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Metabolic Jet Lag when the Fat Clock is out of Sync

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Abstract

There is a growing appreciation of the importance of circadian regulation in energy homeostasis, and the dysregulation of the circadian clock has been associated with obesity and metabolic abnormalities. A new study shows that adipocyte-specific deletion of a core circadian clock gene, *Bmal1*, in mice shifts the timing of their feeding behavior, resulting in obesity (aaa-bbb).

Most of us have tried to disable our circadian clock mechanisms. For example, when we desperately try to meet an important deadline or finish an exciting time course experiment, we do what it takes to keep us going until the mission is complete. A common strategy involves excessive feeding on comfort foods, as well as a high coffee intake. Not exactly the hunter-gatherer life style people were evolutionarily wired for, but it gets us by. Although these short-term fixes are effective, in the long run, too little sleep or irregular sleep patterns are associated with serious consequences for health. Night-shift workers are more at risk for obesity, metabolic syndrome and even some forms of cancer^{1,2}, and, a decrease in the number of hours slept at night prompts a decrease in insulin sensitivity³.

Circadian clocks are the main drivers of cyclical changes in biochemical pathways, allowing an organism to be prepared for regular environmental changes. This rhythmicity also has a strong influence on metabolic processes, and we are just starting to understand the underlying mechanisms. A highly conserved set of proteins constitutes the system's circadian machinery. The proteins encoded by the *BMAL1* and *CLOCK* genes are at the core of this machinery; they form heterodimers and function as transcription factors that bind to cis-acting E-box elements found within promoters or enhancers of key target genes involved in circadian control. The *Cryptochrome (Cry)* and *Period (Per)* genes are the best characterized downstream transcriptional targets for Clock and BMAL1. The Cry and Per proteins also heterodimerize and are part of a negative feedback loop that down-regulates BMAL1 expression. The turnover of these proteins is highly regulated, which, together with the negative feedback loops, result in an oscillating expression pattern over each 24-h cycle.

The primary circadian 'clock' in mammals is located in the brain, in the suprachiasmatic nuclei (SCN), a distinct group of cells located in the anterior hypothalamus. Destruction of the SCN results in the complete absence of a regular sleep-wake rhythm. Surprisingly, endogenous circadian clocks are also found in many peripheral tissues. Thus, there is no such thing as a primary clock in the body; rather, many clocks exist, which communicate through interdependent feedback mechanisms. So far, two metabolically relevant tissues have been targeted for genetic ablation of clock components in mice. Lamia et al.⁴ disrupted

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Bmal1 in hepatocytes, which caused fasting hypoglycemia and enhanced glucose clearance. The authors concluded that hepatic BMAL governs the cyclical expression of biochemical pathways that offset the systemic fluctuations of carbohydrate ingestion at regular meal times. In contrast, Marcheva et al.⁵ showed that deletion of *Bmal1* in pancreatic β -cells prompts impaired glucose tolerance due to reduced insulin secretion, and ultimately results in a reduced proliferative potential of pancreatic islets.

In this issue of *Nature Medicine*, Paschos et al.⁶ fill an important gap in our knowledge of circadian control of metabolism by examining the specific role of BMAL1 in adipocytes and macrophages in mice. They found that *Bmal1* could be deleted in macrophages without detectable consequences, but the loss of *Bmal1* in adipocytes (Ad-*Bmal1*^{-/-} mice) affected the circadian rhythm in the brain, thus placing adipocyte BMAL1 center stage in the control of systemic energy homeostasis. The authors reported that Ad-*Bmal1*^{-/-} mice have an increased expansion of adipose tissue and ultimately develop obesity. These mice display normal circadian rhythms in locomotor activity. However, they have lower energy expenditure and their food intake rhythm is disrupted. These changes do not affect the total number of calories consumed, but the Ad-*Bmal1*^{-/-} mice seem to display the rodent equivalent of 'night eating syndrome'. In other words, they have a higher food intake during the light phase and compensate with a lower food intake during the dark phase, the main period of food intake and activity in wild-type mice. This is associated with a reduction in total energy expenditure and provides the underlying mechanism for the obese phenotype in these mice. In fact, wild-type mice who are restricted access to food during the light phase (so, they are only allowed to eat during periods of activity at night) are resistant to the negative impacts of a high-fat diet, such as obesity and insulin resistance, despite consuming a similar number of calories compared to mice on a high-fat diet who do not have restricted feeding times⁷. Thus, the work of Paschos et al.⁶ indicates that circadian clock in adipocytes affects the feeding rhythm of mice, which in turn exerts a profound impact on whole-body energy homeostasis. How is this possible?

Through a series of elegant experiments, the authors provide evidence for a mechanism in which disruption of the circadian rhythm in adipocytes triggers a reduced capacity for synthesis of long-chain polyunsaturated fatty acids (PUFAs) by these cells⁶. Loss of *Bmal1* in adipocytes results in a reduction in the expression of two genes, *Elovl6* and *Scd1*, which encode key enzymes for the biosynthesis of PUFAs. Reduced amounts of these enzymes result in lower plasma concentrations of PUFAs. This effect is further exacerbated by reduced lipolysis at crucial time points during the light phase. As a consequence, the reduced concentrations of circulating PUFAs lead to decreased hypothalamic PUFA concentrations during the light phase. This reduction leads to an upregulation of orexigenic peptides and a downregulation of anorexigenic peptides in the hypothalamus - changes that promote food intake. Importantly, the authors showed that dietary PUFA supplementation could rescue the obesity phenotype of the Ad-*Bmal1*^{-/-} mice.

The Ad-*Bmal1*^{-/-} mice therefore provide strong evidence for the existence of a PUFA-mediated communication axis between fat stores and the brain, and show that changes in the local production and release of these key lipid messengers are sufficient to evoke a profound dysregulation of food intake patterns. The functional consequences of this relatively mild imbalance of the circadian rhythm in the adipocyte are quite surprising and more severe than would be expected given the extent of the disruption. Of further interest, the obese phenotype of the Ad-*Bmal1*^{-/-} mice is not associated with any other signs of impaired metabolic parameters, suggesting that simultaneous protective mechanisms function to allow expansion of fat mass without other adverse metabolic consequences.

The apparently ‘healthy’ adiposity that is associated with a local disruption of the *Bmal1* in adipocytes deserves further study. What are these additional changes that allow the increased overall fat mass in the *Bmal1*^{-/-} mice? Several candidate mechanisms that enable a fat pad to expand in a non-pathological way, i.e. mechanisms that are beneficial for systemic metabolic regulation have recently been described (reviewed in ref. 8). These include reduced fibrosis and improved angiogenesis. Future studies will be required to unveil the crucial components that act locally in adipose tissue in the *Bmal1*^{-/-} mouse model, a mouse which highlights yet another novel facet of adipocyte physiology.

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Figure 1.

BMAL1 has been eliminated from a variety of cell types. While hepatocytes lacking BMAL1 fail to adjust to diurnal variability of glucose availability, pancreatic β cells lacking BMAL1 prompt an impaired insulin release. The lack of BMAL1 in adipocytes leads to changes in diurnal food intake patterns due to changes in polyunsaturated fatty acid levels (PUFAs), thereby establishing a PUFA-based communication axis between the adipocyte and critical centers in the hypothalamus. The net result is an overall increase in fat mass and, ultimately, obesity.