CellPress

Feature Review

Daily Eating Patterns and Their Impact on Health and Disease

Amir Zarrinpar,[1,2,*] Amandine Chaix,[1] and Satchidananda Panda[1,*]

Cyclical expression of cell-autonomous circadian clock components and key metabolic regulators coordinate often discordant and distant cellular processes for efficient metabolism. Perturbation of these cycles, either by genetic manipulation, disruption of light/dark cycles, or, most relevant to the human population, via eating patterns, contributes to obesity and dysmetabolism. Time-restricted feeding (TRF), during which time of access to food is restricted to a few hours, without caloric restriction, supports robust metabolic cycles and protects against nutritional challenges that predispose to obesity and dysmetabolism. The mechanism by which TRF imparts its benefits is not fully understood but likely involves entrainment of metabolically active organs through gut signaling. Understanding the relationship of feeding pattern and metabolism could yield novel therapies for the obesity pandemic.

Trends

Central circadian pacemakers, sleep/wake homeostasis, and feeding/fasting rhythms coordinate distant metabolic processes for efficient metabolism through endocrine and neuronal signals.

Each cell has autonomous circadian clock components that interact with key metabolic regulators and effect cellular metabolic efficiency.

Obesity and dysmetabolism can be induced by perturbing these physiological or cellular cycles either via genetic manipulation, disruption of light/dark cycles, and by feeding patterns.

TRF promotes synchrony of feeding/fasting rhythms with the central circadian pacemaker, resulting in more-robust circadian and metabolic cycles, and prevents and treats obesity and its metabolic consequences.

Entrainment of feeding/fasting rhythms is entrained by gut signaling which can by mediated by multiple potential candidates, including the gut microbiome, bile acids, incretins, nutrients, and secondary luminal metabolites.

Circadian Rhythms and Metabolism

More than one-third of adults in the USA are obese [1], and this exerts a significant burden on national healthcare spending [2]. In the past, an underappreciation of the complexity of body-weight regulation led to ineffective or scientifically unsound recommendations [3]. In recent years, tremendous resources have been committed to curtail obesity, and these efforts have had some success [4]. From 2003 to 2012 the prevalence of obesity in the USA has plateaued [1], after increasing consistently in the previous four decades. Recent findings have dramatically improved our understanding of the components of metabolic homeostasis and how their perturbation can lead to obesity. Whereas obesity has long been viewed as a simple behavioral problem of overnutrition, now it is appreciated as a phenomenon involving multiple genetic, epigenetic, and environmental factors, as well as multiple organs and commensal organisms. In this review we discuss one facet of the mammalian metabolic homeostasis – the impact of feeding time on metabolism as a whole.

Daily Rhythms: The Central Circadian Pacemaker and the Sleep/Wake Cycle

From cyanobacteria to humans, the majority of organisms have physiological rhythms that cycle with a period of approximately 24 h. The pervasiveness of these rhythms across organisms spanning kingdoms indicates that there is an evolutionary advantage to coordinate cellular machinery to anticipated external stimuli [5,6]. In mammals, virtually every tissue or physiological function exhibits diurnal oscillations. These patterns on a systemic level appear to be temporally coordinated by neuronal and chemical networks which are in turn maintained by various time-keeping mechanisms in the central nervous system (Figure 1) [7]. Central to these rhythms is the endogenous circadian rhythmicity of the hypothalamic **suprachiasmatic nucleus** (SCN), which is entrained by light [8]. The other dominant daily rhythm is the sleep/wake cycle driven by both circadian system and sleep homeostasis [9,10].

[1]Regulatory Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[2]Division of Gastroenterology, University of California, San Diego, La Jolla, CA 92093, USA

*Correspondence:
azarrinpar@ucsd.edu (A. Zarrinpar) and
panda@salk.edu (S. Panda).

The SCN is the dominant circadian pacemaker [11]. Ambient light is detected by specialized retinal ganglion cells that project to SCN neurons via the retinohypothalamic tract, as well as through multi-synaptic, indirect pathways via the thalamus [12]. In turn, SCN output is mediated by circadian variation of its neuronal firing, or release of a number of peptides, including arginine vasopressin (AVP), vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), transforming growth factor-α (TGFα), prokineticin 2, and cardiotrophin-like cytokine. These diffusible and synaptic outputs synchronize and modulate the activity of the autonomic nervous system and the release of hormones from the hypothalamus, which in turn help to maintain vigorous oscillation of circadian proteins in the peripheral tissue, although the mechanisms are not yet well understood.

Sleep/wake homeostasis has been far more difficult to study. However, sleep is essential for maintaining metabolic health [13–15], likely by facilitating the removal of waste byproducts and restoration of necessary metabolites [16]. Although the sleep/wake cycle and the signals from SCN are highly linked, sleep is heavily influenced by a sleep homeostat akin to an hourglass oscillation. For example, a neural sleep factor ('S') rises during waking, and decays during sleep, hence regulating the timing, amount, and intensity of sleep [17]. Melatonin, a pineal gland-derived hormone, plays an important role in synchronizing the sleep/wake cycle and the circadian clock [18,19].

The pathways by which the central circadian system and the sleep/wake cycles control hormonal release, peripheral clock oscillations, and metabolism in other tissues are still being actively investigated. Neurohumoral and neuronal signaling from SCN and brain regions involved in sleep regulation, however, can affect the activity of the hypothalamus and influence the pulsatile release of various hormones, which in turn affect the intermittent release of pituitary hormones [20]. Hence, many hormones that are released by the pituitary are circadian, with their levels oscillating throughout the day. These include plasma levels of cortisol (high in the morning), thyroid stimulating hormone (TSH, high at night), prolactin (high at night), and growth hormone (high at night), which all normally have ~24 h oscillation. In non-diabetic participants, the response to a glucose challenge is very different with the time of day, independently of the route of administration, resulting in higher plasma glucose levels in the evening than in the morning [21]. Post-meal insulin levels also oscillate during a 24 h period, increasing toward the evening and decreasing in the morning. Even sensitivity to insulin is circadian, although not mediated by the hypothalamus [22].

Together, the central circadian pacemaker and sleep/wake homeostasis have tremendous influence over the endocrine system. They can coordinate the physiological activity of various organs with the timing of the release of hormones. As a result, glucose homeostasis, as an example, is highly dynamic; baseline serum glucose and insulin levels, response to glucose or identical meal boluses, and sensitivity to insulin itself, all display circadian fluctuations [21].

Circadian Regulators and Metabolism

Our understanding of the influence of the circadian clock on metabolism has significantly advanced with the discovery of clock proteins that serve as biological clocks. These proteins, expressed in nearly every eukaryotic cell as well as in some prokaryotic organisms, allow each individual cell to have an autonomous, self-sustained mechanism to keep track of a 24 h day [6]. These circadian oscillators are characterized by (i) sustained and persistent period length under stable conditions, (ii) the ability to entrain to external stimuli, and (iii) not being affected by wide variations in temperature. Circadian oscillations are driven by interlocked negative feedback circuits of activators such as **CLOCK**, **brain and muscle ARNT-like 1** (BMAL1) and **retinoic acid receptor-related orphan receptor** (ROR), as well as by inhibitors such as **cryptochrome** (CRY), **period** (PER), and **REV-ERB** (nuclear receptor 1D1/2, NR1D1/2) that act as

Glossary

***Ad libitum*:** literally meaning 'at liberty', where mice have access to food at all times. Mice with *ad libitum* access to normal chow have a diurnal feeding pattern, consuming nearly 75% of their daily calories during the dark/active period. Mice with *ad libitum* access to HFD spread their caloric intake more widely, consuming approximately 50% of their daily calories during the dark/active period.

AMP-activated protein kinase (AMPK): a cellular metabolic regulator important for energy homeostasis. AMPK promotes ATP production and increases the catabolic drive of cells during periods of fasting.

Brain and muscle ARNT-like 1 (BMAL1): also known as ARNTL (aryl hydrocarbon receptor nuclear translocator-like protein 1), is a transcription factor that acts as a positive element in the mammalian cell-autonomous circadian feedback loop. BMAL1 dimerizes with CLOCK to activate *Per* and *Cry* transcription.

CLOCK (circadian locomotor output cycles kaput): a positive transcription factor in the mammalian cell autonomous circadian feedback loop. CLOCK dimerizes with BMAL1 to activate transcription of *Per* and *Cry*.

cAMP response element-binding protein (CREB): a transcription factor that plays a key role in energy homeostasis. It increases the anabolic drive of cells during feeding.

Cryptochrome (CRY): a transcription factor that acts as an inhibitory element in the mammalian cell-autonomous circadian feedback loop. CRY dimerizes with PER and inhibits the transcription of the *Clock/Bmal1* components.

Diet-induced obesity (DIO): wild-type mice fed a HFD *ad libitum* constitute a model used to study dysmetabolism. The mice develop increased adiposity, insulin resistance, leptin resistance, and hepatic steatosis, among other metabolic problems.

Isocaloric diets: two diets that share the same amount of calories, but may differ in their nutrient composition or the timing of their intake.

Period (PER): an inhibitory transcription factor in the mammalian cell-autonomous circadian feedback