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Nutrients and Circadian Rhythms in Mammals

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Summary The circadian rhythm is generally existed in mammalian behavior and metabolic processes, which results from the self-sustained circadian clocks. The mammalian circadian clocks are composed of a master clock located in the hypothalamic suprachiasmatic nucleus (SCN), and of many peripheral clocks in tissues and extra-SCN brain regions. It is indicated that feeding could take over part of the SCN signaling, and affect internal synchrony between the master clock and the peripheral clocks. Thus, recent studies focus more on the relationship between the nutrients and circadian rhythms. Various nutrient components (glucose, amino acid, alcohol) are found to be able to directly affect the circadian rhythm of clock genes. Moreover, the feeding schedule of nutrients is as important as the nutrient components in maintaining a healthy circadian rhythm. Therefore, the circadian homeostasis needs not only balanced nutrient components but also regular timed nutrients.

Key Words circadian rhythm, clock, nutrient components, feeding schedule

The Biological Clock and Circadian Rhythm

In mammals, the approximate 24-h rhythm in behavior and physiology is generally existed, such as wake/sleep cycle, blood pressure, body temperature and concentration of melatonin. The circadian rhythms result from the cell-autonomous and self-sustained oscillators (circadian clocks), which rely on interlocking transcription/translational feedback loops involving a series of clock genes (*Clock*, *Bmal1*, *Per*, *Cry*, *Dec* etc.) and their proteins (*1*). The mammalian circadian clocks are composed of a master clock located in the hypothalamic suprachiasmatic nucleus (SCN), and of many peripheral clocks in tissues and extra-SCN brain regions (*2*). The master clock is mainly entrained by the light cue, while the peripheral clocks are not only affected by the SCN clock but also entrained by the food cue (*3*). Moreover, feeding could take over part of the SCN signaling, and affect internal synchrony between the master clock and the peripheral clocks.

Nutrient Components and Circadian Rhythms

Nutrient components have been identified as important factors to entrain the peripheral circadian clocks (*4*).

Glucose is a particularly potent entraining factor for peripheral clocks (5). Min-Dian Li et al. found that high concentration of glucose increased the transcription levels of *Bmal1* and *Cry1* genes without the alteration of the phase of *Bmal1* cycling, and low concentration of glucose delayed the phase of BMAL1 protein accumulation via western blot (*6*). How could glucose influence the circadian clock and further affect the following metabolic process aroused extensive attention. Some researchers revealed that cellular nutrient sensors such as nuclear receptors were proposed as candidates for the circadian clock entrainment by nutrient components (*7*, *8*). A recent study showed that the O-GlcNAc signaling entrained the circadian clock by inhibiting BMAL1/CLOCK ubiquitination, which may be the molecular mechanism underlying the glucose entrainment of the circadian clock (*6*).

Intraperitoneal injection of amino acids combined with glucose delayed the phase of the liver clock as similar as the effect of delayed feeding (*9*). L-carnosine is a dipeptide of the amino acids β-alanine and L-histidine, which is identified to be related with various physiological alterations (including blood glucose, blood pressure etc.) through the autonomic nerves. Bilateral lesions of the SCN in rat results in destructive effects on the carnosine induced physiological alterations mentioned above (*10*). In our study, we found that L-carnosine administration could accelerate the resetting rate of peripheral clock genes in the hearts, which is regulated by the autonomic nervous system (*11*).

Alcohol is another entraining factor for circadian clocks. Chronic alcohol administration induced the hepatic steatosis and disturbed the circadian clocks in the liver (*12*). Studies in human indicated that the expression level of clock genes in leukocytes of male alcoholic patients were lower than the healthy men (*13*).

Timed Nutrients and Circadian Rhythms

Timed nutrients are as important as nutrient components themselves for maintaining normal circadian rhythms. More and more evidences show that feeding schedules play entraining roles in peripheral clocks and behavior rhythms, which is independent of the SCN signaling (*14*). Arble DM et al. focused on the role of the timed nutrients in weight gain, and found that mice fed

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a high-fat diet only during the 12-h light phase gained significantly more weight than those fed only during the 12-h dark phase (*15*). Recent research showed that feeding time controlled the diurnal rhythm of relative abundance of intestinal microbiota (*16*), which was crucial for the life span (*17*). More studies paid attention to why timed nutrients could significantly affect the circadian system and physiological function. Some studies showed that changes in behavior and physiological functions, such as locomotor activity, body temperature, blood hormones occurred before the anticipatory timed nutrients, were established by restricted daily feeding schedules (*18*). Olivo D et al. found that the anticipatory metabolic activity entrained by feeding schedules exsisted in piriform cortex and olfactory tubercle, but not in suprachiasmatic nucleus (*19*). Timed nutrients shifted the circadian phases of clock genes at the mRNA and protein levels in the gastrointestinal tract but not in the central SCN clock (*20*). Therefore, irregular timed nutrients might induce the alteration of circadian rhythms in the peripheral tissues independent of the SCN, resulting in the uncoupling between the SCN and peripheral clocks, which may further affect the downstream metabolic processes.

Moreover, three meals a day is a well-established human feeding habit, and the breakfast is always regarded as one of the most important meals of the day. In our study, we found that the first meal of the daily cycle activated the transcription of peripheral clock genes and determined their phases, while the daily last meal was tightly related to lipid metabolism and adipose tissue accumulation (*21*).

The Connection between Nutrients and Circadian Rhythms

Studies mentioned above review the relationship between the nutrients and circadian rhythms. Then, how are the circadian rhythms entrained by various nutrients? Studies on the nutrient sensors identified several crucial metabolic factors being able to integrate the nutrient signals with the circadian clock. SIRT1 is a member of the sirtuin family, which plays an important role in regulating many proteins involved in response to nutrients (*22*). In the liver, the rhythmic activity of SIRT1 lies on the level of NAD^+,which is controlled by the BMAL1/CLOCK heterodimer (*23*). In return, SIRT1 regulates the circadian clock via the deacetylation of BMAL1 and PER2 proteins then further influencing the clock function (*24*). Therefore, NAD^+-dependent SIRT1 functions as a sensor linking the nutrients and the circadian clocks. Moreover, REV-ERBα is a transcription factor regulating adipogenesis, which can inhibit the transcription of *Bmal1* (*25*). RORα is a nuclear receptor involved in both lipogenesis and lipid storage, which can activate Bmal1 transcription (*26*). Glucocorticoids (GC) and its receptor (GR) have also been identified as an important link between circadian clocks and nutrients (*27*). Studies have shown that liver-specific GR mutation display accelerated phase shifting in response to restricted feeding schedule in daytime (*28*), while injection of corticosterone do not cause the phase shifting induced by restricted feeding (*29*).

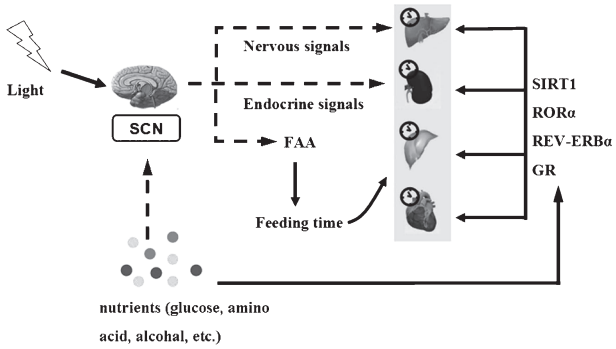

Fig. 1. Peripheral clocks are entrained by nutrients and SCN-derived resetting cues. SCN clock transmits messages to peripheral clocks via nervous and endocrine signals. Nutrients could take over part of the SCN signaling to affect the peripheral clocks via some nutrient sensors such as SIRT1, REV-ERBα, RORα, GR. Nutrients information also goes to the hypothalamus, then produces FAA before feeding time.

Concluding Remarks

Various nutrient components, timed nutrients, the time interval between meals, and nutrients amount all can entrain the circadian clocks, which may further affect the downstream metabolic processes. Life-long calorie-restricted diet could extend the life span in mice (*17*). Eating at the active phase reduces weight gain compared to that at the rest phase (*15*). Time-restricted feeding (TRF) can prevent nutritional challenges and has the protective effect on maintaining relative physiological homeostasis, which is hard to be interrupted by occasional irregular eating (*30*). Therefore, the circadian homeostasis needs not only balanced nutrient components but also regular timed nutrients.

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