

Atilla Engin

Abstract

The biological clocks of the circadian timing system coordinate cellular and physiological processes and synchronizes these with daily cycles, feeding patterns also regulates circadian clocks. The clock genes and adipocytokines show circadian rhythmicity. Dysfunction of these genes are involved in the alteration of these adipokines during the development of obesity. Food availability promotes the stimuli associated with food intake which is a circadian oscillator outside of the suprachiasmatic nucleus (SCN). Its circadian rhythm is arranged with the predictable daily meal-times. Food anticipatory activity is mediated by a self-sustained circadian timing and its principal component is food entrained oscillator. However, the hypothalamus has a crucial role in the regulation of energy balance rather than food intake. Fatty acids or their metabolites can modulate neuronal activity by brain nutrient-sensing neurons involved in the regulation of energy and glucose homeostasis. The timing of three-meal schedules indicates close association with the plasma levels of insulin and preceding food availability. Desynchronization between the central and peripheral clocks by altered timing of food intake and diet composition can lead to uncoupling of peripheral clocks from the central pacemaker and to the development of metabolic disorders. Metabolic dysfunction is associated with circadian disturbances at both central and peripheral levels and, eventual disruption of circadian clock functioning can lead to obesity. While CLOCK expression levels are increased with high fat diet-induced obesity, peroxisome proliferator-activated receptor (PPAR) alpha increases the transcriptional level of brain and muscle ARNT-like 1 (BMAL1) in obese subjects.

A. Engin, M.D., Ph.D. (✉)
Faculty of Medicine, Department of General Surgery,
Gazi University, Besevler, Ankara, Turkey
Mustafa Kemal Mah. 2137. Sok. 8/14, 06520,
Cankaya, Ankara, Turkey
e-mail: dr.aengin@gmail.com

Consequently, disruption of clock genes results in dyslipidemia, insulin resistance and obesity. Modifying the time of feeding alone can greatly affect body weight. Changes in the circadian clock are associated with temporal alterations in feeding behavior and increased weight gain. Thus, shift work is associated with increased risk for obesity, diabetes and cardio-vascular diseases as a result of unusual eating time and disruption of circadian rhythm.

Keywords

Obesity • Circadian rhythm • Clock genes • Suprachiasmatic nucleus (SCN) • N-methyl-D-aspartate receptors (NMDAR) • Brain and muscle ARNT-like 1 (BMAL1) • Cryptochrome circadian clock 1 (CRY1) • Peroxisome proliferator-activated receptor (PPAR) • Adenosine monophosphate-activated protein kinase (AMPK) • Nicotinamide phosphoryl-transferase • Mammalian target of rapamycin (mTOR) • Resistin • Calorie restriction

1 Introduction

The circadian system is a complex feedback network that is closely linked to metabolic homeostasis and involves interactions between the central nervous system and peripheral tissues (Green et al. 2008). Actually the circadian clock controls food processing by regulating the expression of enzymes and hormones which exhibit circadian oscillation (Froy 2007). The circadian clock is generally reset by environmental time cues. The central clock controls peripheral clocks directly and indirectly by virtue of neural, humoral, and other signals in a coordinated manner (Hirota and Fukada 2004). Actually the mammalian circadian system consists of two major oscillators; primarily the central clock mediates synchrony to daily light-dark cycles, whereas food-entrainable circadian oscillator generates activity rhythms by food and are synchronized with regular daily mealtimes (Smit et al. 2013). Nevertheless, central clock entrains peripheral clocks which can be synchronized by non-photic environmental cues (Pardini and Kaeffer 2006). Food processing is controlled through overlapping transcriptional networks that are tied to the clock and are thus time sensitive (Kohsaka and Bass 2007). Moreover, food anticipatory rhythms are under the control of a food-entrainable clock. The mutations of clock genes cannot impair

expression of food anticipatory components (Feillet et al. 2006). Initially undifferentiated stem cells do not possess a functioning canonical molecular clock. Nevertheless, undifferentiated stem cells express a self-sustained rhythm in glucose uptake that is not coincidental with rhythmic expression of clock genes. Thereby rhythmic expression of glucose transporter genes has been thought to be rhythmic transcriptional regulator of glucose utilization (Paulose et al. 2012). Indeed, a large number of nuclear receptors involved in lipid and glucose metabolism has been found to exhibit circadian expression (Yang et al. 2006). Since pancreatic islets possess self-sustained circadian gene and protein oscillations of the transcription factors CLOCK and brain and muscle ARNT-like protein 1 (BMAL1), the beta-cell clock coordinates insulin secretion according to the sleep-wake cycle (Marcheva et al. 2010). In particular disrupted environmental light-dark cycles abolish the normal oscillation of peripheral clocks and induce internal de-synchrony in mammals (Oishi et al. 2015). Furthermore disruption of the traditional sleep/wake cycle is coupled with a tendency to eat at irregular times (Marcheva et al. 2013). Nutritional status is sensed by nuclear receptors and co-receptors, transcriptional regulatory proteins, and protein kinases, which synchronize metabolic gene expression and epigenetic modification, as

well as energy production and expenditure with behavioral and light-dark cycle (Mazzocchi et al. 2012). Eventually, circadian disruption alters the metabolic hormone levels and increases weight gain by changing the morphology of medial prefrontal neurons (Karatsoreos et al. 2011). However, mammalian central oscillators are regulated differently from peripheral oscillators (Glossop and Hardin 2002). Feeding and meal timing are potent regulators of circadian rhythm in peripheral tissues. Temporal feeding restriction under light-dark or dark-dark conditions can change the phase of circadian gene expression in peripheral cells by leading to an uncoupling of peripheral oscillators from the central pacemaker (Damiola et al. 2000).

Actually circadian rhythms in gene expression synchronize biochemical processes and metabolic fluxes with the external environment, allowing the organism to function effectively in response to physiological challenges (Mazzocchi et al. 2012). Even though the biological clocks of the circadian timing system coordinate cellular and physiological processes and synchronizes these with daily cycles, feeding patterns also regulates circadian clocks in mammals. While acute food restriction promotes arousal and food seeking behavior, chronic food restriction induces physiological adaptations to facilitate the extraction and storage of energy from ingested nutrients and to reduce energy expenditure (Patton and Mistlberger 2013). All transcript levels of the clock genes and adipocytokines such as adiponectin, resistin, and visfatin show circadian rhythmicity. The rhythmic expression of these genes is mildly attenuated in obesity (Ando et al. 2005). Consequently, it may be asserted that dysfunctions of molecular clock genes and these adipokines are involved in the development of obesity (Kaneko et al. 2009).

2 Master Circadian Clock System: The Suprachiasmatic Nucleus and Related Network

In mammals, master circadian clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus as the central circadian pacemaker

(Welsh et al. 2010). Circadian oscillations in expression of mammalian “clock genes” are detected not only in the SCN but also in peripheral tissues (Welsh et al. 2004). The SCN are distinguished from those in other brain regions and peripheral tissues regarding the capacity to generate coordinated rhythms and driven oscillations in other cells (Farnell et al. 2011). Although the individual cells of the SCN are capable of functioning independently from one to another, the SCN leads to coordination of circadian rhythms among its neurons and neuronal subpopulations by forming a circadian network through intercellular coupling (Mohawk and Takahashi 2011). Thereby a large population of circadian oscillator cells of the SCN are entrained to daily light-dark cycles via a direct input from intrinsically photoreceptive retinal ganglion cells (Dibner et al. 2010). Light-evoked information is perceived primarily by melanopsin-expressing retinal ganglion cells and these signals are transmitted via the retinohypothalamic tract (RHT) to the SCN (Gooley et al. 2001).

The efferent SCN projections mainly target neurons in the medial hypothalamus surrounding the SCN. The activity of these pre-autonomic and neuro-endocrine target neurons is controlled by differentially timed waves of vasopressin, gamma-aminobutyric acid (GABA), and glutamate release from SCN terminals (Kalsbeek et al. 2006a). Control of the pre-autonomic and neuro-endocrine target neurons by vasopressin, GABA, and glutamate substantially depends on the light-dark cycle. Furthermore, four different phenotypic subpopulations are defined among SCN neurons which contain the same neurotransmitters (Kalsbeek et al. 2006b). Both sympathetic and parasympathetic pre-autonomic neurons also receive excitatory inputs, either from the biological clock or from non-clock areas, but the timing information is mainly provided by the GABAergic outputs of the biological clock (Kalsbeek et al. 2008). Under reverse light/dark conditions, responses to suprachiasmatic afferents of thalamic paraventricular nucleus neurons are in accordance with their membrane potential-dependent properties. This indicates the existence of glutamatergic and GABAergic neurotransmission from the suprachiasmatic nucleus to its target neurons (Zhang et al. 2006).

In this manner exposure to light synchronizes the circadian clock to the environmental light-dark cycle through the release of glutamate into the SCN. Hence N-methyl-D-aspartate (NMDA)-type glutamate receptors play a critical role in mediating the phase shifting effects of light (Novak and Albers 2002). N-methyl-D-aspartate receptors (NMDARs) located at glutamatergic synapses, which are formed between retinal ganglion afferents and SCN neurons, partly mediate light-induced phase resetting (Clark and Kofuji 2010). NMDA-evoked currents in SCN neurons also peak during the night. Meanwhile the synaptic release of glutamate will always move cells toward the glutamate equilibrium potential (Colwell 2001). Thus activation of NMDARs is a critical step in the transmission of photic information to the SCN (Mintz et al. 1999). NR2B is a major NMDAR subtype within the SCN and is known to be sensitive to modulation (Clark and Kofuji 2010). Indeed, NR2B subunit of NMDAR-mediated responses within SCN neurons contribute to light-induced phase shifts of the mammalian circadian system (Wang et al. 2008). Moreover GABAergic transmission-related synaptic communication has a critical role in the synchronization of circadian rhythms in individual SCN neurons (Shirakawa et al. 2000). In this case GABA regulates the phase of the circadian clock through both pre- and postsynaptic mechanisms (Mintz et al. 2002). Presynaptically, spontaneous postsynaptic GABAergic current frequency varies with the length of the day, whereas postsynaptically, the photoperiod affects GABAergic activity within the SCN by changing the equilibrium of GABA-evoked current. The ratio of GABAergic excitation to inhibition determines the photoperiod-induced phase distribution in the SCN network (Farajnia et al. 2014). Furthermore, terminals of the retino-hypothalamic tract (RHT) terminate not only on peptidergic SCN cells but also on gastrin-releasing peptide (GRP) cells. Expression of chemical messengers released by these retinorecipient cells results from an interaction of GRP with other transmitter substances, such as GABA, glutamate, the neuropeptide vasoactive intestinal polypeptide (VIP), and substance P (Antle et al. 2005; Antle and Silver 2005). The

primary neurotransmitter in the ventral SCN is VIP. VIP is expressed at high levels in the neurons of the SCN and regulates the long-term firing rate of SCN neurons through a VIP receptor 2-mediated increase in the cAMP pathway. VIP-containing neurons process light information received from the RHT and then transfer this information to the dorsal SCN (Antle et al. 2009; Kudo et al. 2013). However, Atkinson et al. have argued that cAMP-mediated signaling is not a principal regulator of cyclic nucleotide-gated channel function in the SCN (Atkinson et al. 2011). Synchronisation of cellular clocks by VIP in the SCN is paracrine and is mediated via the cytosolic pathways upstream of the intracellular transcriptional/translational feedback loops (Hastings et al. 2014). Lacking VIP or its receptor in SCN, damps and desynchronizes cryptochrome circadian clock 1 (CRY1) expression in cells (Maywood et al. 2013).

On the other hand, the amplitude of calcium flux rhythm is involved in both the circadian rhythms of the input and output signals. Therefore, the difference in amplitude could reflect the different roles in circadian oscillation between clock gene and calcium (Enoki et al. 2012). Lowering the extracellular concentration of potassium or blocking Ca^{2+} influx in SCN causes membrane hyperpolarization and reversibly abolishes the rhythmic expression of period circadian clock 1 (PER1). Transmembrane Ca^{2+} flux is necessary for molecular rhythmicity in the SCN. Periodic Ca^{2+} influx due to circadian variations in membrane potential is a critical process for circadian pacemaker function (Lundkvist et al. 2005). Additionally, calcium-activated potassium channels in the SCN is controlled by the intrinsic circadian clock and regulates daily oscillation of spontaneous firing rate (Meredith et al. 2006). In mammals, there is increasing evidence that voltage-dependent calcium channels (VDCCs) may contribute to the clock function of SCN cells. Circadian regulation of calcium channels in SCN cells is compatible with their potential involvement in intercellular coupling and coordination of molecular oscillations between SCN clock cells (Nahm et al. 2005).

The mechanisms other than Ca^{2+} -dependent synaptic transmission can also synchronize neurons in the mammalian hypothalamus (Bouskila and Dudek 1993). In this respect the inhibitory/excitatory ratio of GABAergic activity indicates the phase-synchronization of individual SCN neurons. The protein connexin-36 (Cx36) interconnects between gap junctions of the excitatory projection neurons of the inferior olivary nucleus and inhibitory interneurons of the neocortex, hippocampus, and thalamus (Connors and Long 2004). Moreover, many SCN neurons are self-sustained oscillators that have the intrinsic capacity to generate circadian rhythms in electrical activity. During the night, the SCN neuron populations are electrically inactive and are most responsive to excitatory or depolarizing stimulation (Colwell 2011). Actually in the absence of chemical synaptic transmission, many neurons in the SCN communicate via electrical synapses. However, synchronization is achieved in pairs of electrically coupled neurons only (Long et al. 2005). Surprisingly, Pfeuty et al. showed that blocking electrical synapses may increase the synchrony of neuronal activity (Pfeuty et al. 2003). In this case electrical and inhibitory synapses may cooperate, both promote synchrony or may compete. Eventually combining electrical synapses with inhibition amplifies synchrony, whereas electrical synapses alone desynchronizes the activity of the neurons (Pfeuty et al. 2005). It is well known that the most important stimulus for the SCN is light. In contrast to a long photoperiod, in a short photoperiod electrical activity rhythm of the SCN is robust due to highly synchronized single-cell activity patterns. Photoperiod-induced changes in the expression of clock genes coincide with the photoperiod-induced changes in the electrical rhythm of the SCN (Ramkisoensing and Meijer 2015). Gap junction-mediated coupling improves the connectivity of neuronal networks. Thus electrical synapses containing Cx36 are critical for the generation of synchronous inhibitory activity (Deans et al. 2001).

Photic resetting of the SCN pacemaker involves induction of PER1 and PER2 and the subsequent communication among distinct cell

populations. Activation of the 3′/5′-cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) pathway and PER1 are key steps in mediating downstream events of SCN neurons (Gamble et al. 2007). The transcriptional feedback loops of the SCN are supported by cytoplasmic cAMP signaling, which determines their canonical properties of amplitude, phase and period. Daily activation of cAMP signaling is driven by the transcriptional oscillator, in turn regulates progression of transcriptional rhythms. Thus, output from the current cycle constitutes an input into subsequent cycles (O'Neill et al. 2008).

While the photic information received by classical rod/cone photoreceptors and intrinsically photoreceptive retinal ganglion cells influence phase and period of circadian rhythms, the median raphe serotonergic pathway and the neuropeptide Y (NPY)-containing pathway from the thalamic intergeniculate leaflet (IGL) contributes to circadian rhythm regulation (Morin 2013). Subsequent to light information reaches the SCN through the RHT, axons of retinal ganglion cells release glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) at synaptic contacts with SCN neurons (Hannibal 2002, 2006). Furthermore, PACAP enhances alpha-amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid (AMPA)- and NMDA-evoked calcium transients. Actually PACAP is a potent modulator of glutamatergic signalling within the SCN in the early night (Michel et al. 2006). Upon light stimulation, photoentrainable cells exhibit calcium/CREB protein phosphorylation that leads to temporally gated acute induction of the PER2 gene, followed by the phase-dependent changes in PER2 circadian rhythm. CREB activating stimuli can affect amplitude as well as phase of cellular rhythms (Pulivarthy et al. 2007). The net result of RHT stimulation is an increase in firing rate of SCN neurons. These retinal-evoked excitatory postsynaptic responses in the SCN are mediated by NMDA and AMPA/kainate (KA) ionotropic glutamate receptors (Michel et al. 2002). PACAP acts presynaptically to regulate the release of glutamate onto SCN neurons. Hence PACAP enhances both NMDA-evoked and AMPA-evoked

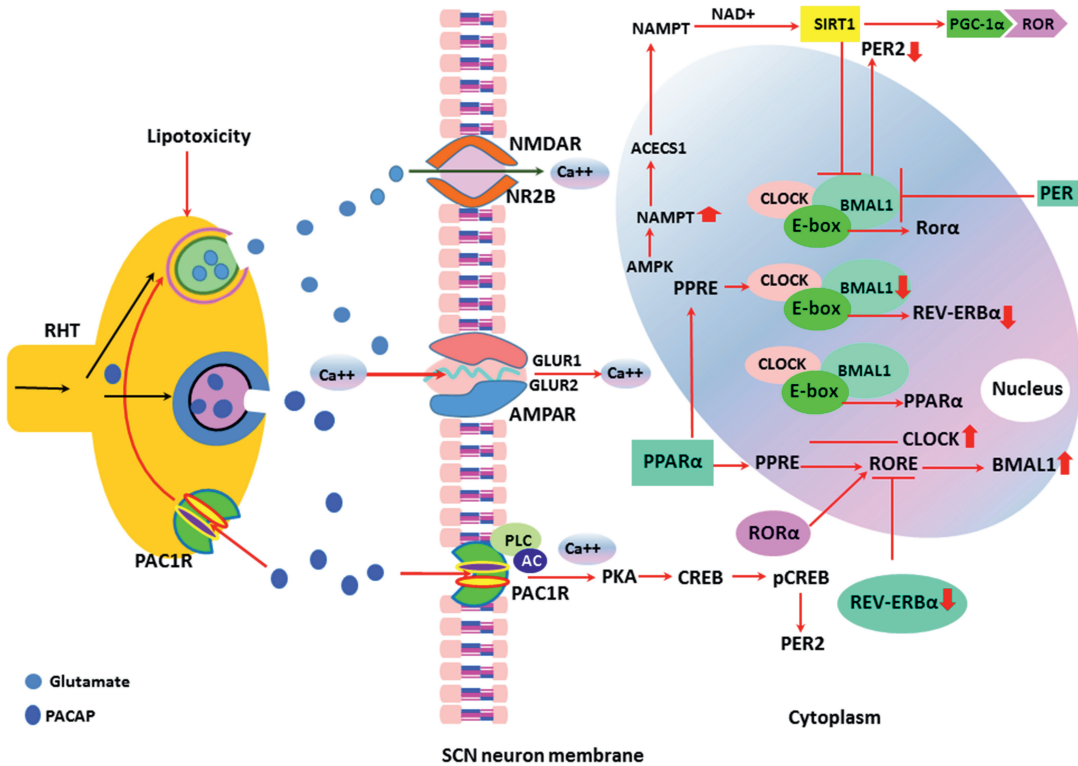


Fig. 2.1 Light-evoked signals are transmitted via the RHT to the SCN. Exposure to light synchronizes the circadian clock to the environmental light-dark cycle through the release of glutamate into the SCN. Activation of NMDARs is a critical step in the transmission of photic information to the SCN. NMDAR-mediated responses within SCN neurons contributes to light-induced phase shifts of the mammalian circadian system. Upon heterodimerization, CLOCK and BMAL1 bind to E-boxes in the promoter region of multiple target genes. In first negative feedback loop upon accumulation of their translation products in the cytosol PER and CRY isoforms heterodimerize and translocate back into the nucleus, subsequently inhibit the transcriptional activity of CLOCK–BMAL1. In second negative feedback loop, CLOCK and BMAL1 induces the transcription of REV-ERB α and ROR α . ROR α and REV-ERB α regulate lipid metabolism and adipogenesis. ROR α stimulates and REV-ERB α inhibits Bmal1 transcription. Accumulation of REV-ERB α protein results in repression of BMAL1 transcription, through binding of REV-ERB α to the RORE within the BMAL1

promoter (RHT Retino-hypothalamic tract; ROR α Retinoic acid-related orphan receptor α ; SCN suprachiasmatic nuclei; PER Period protein; CREB adenosine 3'5' monophosphate (cAMP) response element binding protein; PACAP Pituitary adenylate cyclase-activating polypeptide; NAMPT Nicotinamide phosphoribosyltransferase; CLOCK Circadian locomotor output cycles kaput; NAD⁺ Nicotinamide adenine dinucleotide; PLC Phospholipase C; AC Adenyl cyclase; PKA Protein kinase A; pCREB Phosphorylated CREB; AMPK AMP-Activated protein kinase; PPAR α Peroxisome proliferator-activated receptor α ; PPRE Peroxisome-proliferator response element; PGC-1 α PPAR-gamma coactivator; SIRT1 Silent information regulator 1; BMAL1 Brain and muscle ARNT-like 1; PAC1R PACAP type I receptor; RORE Retinoic acid-related orphan receptor response element; ACECS1 Acetyl-CoA Synthetase 1; NMDAR N-methyl-D-aspartate (NMDA)-type glutamate receptor; AMPAR Amino-methyl propionic acid (AMPA) ionotropic glutamate receptor)

currents in SCN neurons (Michel et al. 2006) (Fig. 2.1).

In fact, homeostatic systems have been adapted to respond to diurnal light/dark cycle (Kitazawa 2013). Peripheral clock mediated circadian expression of muscarinic acetylcholine

receptor proteins, and parasympathetic signaling are essential in conferring circadian time information (Bando et al. 2007). Sympathetic efferents from the SCN can substitute for light cycle information, while other external cues may reach tissues through other efferents or non-neural

pathways (Vujovic et al. 2008). Consequently, the SCN imposes its rhythm onto the body via the secretion of hormones besides the parasympathetic and the sympathetic autonomous nervous systems. A reciprocal connection between the arcuate nucleus (ARC) and the SCN is used to transmit feeding related signals to the SCN (Buijs et al. 2006). More often non-photoc inputs to the clock may be used to reset or strengthen circadian rhythms in humans (Webb et al. 2014). Two features of the mammalian circadian system provide flexibility in circadian programming to utilize casual regularities, which are social stimuli or food availability. In particular latter is sensitive to stimuli associated with food intake which is a circadian oscillator outside of the SCN. Its circadian rhythm arranges with the predictable daily mealtimes (Mistlberger and Antle 2011). On the other hand, food anticipatory activity is driven by a food-entrainable oscillator which does not require a functional molecular clock (Mohawk et al. 2012). Thus, food anticipatory activity is mediated by a self-sustained circadian timing and its principal component is food entrained oscillator (Mistlberger 2009). Nevertheless, the hypothalamus has a crucial role in the regulation of energy balance rather than food intake (Berthoud 2002). Thereby hypothalamic neurons have the capacity to sense and alter their activity in response to fluctuations in local nutrient concentrations (Moran 2010). The dorsomedial hypothalamic nucleus (DMH) and other brain regions express circadian clock gene rhythms which are sensitive to daytime feeding schedules (Moriya et al. 2009). In fact, the dorsomedial hypothalamus is not essential for the expression of the food-entrainable oscillator. However under conditions of food restriction, food anticipatory behavior originates from a neuronal network comprising an interaction between the DMH and SCN (Acosta-Galvan et al. 2011). Furthermore, daily variations in plasma fatty acid concentrations might be detected by the hypothalamus and brain stem. Thus, fatty acids or their metabolites can modulate neuronal activity by brain nutrient-sensing neurons that are involved in the regulation of energy and glucose homeostasis (Migrenne et al. 2011). Another valid signal on timing of the

food-entrained oscillator is insulin. The timing of three-meal schedules indicates close association with the plasma levels of insulin and preceding food availability (Dailey et al. 2012). Fatty acid overload impairs neural control of energy homeostasis and contributes to obesity (Migrenne et al. 2011). In this case hypothalamic “metabolic-sensing” neurons respond to oleic acid by using the fatty acid translocase/receptor (FAT/CD36) (Le Foll et al. 2009). CD36-mediated ventromedial hypothalamic neuronal fatty acid sensing ability is important in the physiological regulation of both energy and glucose homeostasis (Le Foll et al. 2013). Impairment of lipid metabolism and accumulation of specific lipid species in the hypothalamus play a major role in hypothalamic lipotoxicity by integrating peripheral signals with classical neuropeptide-based mechanisms (Martínez de Morentin et al. 2010). In this manner the circadian clock controls acetyl-CoA levels and fatty acid synthesis. Acetylation of acetyl-CoA Synthetase 1 (AceCS1) is cyclic and that its rhythmicity requires a functional circadian clock and the Nicotinamide adenine dinucleotide⁺ (NAD⁺)-dependent deacetylase silent mating type information regulation 2 homolog 1 (SIRT1) (Sahar et al. 2014). Fasting increases hypothalamic SIRT1 expression and decreases forkhead box O1 (FOXO1) acetylation. Thus SIRT1 regulates the central melanocortin system in a FOXO1 dependent manner. Whereas inhibition of the fasting induced SIRT1 activity results in up-regulation of the S6K pathway. By this way hypothalamic SIRT1 regulates the food intake and body weight (Cakir et al. 2009). Actually SIRT1 is required for the circadian transcription of several core clock genes, including BMAL1, RAR-related orphan receptor gamma (ROR gamma), PER2, and CRY1. SIRT1 binds CLOCK-BMAL1 and promotes the deacetylation and degradation of PER2 (Asher et al. 2008). Nicotinamide phosphoribosyltransferase (NAMPT) biosynthesis and NAD⁺ levels display circadian oscillations. Inhibition of NAMPT promotes oscillation of the clock gene PER2 by releasing CLOCK: BMAL1 from suppression by the NAD⁺-dependent deacetylase, SIRT1 (Ramsey et al. 2009) (Fig. 2.1).

3 Food-Entrainable Circadian Rhythm

Ongoing meal or food availability-dependent circadian timing system is called food-entrainable system which is characterized by food-anticipatory processes depending on a circadian clock (Challet et al. 2009). Desynchronization between the central and peripheral clocks by altered timing of food intake and diet composition can lead to uncoupling of peripheral clocks from the central pacemaker and to the development of metabolic disorders (Oosterman et al. 2015). Actually meal time is a potent synchronizer for peripheral oscillators with no clear synchronizing influence on the suprachiasmatic clock. Therefore, food anticipatory rhythm is under the control of a food-entrainable clock (Feillet et al. 2006). For light entrained rhythms, constant conditions mean constant light or constant darkness. Whereas for food anticipatory activity constant condition is food deprivation (Carneiro and Araujo 2012). Hence, the changes in the metabolic activity can lead to an uncoupling of peripheral oscillators from the central pacemaker (Damiola et al. 2000). Food-entrainable oscillators locate elsewhere that generate rhythms of food-anticipatory activity and synchronizes to daily feeding schedules (Landry et al. 2006). It is known that the DMH is critical for the expression of circadian rhythms and in any way it receives input from systems that monitor food availability. However, DMH is not the site of oscillators or entrainment pathways necessary for food-anticipatory activity, but may participate in this circadian function (Gooley et al. 2006). The rhythmicity in the SCN remained phase-locked to the light-dark cycle, whereas feeding cycles can entrain the peripheral oscillator independent of the SCN and the light cycle (Stokkan et al. 2001). Mammals demonstrate feeding rhythms in behavior. Periodic availability of food and periodic feeding dictate adaptive behavioral and appropriate metabolic responses. Recently defined a nutrient anticipation metabolic oscillator (NAMO) is thought to arrange metabolic processes in visceral organs. NAMO is similar with the food anticipatory oscillator in the

central nervous system (Khapre et al. 2014). Actually the mammalian target of rapamycin (mTOR) signaling pathway controls many processes that generate or use large amounts of energy and nutrients (Laplane and Sabatini 2012). It was shown that mTOR/the eukaryotic translational initiation factor 4E binding protein 1 (4E-BP1)-mediated translational control regulates entrainment and synchrony of the master clock (Cao et al. 2013). mTORC1 couples nutrient abundance to cell growth and proliferation by sensing and integrating a variety of inputs arising from nutritional status (Kim et al. 2013). These evidences suggest that NAMO may signal to the circadian clock through mTORC1 (Khapre et al. 2014).

Functional clock genes of gastrointestinal tract are molecular core components of the circadian clock. Synchronization of gastrointestinal clock genes during the daytime feeding in nocturnal animals is independent to the central clock and is not mediated through the vagal nerve (Hoogerwerf et al. 2007). Food-entrained oscillator consists of an unidentified network between the central and peripheral structures. However, clock genes and their metabolic oscillations are not essential for the persistence of food-anticipatory activity (Escobar et al. 2009). In mammals, peripheral and brain oscillators are synchronized indirectly and the SCN output pathways serve as input pathways for peripheral tissues (Dibner et al. 2010).

4 Food-Entrained Oscillator and Clock Genes

Light- and food-entrainable circadian rhythms share many properties, including limits of entrainment in the circadian range, free running under constant conditions and transients following phase shifts, but not neural basis (Mistlberger 1994). Functional CLOCK-based oscillators are not necessary for food-entrained circadian locomotor rhythms. However, both food and light temporally control locomotor behavior and that each circadian clock system can operate independently of the other. Although under normal ad

libitum conditions, these two systems are in phase with each other, but daytime food restriction disturbs the synchrony (Pitts et al. 2003).

The mammalian circadian clock is based on a transcription-translation feedback loop in which CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 proteins act as transcriptional activators of Cryptochrome (CRY) and Period (PER) genes. These genes encode proteins that repress CLOCK-BMAL1 with a 24-h periodicity. In the presence of CRY, nuclear entry of PER inhibits transcription by displacing CLOCK-BMAL1 from the promoter (Ye et al. 2014). CLOCK dimerizes with BMAL1 to activate transcription. BMAL1 can also dimerize with other CLOCK homologs, such as neuronal PAS (PER, ARNT, SIM) domain protein 2 (NPAS2), to activate transcription and sustain rhythmicity (Asher and Schibler 2006; Debruyne et al. 2006). Eventually the regulatory targets of CLOCK:BMAL1, PER1, PER2, and PER3 genes together with the CRY1 and CRY2 genes function as negative regulators by blocking CLOCK:BMAL1-mediated transcriptional activation (Froy et al. 2002). On the other hand, many clock gene products function as transcription factors, which possess PAS and basic helix-loop-helix (bHLH) domains involve in protein-protein and protein-DNA interactions, respectively. These factors ultimately activate or repress their own expression and, thus, constitute self-sustained transcriptional feedback loops (Froy and Miskin 2010).

In homozygous CLOCK/CLOCK mice, the circadian rhythms are severely disrupted in constant darkness, but the locomotor behavior in light-dark cycle is less affected. This indicates that CLOCK protein is a necessary component of the light-entrainable oscillator (Vitaterna et al. 1994), whereas food-anticipatory activity is sustained in homozygous CLOCK/CLOCK mice under both entrained and constant conditions. This would suggest that the food-entrainable oscillator is not a CLOCK-based oscillator and therefore utilizes a different circadian molecular mechanism than that of the SCN (Pitts et al. 2003). The transcriptional regulation of CRY1 and CRY2 is under CLOCK control in both the SCN and in peripheral clocks. Direct inhibitory

effect of the CRY1 and CRY2 proteins on the CLOCK-BMAL1-E box complex inhibits transcription by directly interacting with the PER proteins and translocating them into the nucleus for subsequent transcriptional effects (Kume et al. 1999). When the levels of cytosolic PER and CRY proteins rise, they associate, translocate to the nucleus, and repress their own gene transcription through direct interaction with CLOCK/BMAL1. The molecular clock consists of the three transcriptional regulatory feedback loops. The CLOCK incorporates to CLOCK, BMAL1 and ROR as transcriptional activators, PER, CRY, and REV-ERB as transcriptional repressors, and casein kinase 1 as a posttranslational regulator (Bechtold 2008). In this case, casein kinase I epsilon regulates the circadian clock by periodic phosphorylation of the proteins PER1 and PER2, controlling their stability and localization (Virshup et al. 2007). Nervous system-specific deletion of BMAL1 creates a marked deficit in entrainment of locomotor activity by periodic feeding. This is accompanied by reduced food intake and subsequent loss of body weight. That means SCN-independent food-entrained oscillator in the nervous system requires BMAL1 and plays a critical role in the adaptation of circadian locomotor activity and food intake to periodic feeding (Mieda and Sakurai 2011). While the SCN directly entrains feeding behavior to the light-dark cycle, daytime feeding shifts the timing of PER expression in the liver (Damiola et al. 2000; Hara et al. 2001). Day time restricted feeding forces the food-entrainable oscillator and SCN, which are normally in synchrony, to be out of phase with each other (Pitts et al. 2003).

5 Metabolic Feedback and Clock Genes

CLOCK genes are expressed in both subcutaneous and visceral fat tissues. Visceral obesity-associated cardiovascular risk is an indicator of the potential role of these clock genes in the metabolic disturbances (Gómez-Abellán et al. 2008). Metabolic dysfunction is associated with circadian disturbances at both central and peripheral levels

and, eventual disruption of circadian clock functioning can lead to obesity (Delezie and Challet 2011). Circadian oscillator genes (*Npas2*, *BMAL1*, *PER1-3*, and *CRY1-2*) and clock-controlled downstream genes (*REV-ERB alpha*, *REV-ERB beta*, *Dbp*, *E4bp4*, *Stra13*, and *Id2*) both are expressed in adipose tissues. Furthermore, temporally restricted feeding causes a coordinated phase-shift in circadian expression of these genes (Zvonic et al. 2006). In particular *REV-ERB alpha* acts as a major circadian regulator of *BMAL1* expression in the SCN and in the liver. *REV-ERB alpha* also participates in the regulation of circadian *CLOCK* expression (Preitner et al. 2002). The expression levels of *BMAL1* and *REV-ERB alpha* are attenuated in high fat diet-induced obesity as well as in genetically obese animals. While *CLOCK* expression levels are increased with high fat diet-induced obesity, *CRY1* expression levels are decreased. In addition, peroxisome proliferator-activated receptor (PPAR) α increases the transcriptional level of *BMAL1* (Kaneko et al. 2009).

Thus the diurnal effect dominates the transcriptome of the human adipose tissues, with more than 25% of the transcribed genes being diurnally regulated. The genes linked to *PER1*-led oscillations are defined as a novel point of obesity (Loboda et al. 2009). All transcript levels of the *CLOCK* genes and adipocytokines show 24 h rhythms. However, the rhythmic expression of these genes is attenuated in obesity (Ando et al. 2005) (Fig. 2.1).

Loss of *BMAL1* expression leads to a significant decrease in adipogenesis and gene expression of several key adipogenic/lipogenic factors. Contrarily over-expression of *BMAL1* in adipocytes increases lipid synthesis (Shimba et al. 2005). Several master lipid metabolism regulators and enzymes involved in triglyceride metabolism sustain their circadian expression in clock-disrupted animals (Adamovich et al. 2014). Lipid biosynthesis is regulated by sterol regulatory element-binding proteins (SREBP). The orphan receptor *REV-ERB alpha* participates in the circadian modulation of SREBP activity and expression, as well as SREBP targets, fatty acid synthase and acetyl-CoA carboxylase α ,

independently of feeding regimen. *REV-ERB alpha* also controls the timing of cyclic accumulation of SREBP in the nucleus (Le Martelot et al. 2009). Disruption of clock genes results in dyslipidemia, insulin resistance and obesity. The nuclear receptor *REV-ERB alpha* plays an important role in keeping proper timing of the clock by cross-talking with several other nuclear receptors involved in energy homeostasis (Duez and Staels 2008). Elevated levels of palmitate, a predominant saturated fatty acid in diet and fatty acid biosynthesis, alter cellular function. It is likely that palmitate-induced signal transduction cascades lead to changes in circadian transcript expression such as an increase in *BMAL1* and *CLOCK* and a decrease in *PER2* and *REV-ERB alpha* through AMPK-mediated regulation (Lee and Kim 2013).

REV-ERB alpha is a target gene of PPAR- γ in adipose tissue. Expression of *REV-ERB alpha* promotes the effect of PPAR- γ on adipocyte differentiation and insulin sensitivity (Fontaine et al. 2003). PPAR- γ coactivator-1 α (PGC-1 α) is necessary for appropriate adaptation to the metabolic and physiologic stressors and plays a central role in the maintenance of glucose, lipid and energy homeostasis (Leone et al. 2005). Additionally, PGC-1 α stimulates the expression of *CLOCK* genes, notably *BMAL1* and *REV-ERB alpha* (*Nr1d1*), through co-activation of the ROR family of orphan nuclear receptors. Furthermore, PGC-1 α deficiency causes both metabolic and circadian abnormalities (Liu et al. 2007).

In addition to PGC-1 α , the circadian expression of the PPAR genes are regulated by peripheral oscillators in a *CLOCK*-dependent manner. *CLOCK* and *BMAL1* play an important role in lipid homeostasis by regulating the transcription of a key protein, PPAR α (Oishi et al. 2005). The promoter activities of PPAR target genes acyl-CoA oxidase (AOX), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase and cellular retinol binding protein II (CRBP II) are increased by the expression of *CLOCK/BMAL1* via the peroxisome PPAR response element (PPRE) (Inoue et al. 2005). Increased body mass, higher levels of plasmatic and hepatic triglycerides, higher levels of pro-

inflammatory and lower levels of anti-inflammatory adipokines, impairment of glucose metabolism, abnormal fat pad mass distribution, higher number of larger adipocytes, hepatic steatosis, higher expression of lipogenic proteins in high-fat diet are associated with the decreased expression of PPAR alpha and carnitine palmitoyltransferase I (CPT-1) in liver, and diminished expression of PPAR gamma and adiponectin in white adipose tissue (Magliano et al. 2013). Increase in the BMAL1 transcriptional level of obese subjects and insulin resistance by PPAR alpha indicates the involvement of PPAR alpha in the attenuation of circadian rhythms in the nucleus of the solitary tract in obesity (Kaneko et al. 2009).

When Clock-mutant mice fed with a high-fat diet, CLOCK mutation causes less triglyceride accumulation in the liver through the suppression of *Acs14* and *Fabp1* gene expression compared to wild-type (Kudo et al. 2007). Thus high-fat diet-induced obesity alters the circadian-clock system. Obesity with or without metabolic syndrome are highly correlated with the expressions of circadian-clock genes including *PER1-3*, *CRY1-2*, *BMAL1*, *Dbp*, *E4BP4*, *CK1*, *PEPCK*, *PDK4* and *NHE3* (Hsieh et al. 2010).

The circadian clock synchronizes mitochondrial ATP production to meet daily alterations in cellular energy demands. AMP-activated protein kinase (AMPK) is activated by liver kinase B1 when the AMP/ATP ratio increases. This information is translated into SIRT1-dependent deacetylation of the transcriptional regulators PGC-1alpha and FOXO1 (Cantó et al. 2010). AMPK activation is linked to regulation of the circadian clock, which couples daily light and dark cycles to the control of energy demand in a wide variety of tissues and the hypothalamus (Bass and Takahashi 2010). The activities of AMPK display circadian rhythms in peripheral tissues as a crucial cellular energy sensor. AMPK transmits energy-dependent signals to the mammalian clock by driving the phosphorylation and destabilization of CRY and PER proteins. In addition, AMPK subunit composition, subcellular localization, and substrate phosphorylation are dependent on clock time (Jordan and

Lamia 2013). The loss of AMPK signaling in vivo stabilizes CRYs and disrupts circadian rhythms. AMPK-mediated phosphorylation of CRY and Casein kinases I regulates the negative feedback control of circadian clock by proteolytic degradation of PER2. AMPK can also modulate the circadian rhythms through another metabolic sensor the NAD⁺-dependent type III deacetylase SIRT1 (Lee and Kim 2013). SIRT1 controls DNA repair, apoptosis, circadian clocks, inflammatory pathways, insulin secretion and mitochondrial biogenesis (Chalkiadaki and Guarente 2012), whereas AMPK controls the expression of genes involved in energy metabolism in muscle by acting in coordination with SIRT1. AMPK enhances SIRT1 activity by increasing cellular NAD⁺ levels, resulting in the deacetylation and modulation of the activity of downstream SIRT1 targets that include the PGC-1alpha and the FOXO1 and FOXO3a transcription factors (Cantó et al. 2009). AMPK is upstream of extracellular-signal-regulated kinase (ERK) and mTOR complex 1 (mTORC1) but downstream of adenylyl cyclase in regulating the circadian rhythm of photoreceptor L-type voltage-gated calcium channels (L-VGCCs) (Huang et al. 2015).

AMPK also increases the NAMPT expression and intracellular NAD⁺ levels, which induces deacetylation of SIRT1 (Cantó et al. 2009). The circadian regulation of the NAMPT-SIRT1-PGC-1alpha pathway is achieved by AMPK. Conversely the circadian rhythm is disrupted in AMPK-deficient animals (Um et al. 2011). Hypothalamic metabolic sensors play an important role in the control of feeding and energy homeostasis. In this regard PAS kinase (PASK), AMPK and mTOR are important nutrient sensors of glucose metabolism and cellular energy requirement. Hypothalamic AMPK and S6K1 are highly activated under fasted/re-fed conditions. PASK function has critical importance for preserving the nutrient effect on AMPK and mTOR/S6K1 pathways (Hurtado-Carneiro et al. 2014). Alteration of hypothalamic AMPK activity is sufficient to change food intake and body weight. Acetyl-coenzyme A carboxylase/malonyl-coenzyme A/carnitine palmitoyltransferase-1/

fatty acid oxidation and mTOR signaling are putative downstream pathways for food intake regulation in response to hypothalamic AMPK (Minokoshi et al. 2008). On the other hand, defects in the genes encoding leptin or its receptor lead to hyperphagia and severe obesity. Diet-induced obesity alters alpha2-AMPK and signal transducer and activator of transcription 3 (STAT3) signaling in hypothalamus and subsequently impairs the effects of leptin on these signaling pathways. Defective responses of AMPK to leptin may contribute to resistance to leptin action on food intake and energy expenditure (Martin et al. 2006a). Eventually AMPK is a principal mediator of the effects of leptin on fatty-acid metabolism (Minokoshi et al. 2002). Furthermore, a high-fat diet modulates carbohydrate metabolism by amplifying circadian variation in glucose tolerance and insulin sensitivity (Rudic et al. 2004). In fact, adipose tissue is most vulnerable to clock gene disruption secondary to obesity, which is associated with marked disruption of downstream clock-regulated genes in cellular metabolic homeostasis including AMPK and of AMPK protein. Despite the diversity between rhythm loss and impairment of tissue insulin signaling, adipose tissue is most sensitive to rhythm loss. This discrepancy suggested that insulin resistance and clock gene dysfunction in obesity may arise by different mechanisms (Prasai et al. 2013).

The DNA-binding activity of the Clock:BMAL1 and NPAS2:BMAL1 heterodimers is regulated by the redox state of NAD cofactors. The reduced forms of the redox cofactors, NAD(H) and NADP(H), strongly enhance DNA binding of the Clock:BMAL1 and NPAS2:BMAL1 heterodimers, whereas the oxidized forms inhibit (Rutter et al. 2001).

Expression of NAMPT protein and NAMPT-RNA oscillations are circadian in nature with a reduction in NAMPT protein levels prior to the onset of the dark period. The rhythmic oscillation in RNA and protein levels of NAMPT leads to a circadian oscillation of NAD⁺ levels (Ramsey et al. 2009). NAD⁺ dependent deacetylase SIRT1 is a regulator responsible for various biological effects, depending on its localization in organism. Hence NAD⁺ dependent histone

deacetylases are very important for the mammalian metabolic clock (Rehan et al. 2014). SIRT1 and NAMPT constitute essential parts of the mammalian circadian clock feedback cycle. NAMPT is under the transcriptional regulation of a CLOCK-BMAL-SIRT1 complex, which increases the conversion of NAM to NAD⁺. This in turn activates SIRT1, which reactivates NAMPT expression (Nakahata et al. 2009; Ramsey et al. 2009). NAD displays circadian oscillation and modulates CLOCK:BMAL1-mediated circadian transcriptional regulation through SIRT1. Actually this cycle exhibits a new function of NAD as a “metabolic oscillator” (Imai 2010). SIRT1 levels are responsive to environmental stimuli such as daylight, cell stress, and calorie restriction. SIRT1 binds to and deacetylates a number of important transcription factors, such as PPAR-gamma, PPAR-alpha, PGC-1alpha, and FOXO1. These transcription factors manage metabolic responses such as insulin secretion, gluconeogenesis, and fatty acid oxidation (Haigis and Sinclair 2010). SIRT1 functions as a molecular regulator of CLOCK-mediated histone acetyltransferases (HAT). Thereby SIRT1 transduces signals originated by cellular metabolites to the circadian machinery. Furthermore, SIRT1 also modulates the circadian machinery by controlling the acetylation levels of BMAL1. The histone deacetylases (HDAC) activity of SIRT1 is regulated in a circadian manner (Nakahata et al. 2008). Thus, the cross talk between the biological clock and the NAMPT/NAD⁺/SIRT1 pathway provides a connection between the circadian system and nutrient-sensing pathways (Marcheva et al. 2013). CLOCK/BMAL1 binds to the SIRT1 promoter to enhance its expression and regulates hepatic insulin sensitivity by SIRT1. In addition, constant darkness-induced circadian misalignment in mice decreases hepatic BMAL1 and SIRT1 levels and induces insulin resistance. Actually CLOCK and BMAL1, two core circadian transcription factors, are correlated with hepatic insulin sensitivity (Zhou et al. 2014).

Poly(ADP-ribose) polymerase 1 (PARP-1) modulates the activities of several transcriptional

regulatory proteins either by direct protein-protein interaction or by NAD⁺-dependent poly ADP-ribosylation (Hassa et al. 2006). PARP-1 poly ADP-ribosylation activity is circadian and regulated by feeding. PARP-1 binds to CLOCK-BMAL1 in a daytime-dependent manner and poly ADP-ribosylates CLOCK in a circadian manner. Poly ADP-ribosylation of CLOCK reduces the DNA-binding activity of CLOCK-BMAL1 and its interaction with the PER and CRY proteins (Asher et al. 2010).

The ratio between oxidized and reduced forms of NAD and NADP cofactors or increased levels of oxidized cofactors, NAD⁺ or NADP⁺ decrease the ability of CLOCK/BMAL1 and NPAS2 (neuronal PAS domain-containing protein)/BMAL1 to bind to DNA, suggesting that cellular redox changes may be sufficient to entrain clocks. NPAS2 promote transcription of PER (Rutter et al. 2001). Therefore, the nuclear redox state is similarly fundamental for the activation of several redox-regulated transcription factors including CLOCK, NPAS2 (Rutter et al. 2001) and REV-ERB beta (Gupta and Ragsdale 2011). Sensing and responding to oxidative cycles in cellular environments could have driven the evolution of circadian rhythms, and maintained the intrinsic link between clocks and metabolism (Edgar et al. 2012).

CLOCK-mediated acetylation together with the SIRT1 deacetylation cycles are central mechanisms in the CLOCK-directed rhythmic expression of clock-responsive genes (Bechtold 2008). As mentioned above, alterations in NAD levels could change activities of important enzymes in metabolic pathways. Thereby NAD would also affect NAD-dependent deacetylase SIRT1 or PARP (Revollo et al. 2007). While the reduced forms, NADH and NADPH increase binding of the clock heterodimers, the oxidized forms, NAD⁺ and NADP⁺ decrease their binding. Although NAD⁺ is involved in cellular redox reactions within the mitochondria, it also serves as a substrate for the nutrient-responsive SIRT. In this case the activity of SIRT1 is directly coupled to the redox status, as well as it negatively regulates the activity of CLOCK/BMAL1 (Ramsey and Bass 2011).

Genotype and haplotype analysis in 537 individuals associated with metabolic risk of insulin resistance revealed that genetic variation in the CLOCK genes play a significant role in the development of obesity (Scott et al. 2008). Indeed, CLOCK polymorphism and related haplotypes increase the risk of overweight or obesity by 1.8-fold via altering circadian rhythmicity (Sookoian et al. 2008). Actually the photic regulation of the circadian system can be altered by eating a diet enriched in saturated fatty acids and leads to abdominal adiposity. In this case photic induction of two regulatory proteins, c-FOS and P-ERK, in the suprachiasmatic CLOCK are also markedly reduced during the high fat feeding (Mendoza et al. 2008). Although genetic variation at the CLOCK gene is associated with the metabolic syndrome features, no association is found between CLOCK gene polymorphism and fasting state lipid profiles. However, CLOCK polymorphisms interact with fatty acids to modulate metabolic syndrome traits. Therefore, genetic effects on insulin resistance and obesity phenotypes could be modulated by the dietary intake of the monounsaturated fatty acid (MUFA) or saturated fatty acids (Garaulet et al. 2009). In a total of 1100 individual participants who have CLOCK single-nucleotide polymorphisms, the energy intake with total fat, protein and carbohydrate consumptions are found to be significantly higher in minor allele carriers than in non-carriers. Subjects with the minor allele are 1.33 times more likely to have high energy intake than non-carriers (Garaulet et al. 2010b). Carriers of the minor allele C are also less successful in losing weight due to shorter sleep duration, higher plasma ghrelin concentrations. Moreover, they have shown less compliance with a Mediterranean diet pattern (Garaulet et al. 2011). On the other hand, PER2 polymorphisms have been linked with abdominal obesity, and unhealthy feeding behavior phenotypes (Garaulet et al. 2010a). Despite the CLOCK and PER2 gene polymorphism, NAMPT1 gene polymorphism is a rare single-nucleotide type, which is associated with protection from obesity (Blakemore et al. 2009).

Timing of food intake is associated with genetic variance in CLOCK. In 420 overweight/

obese patients undergoing a 20-week weight-loss diet, those who ate their main meal late lost significantly less weight than early eaters. This difference in weight loss success could not be explained by differences in caloric intake only (Garaulet et al. 2013a). Actually unusual feeding time can produce a disruption of the circadian system which might produce metabolic consequences for the development of obesity and for unsuccessful weight loss in humans (Garaulet and Gómez-Abellán 2014). Indeed, unusual feeding time induces internal desynchronisation through decoupling of peripheral oscillators from the central clock (Lowrey and Takahashi 2004). Association between food timing and obesity has been also verified in shift workers. The majority of evidences indicates that shift workers are more prone to obesity than day workers (Lowden et al. 2010). Additionally, there are considerable epidemiological evidences indicating that shift work is associated with increased risk for obesity, diabetes and cardio-vascular diseases as a result of unusual eating time and disruption of circadian rhythm (Antunes et al. 2010). In a retrospective cohort study that was conducted involving 21,469 healthy individuals who slept less than 6 h at night were more likely to experience weight gain and to become obese (Kobayashi et al. 2012). The pooled odds ratio that linked short-duration sleep to obesity is 1.89 in children and 1.55 in adults in a total of 634,511 participants (Cappuccio et al. 2008). Furthermore, the prevalence of short sleep duration associated-metabolic syndrome is 8.7% (Kobayashi et al. 2011). Virtually sleep deprivation during only a single night induces insulin resistance via multiple metabolic pathways in healthy subjects (Donga et al. 2010). Sleep restriction with less than 6-h at night for 7 days is associated with serious insulin resistance without significant alterations in the insulin secretory response (Buxton et al. 2010). Shorter REM sleep during the second part of the night is also associated with dysregulation of the HPA-axis and reduced insulin sensitivity (Gonissen et al. 2013). Briefly, a sleep duration less than 6 h or more than 9 h is associated with increased prevalence of diabetes mellitus and impaired

glucose tolerance (Gottlieb et al. 2005). Additionally, sleep deprivation may alter the ability of leptin and ghrelin to accurately signal caloric need and produce a misperception for accurate energy availability (Knutson and Van Cauter 2008). Actually feeding requires the maintenance of wakefulness and the orexin system, which has a key role in the interaction between feeding and arousal. Deficiencies in the orexin system are associated with sleep disorders (Spiegel et al. 2009).

Individuals who have an excessive night time light exposure at home are associated with increased body mass, waist circumference and triglyceride levels, and poor cholesterol balance (Obayashi et al. 2013). The effects of dim light at night and high-fat diet appear additive. Thus, animals exposed to dim light at night that are fed high-fat diet display the greatest increase in body mass and exaggerated peripheral inflammation (Fonken et al. 2013b). Furthermore, continuous exposure to light induces the complete loss of circadian rhythm in energy metabolism and insulin sensitivity decreases due to reduced amplitude of the central clock (Coomans et al. 2013). Constant light desynchronizes clock neurons but does not compromise their ability to regenerate circadian rhythms (Ohta et al. 2005). Indeed, constant light has both acute and long-term disruptive effects on developing biological clocks of infants. Thereby cyclic light conditions have been recommended in neonatal intensive care units (Ohta et al. 2006).

Otherwise, peripheral circadian de-synchrony is an early indicator of metabolic disruption in shift workers due to sleep deprivation-mediated disruption of circadian rhythms. Imposing a strict dark phase feeding rhythm can be employed to reset peripheral clocks and alleviate metabolic perturbations. Strengthening the peripheral circadian rhythm by imposing metabolic rhythms via limiting food intake during the night may counteract comorbidities seen in human shift workers (Barclay et al. 2012). Nevertheless, circadian rhythms in clock expression persist during light at night; however, the amplitude of PER1 and PER2 rhythms is attenuated in the hypothalamus. Changes in the circadian clock are associated with temporal alterations in feeding behavior and

increased weight gain (Fonken et al. 2013a). Thus reduced total daily energy expenditure in humans during nightshift schedules and reduced energy expenditure in response to dinner represent contributing mechanisms in the risk of weight gain. During the biological night, when the circadian clock is promoting sleep, working and eating may increase the risk of weight gain and obesity (McHill et al. 2014). In this manner the increase in exposure to light at night parallels the global increase in the prevalence of obesity and metabolic disorders (Fonken and Nelson 2014). Caloric intake during typical sleep time leads to greater weight gain than the same caloric intake during typical wake time (Arble et al. 2009). Eventually disruption of the timing of food intake and other metabolic signals at dim light at night leads to excess weight gain (Fonken et al. 2010).

Additionally, appetite-regulating hormones are altered during circadian misalignment. Thus, insufficient sleep reduces leptin and increases ghrelin (Bayon et al. 2014). In fact, the term of “circadian misalignment” describes either inappropriately timed sleep-wake or misalignment of sleep/wake with feeding rhythms, or misaligned central and peripheral rhythms (Baron and Reid 2014). In any case, circadian misalignment during nightshift schedules disturbs the metabolic physiology and contributes to the adverse metabolic health outcomes by reducing total daily energy expenditure (McHill et al. 2014). Later relative timing of meals, particularly eating close to sleep, could lead to weight gain due to a greater number of eating occasions and higher total daily caloric intake (Reid et al. 2014). Actually three major hormones, leptin, ghrelin and NPY, have been shown to exhibit circadian oscillation in metabolism. The progressive derangements in temporal communication imposed by environmental shifts in energy intake may force a positive energy balance culminating in excessive weight gain and obesity (Kalra et al. 2003). Thus, disruption in the rhythmic communication in the leptin-ghrelin-NPY feedback loop results in the loss of hypothalamic control, leading to abnormal weight gain and obesity (Kalra et al. 2005). The central circadian clock regulates leptin

expression. Even so feeding time cannot be affected by the rhythmicity of leptin release, ablation of the SCN and the regular feeding has been shown to eliminate leptin circadian rhythmicity (Kalsbeek et al. 2001). Leptin is systematically lower when the behavioral cycle is misaligned with the circadian cycle. Leptin suppression is maximal when the behavioral cycle is misaligned by 12 h with the circadian cycle (Scheer et al. 2009).

The expression of receptors for metabolic hormones, such as leptin and ghrelin, allows the ARC to sense the information from the periphery and signal it to the central nervous system. Anatomical and functional pathway for peripheral hormonal feedback to the hypothalamus may serve to modulate the activity of the SCN (Yi et al. 2006). In particular, the ghrelin receptors play an important role in modulating the activity of the circadian system by exerting a direct action on the SCN both under normal conditions and under restricted feeding schedules (Lamont et al. 2014; Yannielli et al. 2007). The SCN also contains leptin receptors. Thus, leptin can directly modulate the electrical properties of SCN neurons and, in this way, may contribute to the mechanism by which metabolic processes influence the circadian clock (Inyushkin et al. 2009). The circadian system importantly contributes to the reduced glucose tolerance observed in the evening compared with the morning. Circadian misalignment reduces glucose tolerance (Morris et al. 2015). Daily blood glucose homeostasis is also controlled by the hypothalamic clock in the SCN as well as by peripheral clocks. Thereby both CLOCK mutant and BMAL1 deficient animals exhibit delayed recovery from insulin-induced hypoglycemia, impaired glucose tolerance and blunted insulin sensitivity (Kalsbeek et al. 2014). Actually BMAL1 regulates mitochondrial energy metabolism to maintain normal glucose-stimulated insulin secretion. Its circadian disruption leads to diabetes due to a loss of glucose-stimulated insulin secretion (Lee et al. 2011). Loss of glucose-stimulated insulin secretion is frequently depended on the accumulation of reactive oxygen species (ROS) as well as a consequence of mitochondrial uncoupling.

Hence it is fully rescued by scavenging of the ROS or by inhibition of uncoupling protein 2 (Lee et al. 2013).

An endogenous ligand for the G protein-coupled receptors FM-3/GPR66 and FM-4/TGR-1, neuromedin S (NMS) is expressed in the SCN of the hypothalamus. NMS increases proopiomelanocortin (POMC) mRNA expression in the ARC and corticotropin-releasing hormone mRNA in the paraventricular nucleus, and induces c-Fos expression in the POMC neurons of the ARC. Consequently, NMS is implicated in the regulation of circadian rhythm and feeding behavior (Miyazato et al. 2008; Mori et al. 2005). However, Neuromedin U (NMU) isoform has potent actions on appetite and energy expenditure. NMS or NMU dose-dependently decreases food intake, increases metabolic rate, and leads to significant weight loss in animals. The two NMU-binding receptors (NMU-R1 and NMU-R2) are also expressed in the SCN, but their phase angles are different. Furthermore, the expression of NMS mRNA fluctuated within the SCN under light/dark cycling, but not under conditions of constant darkness. NMU mRNA expression shows a circadian rhythm in the SCN shell of rats maintained under constant darkness (Nakahara et al. 2004). Amino acid variants in NMU associate with overweight and obesity, suggesting that NMU is involved in energy regulation in humans (Hainerová et al. 2006). Although NMU mRNA is significantly down-regulated in fasting, contrarily NMU overloading markedly suppresses food intake (Howard et al. 2000).

Another chronobiotic hormone which acts via high affinity G protein-coupled membrane receptors is melatonin. The abilities of this hormone for re-synchronization of sleep and circadian rhythm disturbances have been demonstrated in clinical trials (Barrenetxe et al. 2004). The nocturnal synthesis and release of melatonin by the pineal gland are tightly controlled by the SCN clock and inhibited by light exposure. Thus melatonin signals are used for the synchronization of peripheral oscillators. Moreover, melatonin receptors are also expressed by the SCN, hence endogenous melatonin is able to feedback onto the master clock (Pevet and Challet 2011).

Melatonin is necessary for the proper synthesis, secretion, and action of insulin. Therefore, the activity/feeding phase of the day is associated with high insulin sensitivity, and the rest/fasting is synchronized to the insulin-resistant metabolic phase of the day. The reduction in plasma melatonin levels during shift-work at night induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization leading to obesity (Cipolla-Neto et al. 2014). Ghrelin and serotonin are biochemically and functionally linked to the melatonin, which is an internal transducer of photic environmental changes (Kirsch and Zieba 2012). The neuroendocrine circadian patterns in the night eating syndrome (NES) have been distinguished by an attenuated nocturnal rise in the plasma concentrations of melatonin and leptin, despite a greater increase in the concentrations of cortisol (Birkvedt et al. 2012). Patients with NES characteristically demonstrate a significant change in the timing and amplitude of various behavioral and physiological circadian markers such as reduced amplitudes in the circadian rhythms of food intake, cortisol, ghrelin, and insulin, but increased thyroid-stimulating hormone (TSH) amplitude. In this respect a delayed circadian pattern of food intake with a normal sleep-wake cycle occurs in NES. Thus NES may result from dissociations between central timing mechanisms and putative oscillators elsewhere in the central nervous system or periphery (Goel et al. 2009).

6 Effect of Feeding Regimens on Circadian Rhythms

6.1 Restricted Feeding

Daytime restricted feeding involves food intake for 2–4 h in the middle of the light period. After few days, anticipatory activity may occur (Mistlberger 2009). In this case the expression of alternative circadian oscillators can be strongly affected by daily feeding cycles, which are independent to the SCN (Mendoza 2007). Daily food is consumed in a limited time. When foods are received everyday at the same time for only a few

hours, organism adjusts to the feeding period within a few days (Froy et al. 2008). However, there is an association between food-entrainable oscillations and the expression of mPER1 and mPER2 in the cerebral cortex and hippocampus (Wakamatsu et al. 2001). Food-restricted animals are able to predict meal time, whereas lack of food anticipation is associated with a mutation of PER2. Mutations of CLOCK or PER1 do not impair expression of food anticipatory components, suggesting that these clock genes are not essential for food-entrainable oscillations. By contrast, NPAS2 mutation or CRY1 and CRY2 deficiencies show more or less altered responses to restricted feeding conditions (Feillet et al. 2006). SCN circadian pacemaker is entrainable to restricted feeding under continuous darkness. This suggests that circadian clock system can be reset by a signal associated with feeding time (Abe et al. 2007). Functional CLOCK is not required for an entrainment of peripheral clocks to restricted feeding. The rhythmic expression of REV-ERB alpha is not involved in the restricted feeding-induced circadian expression of BMAL1 mRNA, although REV-ERBalpha has been identified as a major regulator of BMAL1 transcription (Oishi et al. 2002). Food-entrained activity rhythms are likely mediated by a circadian oscillators system, which is sensitive to multiple feeding related inputs (Patton and Mistlberger 2013). Indeed, to restrict the food-availability to a specific period of the day causes profound changes on the behavior and physiology of animals. Increase in gastro-intestinal motility, and activity of digestive enzymes 2–3-h prior to the next scheduled feeding is called food anticipatory activity. Metabolic activities of the anterior piriform cortex, the olfactory tubercle and olfactory bulb increase during food anticipatory activity independent of the geographical time and the metabolic activity in SCN (Olivo et al. 2014). In this case although the mechanism is not known exactly, food intake associated stimuli sensitivity of circadian oscillators outside of the SCN enables animals to uncouple rhythms of behavior and physiology from light-dark cycles and align these with predictable daily mealtimes (Mistlberger and Antle 2011). Uncoupling of the

stimulus associated with food intake from the central pacemaker suggests that nutritional regulation of clock oscillators in peripheral tissues may play a direct role in coordination of metabolic oscillations (Lin et al. 2008). Restricting the timing of meals to light time in contrast to restricted feeding during the night causes internal desynchronization with the loss of phase relationship between central-light entrained and peripheral clocks (Sunderram et al. 2014). In this manner peripheral oscillators become uncoupled from the central pacemaker when food availability becomes restricted, a long-lasting temporal conflict occurs with the central pacemaker. As soon as food availability returns to normal, the SCN clock, whose phase remains unaffected, resets the peripheral oscillators (Damiola et al. 2000). Time-restricted feeding entails the delivery of a certain amount of calories with the standard nutritional intake at specific time intervals of specific duration. Calorie restriction entails an overall reduction in caloric intake, albeit without malnutrition (Redman and Ravussin 2011).

Inter-individual analyses showed that subjects with relatively less REM sleep, particularly during the second part of the night, associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA)-axis, higher cortisol concentrations, reduced insulin sensitivity and a higher homeostatic model assessment of insulin resistance (HOMA-IR) index. There is a negative correlation between total sleeping time and fasting insulin concentrations or between total sleeping time and the HOMA-IR index (Gonnissen et al. 2013). The time-restricted feeding regimen entrained circadian clock and metabolic regulators fix feeding times and prevent high fat diet-induced disruption of the normal cellular metabolic program (Hatori et al. 2012). High-energy food intake in the evening and fasting in the morning have both been associated with the development of obesity. In this regard skipping breakfast impairs postprandial insulin sensitivity and fasting lipid levels in humans (Farshchi et al. 2005). Eventually the synchrony between circadian and metabolic processes plays an important role in the regulation of energy balance and body weight control. Modifying the time of feeding

alone can greatly affect body weight (Arble et al. 2009). Temporal restricted feeding is a potent synchronizer of peripheral oscillators (Mendoza et al. 2005). Thus temporal feeding restriction under light-dark or dark-dark conditions can change the phase of circadian gene expression in peripheral cell types by up to 12 h. Sudden large changes in feeding time, similar to abrupt changes in the photoperiod, reset the phase of rhythmic gene expression (Damiola et al. 2000).

6.2 Calorie Restriction

Calorie restriction limits the amount of daily calorie intake to 60–70% of ad libitum feeding. In mammals, calorie restriction prevents or delays the onset of age-related diseases. In humans, long-termed calorie restriction results in sustained beneficial effects on major risk factors for atherosclerosis, Type 2 diabetes, and inflammation (Fontana 2009). A comprehensive review of 372 recorded comparisons revealed that dietary restriction has little effect on mitochondrial ROS production or antioxidant capacity. However more than half of the observations indicated that oxidative damage is reduced with dietary restriction by increasing antioxidant enzyme activity or the turnover of oxidized macromolecules (Walsh et al. 2014).

Calorie restriction upregulates NAMPT mRNA and protein levels in rat skeletal muscle and white adipose tissue. Inhibition of NAMPT activity attenuates the calorie restriction-induced SIRT3 activity, the calorie restriction-induced decrease of oxidative stress and the calorie restriction-induced improvements of antioxidant activity. Thereby, calorie restriction-induced beneficial effects on oxidative stress, mitochondrial biogenesis, and metabolic adaptation require NAMPT (Song et al. 2014). Analysis of the subjects who are included into different levels of chronic caloric restriction programs revealed that severe calorie restriction and acute fasting increase oxidative damage and decrease antioxidant capacity whereas moderate calorie restriction increases antioxidant capacity due to increase in manganese superoxide dismutase (Mn-SOD)

activity and glutathione (GSH) concentration (Stankovic et al. 2013).

The mTOR pathway integrates nutrient, energy, and mitogen signals to regulate cell growth and cell division (Hay and Sonenberg 2004; Wullschleger et al. 2006). Actually calorie restriction can lead to activation of SIRT1 and suppression of mTOR and S6K1 activation (Ma et al. 2015). Dietary energy restriction reduces levels of phospho mTOR. This signaling pathway acts as a sensor of the nutritional and energetic state in the cell. Its principal upstream regulators are AMPK and Akt, and its downstream targets are the mTOR translation effectors p70 S6K, ribosomal S6 protein (S6) and 4E-BP1 S6K (Jiang et al. 2008). While light stimulates the co-localized activation of p70 S6K and ERK, pharmacological disruption of ERK signaling abolishes light-induced mTOR activity. This means that light-activated signaling coordinates activation of CREB and mTOR-mediated signals in the central pacemaker (Cao et al. 2008). Calorie restricted-fed animals resemble restricted feeding-treated animals, as they usually consume all or most of their food within a short period of time. Thus, due to the temporal component of food intake, calorie restriction similarly to restricted feeding synchronizes peripheral clocks and influences clock-controlled output systems (Froy and Miskin 2010). Calorie restriction entrains the SCN clock, whereas timed meals entrain peripheral oscillators (Froy 2007). When restricted feeding is coupled with caloric restriction, timing of clock gene expression is altered within the SCN, indicating that calorie restriction resets circadian rhythms by changing SCN clock gene expression and effects photic responses of the circadian system (Challet et al. 2003).

The normal alignment of feeding and activity with the environmental light cycle is critical for the maintenance of energy homeostasis (Marcheva et al. 2013).

Contrary to temporal restricted feeding, timed calorie restriction modifies clock gene expression in the SCN. Moreover, both temporal gating of light induced phase shifts and light induction of PER1 are strongly modified with daily calorie restriction. Diurnal hypoca-

loric feeding affects not only the transient regulation of the SCN clockwork and circadian outputs under light/dark cycle but also photic responses of the circadian system. Thus the changes in energy metabolism modulates circadian rhythmicity and gating of photic inputs in mammals (Mendoza et al. 2005). The circadian changes in clock and clock-controlled proteins and their acute responses to light in the SCN demonstrate that metabolic cues induced by a calorie restriction modulate the translational regulation of the SCN clock (Mendoza et al. 2007). In addition to timing of food availability affecting the circadian outputs of the clock, caloric restriction induces phase advances behavioral and physiological circadian rhythms and alters expression of clock genes and neuropeptides in SCN (Challet 2010). Under low-fat diet, adiponectin signaling pathway exhibits circadian rhythmicity. However, fasting and high fat diet alters this circadian expression. High fat diet leads to obesity by changing daily rhythm of clock genes and components of adiponectin signaling pathway (Barnea et al. 2009). When compared high fat diet ad libitum, the timed high fat diet restores the expression phase of the clock genes *CLOCK* and *CRY1* and phase-advanced *PER1*, *PER2*, *CRY2*, *BMAL1*, *ROR-alpha*, and *REV-ERB alpha*. High fat diet provides 18% reduction in body weight and improves insulin sensitivity by 3.7-fold. Timing can prevent the harmful effects of high fat diet (Sherman et al. 2012). Actually the serum resistin levels are associated positively with saturated fat intake and inversely with monounsaturated fat intake. In a cross-sectional study of 6637 randomly recruited adults, the resistin level is also found to be inversely associated with adiposity and with adherence to the Mediterranean diet (Cabrera de León et al. 2014). The diurnal pattern of resistin expression is negatively correlated with the gastric contents and serum insulin. Insulin stimulates resistin expression and that circulating resistin follows a contrary circadian pattern in comparison to insulin (Oliver et al. 2006).

6.3 Intermittent Fasting

Intermittent fasting or reduced meal frequency and caloric restriction extend lifespan and improve the health of overweight humans. These feeding regimens enhance cardiovascular and brain functions and improve several risk factors for coronary artery disease and stroke including reduction in blood pressure and increased insulin sensitivity. The beneficial effects of intermittent fasting and caloric restriction are primarily due to reduced oxidative damage and reinforced cellular resistance mechanisms against stress (Mattson and Wan 2005). Additionally, intermittent fasting results in increased production of brain-derived neurotrophic factor (BDNF), which increases the resistance of neurons to degenerative processes. BDNF signaling may also mediate beneficial effects of intermittent fasting on glucose regulation and cardiovascular functions (Mattson 2005).

Furthermore, caloric restriction, intermittent fasting or every other day feeding regimens provide increased resistance to oxidative, metabolic and excitotoxic insults. In this respect PGC-1 is regulated by several signaling pathways via the connection between intermittent fasting and caloric restriction. These include FoxO transcription factors (through an insulin/insulin-like growth factor-I-dependent pathway), glucagon-stimulated CREB, stress-activated protein kinases (p38 and c-jun N-terminal kinase) and SIRT1 (Martin et al. 2006b). These pathways stimulate the production of protein chaperones, neurotrophic factors and antioxidant enzymes, all of which help cells fight with stress and resist disease (Martin et al. 2006b). Chausse et al. showed that intermittent fasting promotes tissue-specific changes in mitochondrial bioenergetics and tissue redox state. However intermittent fasting surprisingly increases protein oxidative damage without measurable changes in mitochondrial function of the brain unlike the other studies. This restrictive dietary intervention may also be detrimental toward liver oxidative balance, as reflected by the enhanced levels of protein carbonylation and induction of glutathione synthesis

(Chausse et al. 2015). Proteomic analysis of hepatic lipid droplets isolated from animals exposed to intermittent fasting and caloric restriction showed significantly higher levels of proteasome 26S subunit, non-ATPase 9 (PSMD9) (co-activator Bridge-1), macrophage migration inhibitor factor (MIF), transcription elongation factor B (SIII), polypeptide 2 (TCEB2), aminoacylase 1 (ACY1) and fatty acid binding protein 5 (FABP5), and a marked reduction of glutathione S-transferase alpha 3 (GSTA3). In addition, accumulation of diacylglycerols (DAGs) is significantly reduced in hepatocytes of intermittent fasting and caloric restriction animals (Baumeier et al. 2015). If intermittent fasting combined with caloric restriction, liquid meals is an effective strategy to help obese women for decreasing weight and lower coronary heart disease risk (Klempel et al. 2012). Intermittent fasting can affect circadian rhythms differently depending on the timing of food availability and light conditions. This suggests that this regimen affects the SCN clock, similarly to caloric restriction (Froy and Miskin 2010). Actually intermittent fasting is not as dominant as restricted feeding in dictating peripheral rhythms. Nevertheless, intermittent fasting exhibits some similarities with restricted feeding, as reflected by the anticipatory feeding behavior. This precedes food availability or restoration of circadian rhythms under disruptive light conditions, due to the effect on the food entrainable oscillator. Co-activation of both the food entrainable oscillator and the SCN would yield rhythms at two opposite phases leading to the overall arrhythmicity (Froy et al. 2009).

7 Circadian Rhythms and Obesity

The daily variations between sleep/fasting/catabolism and wakefulness/feeding/anabolism are coordinated by a master hypothalamic clock, mainly reseted by ambient light. Peripheral clocks 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 (Challet 2013). Circadian

desynchronization of hormonal rhythms may participate in internal desynchronization and is associated with increase in metabolic risks favoring obesity (Challet 2015). Homozygous *CLOCK* mutation shows an attenuated diurnal rhythm of feeding behavior, as well as profound changes in body weight regulation and fuel metabolism, which leads to obesity. In addition to the severely altered diurnal rhythm in food intake, *CLOCK* mutant animals show a significant increase in energy intake and body weight. *PER2*, orexin and ghrelin are dramatically reduced in *CLOCK* mutant animals at all time points of the light-dark cycle (Turek et al. 2005). *BMAL1/CLOCK* generates circadian rhythm of *C/EBP alpha*-mediated leptin transcription in adipose tissue. *PER* and *CRY* mutant animals show a similar disruption of peripheral clock and deregulation of leptin. Actually coupling of the central and peripheral *CLOCK* controls leptin homeostasis. Hence leptin resistance has an important role in circadian dysfunction-induced obesity and metabolic syndromes (Kettner et al. 2015). In diet induced obesity, expression of *CLOCK* in the ARC is down-regulated. In this case inhibition of *CLOCK* may be involved in leptin resistance and regulation of suppressor of cytokine signaling-3 in ARC (Xie et al. 2013). Leptin and adiponectin are strongly associated with glucose and lipid metabolism. Their synthesis and secretion display circadian rhythms that are disturbed in the obese state, while hyperleptinemia resulting in leptin resistance, adiponectin deficiency has been linked to the pathophysiology of the obesity-related disorders (Szewczyk-Golec et al. 2015).

On the other hand, impaired brown adipose tissue activity is an important mediator in the association between disturbed circadian rhythm and adiposity. Increasing the daily hours of light exposure decreases the uptake of fatty acids from triglyceride-rich lipoproteins, as well as of glucose from plasma selectively by brown adipose tissue (Kooijman et al. 2015). Adipose tissue clock genes regulate the hydrolysis of adipose tissue triglycerides and provide a rhythmic release of free fatty acids and glycerol from adipocytes. Disruption of circadian function decreases overall daily lipolytic activity and

blunts the lipolytic response to fasting (Yoshino and Klein 2013). Saturated fatty acid intake interacts with a high obesity genetic risk score in increasing BMI (Casas-Agustench et al. 2014). Loss of clock gene function or misalignment of circadian rhythms with feeding cycles results in impaired lipid homeostasis (Gooley and Chua 2014). About 13% of 263 lipid metabolites shows circadian variation in humans. Surprisingly inter-individual agreement for lipid metabolites identified as rhythmic is only about 20%. Eventually it is stated that there are different circadian metabolic phenotypes and an extensive diversity in circadian regulation of different lipid species in humans (Chua et al. 2013). In 1465 overweight/obese subjects carrying minor alleles at variants of *SIRT1* and *CLOCK* were found to have a higher resistance to weight loss. This could be related to the chronotype of the subject, their higher plasma levels of ghrelin and less adherence to Mediterranean diet patterns (Garaulet et al. 2012).

8 The Risk of Obesity in Adulthood

Human genetic studies report associations between polymorphisms of *CLOCK* and obesity (Scott et al. 2008). Exposure to maternal obesity from pre-conception to birth as well as high fat diets influences the risk of obesity in the offspring. Hepatic mRNA expression of circadian (*CLOCK*, *BMAL1*, *REV-ERB* alpha, *CRY*, *PER*) and metabolic (*PPAR* alpha, *SIRT1*) genes were strongly suppressed in offspring exposed to both maternal obesity and high fat diet (Borengasser et al. 2014). Maternal obesity and diabetes associated with high birth weight, excessive nutrition in neonates, and rapid catchup growth also increase the risk of adult-onset obesity. Conversely, maternal undernutrition results in low birth weight with increased risk for long-lasting energy balance disorders with the impaired glucose uptake, insulin and leptin resistance, low-grade inflammation, modified sympathetic activity with reduced noradrenergic innervations, and thermogenesis (Lukaszewski

et al. 2013). The hypothalamus-adipose axis plays a pivotal role in the maintenance of energy homeostasis by controlling the nutritional status and energy storage level. The perinatal period largely corresponds to the period of brain maturation, neuronal differentiation and active adipogenesis. Impaired neurogenesis, neuronal functionality, nuclei structural organization and misalignment of circadian rhythms with feeding cycles led to a persistent reprogrammed appetite system that favors the orexigenic pathways, leptin/insulin resistance and hyperphagia (Breton 2013). Offspring from high-fat/high-sucrose-fed dams are heavier and have increased hepatic triglycerides, hepatic glycogen, blood glucose and plasma insulin compared with the offspring from chow-fed dams. In a similar manner supplementation of chocolate and soft drink during gestation and lactation contributes to early onset of hepatic steatosis (Kjaergaard et al. 2014).

The mRNA of *PER1*, *PER2*, *BMAL1*, and *CRY1* clock genes are expressed in human hearts. Although *PER1*, *PER2*, and *BMAL1* mRNAs reveal clear circadian rhythms in the human heart, no circadian rhythm is detected in *CRY1* mRNA (Leibetseder et al. 2009). Furthermore, maternal obesity has a profound influence in the protein expression genes in heart and liver of offspring. The circadian clock undergoes nutritional programming, which may contribute to the alternations in energy metabolism associated with the development of metabolic disorders in early life and adulthood. Metabolic and inflammatory genes, *CPT1b*, *PPAR* alpha, *PER2* show anti-phase oscillations, whereas *BMAL1* has greater oscillation amplitudes (Wang et al. 2015). Offspring exposed to maternal obesity and high fat consumption during development are more susceptible to developing behavioral disorders such as anxiety, depression, attention deficit, hyperactivity and autism spectrum disorders (Sullivan et al. 2014). Additionally, hepatic mRNA expression of circadian; *CLOCK*, *BMAL1*, *REV-ERB* alpha, *CRY*, *PER* genes and metabolic; *PPAR* alpha, *SIRT1* genes are strongly suppressed in offspring exposed to both maternal obesity and high fat diet. Offspring from obese animals may exhibit impaired liver metabolism

in response to high fat diet via reduced PPAR alpha expression prior to the development of obesity (Borengasser et al. 2014). In offspring of obese dams, hepatic fatty acid oxidation decreases due to twofold reduction of hepatic long chain acyl-CoA dehydrogenase and three-fold reduction of SIRT3 protein levels. In this manner mitochondrial dysfunction precedes the development of detrimental obesity associated co-morbidities such as insulin resistance and nonalcoholic fatty liver disease (Borengasser et al. 2011).

The incidence of overweight or obese is increasing all over the world. Weight loss surgery for obesity seems to be the most effective option when other treatment modalities have failed. Surgery results in a greater improvement in weight loss related outcomes and weight associated comorbidities compared with the non-surgical interventions. Very few data have been obtained related to the effect of bariatric surgery on the circadian desynchronization (Colquitt et al. 2014). Severely obese individuals show a decrease in circulating free fatty acid 6 months after biliopancreatic diversion. Malabsorptive bariatric operations are associated with a drastic reduction in 24-h circulating free fatty acid concentrations, improvement of insulin resistance and changes in the pattern of leptin peaks independent of weight loss (Raffaelli et al. 2015). Actually all forms of weight loss surgery lead to caloric restriction, weight loss and decrease in fat mass (Gumbs et al. 2005). While duodenal-jejunal bypass induces marked expressions of glucose transporter-2 (GLUT2) in the liver, gluconeogenic enzymes, phosphoenolpyruvate carboxykinase-1 and glucose-6-phosphatase decrease. In these animals, circadian transcription factors CRY1 and PER2 increase in the liver and decrease in the intestine (Kim et al. 2015).

9 Conclusion

In addition to the influence of dietary nutrients on circadian rhythms, the daily timing of food intake has itself been shown to affect body weight regulation in mammals (Summa and Turek 2014). Altered timing of food intake can lead to uncoupling of peripheral clocks from the central pacer-

maker (Oosterman et al. 2015). In other word, unusual feeding time can cause the disruption of the circadian system which might reveal unhealthy consequences in humans (Garautet and Gómez-Abellán 2014). Late lunch eaters loose less weight and display a slower weight-loss rate than early eaters (Garautet et al. 2013b). Calorie restriction entrains the SCN clock, whereas timed meals entrain peripheral oscillators (Froy 2007).

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Obesity and Lipotoxicity

Engin, A.B.; Engin, A. (Eds.)

2017, VIII, 624 p. 47 illus., 35 illus. in color., Hardcover

ISBN: 978-3-319-48380-1