing the circadian rhythm with out-of-phase feeding could change the stress levels of dams, but the effect of day-restricted feeding on maternal cortisol levels remains to be tested experimentally. Moreover, it is known that chronic stress, permanent activation of the HPA-axis and increased

cortisol levels of dams promotes an impaired metabolic phenotype in offspring (Nyirenda et al., 2001). Human epidemiological studies show that maternal chronic stress (increased cortisol levels, increased anxiety) is associated with low birth weight (small for gestational age)(Reynolds, 2013), which is by itself correlated with increased risk of insulin resistance and type 2 diabetes. However, human clinical or epidemiological studies addressing the role of a changed circadian rhythm and out-of-phase eating has not been performed.

Children born small for gestational age are more insulin resistant and face increased risk of type 2 diabetes (Nielsen et al., 2014), historically shown by the Dutch Hunger Winter Study and epidemiological studies of the Chinese Famine (Li et al., 2010, Roseboom et al., 2011). Rodent models of intrauterine growth retardation, such as restriction of placental blood flow (Gatford and Simmons, 2013) or maternal low-protein diet result in similar phenotypes in offspring; reduced birthweight and adult insulin resistance and impaired glucose tolerance later in life (Bouret et al., 2015). The study by Faria et al show that the effects of a changed eating pattern are decreased birth weight of pups as well as impaired GSIS of male offspring, suggesting fetal metabolic programming could be mediated by the decreased food intake of pregnant and lactating dams. When Faria et al then performed a pair feeding and day-restricted eating experiment, the GSIS of isolated islets from male offspring was decreased compared with the pair-fed control group. It is, however, noteworthy that the islets from the pair-fed offspring group had levels of GSIS in between the ad libitum fed group from the previous experiment and the day-restricted feeding group. Although these comparisons were not made side-by-side, this observation suggests that the effects of changing the circadian eating pattern could be additive to the effect of decreased food intake.

Thus, the novel observation made by Faria et al emphasizes that also circadian rhythm alteration of the mother is able to metabolically program the endocrine pancreas of the offspring *in utero* and in the neonatal period independent from the effect of calorie intake. Moreover, the study suggests that up-regulation of specific microRNAs (miR-29a and miR-34a), previously associated with impaired GSIS (Bagge et al., 2012) and TP53 activation (Chang et al., 2007, Raver-Shapira et al., 2007) could be implicated in the decreased insulin secretion observed. This observation is concordant with the hypothesis that microRNAs play important roles in cellular or whole body metabolic stress response pathways (Vienberg et al., 2016).

The study by Faria et al provides a clear line of translational perspective to be empirically tested in the clinical and or epidemiological setting: The simple message is: Pregnant women should keep their bed time and eat regular meals to ensure the long-term metabolic health of their offspring.

These directions of cause add to the already substantial list of general recommendations for pregnant women, such as performing regular but non-strenuous physical exercise, abstain from any alcohol intake, eating a healthy diet rich in folic acid/vitamin B12 and containing ample amounts of poly-unsaturated fatty acids, and maintain a normal body weight as well as a moderate weight gain over the course of gestation; There is considerable Science in being pregnant!

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Conflict of Interest:

The author has no conflicts of interest

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