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Circadian rhythm in mammals: time to eat & time to sleep

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ABSTRACT

Circadian rhythm is defined as rhythmic fluctuations in physiological processes which enable living organisms to make necessary arrangements for upcoming changes in the environment thereby optimizing their metabolism. Mammalian circadian clock consists of feedback(negative) and feedforward (positive) loops consisting of transcription, translation and posttranslational events. It is believed that there are two kinds of clock functioning in the body.The master clock residing in hypothalamus oscillating in conjunction with light/dark cycle whereas peripheral clocks occur in peripheral tissues and influenced by other environmental factors such as feeding. The rhythmic alterations in activities of metabolic pathways are provided by the coordinated expressions of clock genes and consequently by clock-controlled genes. The current studies indicate that consumption of food at inappropriate times as well as sleep restrictions lead to metabolic dysfunctions due to disruption of circadian rhythm which result in diabetes, obesity and heart diseases. To this end, it is aimed, in this review, to examine interactions among food or sleep, metabolism and circadian rhythm with an insight into metabolomic profiling studies of circadian disturbances by sleep restrictions following an overview of working mechanisms of circadian rhythms in mammals.

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Circadian clocks; metabolism; nuclear receptors; sleep disorders; chronobiology disorders

This review is primarily confined to the mammalian circadian system. Overall, this article has the following objectives: (1) to provide an overview of the structural components and the working mechanisms of the circadian rhythm, (2) to define interrelationship among circadian rhythm, food or sleep and metabolism with an insight into studies for metabolome profiling of circadian rhythm disturbances caused by sleep restrictions.

General concepts of circadian rhythm

Definition of circadian rhythm

Circadian rhythm in living organisms is rhythmic alterations in physiological processes which allows organisms to predict up-coming changes in the light/dark cycle of the environment. This enables life forms to adapt their metabolism to changing environmental conditions so

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that they can perform their activities at the optimal time of the day. Period length indicates the time elapsed for one complete oscillation or cycle in circadian mechanism (http://www.circadian.org/dictionary.html, 9 March 2015, Dictionary of circadian physiology). The periocidity of these rhythms is approx. 24 h. The circadian clock is entrained by external cues, thereby matching the clock with the environment (Langmesser & Albrecht 2006; Yang et al. 2006; Reilly et al. 2007; Duez & Staels 2008; Johnston et al. 2009). Characteristics of biological clock have been reported to include a persistent and sustained period length under constant condition, entrainment to environmental signals such as light and stability across wide variations in temperature (Bass 2012). The persistence of circadian rhythm in the absence of any environmental cue constitutes the endogenous nature of the circadian rhythm (Sehgal 2004).

Residence of circadian clock

Circadian clock can be divided into two parts. In mammals, the main circadian time keeping system is placed in the suprachiasmatic nucleus (SCN) of the hypothalamus which is entrained by light. On the other hand, peripheral organs and tissues include another type of autonomous circadian clock, peripheral clock, which is entrained mainly by food. These food entrainable circadian oscillators are believed to be communicated with the light entrainable oscillators in brain via autonomic innervations and endocrine signalling (Mistlberger 2011; Orozco-Solis & Sassone-Corsi 2014).

Operation of the clock machinery

Mammalian circadian clock consists of feedback (negative) and feedforward (positive) loops of transcription, translation and posttranslational events (Reilly et al. 2007; Mistlberger 2011). Non-transcriptional mechanisms might also be involved (O'Neill & Reddy 2011).

The negative loop

Transcription factors CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain and Muscle ARNT-Like1) heterodimerize and bind to E-box elements of three Period (Per 123) genes and two Cryptochrome (Cry1,2) genes thereby activating their expression. The CRY proteins combine with PER proteins in the cytosol and go back to nucleus where CRY proteins repress the transcriptional activity of CLOCK-BMAL1 dimer. This negative feedback effect of CRYs on their expression, called negative feedback loop, is thought to generate oscillations in the circadian clock (Cermakian & Boivin 2003; Orozco-Solis & Sassone-Corsi 2014). It has been proposed that light sensing photolyases might have given rise to cryptochromes. The cryptochromes belong to the photolyase family of proteins containing photolyases and their relatives, cryptochromes (Tauber et al. 2004). Cryptochromes which exhibits up to 50% sequence identity to some photolyases regulates the circadian rhythm by light-independent and light-dependent mechanisms in animals. Humans and other placental mammals do not have photolyase activity. These proteins may function as circadian photoreceptors. Crptochromes play a central role in the inhibitory branch of the autoregulatory transcriptional loop that makes up the clock (Sancar 2004).

The positive loop

CLOCK-BMAL1 dimer activates the gene encoding a transcription factor REV-ERB-α which can inactivate the Bmal1 and Clock genes. The inactivation of CLOCK-BMAL1 by PER-CRY complexes in the negative loop, indirectly cancels out the inhibitory effect of Rev-erbα on Bmal1 and Clock genes (Cermakian & Boivin 2003).

Period of oscillations

The periocidity of the oscillations is approx. 24 h which is controlled by the phosphorylation, degradation and nuclear translocation of the proteins of the feedback loops. Casein kinases I (CKI) δ and Є phosphorylate PER1 and 2, CRYs and BMAL1. The phosphorylation of the proteins lead to their degradations (Cermakian & Boivin 2003). The phosphorylation of PER2 by casein kinase I Є (CKIЄ)-dependent phosphorylation is an important posttranslational modification leading to a fine tunning in circadian clock possibly through altering turnover rate and translocation of PER proteins (Chang & Reppert 2001).

When mice is shifted from an light/dark cycle to constant darkness (free running conditions), periods of activity shift (advance) slightly in constant darkness, this is because of the fact that the endogenous periocidity of most strains is slightly shorter than 24 h (Sehgal 2004).

Clock and clock controlled genes

Clock genes are important for the generation and regulation of circadian rhythms. Main clock genes in mammals: Clock, Bmal1, Per 123, Cry 12, CKIε, CKIδ, Rev-erbα.

As CLOCK-BMAL1 activities oscillate, the genes controlled by them are also expressed accordingly. Clock controlled genes (CCGs) convey rhythmicity to the metabolism. CCGs can control other transcription factors that regulate related genes in rhythmic fashion. However, the phases of the oscillations might differ among clock genes, CCGs and transcription factors (Cermakian & Boivin 2003). It is estimated that the circadian clock controls the expression of 10–20% genes in the cell (Orozco-Solis & Sassone-Corsi 2014). CCGs are controlled mainly by Clock-Bmal1 dimer. These genes yield D-element binding protein (DBP), E4BP4 (E4 promoter–binding protein 4), secreted molecules (arginine vasopressin (AVP), prokineticin 2 (PK2), transforming growth factor α(TGFα) etc.), factors important for protein synthesis, transport and secretion and ion channels (Cermakian & Boivin 2003; Sehgal 2004).

Epigenetic control of circadian mechanism

Posttranslational modifications of the N-terminal regions of histones including methylation, acetylation, ubiquination and phosphorylation plays a pivotal role in the organization of circadian machinery. Chromatin remodelling in the SCN is initiated in response to light. The activation of CCGs by CLOCK-BMAL1 is linked to circadian oscillations in posttranslational modifications of histones such as acetylation or methylation. Two major enzymes participate in the epigenetic control of clock mechanism:

NAD-dependent SIRT1 histone deacetylase

SIRT1 (Sirtuin 1) acts at the interface between metabolism and circadian clock. SIRT1 influences wide variety of cellular processes including DNA repairs, gluconeogenesis, lipid metabolism and insulin sensitivity. Besides, SIRT1 controls metabolism by deacetylating some key regulatory factors including PGC-1 (Peroxisome Proliferator Activated Receptor Gamma Coactivator 1-Alpha), PPARγ (Peroxisome Proliferator Activated Receptor Gamma) and SREBP-1c). Activity of SIRT1 fluctuates in accordance with circadian time thereby periodically deacetylases the histone at the promotor regions of CCGs and/or BMAL1 and PER2. NAD regulates SIRT1 activity according to its level dictated by circadian time. The circadian clock controls the expression of nicotinamide phosphoribosyltransferase (NAMPT) gene that in turn modulates the synthesis of NAD (Orozco-Solis & Sassone-Corsi 2014).

AMP Kinase

Stimulation of AMP Kinase (AMPK) (a protein that is activated following intracellular nutrient restriction) leads to phosphorylation of CRY and subsequent proteosomal degradation of the repressor CRY. This couples clock function to nutrient state (Bass 2012).

Hormonal and temperature rhythms as circadian phase markers

Temperature

The core body temperature of mammals vary with time of day. The peak is normally during the animal's active phase, and the trough is during the rest period.

Hormones

Levels of numerous hormones in mammalian serum exhibit daily oscillations. These are mainly melatonin and glucocorticoids. Hormone release is regulated by SCN via distinct neuroanatomic pathways. Melatonin can act as an input factor SCN as well as an output factor. It conveys the length of the photoperiod to the rest of the organism. Melatonin is cyclically produced by the pineal gland with levels highest at night. Humans, however, are not photoperiodic and the function of melatonin is unclear although it is known to promote sleep. Levels of corticosteroneare regulated by circadian rhythm. It is secreted by the adrenal glands. There are several routes of SCN control over the corticosterone rhythm. Luteinizing hormone (LH) is also released by the anterior pituitary in a circadian fashion (Sehgal 2004).

Entrainment of circadian clock

Environmental light/dark cycle entrains brain clock (SCN and extra SCN) which modulates sleep, feeding and wakefulness whereas environmental nutrient cycle (fasting/feeding) entrains peripheral clocks (autonomous circadian control) which regulates glucose homeostasis, lipogenesis, sterol turnover, oxidative metabolism and respiration (Bass & Takahashi 2010).

Entrainment by light

Light is the major time cue (zeitgeber) synchronizing the circadian timing system. The retina senses the diurnal changes in environmental light through changes in retinal chemistry induced by light exposure. This message is conveyed to SCN by means of retinohypothalamic tract (RHT) to entrain circadian rhythms throughout the body (Golombek & Rosenstein 2010).

Axons of retinal ganglion cells are projected to the SCN where they release glutamate which causes depolarization of membrane after binding to N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This receptor–ligand interactions initiate a series of kinases leading to induction of Per and Cry transcription thus altering the phase or amplitude of intracellular oscillators (Golombek & Rosenstein 2010; Welsh et al. 2010). As a central pacemaker, the SCN synchronizes other oscillators in the brain and peripheral tissues. This synchronization occurs through autonomic neural connections and hormones as well as through circadian modulation of body temperature and feeding behaviour (Welsh et al. 2010). One of the circadian rhythm that transfers time of day information to the organism is the melatonin cycle which is always at low levels in the blood during the day and at high levels during darkness. The pineal gland is one of the organs that receives a neuronal signal from the SCN. During darkness, the SCN sends a neuronal impulse which causes the discharge of norepinephrine from the postganglionic terminal near pinealocytes. Action of catecolamines on β-adrenergic receptors on the pinealocyte membrane triggers a series of molecular events that induce night-related rise in pineal melatonin synthesis and release (Reiter et al. 2011).

Entrainment by food

The clock is not only synchronized by the day/night cycle but also by feeding schedule. In contrast to light entrainable oscillators, exact localization of food entrainable oscillators is currently not clear. Feeding time (as well as calorie content) functions as a powerful time cue for the circadian rhythms which regulates both the central clock system as well as peripheral clocks (Orozco-Solis & Sassone-Corsi 2014). It is established that autonomous clocks are present in various peripheral tissues. The SCN takes part in synchronization of these peripheral clocks which then can oscillate in an appropriate phase to each other. This synchronization is provided by neuroendocrine pathways and by time of feeding. Restriction of food availability to a certain time period acts as a powerful time cue which modulates circadian rhythms. In nocturnal rodents, restriction of food availability to the day time synchronizes rhythm of food anticipatory activity and gene expression in peripheral tissues. However, the SCN remains entrained to the light/dark cycle which results in an misalignment with many tissues (Johnston et al. 2009).

Sex, age and polymorphism-related variations in circadian rhythm

Human variables exhibit a rhythm with a period equal to 24 h. However, healthy human adults may differ from one another with regard to the persistence of the 24 h periods of a set of variable's rhythms within a given individual. Such an internal desynchronization (or individual circadian dyschronism) was documented. The results suggested presence of genetically controlled variability (Ashkenazi et al. 1993). Circadian rhythmicity in mental functions exhibits sex differences. The night-time impairment in cognitive performance is greater in women than in men (Santhi et al. 2016). The diurnal rhythmicity of cortisol secretion was preserved in old age but the relative amplitude was dampened and the timing of the circadian elevation was advanced. There are marked gender-specific effects of ageing on the levels and diurnal variation in human adrenocorticotropic activity (Van Cauter et al. 1996). The intrinsic circadian period was significantly shorter in women than in men. A significantly greater proportion of women have intrinsic circadian periods shorter than 24 h

(Duffy et al. 2011). In human circadian temperature, rhythm exhibits individual differences in its phase and amplitude varying with morningness-eveningness (Baehr et al. 2000).

In recent years, there has been a significant increase in available information from polymorphic variations and epigenetic modification over clock genes and their asssociated risk of diseases. Polymorphic variations in clock genes can be incrementing the risks of developing a disease. Single nucleotide polymorphisms of clock genes (e.g. Clock, Per2, Per3, Bmal1, Cry1 and Cry 2) have been shown to be associated with various diseases including diabetes, dyslipidemia, bipolar disease, infertility, depresion disease and various forms of cancers. For example; polymorphisms of Bmal1 rs7950226 and rs11022775 have been found to be associated with gestational diabetes mellitus in Greek pregnant women (Valenzuela et al. 2016).

Types of feeding regimens and their effects on circadian rhythm

(1) *Restricted feeding:* The time and duration of food accessibility are limited without any calorie reduction. When food restricted in duration but not in calories, this uncouples the SCN from periphery and circadian rhythm is directly defined by the time of food availability.
(2) *Calorie restriction:* This feeding regimen reduces amount of daily intake calories by 60–75%. The peripheral clocks and clock-controlled systems are influenced. However, in contrast to restricted feeding, calorie restriction entrains the circadian clock in the SCN. When food restricted in duration but not in calories, this uncouples the SCN from periphery and circadian rhythm is directly determined by the time of food availability. When food is restricted in calories, both the rhythms SCN and the periphery are appropriately reset (Froy & Miskin 2007).
(3) *Intermittant fasting (alternate day fasting):*In this condition, food is available ad libitum only every other day. Although this feeding regimen resulted in extended life span, improved glucose metabolism, cardioprotection, neuroprotection compared to ad libitum feeding, underlying mechanism is not yet clear (Froy & Miskin 2007; Challet 2010).

Single nutrients that are capable of entraining or phase-shifting circadian rhythms

Glucose

Glucose has been shown to phase-shift the clock in peripheral tissues probably via down-regulation of Per1 and Per2.

Amino acids

Infusion of a mixture of amino acids to rats resulted in a change in the peak time of Per2 expression in the SCN and liver.

Ethanol

It has been shown that ethanol consumption alters the circadian expression pattern of the Per genes. High levels of liver intracellular NADH generated by alcohol metabolism may affect DNA binding of CLOCK:BMAL1.

Retinoic acid

Which has been shown to upregulate Per1 and Per2 expression and can phase shift Per2 expression. When retinoic acid is administered to cells expressing retinoic acid receptors RARα or RXRα, the ligand–receptor complex competes with BMAL1 for binding to CLOCK. These interactions negatively regulate CLOCK/BMAL1 mediated transcriptional activation of clock gene expression.

Adenosine, caffeine, cholesterol are also known to influence circadian rhythm (Froy 2007).

Clock, metabolism and food

Clock influences metabolism

The rhythmic expression and activity of the metabolic pathways is mainly attributed to the coordinated expression of clock genes (Clock, Bmal1, Per2, Per 1, Per3, Cry 1 and Cry2) in liver and adipose tissues. In addition, BMAL1 has been shown to link the core clock mechanism with lipogenic pathway, because REV-ERBα (the negative regulator of Bmal1) and RORα(the positive regulator of Bmal1) have been shown to regulate lipogenesis. Moreover, they both are known to be modulated by CLOCK-BMAL1. Besides, it is known that PPARα involved in lipid and lipoprotein metabolism. It binds directly to the Bmal1 promotor and in turn the CLOCK:BMAL1 heterodimer regulates PPARα expression (Froy & Miskin 2007).

Food influences clock

Food intake itself can generate entraining signals for peripheral clocks. These signal may involve food metabolites, hormones that are secreted upon feeding and fasting, and/or the intracellular redox state (NADH/NAD ratio) (Schmutz et al. 2012). The changes in the metabolic status of a tissue affects its redox state (Mendoza 2007). Due to its function in various biochemical redox reactions, NAD has been proposed as an link between circadian rhythms and nutrient sensing pathways. Oxidated NAD(P) cofactors modulates the binding of BMAL1 complexes to DNA (Peek et al. 2012). The NAD(P) redox equilibrium depends on the metabolic state of the cell. The ratio between NAD(P)H and NAD(P) dictates the binding of CLOCK/NPAS2 (Neuronal PAS domain-containing protein 2): BMAL1 to E-boxes and could result in phase shifting of cyclic clock gene expression and, as a result, of output gene expression (Froy 2007). Increased levels of NAD and NADP cause diminished binding of CLOCK/BMAL1 suggesting that the redox state may reset molecular clock activity and consequently couple circadian and metabolic cycle. It is probable that circadian control of NAD metabolism couples internal energetic cycles with oscillation in the external nutrient environment. NAD is also an important cofactor for the class III histone and protein deacetylase SIRT1 which is a member of the sirtuin family of NAD-dependent deacetylase (Peek et al. 2012). Since the activity of SIRT1 depends on levels of NAD, clock driven oscillations of NAD may contribute to daily oscillations in many metabolic pathways regulated by SIRT 1 (Peek et al. 2012; Schmutz et al. 2012). AMP-activated protein kinase (AMPK), a central mediator of metabolic signals was shown to be involved in the clock mechanism. AMPK phosphorylates and destabilizes the core clock component CRY1 and may hence act on the oscillator mechanism. Phosphorylation of AMPK and consequently its activity appears to be regulated by nutrients

and consequently by the cellular energy state via the ratio of AMP to ATP. AMPK may transmit nutrient signals directly to the clock by CRY1 (Schmutz et al. 2012).

ROS defence mechanism influences clock

Cyclical oxidation–reduction of peroxiredoxins (which are a family of antioxidant enzymes) participate in redox-regulated cytosolic clocks which can occur without gene transcription. Peroxiredoxins follow circadian cycles of oxidation-reduction (Pan & Hussain 2009). Some of the most abundant proteins in RBC are the evolutionarily conserved enzymes of the peroxiredoxin family, which can inactivate ROS. Class 2 peroxiredoxins contain a cysteine residue in their active site that undergoes oxidation when ROS accumulate. This results in the enzyme's transition from a monomeric to a dimeric state. Peroxiredoxin function is essential for RBC survival (Bass & Takahashi 2011). Driving forces behind their rhythmic cycles of peroxiredoxin oxidation-reduction have been reported as changes in metabolic cycles such as glycolysis and rhythmic variations in the levels of NAD(P)H. Oscillations in the redox status of the cells affect the expression of clock-related genes in many pathways (Pan & Hussain 2009; Welsh et al. 2010). Release of partly reduced intermediates, reactive oxygen species (ROS), during electron transport chain can cause oxidative damage to cellular structures. ROS production occurs in a circadian fashion. As a result, circadian variations can also be observed in many ROS defence systems. Moreover, it may also cause a dyssynchrony between ROS defence mechanisms (e.g. glutathione peroxidase, superoxide dismutase) and ROS production which may expose the organism to oxidative damage at peak times of ROS production (Langmesser & Albrecht 2006). Some antioxidant enzymes have been shown to follow a circadian pattern of expression. The activity of antioxidant enzymes determines the level of ROS production and the ROS production modulates clock genes (Pan & Hussain 2009; Welsh et al. 2010).

Integration of circadian and metabolic systems by nuclear hormone receptors

Nuclear hormone receptors (NHRs) and their ligands may function as nutrient sensors coupling circadian and metabolic pathways. In addition to direct transcriptional regulation of Bmal1 via REV-ERB and ROR, the clock both regulates and is regulated by NHRs. More than a half of approx. 50 known NHRs display oscillations in metabolic tissues (Peek et al. 2012). Circadian times at which expression levels of some NHRs peak are shown in (Table 1). Circadian variations in the levels of NR hormones may trigger metabolic rhythms. Food derived lipid soluble nutrients and hormones activate transcription factors of the nuclear receptor superfamily which comprises numerous regulators of metabolic pathways such as REV-ERBα and RORα and also the PPARs, SREBP1a and 1c (Yang et al. 2006; Kohsaka & Bass 2007; Duez & Staels 2009).

PPARs constitute a potential link between the circadian clock and energy metabolism. The three PPAR family members have been shown to regulate lipid metabolism and energy homeostasis by coordinated action in adipose tissue, liver and muscle. PPARγ is the most abundant in adipose tissue where it activates transcriptional activities for lipid storage and lipogenesis. PPARα is known for its role in promoting hepatic fatty acid oxidation and ketogenesis in response to fasting. PPARδ is more ubiquitously present. It might link diurnal variations in body temperature to circadian clock (Yang et al. 2006). Rev-erbα has been

Table 1. Circadian times (ZT) at which nuclear hormon receptor expression levels peak.

	Time/tissue	Species	Reference
Rev-erbα	ZT4 in WAT, BAT, liver and muscle	Mice	Yang et al. (2006)
	ZT8, liver	Mice	Cho et al. (2012)
Rev-erbβ	ZT8 in WAT, BAT, liver, muscle	Mice	Yang et al. (2006)
	ZT 8 in liver	Mice	Cho et al. (2012)
PPARα	ZT4 in BAT	Mice	Yang et al. (2006)
	ZT8 in WAT		
	ZT12 in liver		
	ZT 16 in liver	Mice	Cho et al., (2012)
	ZT 8 in liver	Mice	Adamovich et al. (2014)
PPARγ	ZT8 in liver	Mice	Yang et al. (2006)
	ZT16 in WAT		
	ZT 4 in liver	Mice	Adamovich et al. (2014)
PPARδ	ZT20 in liver	Mice	Yang et al. (2006)
RORα	ZT12 in WAT	Mice	Yang et al. (2006)
RORγ	ZT16 in BAT and liver	Mice	Yang et al. (2006)
Srebp 1 and 1c	ZT13 in liver	Mice	Yoon et al. (2012)
Srebp-1c	ZT 16 in liver	Mice	Adamovich et al. (2014)
Cry1	ZT20 in liver	Mice	Cho et al. (2012)
Clock	ZT20 in liver	Mice	Cho et al. (2012)
Bmal1	ZT20 in liver	Mice	Cho et al. (2012)

Note: BAT: Brown adipose tissue, WAT: White adipose tissue.

identified as a major repressor of Bmal1 transcription. Rev-erbα modulates lipid, glucose and bile acid metabolism as well as adipogenesis and inflammatory reactions (Yang et al. 2006; Kohsaka & Bass 2007; Duez & Staels 2009). It is induced during normal adipogenesis (Kohsaka & Bass 2007). RORα can activate Bmal1 transcription (Yang et al. 2006; Kohsaka & Bass 2007). It regulates lipid flux, lipogenesis and lipid storage in skeletal muscle. SREBP1a and 1c are master regulators of hepatic lipogenesis (Kohsaka & Bass 2007).

Blood concentrations of glucose and many hormones (insulin, ghrelin and leptin) show circadian variations in animals and in humans. Insulin sensitivity is also subjected to daily alterations. Glucose tolerance decreases during the day, whereas glucose-stimulated increase in insulin is higher in the morning. Circadian periods or times at which levels of various carbohydrate metabolism parameters peak can be seen in (Table 2). A clock mutation especially in liver and muscle results in a modest effect on glucose tolerance and insulin sensitivity. Whole body deletion of Bmal1 leads to increased fat mass, impaired glucose tolerance and decreased insulin sensitivity and secretion together with blunted gluconeogenesis. Overexpression of CRY1 in mice resulted in altered glucose homeostasis (Duez & Staels 2010). Depletions of both Rev-erbα and Rev-erbβ functions in mice profoundly disrupted circadian expression of core circadian clock and lipid homeostatic gene networks. Genes expressed in a circadian manner that lose rhythm in the absence of Rev-erbα and Rev-erbβ are associated with insulin signalling pathway, biosynthesis of unsaturated fatty acids, porphyrine metabolism, TCA cycle, glycerophosholipid metabolism and ABC transporters (Cho et al. 2012). PPARα is also rhythmically expressed in liver and regulates diurnal variations in the expression of fatty acid synthase (FAS) and HMG-CoAR, two enzymes involved in lipid and cholesterol synthesis, respectively. Rev-erbα and RORα play also a crucial role *in vivo* in the control of lipid metabolism by regulating the expression of liver apolipoproteins, SREBP and the fatty acid elongase elovl3. Both Rev-erbα deficient and RORα mutated mice are dyslipidemic. Rev-erbα also regulates bile acid metabolism by downregulating Cyp7A1 expression.

Table 2. Circadian periods/times at which levels of various carbohydrate metabolism parameters peak.

	Active period	Inactive period	Specified circadian time	Species	Reference
Muscle	Glycolytic metabolism ↑			Human ?	Bass and Takahashi (2010)
Liver	Glycogen synthesis ↑	Gluconeogenesis ↑ Glycogenolysis ↑		Human ?	Bass and Takahashi (2010)
Pancreas	Insulin secretion ↑	Glucagon secretion ↑		Human ?	Bass and Takahashi (2010), Bass (2012)
Liver/muscle		İnsülin sensitivity ↑		Human	Bass (2012)
SGLT1 mRNA exp.			Peaks at 20:00	Mice	Pan and Hussain (2009)
GLUT5 mRNA exp.			Peaks at 20:00-24:00	Mice	Pan and Hussain (2009)
GLUT2 mRNA exp.			Peaks at 24:00	Mice	Pan and Hussain (2009)

RORα regulates an enzyme of alternative bile acid synthesis pathway (oxysterol 7α-hydroxylase (CYP7B1) (Duez & Staels 2010).

Circadian clocks and feeding time regulate the oscillations and levels of hepatic triglycerides in mice

The circadian clocks and feeding time dictate the phase and levels of hepatic triacylglycerol (TG) accumulation, however oscillations in TGs can persist in the absence of a functional clock.The circadian expression of several hepatic enzymes participating TG metabolism (glycerol3-phosphate pathway) is clock dependent whereas other enzymes retain their circadian expression in the absence of a functional clock and respond to feeding. Night-time feeding of Per1 and Per 2 null mice resulted in a significant increase (about 25%) in hepatic TG content, whereas in wild type (WT) mice, 2 weeks of night-time feeding drastically reduced the total hepatic TG content. Taken together, both feeding and clock-dependent mechanisms not only dictate the phase of hepatic TG acumulation, but also play a prominent role in determining the total hepatic TG levels throughout the day (Adamovich et al. 2014).

Clock is important for food and circadian regulation of macronutrient absorption

Clock controls circadian and food-entrained regulation of intestinal carbohydrate (Table 2) and peptide absorption by regulating key transporters. Higher monosaccharide and lower peptide absorption in Clock mutant mice were reported. Genes involved in TG synthesis and secretion can be divided into those that respond to food (diacylglycerol acyltransferase 1 (DGAT1), monoacylglycerol acyltransferase 2 (MGAT2) and Apo A-I) or food and light (microsomal triglyceride transfer protein (MTP), Apo B, Apo A-IV, DGAT2). Light and food entrained regulation of intestinal genes requires normal clock activity (Pan & Hussain 2009). Circadian periods or times at which levels of various lipid metabolism parameters peak is shown in (Table 3).

Food consumption, nutrient composition and circadian time

Timing, frequency and volume of food intake as well as the nutrient composition of food have been shown to alter circadian rhythm. Studies indicate that consumption of food at inappropriate times leads to imbalanced metabolic function due to disruption of circadian function. For example, in mice and rats, food intake restricted to incorrect times of day shifts the phase of the molecular clock in peripheral tissues, but not that in the central clock (SCN) which results in misalignment between central and peripheral clock rhythms. Consequently, altered expression pattern of key metabolic enzymes and weight gains can occur (Schroeder & Colwell 2013).

Time-restrictive feeding

Time-restrictive feedings have been reported to alter significantly cholesterol and glucose homeostasis in mice. Daily expression of low density lipoprotein receptor (LDLR) and LDLR regulatory factors including SREBPs are severely affected (phase-shifted) by time-restrictive feeding regimen in the mouse liver. Homeostatic regulation of blood glucose are also significantly altered by a shift in usual meal time. Fasting glucose levels were also found to be significantly higher in mice fed time-restrictively. Insulin resistance exacerbated as the day time feeding regimen continued. Disturbed cholesterol and glucose homeostasis might have important metabolic consequences for shift workers as well as other conditions with circadian rhythm disturbances. Just a week of time restrictive feeding was reported to affects differentially the metabolic rhythms, thereby destroying synchronization among the metabolic pathways (Yoon et al. 2012).

Calorie restriction

Calorie restriction resets circadian clock which extends lifespan. Transgenic mice overexpressing in the brain the urokinase-type plasminogen activator consume 30% less food in comparison to their wild type. These transgenic mice were used in researches to investigate calorie restriction and longevity. These mice exhibited higher amplitude in the expression of several clock genes in liver and in rhythms of food intake and body temperature. The marked circadian rhythms displayed in these mice brought about by calorie restriction was linked to increased lifespan. NAD-dependent deacetylases (SIRT1) was thought to mediate the calorie reduction induced longevity (Froy & Miskin 2007).

Period dependent feeding and food composition

It was found that early nocturnal fasting in nocturnal mice alters the peripheral clock and increases *de novo* lipid synthesis leading to obesity. Early nocturnal fasting enhanced hepatic Srebp-1c, a master regulator of lipogenesis and repressed PPARα without any shift in the circadian peak from those of the control. On the other hand, early nocturnal feeding strongly affected other downstream genes, specifically fatty acid synthase (Fas), acetyl-CoA carboxylase (Acc) and glycerol-3-phosphate acyltransferase (Gpat1), shifting their peak time from the end of the nocturnal period to the early diurnal period in both the liver and fat tissues (Yoshida et al. 2012).

High fat feeding at the beginning of active period appears to be important in enabling metabolic adaptation to high carbohydrate meals consumed at later time points. On the contrary, high carbohydrate input at the beginning of the waking period significantly impairs

Table 3. Circadian periods/times at which levels of various lipid metabolism parameters peak*.

	Active period	Inactive period	Specified circadian time	Species	Reference
Lipid absorption	Peaks at the beginning, together with lipase activity and chylomicron synthesis				Bray and Young (2011)
MTP activity	Peaks at the beginning				Bray and Young (2011), Pan and Hussain (2007)
Intestinal MTP activity, protein and mRNA	High			Mice	Pan and Hussain (2009), Pan and Hussain (2007)
PL synthesis & activity of key PL metabolism enzymes		Peaks during the phase			Bray and Young (2011)
TG synthesis	Peaks in the second half			Mice	Bray and Young (2011), Bray et al. (2010)
CE synthesis		Peaks			Bray and Young (2011)
Plasma lipoproteins	High			Rodents, Humans	Hussain and Pan (2012)
Apo B-100 mRNA	High			Mice	Pan and Hussain (2009)
Apo A-IV mRNA	High			Mice	Pan and Hussain (2009)
FAS expression	High			Mice	Pan and Hussain (2009)
Stearoyl CoA desaturase (SCD-1) expression		High		Mice	Pan and Hussain (2009)
DGAT1, DGAT2, MGAT2, FABP1 expression			Highest at meal times	Mice	Pan and Hussain (2009)
Muscle	Fatty acid uptake ↑			Human ?	Bass and Takahashi (2010)
Fat tissue	Lipogenesis ↑ Adiponectin production ↑	Lipid catabolism ↑ Lipid secretion ↑		Human ?	Bass and Takahashi (2010)
Liver	Cholesterol synthesis ↓ Bile acid synthesis ↓			Human ?	Bass and Takahashi (2010)
Plasma TG and cholesterol levels			High at night	Rat and mice	Pan and Hussain (2007)
Absorption of triolein and cholesterol			High at 24:00	Rat and mice	Pan and Hussain (2007)
Adipose tissue		Fat accumulation ↑		Human	Bass (2012)
Ldlr mRNA			Peaks at ZT13	Mice	Yoon et al. (2012)
Apo B mRNA			Peaks at 20:00	Mice intestine	Pan and Hussain (2009)
Apo A-IV mRNA			Peaks at 18:00-20:00	Mice intestine	Pan and Hussain (2009)
DGAT-2 mRNA			Peaks at 16:00	Mice intestine	Pan and Hussain (2009)
FAS mRNA			Peaks at 4:00 and 24:00	Mice intestine	Pan and Hussain (2009)
SCD-1 mRNA			Peaks at 12:00	Mice intestine	Pan and Hussain (2009)
DGAT-1 mRNA			Peaks at 16:00 and 20:00	Mice intestine	Pan and Hussain (2009)

MGAT-2 mRNA	Peaks at 8:00	Mice intestine	Pan and Hussain (2009)
Apo A-I mRNA	Peaks at 8:00	Mice intestine	Pan and Hussain (2009)
FABP-I mRNA	Peaks at 8:00	Mice intestine	Pan and Hussain (2009)
ACAT-2 mRNA	Peaks at 8:00	Mice intestine	Pan and Hussain (2009)
MTP activity, mRNA	Peaks at 20:00	Mice intestine	Pan and Hussain (2009)
Agpat2 mRNA	Peaks at ZT0	Mice liver	Adamovich et al. (2014)
Agapt1 mRNA	Peaks at ZT16	Mice liver	Adamovich et al. (2014)
Lpin1 and 2	Peaks at ZT12	Mice liver	Adamovich et al. (2014)

*Zeitgeber Time (ZT): ZT0 is the time the light is turned on and ZT12 is the time the light is turned off.

metabolic flexibility for responding to high fat meals at later time points. As a result, consumption of high fat meal at the end of the active phase leads to increased weight gain, adiposity, glucose intolerance, hyperinsulinemia, hypertriglyceridemia and hyperleptinemia that constitute cardiometabolic syndrome in mice. These studies suggest that metabolic homeostasis is dependent on an intact and harmonius circadian system and an appropriate time of feeding (Bray et al. 2010).

It has been reported that influences of dietary fats/oils on postprandial inflammatory changes associated with atherosclerosis might depend not only on their fatty acid compositions but also on their ingestion times. As far as the atherogenic inflammatory changes are concerned, differentiation between the reciprocal interactions of type of dietary fats/oils and their ingestion time (either in active or inactive period) occurs. Sunflower oil load activated greater number of inflammatory CD markers in passive period whereas the butter load in active phase compared to their counter period (Otlu et al. 2016).

Reprogramming circadian clock by high fat diet

High fat diet (HFD) induces transcriptional reprogramming within the clock that reorganizes the relationships between the circadian transcriptome and the metabolome. It has been reported that this reprogramming occurs via three mechanisms: either loss or induction or a phase advancement of oscillating genes (Eckel-Mahan et al. 2013).

Metabolic pathways whose oscillation was uniquely lost in HFD include ubiquitin mediated proteolysis and insulin signalling. Transcription factors oscillation of which induced by HFD were PPARγ and SREBP-1 and SRF in livers of mice (Eckel-Mahan et al. 2013). However, HFD generates both tissue and gene specific changes in expression levels of circadian clock (Bmal1 and Per2) and some nuclear receptor genes. In fat tissues, levels of Rorα, Rxrα and Pparγ were decreased in HF-fed compared to row chow fed mice. It was found that levels of Pparγ, Srebp-1c Acc and Fas each peaked at the same time of day in both fat and liver. However, in HF-fed animals, expression of each of these factors was no longer synchronous in liver and fat. Parameters altered by HF-diet in animals have been reported as increased levels of leptin and glucose during both light and dark period, increased insulin and FFA levels during dark period and decreased amplitude of corticosterol rhythm (Kohsaka et al. 2007). HFD also leads to changes in behavioural periodicity, disruption of the molecular clock in the liver and in β cells of pancreas, alterations in the rhythm of metabolic genes in the liver, impairment of insulin secretion and increase in weight which are all signs of metabolic syndrome (Schroeder & Colwell 2013).

Sleep restriction, circadian rhythm and health

Sleep is under the simultaneous control of a circadian process and a homeostatic process. The homeostatic control of sleep serves to balance sleep and wakefulness. Longer periods of wakefulness are followed by longer periods of sleep and shorter periods of wakefulness require less sleep for recovery. On the other hand, the circadian control of sleep serves to place wakefulness during the day and sleep during the night.

Ultradian day refers to a research programme using artificial sleep-wake cycles that are extremely short in duration which permits the study of sleep and wakefulness at many different circadian phases while 24 h homeostatic balance between sleep and wakefulness is intact (Sehgal 2004).

Circadian disruption induced by chronic sleep restriction in humans has been reported to decrease insulin secretion by 32% and lead to insufficient glucose homeostasis and the resulting higher glucose level. This outcome has been related to the increased risk of diabetes in those subjects who exposed to chronic sleep restriction. In order to minimize the health risk associated with diabetes in shift workers, correcting misalignment of central and peripheral circadian oscillators through strengthening the circadian rhythm synchronizers i.e. daily cycles of light and meals has been suggested (Buxton et al. 2012). In a separate study, impact of five nights of sleep restriction on glucose metabolism was investigated. Glucose and insulin levels were found to be increased. Short term sleep restrictions led to changes in glucose metabolism as well as adrenal reactivity. It was suggested that repeated sleep restriction might increase the risk for type 2 diabetes (Reynolds et al. 2012).

Recent works provide a potential link between circadian rhythm disruption caused by insufficient sleep and negative health outcomes including obesity and cardiovascular diseases. Transcriptome analysis revealed that 711 genes were up- or down-regulated by insufficient sleep. Sleep deficiency reduced the circadian amplitude of genes with a circadian expression profile. Genes affected by insufficient sleep were associated with circadian rhythms, sleep homeostasis, oxidative stress and metabolism (Moller-Levet et al. 2013). With 24 h wakefulness, reduced amplitude of daily rhythms was also reported by other workers (Davies et al. 2014). Findings of sleep deprivation also revealed a significant shift in lipid metabolism with higher level of phospholipids in both rats and humans and evidence of a systemic oxidative environment. Two metabolites, oxalic acid and diacylglycerol 36:3, were found to be robustly reduced in both species. The use of these two metabolites as cross-species markers of sleep dept was suggested (Weljie et al. 2015). This clearly indicates the interrelationship of sleep homeostasis, circadian rhythmicity and metabolism.

Some instances of insomnia could be due to disorders of circadian system. They include Advanced Sleep Phase syndrome (ASPS) and Delayed Sleep Phase Syndrome (DSPS). Autosomal semidominant mutations in rodents with short or long circadian periods have been shown to be associated with similarly advanced or delayed sleep-wake rhythms. Humans with a mutated Per2 gene display a specific sleep disorder. ASPS has been documented in humans. ASPS is characterized by a normal sleep pattern, but it is advanced by approx. 4 h. These patients feel very sleepy abnormally early in the evening and then wake up very early in the morning. ASPS is inherited as a simple autosomal dominant disorder, indicating that it is a single-gene mutation. DSPS has also been associated with a structural polymorphism in the hPer3 gene. DSPS patients have difficulty in falling asleep before 2 or 3 am and consequently will not wake up spontaneously until late in the morning. (Refinetti 2000; Sehgal 2004).

Future clinical perspectives in circadian rhythm

Significance of misalignment between central and peripheral clocks

Some of the metabolic consequences of circadian disruptions have been suggested to arise from a misalignment of central pacemaker with peripheral pacemaker. Changing the timing of feeding and thereby forcing a nocturnal rodent to eat during day time shifts the phase of clock gene expression in peripheral tissues while expression in the SCN remains entrained

to the light/dark cycle irrespective of feeding schedule. This leads to a phase misalignment of peripheral oscillators with respect to that of the central circadian pacemaker which might play a role in metabolic dysregulation. As a result of the dyssnchronization, coordinated response to a meal might be disturbed thus leading to unusual response to food intake. Peripheral oscillators of metabolism coordinate both metabolic and circadian pathways needed for optimal hepatic lipid metabolism and homeostasis (Cermakian & Boivin 2009; Duez & Staels 2010; Buxton et al. 2012). The challenges lying ahead for researchers is to determine biomarkers for determining desynchronization between central and peripheral circadian clocks.

Determination of internal body time by blood metabolomics

Shift working, jet lag and other irregular lifestyles cause changes in the internal body time of individuals. In addition, genetic differences also cause changes in the internal body time of individuals. Time-table method has been proposed as an tool to detect internal body time differences caused by abnormal environments or genetic differences by quantifying clock controlled metabolites in plasma. Recent studies indicate that a molecular time table can be a convenient diagnostic tool. The measurement of internal body time by blood metabolomics, the molecular-timetable method, is conducted by measuring the body time of the day by profiling the rhythmic alterations of substances in the blood which requires quantification of many clock-controlled metabolites in human or mouse plasma. The internal body time detection method is essential for the development of chronotherapy for treatment aproaches considering interindividual differences as well as for efficient time-restricted feeding to avoid or cure obesity. Thus, the body time information proposed by various workers can be employed to maximize potency and minimize toxicity during drug administration and thus will lead to highly optimized and personalized medicine in the future (Minami et al. 2009; Kasukawa et al. 2012).

Concluding remark

A large body of evidence from both human and animal studies now indicates a relationship between circadian disorders and altered metabolism. Various feeding time and nutrient compositions, irregular life style, sleep restrictions have an impact on the circadian rhythmicity and on the synchrony between the central and peripheral clocks which might result in metabolic diseases including diabetes, insulin resistance, hyperlipidemia, obesity. Present studies on quantification of clock controlled plasma metabolites might pave the way for sensitive and accurate detection of circadian rhythm disorders and for maximizing the effciency of drug administration by considering internal body time of individuals.

Disclosure statement

No potential conflict of interest was reported by the authors.

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