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METABOLISM

Ketogenic diet rewires circadian clock

The circadian clock is an important factor in maintaining metabolic homeostasis. Certain diets are known to affect circadian functions, particularly in the liver; however, whether other organs are affected and the underlying mechanisms have been unclear. Now, new research published in *Cell Metabolism* suggests that a ketogenic diet has different effects on the circadian clocks of the intestine and liver.

"The effects of a ketogenic diet are such that the conceptual links with the circadian clock appeared important," explains corresponding author Paolo Sassone-Corsi. Previous work indicated that a high-fat diet could reprogramme the circadian clock. "The question here being, would another nutritional challenge be able to do so, and in different organs?" says Sassone-Corsi.

> "…a ketogenic diet has different effects on the circadian clocks of the intestine and liver"

The researchers fed 8-week-old C57BL/6 mice either a ketogenic diet or a control chow diet for 4 weeks. Mice fed the ketogenic diet lost weight in the first 2 weeks and then stabilized at a weight similar to that of chow-fed mice. Calorimetric analysis showed that rhythmicity in the respiratory exchange ratio was abolished in mice on the ketogenic diet but oscillated along the circadian cycle in chow-fed mice. The researchers then used high-throughput transcriptomics of liver tissue and ileal intestinal epithelial cells (IECs) to identify whole-genome changes in gene expression.

In mice fed the chow diet, the number of genes that were cyclically expressed was similar in the liver and intestine. However, cyclic gene expression was much higher in the liver samples from mice on the ketogenic diet. Under ketogenic conditions, 2,339 genes displayed circadian expression in the liver, compared with 719 under chow conditions; 801 additional genes were cyclically expressed in the liver under both nutritional regimens. The ketogenic diet had the opposite effect in IECs; 785 genes were found to be expressed cyclically under the ketogenic diet, 996 under the chow diet and 515 under both dietary conditions.

The transcriptomic analysis also revealed that the peroxisome proliferator-activated receptor-α (PPARα) signalling pathway was enriched in mice fed a ketogenic diet, with the cyclic activation being particularly marked in IECs. On further investigation of the mechanisms underlying this effect, the researchers found that serum levels of β-hydroxyl-butyrate (a ketone body that inhibits histone deacetylases) oscillated in a diurnal cycle in mice fed the ketogenic diet, which could contribute to the oscillation in genes involved in the PPARα signalling pathway in the gut. This finding also directly links nutrition to epigenetic control.

The authors speculate that their work could have a range of implications for future research, particularly relating to determining whether histone deacetylases can be targeted in a time-specific manner. "Future studies will be centred on how time-specific nutrition modulates metabolism through epigenetic mechanisms," suggests Sassone-Corsi.

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ORIGINAL ARTICLE Tognini, P. *et al.* Distinct circadian signatures in liver and gut clocks revealed by ketogenic diet. *Cell Metab.* **26**, 523–538 (2017)