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Critical Review

Chrono-biology, Chrono-pharmacology, and Chrono-nutrition

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Abstract. The circadian clock system in mammals drives many physiological processes including the daily rhythms of sleep–wake behavior, hormonal secretion, and metabolism. This system responds to daily environmental changes, such as the light–dark cycle, food intake, and drug administration. In this review, we focus on the central and peripheral circadian clock systems in response to drugs, food, and nutrition. We also discuss the adaptation and anticipation mechanisms of our body with regard to clock system regulation of various kinetic and dynamic pathways, including absorption, distribution, metabolism, and excretion of drugs and nutrients. "Chrono-pharmacology" and "chrono-nutrition" are likely to become important research fields in chrono-biological studies.

Keywords: circadian rhythm, Period 2 gene, liver, obesity, metabolism

1. Molecular mechanisms of the circadian clock system

The circadian clock system has been widely maintained in many species, from prokaryotes to mammals. "Circadian" means "around [a] day" in Latin, and therefore "circadian rhythm" refers to a cycle of approximate 24 h. The earth rotates once every 24 h, and the circadian system has evolved to adjust functions and behavior to this cycle in order to efficiently utilize sunlight for photosynthesis in the case of plants and cyanobacteria and to obtain food in the case of animals. One of the most important features of our circadian system is that circadian clocks can endogenously maintain time under constant darkness and without external stimuli, suggesting that our body has its own internal clocks. In 1972, Moore and Eichler (1) investigated the effects of destroying the suprachiasmatic nucleus (SCN) in the rat hypothalamus. Their results revealed the loss of sleep-wake cycles and corticosterone rhythms. Since then, the SCN is regarded as the location of the master clock system in mammals. The SCN receives light–dark information directly through the retinal–hypothalamic tract and organizes the local clock in the peripheral tissues through multiple pathways involving neural and hormonal functions (2, 3). The molecular mechanism of the circadian system in mammals has been well studied over the past two decades. The transcriptional–translational feedback loop of the major clock genes *Bmal1*, *Clock*, *Per1/2*, and *Cry1/2* is the main component of the circadian system (2) (Fig. 1A). *Bmal1* and *Clock*, which are transcriptional activators, play a positive role in activating the *Per* and *Cry* genes through a specific promoter sequence known as the E-box. *Per* and *Cry* are translated into proteins in the cytoplasm and are then transported back into the nucleus after interacting with each other, and they subsequently stop their transcription by binding to BMAL1 and CLOCK. Thus, *Per* and *Cry* are rhythmically expressed over a 24-h period. This transcriptional regulation induces rhythmic expression of approximately 10% of all genes in each peripheral cell (4 – 6). In addition to such transcriptional regulation of the circadian clock, post-transcriptional regulation and translational regulation have recently been reported to play important roles in maintaining circadian rhythms. Genome-wide RNA-seq and Chip-seq analyses found that only 22% of the rhythmically oscillating messenger RNAs are driven by *de novo* transcription, with RNA polymerase II recruitment and chromatin remodeling also exhibiting such rhythms (7). Furthermore, it was reported that the non-transcriptional redox cycle has a 24-h rhythm in

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Invited article

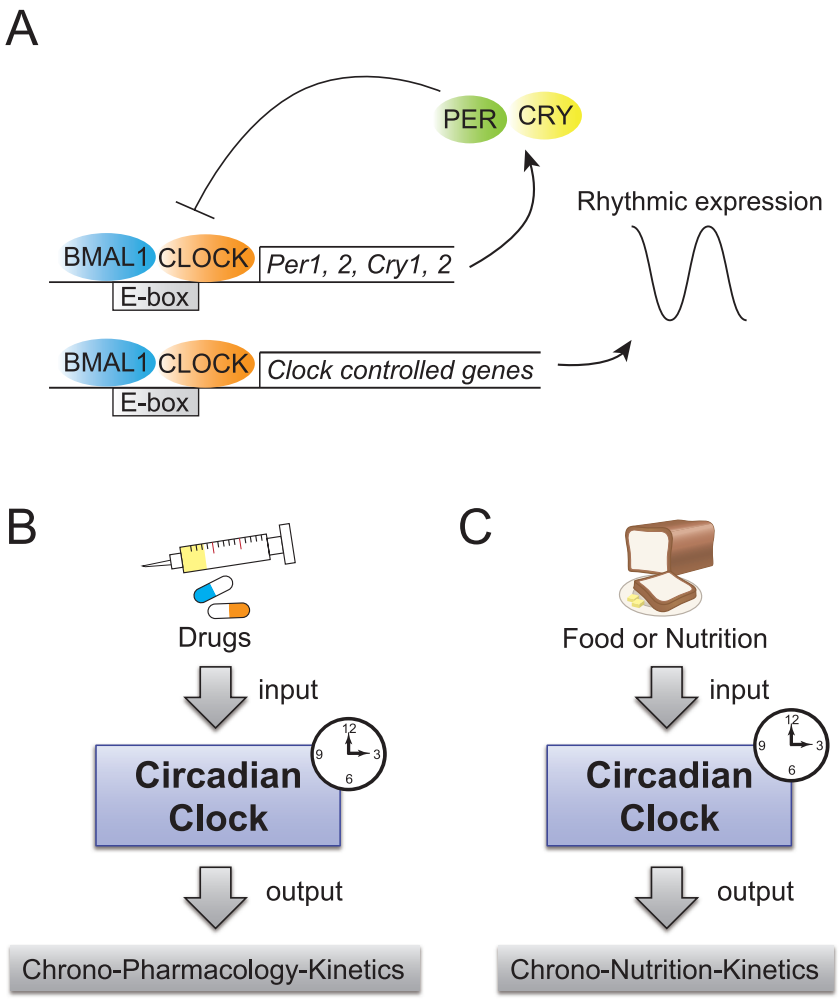

Fig. 1. Framework of the Introduction. A) Schematic diagram of feedback loop of circadian clock genes. B, C) Schematic diagram of "chrono-pharmacology (B)" and "chrono-nutrition (C)", respectively. In both strategies, there are two aspects. The first is that circadian changes affect functions such as the absorption, distribution, metabolism, and excretion of drugs or nutrients. Considering these factors when determining the timing, amount, and composition of drug administration or food intake can be beneficial for enhancing the power of the drug and functional food effects and for improving human health and diseases. The second aspect is that similar to light stimulation, drugs and nutrients can serve as stimuli for changing the phase of circadian clocks.

human red blood cells, which have no DNA or nucleus. This redox rhythm of peroxiredoxins was shown not only in human blood cells, but also in other eukaryotic cells (8, 9). In the SCN, the redox state regulates the rhythmic output activity concerning the neuronal firing of SCN neurons (10). These observations indicate that our understanding of the circadian clock system is expanding and that the system employs complicated processes to generate accurate clock rhythms. For an important issue, the circadian expression phases of clock and clock-controlled genes are anti-phase between human (diurnal) and mice/rats (nocturnal) in the brain excluding the SCN and peripheral tissues. Whereas, in the SCN, the phases of clock gene expression rhythms are same in both diurnal and nocturnal animals. Although the mechanism of this anti-phasic change from the SCN to the other organs is still unknown, the findings of many circadian functions in rodents could be applied to humans by changing the phase of circadian regulation to the anti-phase of it.

A particular feature of the circadian system is "entrainment to 24-h oscillation" by external or internal signals because the oscillation period of the circadian clock is not *precisely* 24 h, but *approximately* 24 h. Light information obtained via retinal input is the typical external entrainable factor in mammals. In addition to light, entrainable factors include food, temperature, exercise, and drugs. Among these factors, food is the best synchronizer (i.e., comparable with light) (11 – 14).

2. Chrono-pharmacology and chrono-nutrition

A well-known aspect of circadian rhythm is so-called "chrono-pharmacology", which is used to determine the timing of drug administration in relation to circadian changes in targeted kinase activity, the protein quantities needed to enhance the potency of a drug, and/or the absorption and excretion of a drug (Fig. 1B). Chrono-pharmacology enables us to maintain or improve human health by speculating the state of metabolic activity

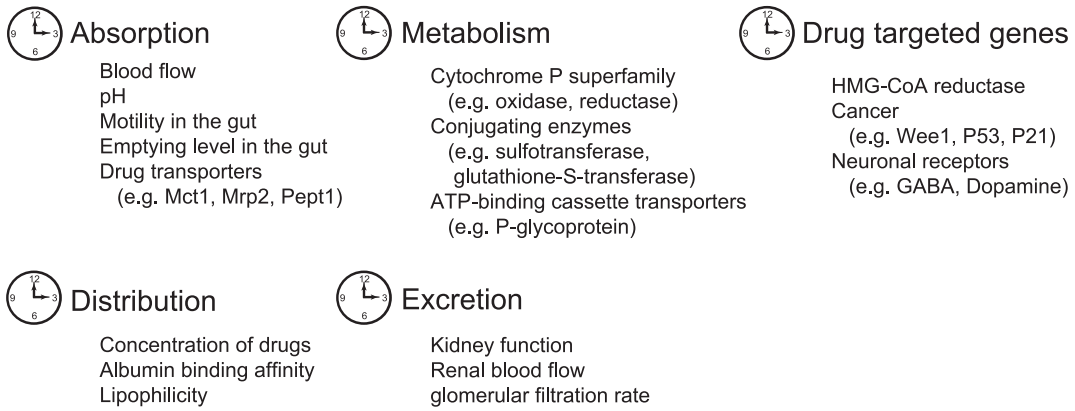

Fig. 2. A framework of the aspect of chrono-pharmacology: circadian regulation of drug functions. Drug absorption, distribution, metabolism, and excretion (ADME) and drug-targeted genes are influenced by the circadian system. In each aspect, representative factors and keywords that we discussed in this review are indicated in this figure.

and it also enables optimal timing of food intake by understanding the circadian changes in the digestive system. In another aspect of chrono-pharmacology, many drugs have been investigated for the powerful tool of regulating the circadian system in mammals. These drugs can be useful for the therapy of circadian disorders, such as circadian rhythm sleep disorders and jet lag. Recently, the term "chrono-nutrition" has also been used to refer to the relationship between food and the circadian clock system (Fig. 1C). In addition, we can change the timing of our internal clock by altering the timing of food intake. Consequently, chrono-nutrition has been defined to encompass the following two aspects: i) timing of food intake or contribution of food components to the maintenance of health and ii) timing of food intake or contribution of food components to rapid changes in or resetting of our system of internal clocks. Therefore, as is the case in chrono-pharmacology, chrono-nutrition will be a common strategy to keep our health through the circadian rhythm system. In this review we focused on these four aspects of chrono-pharmacology and chrono-nutrition in each section.

3. Chrono-pharmacology: circadian regulation of drug functions

3.1. Pharmacokinetics

Drug absorption, distribution, metabolism, and excretion (ADME) are influenced by circadian systems (Fig. 2). Drug concentrations in the blood and the target tissue are regulated by these processes, which can be used to determine the pharmacological effects of drugs. Absorption of orally administered drugs depends on several factors such as blood flow, pH, and motility or the emptying level of the gastrointestinal tract. Many studies have provided evidence showing the importance of the circadian clocks in gut physiology (15 – 19). Drug absorption is dependent on the drug transporters expressed in the gut. Several lipid transport proteins including microsomal transport protein, which is important for fatty acid transport, are regulated by circadian clocks, suggesting that lipophilic drugs may also be under their control in mice (20 – 22). Thus, circadian patterns of absorption are especially pronounced in lipophilic drugs, and absorption is higher during the active phase than at the inactive phase in mice (23). Multi-drug-resistance 1a, a xenobiotic efflux pump, exhibits a circadian pattern of action, and its gene expression is directly regulated by core clock genes in mice (24, 25). Several drug efflux pumps such as Mct1, Mrp2, Pept1, and Bcrp also show circadian expression patterns in rats (26). As a result of diurnal variations in the functions of transporters and efflux pumps, drug absorption is sensitive to the time of administration.

The following three factors may contribute to the volume of distribution of a given drug: concentration, albumin binding affinity, and lipophilicity. The degree of protein binding between drugs varies in a diurnal manner and correlates with changes in plasma albumin levels (27).

The xenobiotic metabolism system comprises three groups of proteins with distinct and successive functions (28). The first group involves drug functionalization and consists of the microsomal cytochrome P superfamily of enzymes, which have oxidase, reductase, or hydroxylase activities. Many cytochrome P450 genes exhibit circadian expression profiles in mice and rats (4, 29 – 31). The second group involves drug conjugation and consists of conjugating enzymes such as sulfotransferase, glutathione-S-transferase, N-acetyltransferase, and gluc-

uronotransferase. Conjugation helps to make lipophilic compounds hydrophilic enough to subsequently facilitate their excretion. For example, diurnal variation in hepatic glutathione-S-transferase, a conjugation reaction enzyme, shows high activity during the light period in mice (31, 32). The third group contains ATP-binding cassette transporters like multi-drug resistance-associated proteins and P-glycoprotein, which facilitate the transport of xenobiotics from outside the cell. The daily rhythms of the gene expression of ATP-binding cassette transporters were recently reported in mice and rats (24, 25, 33, 34).

The circadian clock system plays a key role in changes in drug toxicity by influencing drug metabolism in the liver and intestine and excreting the metabolites via bile and urine. It is known that biliary excretion of bile acids, lipids, and xenobiotics follows a circadian rhythm, with maximum excretion during the dark period in rats (35, 36). Bile acid synthesis involves cholesterol-7a-hydroxylase, a rate-limiting enzyme that converts cholesterol into bile acids, whose rhythmic expression is regulated directly by the transcriptional repressor REV-ERBa in rodents (37 – 39). Drug excretion is influenced by kidney functions such as renal blood flow, glomerular filtration rate, and urine volume. Renal blood flow exhibits a significant circadian rhythm: it shows a peak during the active phase, which is twice the level of the peak seen during the resting phase in human and rats (40, 41). Circadian oscillations in glomerular filtration rate are apparently synchronized with those of renal blood flow and systemic hemodynamics, with a 50% change at the day-night transition (42). The day-night differences in the urinary excretion of some drugs have already been examined in rodents (43 – 45), but the detailed mechanisms of ADME in relation to the circadian system are not fully understood. Taking altogether, we should consider how the circadian clock system affects drug pharmacology.

3.2. Pharmacodynamics

Circadian systems not only affect ADME, but also regulate drug-targeted receptors, drug-targeted transporters/enzymes, drug-targeted intracellular signaling systems, and drug-targeted gene transcription. Gene array experiments using mice with mutations or with a disrupted circadian clock system have provided new discoveries demonstrating the pivotal role of the molecular clocks in target function and drug efficacy. For example, it is recommended to take statin drugs (inhibitors of HMG-CoA reductase) in the evening because HMG-CoA reductase is most active at this time in humans. Circadian mechanisms also play critical roles in cancer and chemotherapeutics, and cell cycle-related genes and enzymes including *Wee1*, *P53*, and *P21* have shown circadian changes in their expression and functions in rodents (46, 47).

In the central nervous system, many receptors including adrenergic, GABAergic, serotonergic, cholinergic, dopaminergic, and opiate receptors have shown daily expression rhythms under light–dark or constant darkness conditions in rodents (48, 49). For enzymes, the level of monoamine oxidase A, which metabolizes catecholamines and serotonin, is regulated by the circadian clock system in mice and is the target molecule of antidepressants that inhibit this activity (50). GSK3β is a target enzyme for lithium that exhibits circadian rhythms in enzyme activity and gene expression in rodents, suggesting that the chrono-pharmacological aspects of lithium should be considered (51). Serotonin shows circadian rhythmicity in several brain regions, including the SCN, pineal gland, and striatum; and it peaks during the light–dark transition but persists under constant darkness in mice (52 – 54). The RNA expression levels of the serotonin transporter and its uptake activity in the mouse midbrain are significantly higher in the dark phase than in the light phase (55 – 57). These papers strongly suggest the importance of the time-dependent effect of antidepressants. Overall, in addition to drug formulations and routes of administration, the effect of circadian rhythms should be taken into account when treating a disease with drugs.

4. Chrono-pharmacology: drug input to the circadian clock

4.1. Neuropharmacology

The SCN receives both environmental cues, such as the light–dark cycle, and additional information from other brain areas. Exogenous melatonin and ramelteon (Rozerem; Takeda Pharmaceuticals, Osaka) are notable for their effects on the circadian rhythm of the SCN, and they function as non-photic entrainers which phase-advance SCN circadian rhythms when injected in the middle of the active phase in mice (58, 59). Similarly, benzodiazepines also entrain the circadian rhythm of the SCN when injected late at night (60). In hamsters, serotonin 1a/7–receptor agonists phase-advance the circadian locomotor activity rhythm by reducing *Per1* and *Per2* gene expression in the SCN (61). Lithium lengthens the locomotor activity rhythm in rodents by inhibiting GSK3β in the SCN (51). General anesthesia also affects circadian rhythms; some types of anesthesia phase shift, while others reduce the rhythmic amplitude of clock gene expression in mice (62). Taken together, many central nervous system drugs are able to modulate circadian rhythm through their target receptors and enzymes (Fig. 3).

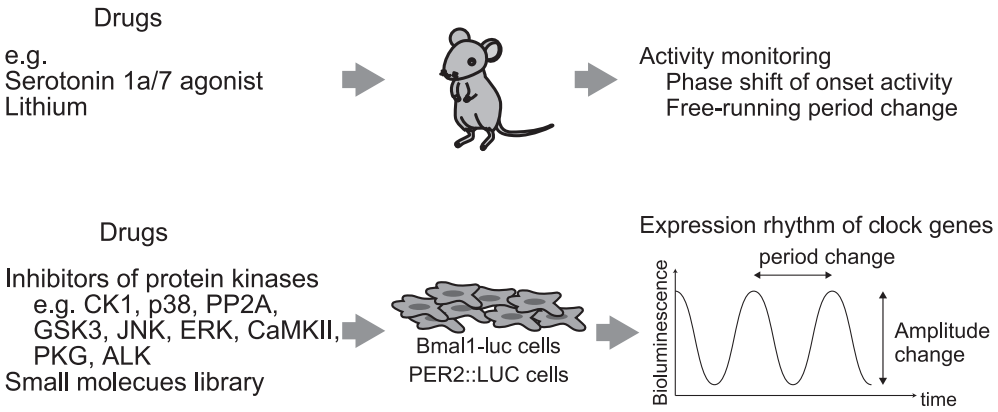

Fig. 3. Framework of the aspect of chrono-pharmacology: drug input to the circadian clock. Several studies have tried to seek drugs that affect the circadian system by measuring behavioral changes in vivo or clock gene expression changes in vitro. In both conditions, phase, period, and amplitude are the important factors for considering the effect of drugs on the circadian system. Representative drugs we discussed in this review are shown on the left side.

4.2. Small molecules

As the molecular composition of the core oscillator is largely understood, we are interested in understanding clock modification by small molecules (Fig. 3). This strategy can yield a new understanding of basic clock biology and will be useful for developing putative therapeutic agents for clock-associated diseases. In several studies, reporter assays have involved stable cell lines expressing either luciferase alone from an exogenous Bmal1 promoter (63 – 67) or PER2::LUCIFERASE fusion proteins from the endogenous Per2 promotor (68), corresponding to mRNA or protein rhythm, respectively. Bioluminescence was monitored for several days to determine the oscillation period and amplitude. As light pulses cause phase delay and phase advance when light stimuli are provided in the early evening and late at night, respectively, small molecules can phase-shift the oscillation rhythm depending on the time of their application. These screening methods enabled us to find small molecules capable of modifying the core loop of the clock, as well as the input and output pathways of the core clock. Several studies have demonstrated the feasibility of developing a "clock drug" to alter clock gene expression and rhythms (63 – 65, 68).

To date, around 200,000 compounds have already been screened and characterized as period lengthening or shortening; phase delaying, phase advancing, or phase attenuating; and amplitude enhancing or amplitude reducing. Compounds with period-lengthening activity include casein kinase 1 inhibitor, p38 inhibitor, JNK inhibitor, and PP2A inhibitor, while compounds exhibiting period-shortening activity include DNA topoisomerase II inhibitor, PKC agonist, CDK inhibitor, and GSK3β inhibitor. Various kinase inhibitors including U0126 (ERK), KN-62 (CaMKII), KT5823 (PKG), and SB431542 (ALK) attenuate phase shifts (69 – 74). Inducer of cellular c-AMP, phosphodiesterase inhibitor (rolipram), and secondary inducer of cAMP cause a phase delay and enhance amplitude (68). Agonists of *Rev-erbα* or *Rev-erbβ* reduce amplitude (75, 76), whereas some compounds enhance amplitude while shortening the period (68). Thus, by chemical biology screening or targeted ligand development, it will be beneficial to find small molecules capable of manipulating the clock. Other approaches are also available. Many medicinal drugs, including Chinese traditional medicines, are used to treat diseases. However, the effects of these drugs on the circadian system are not known. As we describe in the next section, we have the opportunity to find functional foods and nutrients.

5. Chrono-nutrition: circadian regulation of physiological functions

5.1. Digestion and absorption

Digestion and absorption in the stomach and intestines follow circadian rhythms in mammals, and these rhythms are regulated by rhythmically expressed clock genes in the gut as well as by daily food intake (15, 18). For chrono-nutrition, we can consider digestion and absorption (Fig. 4). The circadian rhythms of expression clock genes in the digestive organs have already been carefully investigated. Interestingly, the data suggest that the phases of the rhythms in clock gene expression differ among the cranio-caudal axes of the gut in mice (77). The phase in the upper gut appears to be phase-advanced compared with that in the lower gut, suggesting that the upper gut is entrained faster than the lower gut by

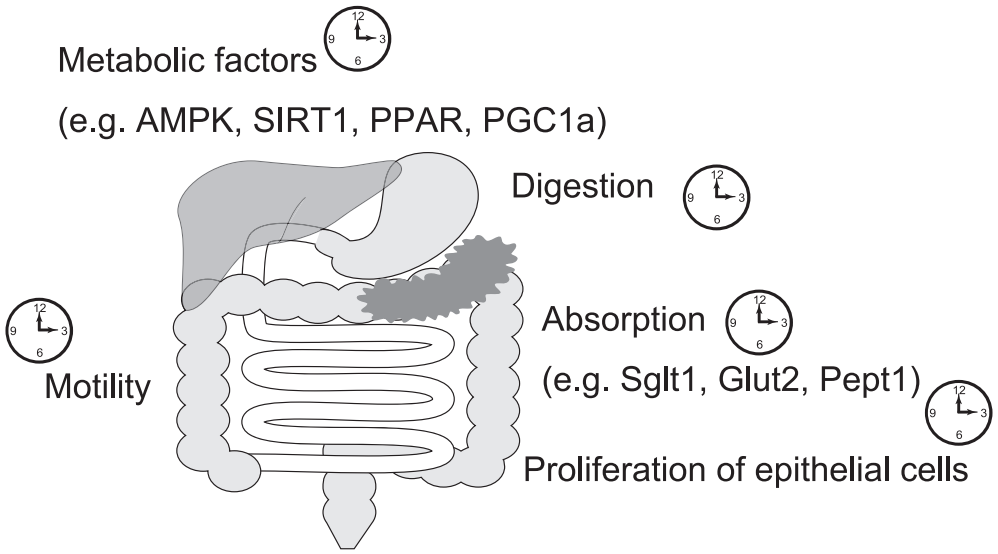

Fig. 4. Framework of the aspect of chrono-nutrition: circadian regulation of nutrition functions. Food/nutrition digestion, absorption, and metabolism are influenced by the circadian system. In addition, motility and proliferation of epithelial cells in digestive tubes including the colon have circadian rhythms.

varying the speed of food and nutrition delivery. Microarray analysis of the distal colon revealed that 3.7% of all genes have a circadian pattern of gene expression and that these genes are related to cell signaling, differentiation, proliferation, and death in mice (78). The scheduled-feeding paradigm in the daytime for nocturnal mice showed a phase shift in the rhythms of clock gene expression in the gastrointestinal tract (79). Therefore, nutrient signaling can affect gut circadian systems.

Colonic motility in humans is also known to have a circadian rhythm. A study showed frequent movement of the colon during the day and minimal movement during the night (80). Mice have a similar day–night rhythm in colonic motility, which is regulated by clock genes and neuronal nitric oxide synthase activity (80). Stool weight, the colonic contractile response of acetylcholine (measured by colonic organ culture), and intracolonic pressure (measured by the telemetry system in the wild type) all showed clear circadian rhythms; however, these rhythms were disrupted in *Per1* and *Per2* double-knockout mice or in nNOS-knockout mice. The intestinal digestive enzyme sucrase also follows a circadian change in activity, peaking before feeding time (81). Therefore, the digestive system undergoes circadian changes in both rodents and humans.

Several studies have reported circadian variations in the intestinal absorption of glucose, peptides, lipids, and drugs by several transporters. Isolated rat small intestine showed increased absorption of glucose and water at nighttime compared with daytime (82). Sodium/glucose cotransporter 1 (*Sglt1*), glucose transporter 2 (*Glut2*), and *Glut5* have clear circadian oscillations in their expression (83, 84) and are regulated by clock genes through E-box activity (85). Furthermore, *Sglt1* is regulated by PER1 activity independent of the E-box (86). Sglt1 and Pept1 were phase-entrained by a scheduled feeding experiment. Therefore, these transporters are directly regulated by feeding conditions (87). In *Clock* mutant mice, peptide transportation was reduced, but lipid absorption was high (21). In contrast, *Nocturnin* (i.e., clock-regulated deadenylase)-knockout mice showed that lipid absorption was reduced because of reduced chylomicron transit (88). Expression of the sodium pump (*Atpa1a*), sodium channel (*γEnac*), sodium transporters (*Dra*, *Ae1*, and *Nhe3*), and the Na^+/H^+ exchanger regulatory factor (*Nherf1*) in rat colonic mucosa showed circadian variations, suggesting that NaCl absorption in the colon was under circadian regulation (89). The drug transporters Mdr1, Mct1, Mrp2, Pept1, and Bcrp also showed circadian expression in rat jejunal mucosa (26). Taken together, these data show that many important transporters are under circadian regulation, and circadian disruption leads to abnormal absorption.

5.2. Intestinal epithelium

Self-renewing epithelial cells arise from the stem cells located in the lower part of the intestinal crypts. Measurement of thymidine or Brdu incorporation has shown that the circadian rhythm mediates the proliferation of the intestinal epithelium in both humans and rodents (90 – 93). This rhythm persisted under fasting in mice (94), and expression was dramatically enhanced

by re-feeding (93).

The detailed mechanism of the circadian control of cell proliferation remains largely unknown, but three mechanisms have been proposed. First, wee1, a negative regulator of the G2/M transition, is likely a clock-controlled gene in colonic epithelial cells because its promoter contains an E-box (46), and wee1 gene expression exhibits circadian changes (77, 95). Second, the proliferation level is controlled by extrinsic luminal signals, neural output signals (glucocorticoids), gastric hormones (gastrin and neurotensin), and growth factors (EGF) because all show a circadian pattern (96). Third, rhythmic food intake may control daily rhythm in the cell cycle through the enteric nervous system.

5.3. Metabolism and energy expenditure

The circadian system in mammals tightly regulates energy metabolism. This seems reasonable given that clock gene mutations or deletions are reported to lead to dysfunctions in energy metabolism (3). *Clock* mutant mice show an attenuated feeding rhythm and obesity when fed a regular diet or high-fat diet (HFD) (97). *Per2*$^{-/-}$ mice showed disrupted feeding rhythms and obesity due to disrupted glucocorticoid rhythms when fed a HFD (98). *Per2*$^{-/-}$ mice also experienced disruptions in the circadian rhythm of alpha MSH, which regulates feeding behavior in the hypothalamus. *Rev-erbα* and *Rev-erbβ*, which play roles in the functioning of nuclear receptors and core clock genes, were reported to regulate lipid metabolism (99, 100). Antagonists of *Rev-erbs* can improve or prevent HFD-induced obesity and circadian disruption in mice (76). *Bmal1*-knockout mice showed obesity and lower insulin secretion compared with wild-type mice (101). Adipocyte-specific deletion of *Bmal1* led to obesity, and interestingly, a shift in food intake timing from nocturnal to diurnal, which was caused by a change in the levels of circulating polyunsaturated fatty acids and nonesterified polyunsaturated fatty acids in the hypothalamic neurons (102). Thus, circadian clock disruption causes energy metabolism dysfunction, suggesting that the circadian system tightly regulates metabolic functions.

Important metabolic factors like AMPK, *Sirt1*, *Pparα*, and *Pgc1α* follow circadian rhythms in their activity and act as important regulators of core circadian mechanisms. AMPK, which is a nutrient sensor in peripheral tissues, acts in the destabilization of CRY protein in the core of the circadian system (103). *Sirt1*, an anti-aging gene regulated by nicotinamide adenine dinucleotide (NAD^+), regulates the histone acetyltransferase activity of CLOCK protein (104, 105) and promotes deacetylation and degradation of PER2 (106). *Pparα*, which is a nuclear receptor for lipid metabolism in the liver, binds with PER2 (107) and promotes *Bmal1* expression through PPRE in the promoter of *Bmal1* (108). *Pgc1α*, a transcriptional coactivator for the regulation of energy metabolism, is also involved in circadian regulation and promotes the expression of *Bmal1* and *Rev-erbα* through the RORE site (109). Thus, the core metabolic genes are tightly related to the clock systems, and their activities undergo circadian changes.

6. Chrono-nutrition: food input to the circadian clocks

6.1. Food anticipatory activity (FAA)

Daily scheduled feedings, restricted to only a few hours throughout the day, induce time-specific arousal in rodents (i.e., FAA) (Fig. 5). FAA appears roughly 2 – 3 h before feeding time and is thought to indicate that mice are anticipating food at the scheduled time. Therefore, it is believed that mice can learn and remember the timing of regular feedings through their internal, food-entrainable oscillator (FEO). In addition to FAA, food can entrain clock-gene expression rhythms in many areas of the brain and in almost all peripheral tissues, but not in the SCN. After cloning core clock genes in the 1990s, several studies investigated the entrainment of peripheral clocks by using scheduled

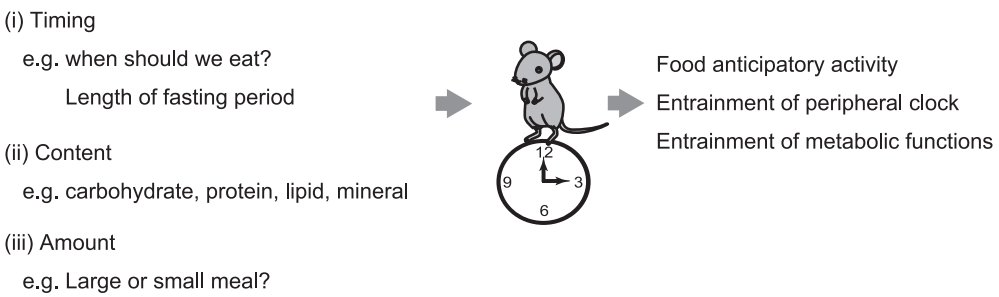

Fig. 5. Framework of the aspect of chrono-nutrition: food/nutrition input to the circadian clocks. Timing, components, and amount of food/nutrition could be important factors to stimulate the circadian system in mammals. Scheduled feeding–induced entrainment of the circadian system can be observed at the behavioral and molecular levels.

feeding experiments. Our group showed that *Per1*, *Per2*, D-site-binding protein, and cholesterol 7 alpha-hydroxylase mRNA expression rhythms in the liver underwent phase shifting and entrainment with daytime feedings in mice (110). However, the *Per1* and *Per2* expression rhythms in the SCN did not undergo phase shifting with scheduled feedings. Similar results were reported in the field of circadian research at the same time. Stokkan et al. (111) reported that the liver clock phase was initially shifted by 10 h within 2 d. Damiola et al. (112) reported that this food-induced phase resetting occurs faster in the liver than in the kidney, heart, or pancreas. In essence, food appears to be a strong entrainable factor with respect to mammalian clocks. In addition, this entrainment will fix the timing of food digestion and metabolism by controlling clock-regulated output genes in the peripheral tissues.

To investigate the location or mechanism of the FEO, many researchers have tried to diminish FAA in mice by using knockout, mutant, or specific brain-part–lesioned mice. In lesion studies, the dorsomedial hypothalamus (DMH), which plays a role in regulating eating behavior, is reported to be one of the possible locations of the FEO. Several studies have demonstrated that DMH-lesioned mice and rats showed a significant reduction in FAA formation (113 – 115). However, the ability to induce FAA was still present in DMH-lesioned mice (116, 117). The decisive data provided by Acosta-Galvan et al. (117) indicate that DMH-lesioned mice have reduced FAA, whereas both DMH- and SCN-lesioned mice have increased FAA. This result suggests that the DMH is part of the FEO but not a prerequisite for the induction of FAA. Furthermore, the data suggest that the SCN inhibits FEO entrainment because the SCN is entrained by light–dark information through the retina. In view of these results, the FEO is thought to be a large network structure in the brain. Therefore, it is difficult to ascertain the location of the new oscillator, as with the SCN.

Circadian clock genes are thought to be involved in the FEO mechanism. However, several controversial papers have been published on the subject. *Per2* mutant/knockout mice and *Bmal1*-knockout mice were reported to exhibit normal FAA or reduced FAA in different studies performed in different laboratories (118 – 121). Recently, Mieda and Sakurai (122) showed that nervous system-specific *Bmal1* deletion caused a reduction in the entrainment ability of the scheduled-feeding paradigm, suggesting that *Bmal1* is an essential component of the FEO. Additionally, Takasu et al. (123) demonstrated that clock-gene mutant or knockout mice have different abilities for adapting to different periodic feeding paradigms (T-cycle experiment). In fact, FAA can be induced in $Cry1^{-/-}$ mice (short-period mutant) with 22-h periodic feedings, but not in $Cry2^{-/-}$ (long-period mutant) or wild-type mice. Taken together, mice may use the circadian system to remember feeding times and induce FAA.

To understand the FEO mechanism, we have to consider the motivation of food intake during FAA and before feeding. Ghrelin secreted from the stomach acts as a circulating hormone to relay the hunger state to the hypothalamus before food intake. Ghrelin-receptor–knockout mice showed significantly reduced FAA formation during a daytime-scheduled feeding experiment (124, 125). However, normal FAA formation in preproghrelin-knockout mice has been reported (126). Orexin (hypocretin), which is an important neuropeptide for promoting wakefulness and locomotor activity, was reported to be involved in food anticipation. Orexin neuron–ablated mice showed a severe deficit in FAA increase with scheduled feedings (127, 128). In orexin neurons in the lateral hypothalamus, fos expression exhibits rhythms that shift in response to scheduled feedings. Therefore, the orexin neurons and lateral hypothalamus are involved in the FEO. Melanocortin-3 receptor–deficient mice also showed decreased FAA formation (129), reduced food intake, and melanocortin-3–receptor expression in the hypothalamus. More recently, Sirt1, the NAD-dependent deacetylase, was reported to be involved in the FEO (130). Researchers have reported that brain-specific *Sirt1*-knockout show decreased FAA in the daytime-scheduled feeding paradigm, and *Sirt1* was shown to upregulate the expression of the orexin type 2 receptor in the hypothalamus in response to scheduled feedings. Taken together, hunger, or the motivation for food intake, appears to mediate the mechanism of FEO formation in hypothalamic nuclei.

6.2. Food timing

A recent chrono-nutritional study provided some insight into the optimal timing of food intake for maintaining body weight and health (Fig. 5). Although it has always been speculated that eating late at night carries a high risk of developing obesity, there is minimal evidence to support this hypothesis. Recently, several clinical studies have demonstrated this phenomenon. Hsieh et al. (131) showed that subjects with short sleep duration (< 5 h) had significantly higher risk for developing obesity, diabetes, and poor sleep and eating late dinners than subjects with a longer sleep duration (> 5 h). Baron et al. (132) reported that late sleepers (midpoint of sleep > 5:30 AM) consumed more calories at dinner and after 8:00 PM and were more at risk for obesity than normal sleepers (midpoint of sleep < 5:30). Clinical studies in a laboratory setting showed that adults with insufficient sleep for 5 consecutive days experienced increased total

daily energy expenditure, but the energy intake after dinner increased and exceeded the energy needed to maintain an energy balance (133). In addition, humans and rats selected foods with a higher fat composition at dinner time than at breakfast time (134, 135), suggesting a nutritional preference that leads to obesity with late-night feeding. These findings indicate that late dinners carry the risk of obesity in humans.

The same findings were found in rodents. Scheduled food intake (e.g., HFD) during only light periods caused higher weight gain than food ingested at night (136). Mice maintained under dim lighting conditions at night-time (i.e., light at night) showed increased food intake during the daytime. As a result, their body weight increased compared with mice maintained under normal light–dark conditions (137). Consumption of a HFD at the end of the dark period induced increased weight gain, adiposity, glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and hyperleptinemia (138, 139). Similarly, mice fed breakfast only showed body weight gain, hyperinsulinemia, hyperleptinemia, and decreased expression of β-oxidation-related genes in adipose and hepatic tissue compared with mice fed a bigger breakfast and a smaller dinner (140). Therefore, the timing of food intake is an important factor for maintaining appropriate body weight. However, the reason for this phenomenon is still unknown.

One reason may be the phases of clock gene expression that change with the timing of food intake. Late-night dinners may cause changes in clock gene expression in the peripheral tissues. Our group reported that food volume and starvation intervals are important factors for determining the peripheral clock phase (141, 142). A feeding schedule of 2 meals per day in mice induced only one peak in the rhythm of clock gene expression in peripheral tissues (141, 143). On the other hand, a feeding schedule of 2 – 3 meals per day in mice, with food intake following a longer fasting interval, was more effective at entraining the peripheral clock phase than other feeding schedules. In the study by Kuroda et al. (142), food timing mimicked human eating patterns. Food at Zeitgeber time (ZT, ZT 0 = lights on) 12 was set to breakfast, food at ZT 18 (middle of the dark period) was set to lunch, food at ZT 1 or ZT 4 was set to dinner, and food at ZT 4 was set to late dinner. In fact, mice fed at ZT 12 (breakfast), ZT 18 (lunch), and ZT 1 (dinner) were entrained by food at ZT 12, because this feeding was 11 h after the last meal (ZT 1), whereas the other meal came 6 or 7 h later. However, mice fed at ZT 12, ZT 18, and ZT 4 (late dinner) were entrained by food at ZT 4 (late dinner) because this feeding came 10 h after the last meal at ZT 18, whereas food at ZT 12 came 8 h later. This suggests that dinner is more effective at resetting the clock phase if the dinner time is late at night. Moreover, such a phase change may cause late-night dinner-induced obesity.

High-fat food intake leading to obesity induced a long free-running period of locomotor activity rhythms and decreased the amplitude of clock or clock-controlled gene expression rhythms in hepatic and adipose tissue (144). However, two recent studies have shown promising results which suggest that eating according to the same daily schedule can diminish HFD-induced obesity. Scheduled high-fat feedings for 8 h during the dark period (145) or for 4 h during the light period (146) without calorie restriction prevented obesity. These studies suggest that regulating the timing of food intake can improve the amplitude of the clock and clock-controlled metabolic-related gene expression rhythms, nutrient utilization, energy expenditure, and insulin sensitivity. Similarly, our group demonstrated that scheduled access to food during the active phase led to a recovery from disrupted locomotor-activity rhythms and disrupted *Per2* expression rhythms in *db/db* mice, known causes of severe obesity, type 2 diabetes, and low-amplitude cycles of clock genes (147).

For night shift work–induced obesity in rats and mice, scheduled food access proved helpful for preventing obesity. Extensive epidemiological studies of rotating night shift work revealed that nurses who worked for longer periods during their shift carried a higher risk of type 2 diabetes than nurses who worked shorter shifts (148). Karatsoreos et al. (149) reported that a 20-h light-dark cycle in mice induced obesity and irregular release of metabolic hormones, as well as decreased dendritic length in the prelimbic prefrontal cortex. To avoid these effects, scheduled feedings during the dark period with restricted arousal for 8 h during the light period prevented obesity induced ad libitum (150). Similarly, scheduled feeding of night shift work mice during the normal dark phase was shown to prevent dyssynchrony of rhythmically expressed hepatic genes in microarray analysis (151). Therefore, meal timing is important for preventing obesity.

In addition to obesity, rotating night shift work carries a higher risk of developing cancer. According to a large-scale prospective cohort in Japan, there was a significant increase in the risk of prostate cancer (152). WHO's International Agency for Research on Cancer determined in 2007 that rotating night shift work is a probable factor in cancer. In mice, chronic jet lag also accelerated malignant growth (153). Intriguingly, on a similar manner related to obesity, scheduled feeding was effective at reducing the speed of cancer growth, especially when food was given during the light period in mice (154). Scheduled feedings can change the amplitude of

circadian clock gene expression rhythms and tumor genes, such as *Hspa8*, *Cirbp*, and *Ccna2*. Therefore, the timing of food intake can improve not only obesity, but also cancer growth, by changing the strength of circadian systems in a chronic jet lag model for mice. Chronic jet lag also induced increased mortality in aged mice (155) and dysregulation of the inflammatory response by endotoxemic shock (156) and experimental colitis (157). These phenotypes might be improved by temporal regulation of food ingestion. Chrono-pharmacology kinetics can also be manipulated by the food timings. Matsunaga et al. (158) investigated whether the level of hepatotoxicity and mortality after injecting acetaminophen in mice had circadian rhythms through CYP2E1 and hepatic glutathione activities. In addition, this rhythmic response of acetaminophen could be manipulated by scheduled feeding during the light phase. Similar manipulations of food timings on the chrono-pharmacology kinetics were reported in the activity of sodium valproate (159) and in the nephrotoxicity of gentamicin (160). Thus, considering regulation of eating timings might be helpful for the drug therapy of diseases.

6.3. Nutritional signals

Understanding the mechanisms of food entrainment in the circadian system will contribute to chrono-nutritional therapy concerning the functionality of food and nutrition (Fig. 5). FAA is an index of the FEO, and clock gene entrainment in peripheral tissues is another good index of the FEO. This peripheral entrainment appeared 1 – 2 d after starting the scheduled feedings, whereas FAA appeared within 3 – 5 d (115, 161). Therefore, FEO may be located in the peripheral tissues. In fact, the expression of many genes, including clock genes in the liver, changed rapidly with daytime re-feeding. In microarray analysis of the hepatic genes, Vollmers et al. (162) showed that re-feeding downregulated the CREB- and FoxO1-targeted genes but upregulated SREBP- and ATF6-targeted genes. In addition, *Per1* was downregulated, while *Per2* was upregulated by daytime re-feeding. Similarly, *Per2* (161, 163) and *Dec1* (163) were upregulated, while *Rev-erbα* was downregulated by re-feeding (161). The induction of *Per2* expression by food is regulated by insulin signaling. Balsalobre et al. (164) showed that multiple signaling pathways, including insulin signaling, can induce *Per2* expression. Similarly, insulin directly induced *Per2* expression in hepatic tissue and three-dimensionally cultured hepatocytes (161, 165, 166). In addition, our recent study demonstrated that rapidly digested starches cause higher blood glucose and higher insulin secretion and induce a larger phase shift in the rhythms of liver *Per2* expression (167). Therefore, food-induced insulin secretion is an important signal for food entrainment in the liver. However, this pathway is not necessary to demonstrate FAA or entrain peripheral clocks. Because streptozotocin induced pancreatic beta cell destruction, which causes the loss of insulin production, it cannot be used to protect against food-induced FAA or phase shifts in hepatic clock genes (168, 169). Taken together, insulin signaling is one of the most important factors for food entrainment, but the unknown mechanisms of the peripheral FEO remain to be elucidated. Poly (ADP-ribose) polymerase 1 (PARP-1), a NAD^+-dependent ADP-ribosyltransferase, is a possible factor of food entrainment. PARP-1 binds and poly(ADP-ribosyl)ates CLOCK, and PARP-1–knockout mice exhibit impaired food entrainment of clock gene expression rhythms in the liver (170). AMPK, a nutrient sensor, is another possible factor for food entrainment. AMPK is activated by fasting or low glucose levels. It then phosphorylates and destabilizes CRY1 protein (103). Diet-induced heat production is also a possible factor of food entrainment. Heat stimulation and body temperature cycles are now reported to be entrainable factors of peripheral clock genes (171 – 173). Recent evidence by Gerber et al. (174) suggests another possible factor; they found through unique screening of transcription factors that the serum response factor has rhythmic transcriptional activity in humans and rodents. In contrast, the glucocorticoid hormone negatively affects food entrainment in peripheral tissues. Adrenalectomized mice showed faster entrainment by food compared with sham-operated mice, and hepatocyte-specific glucocorticoid receptor–null mice showed faster entrainment to restricted feeding than wild-type mice (175). In summary, the mechanisms underlying peripheral clock gene entrainment by food remain a mystery.

The next question is what kind of nutrition has the power to induce entrainment in the circadian clock system. Our group focused on the composition of the standard diet AIN-93M [14% casein, 47% cornstarch, 15% gelatinized cornstarch, 10% sugar, 4% soybean oil, and others (e.g., fiber, vitamins, and minerals)] (176). We changed the composition of nutrients during a daytime scheduled feeding experiment (only 2 d feeding) and checked for phase entrainment in liver rhythm by ex vivo cultured hepatic PER2::LUC bioluminescence. The results showed that 100% of the cornstarch or soybean oil could induce a phase shift, but other nutrients could not. In addition, a combination of glucose and casein without oil, vitamins, or fiber could entrain the liver clock phase. A high-salt diet also changed the peripheral clocks by increasing glucose absorption through the upregulated *Sglt1* and *Glut2* in the jejunum (177). Similarly, streptozotocin-induced insulin-deficient

mice, which have high blood glucose levels, showed a phase-advanced peripheral clock phase (178). In contrast, ketogenic diets, accompanied by hypoglycemia, caused phase-advanced peripheral clocks (179). However, this effect was caused by a shortened circadian free-running period of the SCN and a behavioral phase in the normal light–dark cycle. A palatable non-nutritive mash with restricted access induced FAA (180). A palatable snack (chocolate) in the daytime also elicited FAA and *c-Fos* expression in the corticolimbic area (181), and this entrainment is thought to be mediated by ghrelin (182). Scheduled access to high-fat chow ad libitum caused FAA and *c-Fos* activation in the hypothalamus (183). These results suggest that glucose or a palatable snack can induce the FEO. Other nutritional ingredients such as caffeine can lead to considerable changes in the circadian system. Caffeine was reported to lengthen the circadian clock period (i.e., in the SCN and peripheral clocks) and behavioral rhythms (184). Caffeine is an antagonist of adenosine receptors and an inhibitor of phosphodiesterase, which increases cAMP concentrations. Taken together, functional nutrition may become an increasing topic of relevance in the future.

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