METABOLISM

Paternal circadian disruption affects offspring health

Lassi, M. et al. *Sci. Adv.* **7**, eabg6424 (2021)

Most organisms, including humans, exhibit circadian rhythms that allow them to align their physiology and behavior to the rhythmic fluctuations in the environment (e.g. the light-dark (LD) cycle). Disruption of these rhythms is associated with negative health outcomes such as premature aging and metabolic syndrome. Emerging research from animal models suggests that the effects of circadian disruption persist across generations. Most notably, studies in rodents have shown that disruption of maternal circadian rhythms, before and during gestation, adversely affects offspring health; however, to date, the role of paternal circadian rhythms in offspring health has been largely overlooked.

In a new study published in *Science Advances*, a team of investigators led by Raffaele Teperino from the German Research Center for Environmental Health Neuherberg shows that circadian disruption in male mice before mating modifies offspring feeding behavior and metabolic health; the findings also provide evidence for a role of seminal plasma corticosterone in the intergenerational transmission of the effects of circadian disruption.

To understand the effect of paternal circadian disruption on offspring health, the team submitted C57BL/6J male mice (F0 males) to a 30-day restricted feeding (RF) schedule — with access to food limited to 12 hours from 6:00 a.m to 6:00 p.m — before mating them to females and analyzing the phenotype of their progeny. The choice of the circadian disruption protocol was based on previous studies that had established that changing the feeding time of mice from the phase of activity (dark period of the LD cycle) to the phase of rest (light period) acts like a "Zeitgeber" (ZT, referring to any cue that can influence the timing of the internal clock) and generates a 12-h shift in the body clock.

Here, Lassi et al. show that 30-day RF modified the pattern of 24-h corticosterone

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secretion in F0 male mice, as well as the expression of core clock genes in the liver, thereby confirming that the RF protocol was sufficient to disrupt the circadian rhythm of the mice. Corticosterone is a potent internal regulator (or ZT) of the circadian clock and regulates clock gene expression in various tissues. In normal conditions, corticosterone secretion follows a robust circadian rhythm, and previous studies have shown that alteration of the corticosterone rhythm results in clock desynchronization and compromises metabolic homeostasis.

F1 males born from the mating of RF males to age-matched females on ad libitum feeding schedule (F1-RF mice) developed normally and showed normal growth curves from weaning to ~10 months. However, metabolic phenotyping revealed that F1-RF males showed an increase in daily food intake, were hyperglycemic and had a disrupted corticosterone rhythm compared with F1 males of control fathers (F1-C). Analysis of RNA-seq also indicated profound alterations of oscillatory genes and core clock components in the liver and hypothalamus of F1-RF mice.

Hypothesizing that corticosterone in the seminal plasma —the acellular part of the semen — could mediate the effects of paternal circadian disruption on offspring phenotype, the team measured corticosterone concentration in seminal plasma of control and RF F0 males at different ZT. In control mice, seminal plasma corticosterone concentration oscillated within 24 h following the pattern observed in the serum with an anticipatory peak at the beginning of the night phase, whereas corticosterone rhythmicity was severely dampened in the seminal plasma of RF F0 males with a significantly less pronounced peak at the day-night transition.

To test whether corticosterone level in the seminal plasma is an important factor for the intergenerational consequences of paternal circadian disruption, the team generated a new cohort by breeding parental mice during the day (between ZT1 to ZT3, instead of day-night transition from ZT10 to ZT12 for previous cohorts) when corticosterone levels in the seminal plasma were not different between control and RF males. Phenotyping of F1 mice revealed that day breeding normalized the hyperphagia, hyperglycemia and the corticosterone phenotypes observed in F1-RF animals, thereby confirming the role of seminal plasma corticosterone levels in the intergenerational phenotype.

"Together, our results show that paternal circadian rhythm is important for offspring feeding behavior and metabolic health, reinforce the role of seminal plasma in acquired inheritance, and propose corticosterone as an important molecule for parental communication at conception and offspring phenotype," conclude the investigators in their report.

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Published online: 16 June 2021
https://doi.org/10.1038/s41684-021-00797-w