

# Circadian clock misalignment and consequences

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Credit: Vera Kratochvil/public domain

(Medical Xpress)—Shift work sleep disorder comprises a group of symptoms including insomnia, proneness to accidents and inattentiveness that typically afflict people whose work schedules shift between day and night, disrupting their normal circadian cycles. The disorder heightens such health risks as obesity, diabetes, heart disease and may be implicated in increased incidence of cancer.

Normally, the light-entrained circadian clock, which is located in the brain's suprachiasmatic nucleus, controls the alternating diurnal active phase and the rest phase. In humans, the active phase is during the light period and the rest phase is the dark period; in mice, it is the opposite. While a night worker on a reliable and unchanging schedule can adapt to some extent, most health experts maintain that night work is not ideal for the vast majority of workers.

It is known that many of the metabolic factors associated with the disorder arise from shifting the eating schedule from the active phase to the rest phase, but the actual mechanisms have not been studied. Now, a group of researchers from the University of Strasbourg and the Centre National de la Recherche Scientifique have published two related studies in the *Proceedings of the National Academy of Sciences* that reveal, for the first time, the origin and identity of the metabolic signals generated when feeding is shifted to the rest cycle.

The researchers studied a group of eight- to 12-week-old male mice. Control mice received open feeding during both active and rest cycles; the test group received restricted feeding (RF) only during the rest cycle, and fasting during the active cycle. As the metabolism expressed by the two groups diverged, the researchers were able to determine how the RF mice developed [metabolic syndrome](#) in response to restricted feeding.

In the first paper, the researchers documented how shifting the master central circadian clock via RF leads to metabolic syndrome by misaligning the body's peripheral circadian clocks. They determined that this is caused by the non-expression of receptors in the suprachiasmatic nucleus for glucagon and proliferator-activated receptor alpha. This prevents the master circadian clock from shifting to the new feeding schedule and creates a misalignment that breaks the peripheral circadian clocks.

In the second paper, the researchers demonstrated that the shift of the master circadian cycle induced alterations of two important metabolic pathways that shift the body's peripheral circadian clocks by 12 hours.

The authors write, "Assuming that specific metabolic perturbations generated by switching the feeding time could selectively affect the time of expression of some of the core circadian cycle components, we looked for both metabolic and peripheral [circadian clock](#) alterations at early RF times." These alterations occurred in two phases: First, the shifted eating schedule broke the existing peripheral circadian clocks; this caused reduced insulin secretion, triggering untimely increases in glucagon. Then the new eating cycle generated shifting peripheral circadian clocks. Additionally, RF caused overproduction of corticosterone, causing problems in muscles and heart by inhibiting the shift to the new circadian cycle in those tissues.

**More information:** Shifting eating to the circadian rest phase misaligns the peripheral clocks with the master SCN clock and leads to a metabolic syndrome. *PNAS* 2015 112 (48) E6691-E6698; published ahead of print November 16, 2015, [DOI: 10.1073/pnas.1519807112](https://doi.org/10.1073/pnas.1519807112)

### **Abstract**

The light-entrained master central circadian clock (CC) located in the suprachiasmatic nucleus (SCN) not only controls the diurnal alternance of the active phase (the light period of the human light-dark cycle, but the mouse dark period) and the rest phase (the human dark period, but the mouse light period), but also synchronizes the ubiquitous peripheral CCs (PCCs) with these phases to maintain homeostasis. We recently elucidated in mice the molecular signals through which metabolic alterations induced on an unusual feeding schedule, taking place during the rest phase [i.e., restricted feeding (RF)], creates a 12-h PCC shift. Importantly, a previous study showed that the SCN CC is unaltered during RF, which creates a misalignment between the RF-shifted PCCs

and the SCN CC-controlled phases of activity and rest. However, the molecular basis of SCN CC insensitivity to RF and its possible pathological consequences are mostly unknown. Here we deciphered, at the molecular level, how RF creates this misalignment. We demonstrate that the PPAR $\alpha$  and glucagon receptors, the two instrumental transducers in the RF-induced shift of PCCs, are not expressed in the SCN, thereby preventing on RF a shift of the master SCN CC and creating the misalignment. Most importantly, this RF-induced misalignment leads to a misexpression (with respect to their normal physiological phase of expression) of numerous CC-controlled homeostatic genes, which in the long term generates in RF mice a number of metabolic pathologies including diabetes, obesity, and metabolic syndrome, which have been reported in humans engaged in shift work schedules.

Shifting the feeding of mice to the rest phase creates metabolic alterations, which, on their own, shift the peripheral circadian clocks by 12 hours. *PNAS* 2015 112 (48) E6683-E6690; published ahead of print November 16, 2015, [DOI: 10.1073/pnas.1519735112](https://doi.org/10.1073/pnas.1519735112)

## **Abstract**

The molecular mechanisms underlying the events through which alterations in diurnal activities impinge on peripheral circadian clocks (PCCs), and reciprocally how the PCCs affect metabolism, thereby generating pathologies, are still poorly understood. Here, we deciphered how switching the diurnal feeding from the active to the rest phase, i.e., restricted feeding (RF), immediately creates a hypoinsulinemia during the active phase, which initiates a metabolic reprogramming by increasing FFA and glucagon levels. In turn, peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) activation by free fatty acid (FFA), and cAMP response element-binding protein (CREB) activation by glucagon, lead to further metabolic alterations during the circadian active phase, as well as to aberrant activation of expression of the PCC

components nuclear receptor subfamily 1, group D, member 1 (Nr1d1/RevErb $\alpha$ ), Period (Per1 and Per2). Moreover, hypoinsulinemia leads to an increase in glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) activity that, through phosphorylation, stabilizes and increases the level of the RevErb $\alpha$  protein during the active phase. This increase then leads to an untimely repression of expression of the genes containing a RORE DNA binding sequence (DBS), including the Bmal1 gene, thereby initiating in RF mice a 12-h PCC shift to which the CREB-mediated activation of Per1, Per2 by glucagon modestly contributes. We also show that the reported corticosterone extraproduction during the RF active phase reflects an adrenal aberrant activation of CREB signaling, which selectively delays the activation of the PPAR $\alpha$ –RevErb $\alpha$  axis in muscle and heart and accounts for the retarded shift of their PCCs.

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