論文審査の要旨及び担当者

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（論文審査の要旨）

論文題名：Maternal circadian rhythms during pregnancy dictate metabolic plasticity in offspring
（母児概日リズム連関と代謝可塑性）

In modern society, maternal circadian disruption during pregnancy may significantly impact fetal development and metabolic plasticity. Using environmental and genetic mouse models, this study demonstrated that maternal circadian disruption predisposes offspring to diet-induced obesity by rewiring hepatic circadian rhythms, altering placental efficiency, and disrupting the phase-relationship between the mother and fetus.

At the screening, several key points were discussed. First, the cause of premature death observed in circadian gene knockout mice was questioned. It was explained that previous studies showed early-life knockout of genes such as Bmal1, Cry1, Per2, and Clock leads to developmental changes and premature death. Next, research on the fluctuation of clock gene expression in pregnant mice was explored, highlighting that hypothalamic expression levels peak at mid-gestation, though studies on peripheral organs remain limited. Then, the difference in outcomes between high-fat diet (HFD) and low-fat diet (LFD) induction in experimental groups was addressed. Maternal circadian disruption caused the production of newly rhythmic metabolites under HFD conditions, the driven of de novo oscillation of lipid species may contributing to an exaggerated obese phenotype, while no such effect was observed under LFD conditions. The rationale for using LFD instead of regular chow was also clarified, emphasizing that LFD ensures the only variable difference is the fat content, creating a clearer contrast between groups. Additionally, the higher daytime food intake observed in offspring exposed to HFD was attributed to reduced energy expenditure and arrhythmic feeding behavior, driven by the induction of orexigenic peptides in the hypothalamus, such as Npy and Agrp. Regarding potential epigenetic changes, it was explained that DNA methylation in 4-week-old offspring without diet induction showed minimal differences, though future studies may investigate this further. The possibility of immature liver development in offspring due to maternal CPS was also raised. However, qPCR analysis of liver markers, including Alb, Hnf4a, and Afp genes in the fetal liver indicated no significant differences, suggesting liver maturation was unaffected. Furthermore, leptin resistance in offspring with exaggerated obesity was discussed, linking it to arrhythmic leptin gene expression in the white adipose tissue (WAT) and hyperleptinemia in the serum. Despite this, orexigenic peptides were induced in the hypothalamus during the light phase, pointing to central leptin resistance as a key factor. Finally, the impact of maternal shift work on human offspring metabolism was considered. While studies show maternal shift work is associated with lower birth weight, long-term metabolic observations are limited, representing a potential area for future research.

In light of the above, while the precise mechanisms linking maternal circadian disruption to fetal metabolic disturbances remain incompletely understood, this research has provided valuable insights into how maternal circadian disruption during pregnancy impacts offspring metabolic functions, enhancing our understanding of the developmental origins of health and disease, and Yao Na has successfully completed their dissertation assessment.