CHAPTER FIVE

Circadian Clocks, Food Intake, and Metabolism

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Contents

Abstract

Circadian rhythmicity that has been shaped by evolution over millions of years generates an internal timing controlling the sleep–wake and metabolism cycles. The daily variations between sleep/fasting/catabolism and wakefulness/feeding/anabolism are coordinated by a master hypothalamic clock, mainly reset by ambient light. Secondary clocks, including liver and adipose tissue, are normally synchronized by the master clock, but they are also sensitive to feeding time, especially when meals take place during the usual resting period. Cellular metabolism and circadian clocks are tightly interconnected at the molecular levels. Although the suprachiasmatic clock is not shifted by mealtime under light–dark conditions, nutritional cues can feedback onto it and modulate its function under hypo- and hypercaloric (high-fat) conditions. Food-related reward cues

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are other modulators of the master clock. Circadian disturbances (e.g., desynchronization induced by shift work or chronic jet lag) are frequently associated with metabolic dysfunctions (chronobesity) and vice versa. Pharmacological tools and natural synchronizers (i.e., light and mealtime) can be useful as chronotherapeutic treatments to limit the occurrence of metabolic risk factors.

1. INTRODUCTION

Energy metabolism, food intake, and circadian clocks are tightly interconnected. By providing energy substrates to the organism, feeding is essential for maintaining energy homeostasis. Most often, this does not occur randomly at any time of the astronomical day, but takes place periodically during a certain temporal niche (e.g., daytime or nighttime), depending on whether the species is diurnal or nocturnal, respectively. The daily period of feeding and food foraging also coincides with the period of wakefulness, exercise, high metabolic activity, and anabolism. Conversely, the daily period of fasting corresponds to sleep, low metabolic activity, and catabolism. At a cellular level, glucose availability is maintained with a quite narrow margin of variations throughout 24 h, despite the daily rhythm of food ingestion reported above. The two main sources of energy stores include carbohydrate (i.e., glycogen synthesized in the liver and muscle) and lipid (i.e., triacylglycerols synthesized in the white adipose tissue). During the 12-h period of activity/feeding, glucose supply comes mostly from dietary carbohydrate supply, as well as from glycogen for short-term needs (e.g., exercise). By contrast, during the 12-h period of sleep and fasting (glycogenolysis and lipolysis), energy used to cover basal energy expenditure comes from energy substrates stored in anticipation during the previous period of feeding (concomitant with glycogenesis and lipogenesis).

The 24-h temporal segregation of physiology and behavior is controlled by the circadian system. This timing system is actually comprised of a network of endogenous circadian clocks that generate, via their local or distributed outputs, an internal rhythmicity close to 24 h. At the top of the circadian system is a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Most circadian rhythms in behavior (e.g., sleep–wake cycle) and physiology (e.g., hormonal rhythms, like pineal melatonin, or adrenal glucocorticoids) are controlled by this hypothalamic structure.[1–3] Besides, almost all peripheral tissues, such as liver, muscle,

and skin, express circadian oscillations of the molecular actors of the clockwork, called clock genes.[4,5] The mammalian clock machinery generates autoregulatory transcriptional loops, leading to rhythmic expression of clock genes and clock-controlled genes (i.e., downstream targets of the clockwork). In the core of these oscillatory mechanisms are transcription factors, BMAL1 (Brain and Muscle Aryl hydrocarbon receptor nuclear translocator-Like protein 1) and CLOCK (Circadian Locomotor Output Cycles Kaput), or its analog NPAS2 (Neuronal PAS domain protein 2), that dimerize together to activate the transcription of other clock genes, including three Period (*Per1–3*) and two *Cryptochrome* (*Cry 1–2*) genes via E-box sequences in their promoter, thus defining a main positive loop.[4,6] The PER and CRY proteins then form complexes that are translocated in the nucleus where they inhibit their own CLOCK (NPAS2)/BMAL1-induced transactivation, defining a main negative loop. There are also reinforcing loops comprising other transcription factors, REV-ERB (*Reverse Viral Erythroblastosis oncogene products*) α−β, and ROR (*Retinoic acid-related Orphan Receptors*) α−β−γ that modulate the transcription of *Bmal1*, *Npas2*, and *Clock* via retinoic acid-related orphan receptor response elements. Furthermore, PER/CRY repressor complexes are inactivated via ubiquitination and proteasome degradation by F-box proteins 3 and 21 for the CRYs,[7,8] and β-transducin repeat containing proteins 1 and 2 for the PERs.[9] Besides its role as a transcriptional activator, CLOCK is also a histone acetyltransferase that drives the cyclic acetylation of various targets, including BMAL1.[10] The internal coordination of circadian rhythmicity is structured as a multistep network, in which the master suprachiasmatic clock is a conductor that provides temporal signals to the secondary clocks/oscillators in the brain and peripheral organs via nervous and endocrine messages.[3,11,12] Light perceived by the retina, that contains its own clock, is widely recognized as the most potent synchronizer of the master clock. Nevertheless, several cues associated with feeding (and fasting) also impact circadian functioning at different steps of the circadian system.

The first purpose of this chapter is to provide an overview of the complex physiological interactions between feeding–fasting cycles and the various clocks/oscillators, including feedback effects of nutritional cues on the circadian clocks that control feeding rhythmicity (Fig. 5.1). Another issue that will be covered is the reciprocal disturbances between circadian rhythmicity and metabolic pathologies of energy metabolism. Finally, emerging chronotherapeutic approaches in the field of dieting and prevention of metabolic risks will be briefly introduced.

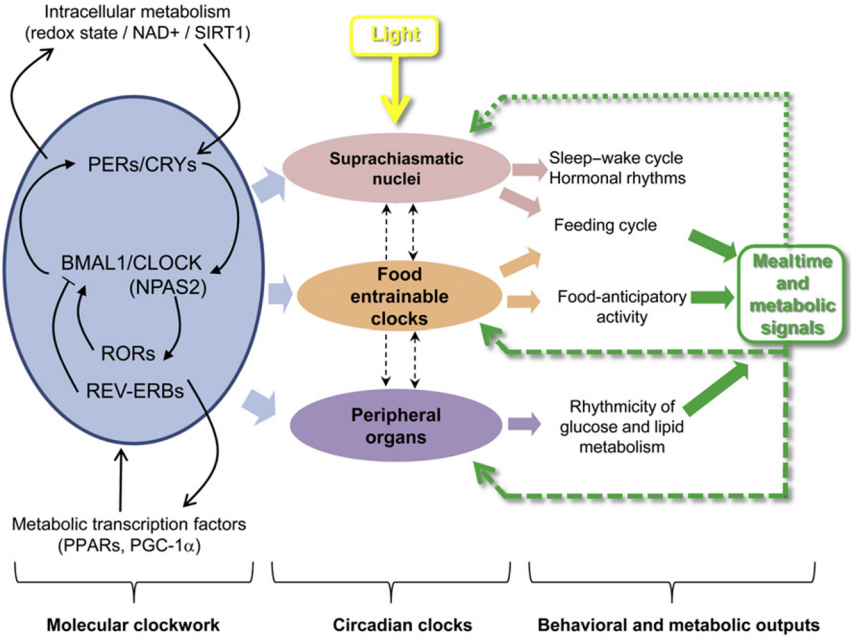

Figure 5.1 The multilevel interactions between circadian clocks and metabolism in mammals. The molecular clock is present in virtually all tissues. The master clock in the suprachiasmatic nuclei and other secondary clock in the brain adjust the phase of behavioral rhythms (sleep–wake and feeding cycles, food-anticipatory activity), while peripheral clocks/oscillators participate in the rhythms of metabolic processes (e.g., glucose tolerance, insulin sensitivity, fatty acid oxidation, fat storage). In turn, mealtime cues and metabolic signals feedback on circadian clocks to modulate their oscillations.

2. PHYSIOLOGY

2.1. Daily rhythm of food intake

Homeostasis of food intake and energy metabolism is regulated by the brain, via a network of cerebral nuclei located in the basal hypothalamus (e.g., arcuate and ventromedial nuclei) and brainstem (e.g., nucleus of the solitary tract and parabrachial nucleus). These structures receive and detect blood-borne metabolic signals from peripheral tissues, such as metabolites (glucose, nonesterified fatty acids) and metabolic hormones (stomach ghrelin, fat leptin and pancreatic insulin, and intestinal gluco-incretins).[13] Although feeding-sensitive variations in clock gene expression have been detected

in these neural structures,[14–16] their functional implication in the daily rhythm of ingestive behaviors remains to be established.

Bilateral lesions of the SCN as well as knife-cuts around them abolish circadian rhythmicity of the feeding/fasting cycle, indicating that the suprachiasmatic clock controls the circadian rhythm of feeding.[17,18] As aforementioned, because suprachiasmatic lesions also produce arrhythmicity of sleep–wake cycle, the concomitant loss of feeding rhythm may partly be an indirect consequence of behavioral arrhythmicity (in that view, destructured sleep timing would be the direct cause of the destructured pattern of food intake). There are experimental arguments outlined below, suggesting that a feeding-entrainable system outside the SCN may also participate in the daily rhythm of food foraging/intake (Fig. 5.1).

Timing of food availability has a major impact on overt rhythmicity. When food access is limited to a few hours every day at the same time (temporal restricted feeding), animals display food-anticipatory activity, that is, a bout of arousal accompanied with food-appetitive behaviors and physical activity prior to the expected food presentation.[19] Such a rhythmic behavior anticipating food presentation on a daily basis is manifest not only in food-restricted adult animals but also in pups nursed daily by the mother shortly once a day.[20,21] Other physiological parameters such as body temperature and corticosterone release also rise before food presentation, in phase with anticipatory behavior.[19,22] In rodents arrhythmic after suprachiasmatic lesions, temporal restricted feeding provides timing cues to the rest of the circadian system, thus restoring behavioral rhythmicity via daily food-anticipatory activity, hormonal rhythmicity, and/or sympathetic activation.[22,23] There are food-entrainable clocks throughout the brain that likely define a multi-oscillatory network coupling several neural oscillators most sensitive to feeding cues. Albeit the anatomic brain substrate that initiates food-anticipatory behavioral activity has been difficult to ascertain, possibly due to its distributed nature, experimental data favor the participation of some structures in the metabolic hypothalamus, the brainstem, and cerebellum.[19,24–26]

Alterations in the diurnal pattern of feeding have been detected in mice with functionally impaired clock genes. The daily pattern of food intake under a light–dark cycle is markedly attenuated in *Clock* mutant mice and in mice with adipocyte-specific deletion of *Bmal1*, food intake during daytime being found greater than that in wild-type mice.[27,28] Other mutations of clock genes, such *Rev-erbα*, do not impair daily pattern of feeding.[29] In mammals, a major modulator of the ultradian meal pattern during the

feeding period is the size of the preceding meal. Indeed, larger meals lead to long intervals until the initiation of the next meal.[30] It is not known yet with certainty whether these ultradian patterns of intermeal lags are disturbed in clock mutant or mice knockout for clock genes.

Furthermore, in addition to the circadian and homeostatic control, food intake can be influenced by the ambient lighting conditions, defining direct effects of light or "masking." In nocturnal mammals, light exposure at night acutely reduces food intake during the active period (i.e., negative masking of feeding), while dark exposure during daytime enhances food intake during the usual sleep/fasting period (i.e., positive masking of feeding).[31]

2.2. Daily variations in energy metabolism

Mammals maintain a relatively high metabolic rate with narrow daily variations, albeit they do not feed continuously. Nonetheless, it is possible to measure with indirect calorimetry daily oscillations in energy expenditure (via oxygen consumption) and in respiratory exchange ratio, also called respiratory quotient (RQ; i.e., the ratio of carbon dioxide produced and oxygen consumed), which is an indicator of metabolized fuels. Lesions of the suprachiasmatic clock suppress circadian rhythmicity of energy expenditure as well as RQ.[32] This observation has been interpreted as meaning that the master clock controls the daily variations in energy metabolism. Alternatively, this arrhythmicity may result from the arrhythmic sleep–wake cycle that would prevent the detection of circadian variations.

When mammals are food deprived for several days under a light–dark cycle, daily rhythms of energy metabolites persist, thus demonstrating that the metabolic rhythmicity does not rely solely on daily feeding–fasting cycles.[33] Temporal restricted feeding can shift the daily rhythms of energy metabolites and RQ as well.[33,34]

Per2-null mice have been found to be leaner due to increased energy expenditure, while 24-h RQ values do not differ from wild-type littermates.[35] *Clock* mutant mice are less active during nighttime compared to wild-type mice and, accordingly, display a reduction in nocturnal energy expenditure.[27] In mice with adipocyte-specific deletion of *Bmal1*, the diurnal rhythm of energy expenditure is dampened, due to reduced expenditure at night without modification of the level of nocturnal activity.[28] The daily variations of the RQ show large interindividual differences in *Cry1*−/−; *Cry2*−/− mice, leading to flattened 24-h average.[36] A mutation of *Rev-erbα* leads to an altered daily rhythm of *in vivo* carbohydrate/lipid utilization, as

highlighted by larger and lower RQ values during night and day, respectively. Thus, lack of REV-ERBα causes not only an increased utilization of fatty acids during both resting (daytime) and acute fasting but also an enhanced nocturnal glucose utilization (used for *de novo* lipogenesis from dietary carbohydrates), as well as diet-induced obesity. Thus, these findings indicate that REV-ERBα is crucial for the daily variations of fuel utilization.[29] Notwithstanding, the molecular mechanisms underlying this temporal partitioning of fuel utilization remain to be further elucidated.

Glucose, the main source of energy for cells, comes from the liver or from dietary carbohydrate via the intestine and circulates easily in the bloodstream. In most tissues, cellular uptake of glucose via facilitated diffusion is controlled by insulin, except for the liver and the brain. Another major fuel source is fat. As hydrophobic molecules, lipids cannot circulate readily in the aqueous blood. As a matter of fact, lipids are transported as particles associating them with hydrophilic molecules, called apolipoproteins. The expression of apolipoproteins is activated and repressed by the circadian factors RORα and REV-ERBβ, respectively.[37–39] The lipid particles in the plasma include chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins, and high-density lipoproteins.

Lipoprotein lipase (LPL) is an enzyme that catalyses the hydrolysis of the triacylglycerols in chylomicrons and VLDL, releasing nonesterified fatty acids and facilitating their cellular uptake.[40] *Lpl* is strongly expressed in tissues that store lipids (i.e., white adipose tissue) or use them as fuel (i.e., muscles and brown fat). Of note, LPL activity displays marked daily variations according to organs, but with opposite timing depending on their role: LPL activity in epididymal fat of nocturnal rats is highest at night for lipogenesis, while it rises progressively from morning to early night in skeletal muscle for fat oxidation.[41] LPL expression and activity are modulated by a number of factors, such as PPARs, insulin, glucose, and fatty acids.[42] Furthermore, CLOCK alone or together with BMAL1 can also transactivate *Lpl* expression.[29,40]

Heme, being notably an iron-containing compound embedded to the hemoglobin, is a crucial component of the intermediary metabolism. Moreover, circadian rhythmicity can be modulated by heme bioavailability, illustrating a systemic link between metabolic and circadian pathways. A decrease in heme biosynthesis shortens the circadian period of *in vivo* body temperature rhythm.[43] Also, heme and inhibitors of heme oxygenase dose-dependently dampen circadian oscillations rhythms of SCN explants from PER2:LUC mice, while pharmacological inhibition of heme synthesis

lengthens the circadian period of SCN PER2:LUC rhythms.[44] At a molecular level, heme was first shown to bind to NPAS2, thereby modulating DNA binding of NPAS2/BMAL1 in response to the presence of carbon monoxide.[45] Further work involved PER2 in heme effects on the molecular clock, but this is still a subject of debate.[46,47] Heme can also serve as a physiological ligand for REV-ERBα and REV-ERBβ to modulate their transcriptional efficiency.[48,49] REV-ERBs are also responsive to carbon monoxide and nitric oxide.[50,51] Other examples of intracellular interactions between the metabolic and circadian systems will be mentioned below.

2.3. Cross talk between molecular clocks and intracellular metabolic pathways

Peroxiredoxins are ubiquitous antioxidant enzymes that detoxify reactive oxygen species, such as hydrogen peroxide. Reduction–oxidation (redox) cycles of peroxiredoxins define 24-h metabolic cycles that can work in the absence of the transcriptional/translational circadian clockwork, for instance in red blood cells.[52] A comparative analysis reveals that these 24-h redox cycles are conserved in all living organisms studied so far, including bacteria.[53] In mammalian nucleated cells, peroxiredoxin oscillations are influenced by the transcriptional/translational circadian clockwork, as shown by altered phase relationships in fibroblasts from *Cry1−/−*; *Cry2−/−* mice.[52]

Redox reactions are involved in multiple biological processes, including the molecular clockwork itself. For instance, the DNA-binding activity of CLOCK/BMAL1 and NPAS2/BMAL1 heterodimers *in silico* is enhanced by the reduced form (NDAH, from NAD^+) of nicotinamide adenine dinucleotide (NAD).[54] Intracellular levels of NAD^+ show circadian oscillations in fibroblasts from wild-type mice, but they are arrhythmic in fibroblasts sampled from *Clock* mutant or *Cry1−/−;Cry2−/−* mice.[55] Synthesis of NAD^+ is largely controlled by the enzyme nicotinamide phosphoribosyltransferase (NAMPT) whose circadian expression is regulated by CLOCK/BMAL1 heterodimers. In turn, NAMPT modulates the molecular clockwork of peripheral clocks (fibroblasts, hepatocytes), thus defining a new feedback loop.[55,56] Another example of interactions between clock mechanisms and redox reactions is given by the fact that transcription repression mediated by heme-bound REV-ERBs is sensitive to redox states.[50]

5′-Adenosine monophosphate-activated protein kinase (AMPK) is an enzyme that plays a key role in the cellular regulation of fatty acid and

glucose metabolism aiming at keeping energy homeostasis via phosphorylation of a number of metabolic enzymes. AMPK is viewed as a cellular sensor of energy status because, beside AMP, it is also activated by many physiological stimuli, such as stress, food deprivation, acute exercise, or hormones (e.g., leptin). Some of AMPK targets are clock components. CRY1 is phosphorylated and destabilized by AMPK.[57] When phosphorylated by AMPK, casein kinase Iε degrades the clock protein PER2, thereby impacting circadian oscillating. Fibroblasts treated with metformin, an activator of AMPK, display a shortened circadian period. Furthermore, *in vivo* injections of metformin produce phase advances of clock gene oscillations in peripheral tissues.[58]

The NAD^+-dependent SIRT1 (Sirtuin 1) histone deacetylase is a redox sensor that has been involved in a multitude of processes related to cellular metabolism, stress, and senescence.[59] In particular, SIRT1 modulates the activity of the metabolic transcription factor PGC-1α (peroxisome proliferator-activated receptor (i.e., PPARγ) coactivator 1α),[60,61] also identified as a modifier of the transcription of clock genes, such as *Bmal1* and *Rev-erbα*, in part via coactivation of RORs.[62] Moreover, SIRT1 binds circadianly to CLOCK/BMAL1 heterodimers, thus adding another functional link between cellular energy state and the molecular clockwork.[63,64]

Strikingly, nuclear receptors recognized as circadian factors, that is, REV-ERBs and RORs, have also been reported having regulatory roles in metabolic function. A pioneer work discovered that REV-ERBα promotes and RORα inhibits *in vitro* adipocyte differentiation.[65,66] BMAL1, whose transcription is regulated by both REV-ERBs and RORs, was also considered to play a prominent role in adipogenesis.[67] More recently, PER2 has been shown to promote adipogenesis via PPARγ (see below).[35] A point that remains to be clarified is whether the effects reported above result from abnormal metabolic function due to noncircadian roles of these circadian factors, or from altered circadian control of metabolic pathways. Furthermore, it is noteworthy that metabolic factors activated by fatty acids, such as PPAR, are tightly linked bidirectionally to the molecular clockwork. Actually, *Rev-erbα* expression in the adipocytes and hepatocytes is induced respectively by PPARγ and PPARα.[65,68] In addition, PPARα in the liver activates the transcription of *Bmal1*, while daily expression of *Pparα* involves BMAL1.[69] Although not exhaustive, this brief overview of multiple and interconnected regulatory loops highlights the now established functional and molecular cross talk between the circadian and metabolic systems (Fig. 5.1).

2.4. Peripheral organs and most brain regions: Clocks entrainable by mealtime

Time when food is eaten has potent phase-resetting effects on the clockwork of all peripheral tissues studied so far, including liver, white adipose tissue, gastrointestinal tract, heart, lung, and kidney[70–72] (Fig. 5.2). The characteristics of the feeding–fasting cycles are critical because both food volume and interval of food deprivation matter to reset the liver oscillations.[73] However, the nature of the feeding-associated signals capable of resetting peripheral oscillators is not yet fully identified. Hormones, such as glucocorticoids and metabolites, like glucose, as well as nutrient sensors, like AMPK, are good candidates.[57,74,75] In the liver, transient upregulation of *Per2* and *Dec1* transcription is observed in the first hour after feeding.[76] Moreover, refeeding-induced insulin secretion leads not only to an upregulation of *Per2* expression but also to downregulated *Rev-erv*α mRNA hepatic levels.[77]

Timing of circadian oscillations is markedly modified by restricted feeding in many, but not all, cerebral regions out of the SCN. For example, daytime feeding modifies the phase of molecular oscillations in the

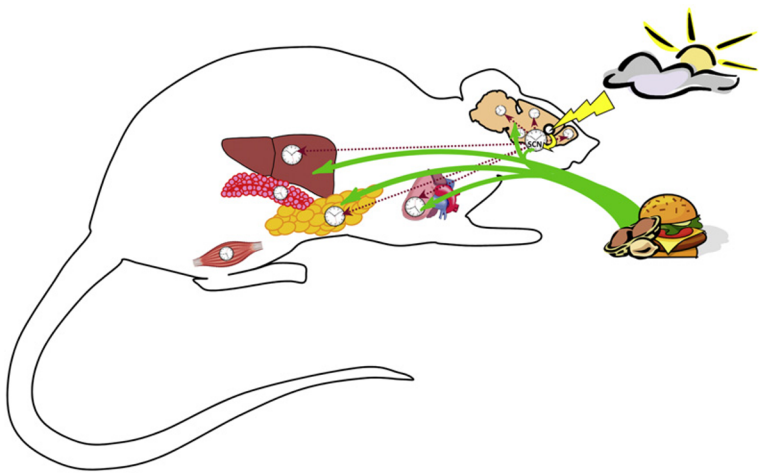

Figure 5.2 The suprachiasmatic nuclei (SCN) contain the master clock that controls sleep–wake cycle and hormonal rhythms. The SCN are the conductor of the many secondary clocks/oscillators in the brain and peripheral organs, in part via temporal messages transmitted by nervous pathways (dotted arrows). Light and feeding time act as synchronizers (filled arrows) at different levels of the multi-oscillatory circadian network.

arcuate and dorsomedial hypothalamic nuclei,[15,78] central amygdala,[25,79] and cerebellum.[80,81] By contrast, circadian oscillations in few brain structures, such as the SCN and the hippocampus, are less sensitive to timed mealtime.[14] The cerebral oscillators or clocks that are sensitive to mealtime define a feeding-entrainable network, some of them being likely involved in the mechanisms of behavioral meal anticipation, as evoked above.

2.5. SCN: The master light-entrainable clock is sensitive to metabolic and reward cues

The mammalian clock machinery described in Section 1 is present in cells of the master suprachiasmatic clock. Compared to the rapid dampening of circadian oscillations in peripheral organs, the very robust self-sustained rhythmicity of suprachiasmatic cells, even when isolated *in vitro*, involves likely a strong intercellular coupling.[82]

Activity of mitochondrial cytochrome oxidase in suprachiasmatic cells is higher during daytime, while lactate dehydrogenase activity increases at night.[83,84] Because the daily variations of cytochrome oxidase activity are no longer detectable in constant darkness, this suggest that the photic inputs play a regulatory role in the rhythmicity of this metabolic process.[83]

The capacity of the suprachiasmatic cells to generate endogenous rhythmicity was initially demonstrated *ex vivo* and *in vitro* with a metabolic readout, namely, the circadian rhythm of 2-deoxyglucose uptake.[85] Of interest, cultured fibroblasts cannot generate such metabolic rhythmicity, despite synchronized clock gene oscillations. However, sustained oscillations of 2-deoxyglucose uptake can be triggered in fibroblasts when they are cocultured without physical contact with immortalized suprachiasmatic cells.[86]

Another powerful demonstration of self-sustained rhythmicity generated by the SCN came from the circadian rhythm of neuronal firing rate in suprachiasmatic slices kept *in vitro*.[87] Electrical properties of neurons are controlled by various regulatory mechanisms, such as conductances of voltage-gated ion channels. Inhibition of oxidative phosphorylation or glycolysis blocks the Na/K pump to depolarize resting potential and increase spontaneous firing in suprachiasmatic cells, thus indicating a metabolic modulation of the Na/K pump.[88] However, the connection between the molecular clock and the rhythmic electrical activity within the master clock remained elusive. It turns out that redox rhythmicity, by itself driven by the molecular clockwork as aforementioned, has a direct influence on the excitability of suprachiasmatic neurons via a modulation of K^+ conductance.[89]

Among stimuli capable of resetting the central clock, light is the most potent (Fig. 5.2). Light cues are first perceived by the retina that contains a circadian clock.[90] Photosensitive ganglion cells containing the photopigment melanopsin send fibers that project to the SCN, either directly via the retinohypothalamic tract or indirectly via the intergeniculate leaflet of the thalamus.[91,92] The way the SCN clock is synchronized to light is characterized by a photosensitive daily period (mainly at night) during which light cues can shift the clock, while the temporal window around midday defines a period during which light has no phase-resetting effect.[91] A newly identified modulator of photic resetting in the SCN is the metabolic transcription factor, PPARβ/δ.[93]

Under light–dark cycle, light can indirectly affect rhythmicity in peripheral organs through signals coming from the SCN via sympathetic projections. This is the case for plasma glucose that, in addition to its circadian control, can be increased by light exposure or stress.[94,95] Furthermore, as already evoked for food intake, the apparent daily sleep–wake cycle can also be modulated by direct, clock-independent responses to light, called "masking" in the circadian field.[96,97]

Daily rhythmicity of release of hormones in the bloodstream is the rule, rather than the exception. In nocturnal rats, plasma levels of both insulin and leptin increase during the early activity period (night).[98–100] Because suprachiasmatic lesions in rodents abolish this rhythmicity (i.e., hormonal rhythms become flattened, usually around the mean level), this reveals a control by the suprachiasmatic clock.[98,100] Studies in functional neuroanatomy have shown that the suprachiasmatic control of endocrine rhythmicity is largely mediated by the sympathetic innervation via hypothalamic relays (i.e., paraventricular and dorsomedial nuclei, and subparaventricular region) receiving vasopressinergic, glutamatergic, and GABAergic inputs from the master clock.[3]

In humans, hormonal rhythmicity is known to depend not only on circadian clocks but also on food intake, sleep, and light. To limit these so-called confounding effects from a strict circadian point of view, human subjects can be maintained for almost 2 days awake to avoid sleep-induced effects, fed hourly isocaloric meals to avoid synchronizing effects of daily mealtime, and in constant dim light to prevent direct or synchronizing effects of light (this experimental situation is the so-called condition of constant routine). Using this paradigm, plasma leptin and insulin show a peak around the minimal body temperature and close to the usual time of

awakening, respectively.[101] Similarly, plasma fatty acids are also found to be under circadian control, with higher levels during subjective daytime.[102]

Contrary to the high sensitivity of peripheral clocks to the feeding cues, the suprachiasmatic clock of food-restricted animals under a light–dark cycle appears to be buffered against any synchronizing effect of mealtime, as shown with the lack of phase shift of either the circadian rhythm of firing rate or clock gene expression in the SCN.[70,103,104] This does not mean, however, that feeding-associated signals do not reach at all the suprachiasmatic cells. When the photic synchronizer is absent, that is in constant dark or constant light, timed meals can, although not systematically, entrain the suprachiasmatic clock.[19,22] Diurnal parenteral nutrition and *in vivo* glucose infusion produce shifts of clock gene oscillations in the master clock.[105]

Calorie restriction and starvation both lead to a major mobilization of energy stores and affect the timing of the sleep–wake cycle. When challenged with calorie restriction, nocturnal animals become active during their usual sleep period (i.e., they become partially diurnal), independently of the time of feeding.[106,107] Conversely, calorie-restricted diurnal rodents change their behavioral timing of activity to nighttime.[108] These modifications in behavioral timing in case of negative energy balance are due in part to the fact that metabolic cues associated with calorie restriction affect the suprachiasmatic clock machinery and its synchronization to light.[107,108] A ketogenic diet is another example of negative energy balance leading to body mass loss, lipid mobilization, and phase-advanced sleep–wake cycle.[109] Nocturnal mice, that have to work for getting food with increasing levels of workload over days, become also partially diurnal. Interestingly, the switch from nocturnal to diurnal pattern of activity coincides with a gradual shift toward a negative energy balance.[110] Whatever the cause, chronic hypocaloric conditions may ultimately change the cellular metabolic state of suprachiasmatic cells, therefore, altering the mechanisms of circadian oscillations. Alternatively or in combination, circulating metabolites (glucose, nonesterified fatty acids) and metabolic hormones may modulate photic resetting according to the metabolic status.

A daily palatable snack in addition to regular food (chow pellets) provided *ad libitum* is able to entrain behavioral rhythms of rats and mice in constant darkness conditions.[111,112] In mice, ingestion of the attractive and palatable snack activates both the reward and arousal systems in the brain, suggesting that the modulatory effects on the master clock involve somehow dopaminergic and orexinergic pathways.[112] The timing of suprachiasmatic

clock and its synchronization to light can be modified by both the negative metabolic drive associated with hypocaloric feeding and the positive hedonic drive associated with palatable pellets. However, the direction of the modulation of light resetting is opposite: the amplitude of the circadian responses to light of the master clock are increased and reduced by hypocaloric and food-related reward cues, respectively. As discussed elsewhere, the orexinergic neurons in the lateral hypothalamus can integrate both kinds of feeding-related cues and may provide a main modulatory afferent pathway to the SCN.[26]

Together, these findings highlight the fact that the multi-oscillatory circadian network is involved in the daily variation of metabolism at all levels of the circadian system. Moreover, mealtime and other nutritional cues can act on the timing of various clocks (Fig. 5.1). This may explain why alterations in circadian timing have deleterious consequences on metabolic health, as detailed in the next part.

3. PATHOLOGY

3.1. Circadian disturbances are associated with metabolic dysfunctions

In most instances, circadian disturbances result from an altered endogenous clockwork or from altered exogenous timing cues. Mutations or KO of clock genes have been frequently linked with disturbances of metabolism. For instance, *Clock* mutant mice show increased adiposity, possibly due to the hypoactivity and hyperphagia reported above.[27] These mutant mice also display reduced gluconeogenesis, but enhanced insulin sensitivity.[113] Mice synthesizing nocturnal melatonin and having disrupted expression of *Clock* in the liver and skeletal muscles show lower glucose tolerance and signs of impaired glycolysis and gluconeogenesis.[114] *Cry1−/−;Cry2−/−* mice suffer from hypertension.[115] *Per2*(*Brdm1*) mutant mice have impaired glucose homeostasis, characterized with hypoglycemia and hyperinsulinemia relative to wild-type mice,[116] while *Per2−/−* mice have reduced lipid stores.[35] Knockout of *Rev-erbα* leads to increased adiposity and chronic hyperglycemia, despite the same daily energy intake of chow diet and daily level of motor activity as those in wild-type littermates.[29] A cardiomyocyte-specific *Clock* mutation in mice leads to increased fatty acid oxidation and decreased cardiac efficiency.[117] Mice bearing a liver-specific deletion of *Bmal1* show a mild hypoglycemia in the afternoon and increased glucose tolerance.[118] Mice with pancreas-specific deletion of *Bmal1* mutant mice are intolerant to glucose and have diminished insulin secretion[119] (Fig. 5.3).

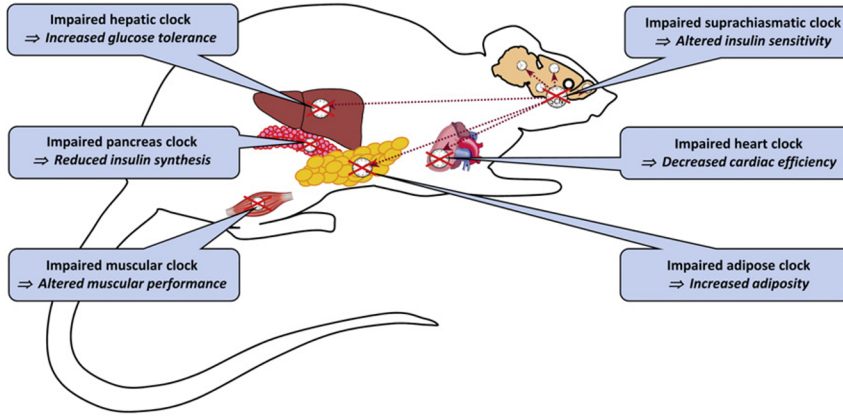

Figure 5.3 Examples of metabolic consequences resulting from impairments of specific circadian clocks in rodents. SCN, suprachiasmatic nuclei.

In humans, polymorphisms in some clock genes have been correlated with metabolic risks. For instance, two *Bmal1* haplotypes are linked with type 2 diabetes and hypertension. Polymorphisms in *Clock* or *Rev-erbα* are significantly associated with high-fat mass.[120,121]

Light being the most potent synchronizer for the master clock, it is not surprising that changes in lighting conditions markedly affect circadian timing, and possibly energy metabolism. The photoperiod (i.e., the relative duration of the light period per 24 h) is perceived by the retina and integrated by the suprachiasmatic clock. Natural fluctuations in food intake, body mass, and adiposity occur recurrently according to seasons in so-photoperiodic species, whose physiology is specifically regulated on a seasonal basis.[122] In these cases, photoperiodic information is translated into neuroendocrine changes via the nocturnal secretion of melatonin by the pineal gland.[123] In rats, whose reproduction is not photoperiod-dependent, free access to sucrose and imposed high-fat feeding do not have the same obesogenic effects depending on the photoperiod. Exposure to short photoperiod (shorter day and longer night) compared to long photoperiod (longer day and shorter night) stimulates spontaneous ingestion of sucrose and promotes fat accretion, suggesting that the photoperiodic environment can modulate metabolic responses.[124] Another important parameter of lighting conditions is the light intensity during the periods of wake and sleep. For example, in spite of nondifferent levels of caloric intake and daily motor activity, mice exposed to dim light at night consume relatively more food

during the light phase than mice exposed to regular light–dark cycle.[125] Also, mice exposed to constant light show larger gain in body gain and changes in daily insulin sensitivity, as compared to individuals kept under a light–dark cycle.[126]

Disruption in circadian rhythmicity can be triggered by light exposure at unusual times of the daily cycle. In humans, transmeridian fast travels (across more than two or three time zones) have become very common following the considerable development of air transport. Physiologically, they cause a transient loss of circadian synchronization, internal regulations being initially out of phase with respect to the new light–dark cycle. Then, day after day, the suprachiasmatic clock will resynchronize to the new cycle and impose an appropriate adjustment of peripheral clocks and oscillators to the local time. The transient period of resynchronisation, relatively proportional to the number of time zones crossed (but dependent on the east–west direction of travel), is accompanied by sleep quality problems, digestive disorders, and several metabolic and hormonal alterations.[127] In particular, carbohydrate oxidation was increased in human subjects exposed to 3 days of jet lag, while protein oxidation was decreased.[128]

Shift work and rotating work schedules trigger chronobiological conflicts between the endogenous clockwork and the ambient light environment as well as mealtime, leading to situations of altered internal temporal organization (e.g., between the master clock and peripheral oscillators or between different peripheral oscillators) and occurrences of desynchronization (misalignment between internal timing and local time). The deleterious effects of chronic desynchronization on metabolic health have been identified in animals. Rats undergoing desynchronization caused by a long-term biweekly change of the light–dark cycle are overweight or have impaired insulin secretion compared to animals maintained in a fixed light–dark cycle.[129,130] Moreover, rats forced to exercise during their usual sleep period show a reversed rhythm of triacylglycerols and increased gain in body mass.[131] Obesity and increased body mass index are commonly observed in large-scale epidemiological studies on night workers and workers with rotating schedules.[132–136] The obesogenic properties of repeated light–dark shifts in animals or chronic shift work in humans leads to the concept that we called "chronobesity."[137]

Mice exposed to light–dark cycles that are too short (i.e., 20 h) to allow daily photic resetting of their master clock show cardiovascular disease, larger gain in body mass, large insulin/glucose ratio, the latter indicating insulin resistance.[138,139] In animal studies, ultimate desynchrony (i.e.,

arrhythmicity) can be induced by complete suprachiasmatic destruction. Of note, mice rendered arrhythmic by suprachiasmatic lesions display hepatic insulin resistance.[140] The consequences of circadian misalignment between the endogenous clockwork and the sleep–wake and feeding–fasting cycles have been studied in humans, using a protocol of forced desynchrony. For that purpose, healthy subjects were exposed to seven recurring 28-h sleep–wake cycles in dim light; this paradigm triggered metabolic alterations in postprandial glucose responses evoking a prediabetic state.[141]

Mealtime being an efficient time giver for peripheral clocks, unusual times of meals in individuals exposed to a light–dark cycle will induce a state of internal desynchronization, the master clock being synchronized by light, while peripheral timing being phase adjusted by feeding times. Thus, it is consistent to find marked chronobiological effects when, regardless of the cause, food intake occurs at unusual hours compared to the normal cycle of sleep–wake cycle. In nocturnal rodents, the metabolic impact of eating chow pellets only during daytime is weak, as in most case, food-restricted rodents do not change their body mass. Different conclusions can be drawn in obese rodents (see below). In them, the spontaneous intake in late afternoon (end of resting period) seems to have the most detrimental effects on energy balance. In humans, the critical period is rather at the beginning of the resting period (early night). Large intake of calories for dinner is associated with increased body mass index.[142] Another study performed in the same girls between childhood and adolescence found that larger energy intake in evening/night meal of children was positively correlated with body mass index few years later.[143] It should be also noted that patients with night eating syndrome have a higher risk of developing obesity.[144] Whether the discrepancies in consequences of meal timing between rodents and humans rely on interspecies or nocturnal–diurnal differences remain to be established. Finally, in shift workers, a high intake at lunch has been identified as a particularly deleterious factor (i.e., it increases the risk of developing a cardiometabolic syndrome). Of note, besides the more fractionated pattern of energy intake, shift workers ingest usually more (+10%) saturated lipids than regular day workers.[134]

Sleep restriction in rats kept in a regular light–dark cycle alters glucose homeostasis (i.e., hyperglycemia and impaired glucose tolerance), while leading to body mass loss without significant change in energy intake.[145] In mice, repeated sleep deprivation during early daytime leads to some metabolic disruption, such as impaired gluconeogenesis.[146] In humans, sleep curtailment is increasing worldwide. Chronic partial sleep deprivation has

been shown to have adverse effects on glucose metabolism, such as impairment of glucose tolerance and insulin sensitivity, both being major risk factors for type 2 diabetes, and sleep deprivation leads to an increase in hunger feeling.[147] Shorter periods of sleep will also increase the daily period available for eating.

Together, these data reveal that unusual timing of light exposure and/or meals in healthy individuals are major contributors of circadian misalignment, perturbing clock rhythmicity, and sleep homeostasis, whose alterations increase the likelihood of metabolic risk factors.

3.2. Metabolic pathologies are frequently associated with circadian disturbances

Now will be described some of the circadian abnormalities observed in genetic and experimental models of obesity and diabetes.

The Zucker rat is an animal model of genetic obesity, caused by a mutation (*fa*) in the gene encoding the receptor of leptin, an anorexigenic hormone synthesized by adipose tissue and acting notably on the metabolic hypothalamus. The *fa* mutation leads to hyperphagia and excessive adiposity. In addition, the Zucker rat maintained under a light–dark cycle displays alterations in daily timing, characterized by phase advances of feeding, locomotor activity and body temperature rhythms.[148,149] In these leptin-resistant rats, the amplitude of clock gene expression is dampened in the liver, but neither in the white adipose tissue nor in the SCN.[150] Mice carrying the *ob* mutation become obese because their adipocytes cannot synthesize leptin. These mice have an increased ultradian activity at the expense of the circadian pattern and an increased daytime activity, while the endogenous period is not affected.[151] The daily pattern of feeding is modified in *ob/ob* mice, with increased intake in the second half of the light period, and greater energy intake in the early and late parts of the dark period.[152] The amplitude of clock gene oscillations in *ob/ob* mice is decreased in the liver and adipose tissue, but not in the SCN. These circadian abnormalities are observed before any detectable metabolic dysfunctions, ruling out a causal role of obesity in the appearance of the circadian perturbations.[153]

Experimental studies in mice have shown that excess energy intake of a high-fat diet is associated with several circadian abnormalities. The period of the endogenous clock suprachiasmatic is elongated relative to that of control mice fed with a standard chow diet.[137,154] Furthermore, the daily period of feeding behavior is lengthened, due to increased food intake during the late part of usual period of rest (daytime in mice).[154] In addition, daily variations

of metabolic hormones in mice fed with high fat are attenuated, with higher and lower plasma levels of leptin and corticosterone, respectively.[137,154] The daily or day–night variations in clock gene expression of peripheral tissues in high-fat fed mice have been found to show either major[154,155] or minor changes.[29,156]

The mouse line carrying the mutation *db*, which invalidates the leptin receptor, is a classical model of obesity associated with severe diabetes mellitus and hypertension. The amplitude of activity–rest rhythm and blood pressure is dampened in *db/db* mice.[157,158] The characteristics of the clock gene oscillations in the liver are significantly altered compared to those observed in *db/+* control mice.[157] Experimental type 1 diabetes induced by streptozotocin, which destroys pancreatic β cells, is associated with several circadian disorders. In particular, the amplitude of oscillations of clock genes is reduced in the liver of diabetic mice.[159] Moreover, the phase-delaying effects of light are increased in streptozotocin-treated mice.[160] In both cases, acute treatment with insulin normalizes circadian alterations.

Obesity in humans is associated with a more flattened and fragmented rhythm of wrist temperature.[161] Moreover, the daily variations in glucose tolerance, which usually decrease throughout daytime in lean subjects, are reversed in obese subjects with or without type 2 diabetes.[162] At a molecular level, clock gene mRNAs in visceral adipose tissue have been correlated with adiposity, at least in women.[163,164] Using serial biopsies of white adipose tissue in the same individuals, no significant change is detected in the characteristics of clock gene oscillations in overweight/obese patients with or without type 2 diabetes, as compared to lean subjects.[165] This study thus contrasts with the majority of findings in animal studies reported above. Whether the differences are due to the type of white adipose tissue (e.g., subcutaneous vs. retroperitoneal), the severity of the metabolic diseases, or interspecific differences clearly warrants further investigations.

4. CHRONOTHERAPEUTICS

4.1. Pharmacology

Besides taking into account the pharmacokinetics of drugs according to the time of the day to improve their efficiency and reduce their side effects (chronopharmacology), targeting drugs that affect the circadian system (so-called chronobiotic drugs) is an emerging and active field of pharmacology. Below are mentioned a few examples of recent advances in that domain, reviewed elsewhere in detail.[166]

Agomelatine is an antidepressant drug with melatonergic (MT1/MT2) agonist and 5-HT(2C) receptor antagonist properties. Because both melatonin and serotonin are known regulators of the master clock and possibly secondary clocks, part of the antidepressant properties of agomelatine can be mediated by its resynchronizing effects on circadian rhythms. Furthermore, physiological doses of melatonin stimulate the activity of several antioxidant enzymes.[167] In the case of the metabolic syndrome, such melatonergic compounds may help to correct the altered sleep–wake cycle.[168]

With respect to the clock gene machinery, REV-ERBα−β are among the rare circadian factors with a known endogenous ligand (i.e., heme). Synthetic REV-ERBs ligands recently developed have significant effects on clock gene expression and less clear resetting effects, as they decrease nocturnal activity in mice, rather than shifting the sleep–wake cycle. Nevertheless, some of these promising compounds have been shown to improve the metabolic profile of obese mice.[169,170] Other hopeful targets to cure metabolic disorders are the closely related members of the ROR family.[171]

4.2. Food composition and feeding time

Even if most animal studies reported above concerned either chow or high-fat diet, the nature of diet-derived nutrients can play a role in the control of peripheral circadian timing. For instance, the daily rhythm of sterol regulatory element-binding protein-1 expression in the liver, where it regulates lipid metabolism, shows differential phase shifts according to various macronutriment regimens (i.e., standard vs. high-carbohydrate, -fat, or -protein).[172]

Several works highlight the fact that excessive food intake during the resting period is deleterious for metabolic health and, conversely, that avoiding it leads to beneficial effects in case of metabolic diseases. Zucker rats display a phase-advanced rhythm of food intake, which begins in the afternoon and not the evening (lights off), as in control rats. It is interesting to note that if food intake is limited exclusively to night (normal feeding period in rats), the overweight of Zucker rats is reduced by 23% compared to those that have a free access to food, despite similar energy intake for the two groups of rats.[149] In the case of *db/db* mice that are obese and severely diabetic, restricting food access to the dark period not only restores a robust rhythm of rest–activity but also ameliorates plasma glucose, insulin, and triacylglycerols.[157]

With respect to diet-induced obesity, the daily period during which high fat is consumed seems important for its obesogenic effects in rodents, as shown by the lack of major adverse metabolic consequences of high-fat feeding when it is restricted to the usual feeding period (nighttime for mice).[173,174] Furthermore, fatty acid composition matters in the altered eating pattern induced by high-fat feeding. In rats, this effect is specifically mediated by saturated fatty acids.[175]

Finally, in animal studies, the adverse effects of desynchronization can be alleviated by timed feeding. The increased gain in body mass of rats desynchronized by a biweekly shift of the light–dark cycle is not observed if food access is limited to the dark period (including during the shifted cycle).[130] Feeding restricted to the dark period in rats (i.e., corresponding to the usual period of food intake) limits body mass gain and desynchronization resulting from forced activity imposed during the resting period (daytime).[176]

4.3. Light and other (de)synchronizers

For applying reliable chronotherapy in humans, it is important to determine internal time for each subject. A recent study reveals that two blood samples taken at 12 h apart from each other are sufficient to estimate individual circadian timing.[177] Adequate timing of light exposure can promote phase adjustment of the master clock. In addition, timed light avoidance can be as useful by preventing photic resetting and allowing transiently endogenous free run. In view of the rather unique and exclusive synchronizing role of light for the suprachiasmatic clock, a means to prevent desynchronization implies strong and appropriate (timed), rather than weak and mismatched lighting information (e.g., light at night).[178] As discussed by these authors, light strategy should combine also appropriate timing of other putative (de)synchronizers (mealtime, exercise) in a global "Zeitgeber hygiene."

In humans also, timed carbohydrate-rich meals can act as a synchronizer of peripheral oscillators.[179] Apart from meal timing, dietary energy density during daytime may modulate overall energy intake. This observation led, for instance, to the recommendation that eating low-density foods in the morning and avoiding high-density foods at night might aid in reducing daily energy intake.[180]

5. CONCLUSION

In spite of the huge literature demonstrating the tight connections between circadian clocks and metabolism in animals, much work remains to be done to confirm in humans the conclusions drawn in nocturnal rodents. Nevertheless, epidemiological studies consistently report an increased prevalence of metabolic risk factors in shift workers and other desynchronizing conditions. Therefore, it is relevant from a clinical point of view to improve basic knowledge and develop models of shift work and other circadian disturbances in day-active animals. In view of the more and more recognized importance of (circadian) timing in pathophysiology, pharmacological and dietary interventions for limiting metabolic risks could take into account circadian rhythmicity to maintain and/or restore a temporal organization appropriately synchronized to local time.

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