Circadian Rhythms & Metabolism

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Circadian timing is historically important

- Circa (about) dia (day): 24 hour cycles in behaviors and physiological processes
- All animal species are shown to follow some type of rhythmic pattern
- Hunter-gatherer societies (even ones that exist today) show intermittent food intake, and have far lower instance of metabolic diseases
- Wild animals vs domesticated
- Most human and animal species have adaptations for intermittent food supply, (long-term energy stores in adipose tissue)
How does our body know what time it is?

Blue light $\rightarrow$ retinal ganglion cells $\rightarrow$ melanopsin $\rightarrow$ SCN $\rightarrow$ pineal gland $\rightarrow$ melatonin $\rightarrow$ acts back on the SCN and also acts on hypothalamus

- Blue light= sun, computer/ phone screens, the lights in our homes
- SCN= Suprachiasmatic nucleus (core clock in brain)
- Melatonin= hormone that regulates sleepiness (high at night), also affects the core clock expression, and can be synthesized from tryptophan in the diet
  - This is RELEASED by pineal gland (which is stimulated by the SCN), and ACTS on the SCN as part of a feedback loop
Our Body’s Core Clock

There is central circadian control via the SCN (pathway shown in this figure), that controls oscillations in certain metabolites.

These oscillations communicate information to peripheral clocks, which are found in various organs.
Central vs peripheral control

We can dramatically affect the oscillations (the efficiency) of our metabolism through our daily patterns in eating, sleeping, and exercise.

Circadian control involves extensive feedback loops, so that small changes can have dramatic effects throughout the entire body.
Crosstalk: clocks and metabolism

**BMAL**: increase gluconeogenesis (produces glucose from non-carb substrates during fasting/ low sugar states)

AMP/ATP ratio → increase **AMPK** → increase glucose uptake and hepatic FA oxidation

**NAD**⁺ is usually produced with energy burning processes, and signals to reduce clock expression

(dotted lines in this figure indicate inhibition)
Crosstalk: clocks and metabolism

Eat → increase blood glucose → glycolysis

→ increase insulin, activate PI3K pathway activation → foxO gene activation
  → NAD+ levels → sirtuins → stat3 → transcription effects
  → lipid metabolism
  → cancer associated mutations

→ pyruvate to lactate conversion produces NAD+ (anaerobic breakdown during exercise)

→ NAD+ is USED during the first part of glycolysis, but is PRODUCED during the last part (oxidative phosphorylation), so in general increased NAD+ indicates energy burning state, so it makes sense that it inhibits BMAL, which would signal gluconeogenesis to provide energy during fasting state
Effects of circadian disruption (epidemiological evidence)

From studies done in shift workers:

- Higher cancer risk
- Insulin resistance and diabetes
- Higher instance of obesity
- Non-Alcoholic Fatty Liver Disease
- Cardiovascular complications
Effects of circadian disruption (experimental evidence)

Phase-shifted mice (light altered, or changes to feeding times) see same risk factors as are shown in epidemiological studies

Mice with mutations or targeted disruptions of core circadian genes that have been generated during the last decade all show impaired circadian behavior and deregulation of circadian patterns in gene expression (Lowrey and Takahashi 2004). In addition to this universal phenotype, other pathological defects are specific for particular circadian mutants. Thus, Clock mutation results in reduced fertility and complications of pregnancy (Miller et al. 2004), obesity and metabolic syndrome (Turek et al. 2005), and sensitization to cocaine (McClung et al. 2005). Period2 deficiency leads to the enhanced voluntary alcohol consumption and alterations in the glutamatergic system (Spanagel et al. 2005), higher sensitivity to radiation and increased tumor formation after irradiation (Fu et al. 2002), and alterations in bone remodeling and bone mass accumulation (Fu et al. 2005). Hence, some circadian proteins play important roles in organ physiology that are not necessarily linked to their circadian function. This is certainly true for BMAL1, since Bmal1−/− mice, in addition to loss of circadian rhythms, display a number of phenotypes including infertility (Kennaway 2005), defective glucose homeostasis (Rudic et al. 2004), idiopathic calcification and ossification of hind limb joints (Bunger et al. 2005), and increased sensitivity to chemotherapy and radiation (Gorbacheva et al. 2005). To further investigate the role of BMAL1 in normal physiology, we monitored a large group of Bmal1−/− knockout (KO) and wild-type mice for their entire lifespan. This revealed that Bmal1 KO animals had reduced lifespan and developed a number of pathologies characteristic of mice with premature aging phenotypes (Tyner et al. 2002; Mounkes et al. 2003; Chang et al. 2004; Trifunovic et al. 2004; Kurosu et al. 2005).
Improving your circadian clock

People often talk about what we eat and how much we eat, but no one really talks about the timing of meals.

Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet.


Abstract

While diet-induced obesity has been exclusively attributed to increased caloric intake from fat, animals fed a high-fat diet (HFD) ad libitum (ad lib) eat frequently throughout day and night, disrupting the normal feeding cycle. To test whether obesity and metabolic diseases result from HFD or disruption of metabolic cycles, we subjected mice to either ad lib or time-restricted feeding (tRF) of a HFD for 8 hr per day. Mice under tRF consume equivalent calories from HFD as those with ad lib access yet are protected against obesity, hyperinsulinemia, hepatic steatosis, and inflammation and have improved motor coordination. The tRF regimen improved CREB, mTOR, and AMPK pathway function and oscillations of the circadian clock and their target genes’ expression. These changes in catabolic and anabolic pathways altered liver metabolome and improved nutrient utilization and energy expenditure. We demonstrate in mice that tRF regimen is a nonpharmacological strategy against obesity and associated diseases.
Improving your circadian clock (shameless product placement)

Panda lab at Salk Institute is examining effects of TRF in humans using an app paired with clinical trials.
Conclusions

- Circadian machinery and metabolic pathways are extensively interconnected
- Our central clock has dramatic effects on how well our body can metabolize things
- Our altered schedules and poor eating habits alter our circadian rhythms, which can lead to metabolic disruption, inflammation, cancer, and a multitude of other health risks
- You can still eat cake, just do it at the right time of day
- Download Bree’s app and help her research