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Circadian-Clock Regulation on Lipid Metabolism and Metabolic Diseases

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Abstract

The basic helix-loop-helix-PAS transcription factor (CLOCK, Circadian Locomoter Output Cycles Protein Kaput) was discovered in 1994 as a circadian clock. Soon after its discovery, circadian clock, Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also call BMAL1), was shown to regulate adiposity and body weight by controlling on the brain hypothalamic suprachiasmatic nucleus (SCN). Farther, circadian-clock genes were determined to exert several of lipid metabolic and diabetes effects, overall indicating that CLOCK and BMAL1 act as a central master circadian clock. Master circadian clock acts through the neurons and hormones, with expression in the intestine, liver, kidney, lunge, heart, SCN of brain and other various cells types of the organization. Among circadian-clock genes numerous metabolic syndrome are the most important in the regulation of food intake (via regulation of circadian-clock genes or clock-controlled genes in peripheral tissue), which lead to a variation in plasma Phospholipids and tissue Phospholipids. Circadian-clock genes affects the regulation of transporters and proteins included in the regulation of Phospholipid -metabolism. These genes have recently received increasing recognition because a pharmacological target of circadian-clock genes may be of therapeutic worth to make better resistance against insulin, diabetes, obesity, metabolism syndrome, atherosclerosis and brain diseases. In this book chapter, we focus on the regulation of circadian clock and summarize its phospholipid effect as well as discuss the chemical, physiology and molecular value of circadian clock pathway regulation for the treatment of plasma lipids and atherosclerosis.

Keywords

Circadian clock; Phospholipids metabolism; lipid metabolism; atherosclerosis; Diet-induced obesity

1. Introduction

Sleep disorders are now a major health threat to our life, may result in more than 22 million Americans suffering from sleep disorder annually [1–15]. At least 38,000 people die

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from heart disease directly complicated by a sleep disorder [1–15]. A sleep disorder now affects almost every ethnicity and cultural society, setting an enormous load on the modern healthcare system in the United States and worldwide. From the numerous complications associated with sleep disorder are major metabolic syndrome, atherosclerosis, hypertension, dyslipidemia, obesity, diabetes mellitus, cardiovascular diseases, several cancers, and certain types of brain diseases such as Alzheimer's disease [1–15]. Emphasizing the consequences of sufficient lipid buffering, atherosclerosis represents, to date, the very high common cause of lipid-related diseases [16–20]. According to sleep being a major risk factor for development of atherosclerosis, ample sleep achieved by either dieting, lifestyle, pharmacology, changes in circadian rhythms, proinflammatory responses and metabolic effects improving sleep quality and pattern, have shown, in numerous pre-clinical studies, many promising effects. For example, the ATP binding cassette subfamily G member 5/8 (ABCG5/8), N-terminal Niemann-Pick C1 (NPC1) intracellular cholesterol transporter 1 (NPC1L1) and Microsomal triglyceride transfer protein (MTTP) inhibitor are adequate to indicate significant improvements in systemic lipid metabolism and atherosclerosis-linked comorbidities [4;21–29]. Further emphasizing, the direct relationship between atherosclerosis and lipid regulation, plasma cholesterols reduced by ABCG5/8, NPC1L1 and MTP inhibitors, which are regulated by circadian-clock genes, most often result in whole resolution of atherosclerosis, an opinion that encouraged the American Heart Association and National Institutes of Health to recommend such inhibitors under assured conditions for the treatment of atherosclerosis. Since the correlation between food intake and Phospholipid regulation is highly confirmed by several basic research studies, inhibitors to inhibit food intake intuitively appear promising to improve Phospholipid metabolism [30–34]. Under this reason, remarkable examples of such strategies are the administration of MTP inhibitor, which not only reduces plasma cholesterol through their MTTP inhibition but also decreases Phospholipid metabolism through their ability to reduce lipid absorption via circadian rhythm regulation of food intake [35;36]. We have shown that the circadian-clock genes can regulate plasma triglycerides and cholesterol, and regulate cholesterol and triglyceride absorption and metabolism [28;29;37–40]. A prominent example of circadian-clock gene regulation, is the circadian-clock with a mutant CLOCK gene, which improve body fat mass and body weight through regulation of intestinal lipid absorption and adipose lipid metabolism [38;40–43]. However, whether circadian-clock genes regulate Phospholipid metabolism is not commonly known.

Phospholipids are polar, ionic compounds composed of an alcohol that is attached by a phosphodiester bridge to either diacylglycerol or sphingosine [35]. There are two classes of Phospholipids: those that have glycerol (from glucose) as a backbone are called glycerophospholipids and those that have a sphingosine (from serine and palmitate) are called sphingophospholipids. Most Phospholipids are synthesized in the smooth endoplasmic reticulum [35]. From there, they are transported to the Golgi apparatus and then to membranes of organelles or the plasma membrane of organelles [44]. They could also be secreted from the cell by exocytosis. Phosphatidylcholine (also called PC) and Phosphatidylethanolamine (also called PE) are the most abundant Phospholipids in most eukaryotic cells [35;45]. The primary route of their synthesis uses choline and ethanolamine obtained either from food intake or from the turnover of the body's Phospholipids

[44]. Sphingomyelin is one of the principal structural lipids of the membranes of nerve tissues. It is synthesized from ceramide (an acyl sphingosine) and phosphatidyl choline. Sphingomyelin is also hydrolyzed into ceramide and phosphoryl choline [46]. Ceramide is further degraded to sphingosine and free fatty acid (FA) [46]. In this book chapter, we summarized the regulation of circadian-clock genes with a special focus on their role to control Phospholipid metabolism. A key central field will thereby be the topic of whether disordering the circadian-clock genes will regulate transcription factors, and will the function of a protein pathway be of chronotherapeutic value to progress Phospholipid metabolism?

2. Origins of the mammalian clock

Several biological, physiological, and behavioral activities show characteristic recurrence with 24-h intervals related to sunrise and sunset. Light entrains the central clock present in two lateral SCN in the hypothalamus via the retinohypothalamic tract. The master circadian clock arises from auto regulatory transcriptional, translational, and posttranslational feedback loops of few transcription factors encoded by “clock” genes, including circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1), neuronal PAS containing protein 2 (NPAS2), period genes (Period1/2/3, *PER1*/2/*3)*, and cryptochrome genes (*CRY1/2*) [24;47–50]. The BMAL1:CLOCK and BMAL1:NPAS2 heterodimers bind to *cis*-acting E-box sequences present in the promoter regions of *PER1/2/3* and *CRY1/2* and enhances their expression, constituting a positive feed-forward loop. Unlike CLOCK and BMAL1, PER1-3 and CRY1-2 protein can dimerize and translocate to the nucleus, then dimerize the PER1–3:CRY1–2 complex, inhibiting the activity of CLOCK:BMAL1 or NPAS2-BMAL1. In the center of the hypothalamus, circadian-clock genes are localized in the SCN and express neuronally and hormonally [16;25;51]. Zhang et al has reported that the liver had the most circadian genes, then kidney as the 2nd, whereas the hypothalamus had the fewest (Figure 1) [52]. SCN is responsible for controlling circadian rhythms, these circadian-clock protein’s neuronal and hormonal activities regulate different body functions in the 24- hour cycle, such as body temperature, wakeup/sleep, and food intake. To activate CLOCK:BMAL1 or NPAS2:BMAL1 there are 450 unique protein modifications [52]. Clock genes also need multiple post-translational modifications, including phosphorylation, ubiquitination, acetylation and SUMOylation to regulate various physiological functions [53–55]. This post-translational modification of BMAL1 is regulated by ubiquitin-specific protease 2 (USP2) [54;55]. USP2 is essential to deubiquitinating PER1, CRY1 and CRY2 in vivo [54–57]. This mechanism was demonstrated by the absence of deubiquitinated Per1, Bmal1, Cry1 and Cry2 in mice deficient in USP2 [55].

BMAL1:CLOCK is a heterodimer formed via CLOCK with 361 amino acids and BMAL1 with 387 amino acids. CLOCK and BMAL1 have the same one, basic, helix-loop-helix (bHLH) binding of protein to DNA via recognized E-box sites, through hydrogen bonding, between serine residues and DNA. As we know, E-box sites are about 20 base pairs upstream of genes with a major 5’-CACGTG-3” canonical motif. CLOCK and BMAL1, or NPAS2 (a paralog of clock) can not only recruit transcription factors to the E-box site, but also can upregulate transcription of the target genes such as, nuclear receptor subfamily

1, group D, member 1 (NR1D1, Rev-erbα), D-Box Binding PAR BZIP transcription factor (DBP), peroxisome proliferator-activated receptor (PPAR) alpha (PPARα), small heterodimer partner (SHP), GATA binding protein 4 (GATA4), and paired box protein 4 (PAX4) [16;24;28;29;40;47–50;58] (Figure 2). These genes can also, through recruitment of histone acetyl transferases, de-condense the nucleosome into heterochromatin allowing transcriptional machinery access to the DNA, such as mutant CLOCK, which down-regulates upstream transcription factor2 (USF2). In addition, USF1 serves as a suppressor of the circadian clock mutant, revealing the nature of the DNA-binding of the Clock:Bmal1 complex in mice [59]. This data also suggests that USF1 and USF2 are an important modulator of molecular and behavioral circadian rhythms in mammals. In addition, it is possible that CLOCK regulates USF2 through the histone acetyl transferase pathway. However, more experiments are required to understand this mechanism.

The reported levels of CLOCK and BMAL protein do not show dramatic circadian oscillations in mammalian brains, however, reflecting the species-related phosphorylation in circadian clock protein show clear circadian oscillations with time-dependent, post-translational regulation [53]. The degradation of CLOCK and BMAL1 is more important for transcription activation of clock-controlled genes through E-boxes in their promoters [60]. For example, estrogen receptors are regulated by CLOCK [61]. CLOCK:BMAL1 proteins can bioaccumulate by proteasome inhibitor MG132 by preventing their protein degradation. MG132 is an inhibitor decreasing E-Box-mediated transcription by interfering with CLOCK:BMAL1 regulation cycles in humans. Whereas in rodents, CLOCK19 protein is hypo-phosphorylated to a higher extent than those of wild-type CLOCK [62]. In vitro studies have also shown several enzymes (such as Casein kinase I/II, Glycogen synthase kinase 3 beta (GSK-3β) and Cyclin-dependent kinase 5) are responsible for CLOCK:BMAL1 degradation [63–65] [66;66;67]. For example, GSK-3β-catalyzed phosphorylation can phosphorylate Ser431 of CLOCK dependent site Ser427 and Thr21 of BMAL1 dependent site with Ser17, to induce higher activity of CLOCK and BMAL1 under unstable conditions. Similarly, protein kinase CR can phosphorylate and stabilize BMAL1 by eliminating BMAL1 polyubiquitination [66;67]. Regulation of CLOCK:BMAL1 phosphorylation affects transcription through alterations in DNA binding [68]. In addition, CLOCK:BMAL1 activity is affected not only by phosphorylation, but also by ubiquitination to induce its transactivation and degradation [69]. For example, SUMOylation and O-GlcNAcylation induce ubiquitination of BMAL1 at Lys259 and at Ser418, respectively, to increase BMAL1 transactivation and degradation [69]. In addition, HECT-type E3 ligase can promote ubiquitination of BMAL1 and CLOCK [66;70;71]. Moreover, there are several studies showing that Sirtuin 1 binds to CLOCK and BMAL1 and deacetylates BMAL1 at lys537 [71], thus preventing CRY1 recruitment and restarting the transactivation of the clock gene. Furthermore, HAT activity required site motif A of CLOCK and acetylation site of BMAL1 are required to rescue the cellular clock-controlled gene rhythm [72;73]. Histone modifications were essential for normal clock function [71;72;74–77]. CLOCK:BMAL1 heterodimers shuttle between the nucleus and the cytosol, thus suggesting that the dimer-protein modulation are involved in several post-translation and transcription levels.

3. Physiological functions of Circadian clock

While major studies indicate that most metabolic functions of circadian clock require transcription and post-translation levels, there is gain experience indicating that circadian clock genes have physiologically related functions on a body metabolism, potentially through several pathways that have yet to be identified. Circadian-clock genes respond to external stimuli and the one prominent effect of the circadian-clock gene is its ability to diurnal control food intake. We have shown that circadian-clock genes and lipid transport proteins are expressed in the small intestinal enterocytes and respond to food entrainment in wild-type mice [38]. Dominant-negative Clock mutant protein mice (*Clock*$^{\Delta 19/\Delta 19}$ or *Clk*$^{mt/mt}$) disrupt the circadian expression and food entrainment of the clock genes [38;41]. In addition, the absorption of lipids was high in Clock mutant mice [38;40]. Our data also suggests that Clock plays an important role in light and food entrainment of intestinal function. To understand the mechanism of Clock genes regulating lipid absorption and metabolism, we studied the role of Clock gene in the diurnal regulation of plasma triglyceride-rich apolipoprotein B-lipoprotein and *MTTP*. Clock mutant mice showed sustained hypertriglyceridemia and high *MTTP* expression. We found that CLOCK-knockdown-activated *MTTP* promoter and reduced SHP, in the Human liver cell line Huh7 cells, CLOCK temporally interacts with the E-box site and increases *SHP* expression, whereas SHP reduces *MTTP* expression by differentially interacting with Hepatocyte nuclear factor 4 alpha and the liver receptor homolog−1 [40]. In *Clock*$^{mt/mt}$ mice, however, the binding of Clock to *SHP* promoter did not show cyclic change and SHP mRNA levels were relatively low and did not change [40]. This data shows that a decreased interaction of *SHP* with these transcription factors is associated with increased *MTTP* expression. Therefore, S*HP* is a clock-controlled gene that transmits information from *Clock* to *MTTP*. Additionally, we showed, for the first time, that *Clock*$^{\Delta 19/\Delta 19}$ mutant protein enhances plasma cholesterol and atherosclerosis in the low density lipoprotein receptor knockout (*Ldlr*$^{-/-}$) and apolipoprotein E knockout (*ApoE*$^{-/-}$) atherosclerosis animal models [29]. In addition, Clock mutant protein affects macrophage function. Macrophages from *Clock*$^{\Delta 19/\Delta 19}$ mice took up more oxidized lipids and were defective in cholesterol efflux. Molecular studies showed that Clock regulates ATP Binding Cassette Subfamily A Member 1 expression and cholesterol efflux in macrophages via Usf2 [29]. In addition, we recently showed that global Bmal1-deficient mice or hepatic-specific Bmal1 knockout mice also have an impaired cholesterol metabolism, display hepatic cholesterol efflux into bile, develop atherosclerosis when fed with an atherogenic diet and potentiate the development of atherosclerotic lesions in the *Ldlr*$^{-/-}$ and *ApoE*$^{-/-}$ atherosclerosis animal models [28]. Liver-specific inactivation of Bmal1 led to elevated plasma low density lipoprotein (LDL) and / very low-density lipoprotein (VLDL) cholesterol levels as a consequence of the disruption of the Pcsk9/Ldl receptor regulatory axis [22;28;78].

Phosphatidylcholine is one of Phospholipid that occupies 70% of VLDL Phospholipids. Phosphatidylcholine biosynthesis is known to be required for VLDL secretion [78]. This has also shown that diurnal variation of VLDL concentration is linked to the clock-controlled production of Phosphatidylcholine. Furthermore, Ma et al. have identified two distinct groups exhibiting rhythmic and non-rhythmic patterns of gene expression during light-dark

cycles, according to database of the circadian regulation of lipid-associated Genome-Wide Association Studies (GWAS) candidate genes in mouse liver [79]. Liver-specific Bmal1 knockout mice increased plasma Ldl/Vldl cholesterol levels through disordered Pcsk9/Ldl receptor expression [79].

In line with this idea, circadian-clock genes affect food intake, body weight, plasma glucose and lipids, has protective effects on the adipose tissue, heart, liver, intestine and affects Phospholipid metabolism via several pathways [4;21;80–82]. In other words, the circadian-clock may through several mechanisms control Phosphatidylcholine (is one Phospholipids that make up 50% of total cellular Phospholipid biosynthesis), as the Phosphatidylcholine phenotype can be copied by different circadian-clock gene mutations [83]. Wild-type mice in normal light and dark cycles, display a rhythmic accumulation of hepatic phosphatidylcholine with a peak at Zeitgeber time (ZT) 22–0. Bmal1-deficient (*Bmal1*$^{-/-}$) mice show elevated phosphatidylcholine levels in the liver associated with an atherogenic lipoprotein profile [78]. To investigate whether the circadian variation of Phosphatidylcholine levels is the result of a circadian regulation of Phosphatidylcholine biosynthesis, Grechez-Cassiau et al. found that Choline Kinase alpha (Chkα) gene is a clock-controlled gene in the liver [78]. Chkα gene expression is regulated by the Rev-erbα and RAR related Orphan Receptor A (Rorα) nuclear receptors [78]. Thus, hepatic phosphatidylcholine is regulated by the circadian-clock gene through a Bmal1-Rev-erbα-Chkα axis and suggests that an intact circadian timing system is important for the temporal coordination of Phospholipid metabolism. The Rev-erbα subtype appears to be a key circadian regulator of Phosphatidylcholine metabolism in the liver through the rhythmic transcriptional repression of the Chkα gene. Thus, a likely mechanism by which hepatic Phosphatidylcholine levels are increased in the *Bmal1*$^{-/-}$ mice is that Chkα up regulates by the high of total Choline Kinase activity [78]. In addition, there is a low Rev-erbα gene expression level in the Per1/Per2 double knockout mice [84]. Twenty-four out of twenty-seven Phosphatidylcholine species were arrhythmic by the lipidomic profiling, although 16% of lipid metabolites were still oscillating in liver [84]. These studies suggest that a genetic disruption of the circadian clock system compromises Phosphatidylcholine homeostasis.

4. Preclinical studies on diurnal rhythm in Phospholipid metabolism

Minami et al. found oscillatory peaks of phospholipids was detected by Liquid chromatography–mass spectrometry (among these time-indicating metabolites) [85]. Fourteen oscillatory peaks were identified as various types of lysophosphatidylcholines with different unsaturated FAs [85]. As mentioned above, in mammalian cells, Phosphatidylcholine is one of all Phospholipid, constituting 50% of total cellular Phospholipids [86], Phosphatidylcholine is also the main circulating Phospholipid in plasma, where it is critical for the assembly and secretion of lipoproteins by the liver. Hepatica Phospholipids enter in bile-salt mediated micelle formation in the intestinal lumen, which facilitates the absorption of lipid-soluble nutrients from the diet [87]. Several studies have shown that serum Phosphatidylcholine is shown to be subjected to temporal control that could be correlated with rest-activity cycles and feeding [84;88]. Phosphatidylcholine plays an important role in mammalian cell signaling [89] as well as in oncogenic signaling

pathways [78;89–91]. Numerous studies have evaluated the circadian-clock genes effect on Phospholipid metabolism. Diurnal rhythm of retinal–Phospholipid–synthetic enzyme has been shown in the retina of rats [92]. Retinal Phospholipid synthetic enzymes showed daily variations, in retinal ganglion cells (RGCs) of chicken when in constant darkness. [^{32}P]Phospholipid display circadian oscillations both in, in vivo chicken kept in constant light, and in cultures of immunopurified embryonic RGCs [92]. Several distinct enzymes, lysophospholipid acyltransferases, phosphatidate phosphohydrolase, and diacylglycerol lipase, in the pathway of Phospholipid biosynthesis and degradation have shown diurnal variation [93]. These activities of these enzymes are high during the subjective day and low at night, as were the metabolic changes observed in the in vivo labeling of Phospholipid in cultures of purified embryonic RGCs [93;94]. In addition, glycerophospholipid synthesis has also shown diurnal rhythm in retinal inner nuclear layer cells [93;94]. Biosynthesis of Phospholipid has shown the circadian cycle by serum shock in cultured quiescent NIH3T3 cells, this cycle is abolished by knock–down Per1 gene, suggesting that the biosynthesis of Phospholipid circadian cycle in cultured fibroblasts depends on the endogenous circadian clock [94;95;95–97]. Ruggiero et al. showed that the diurnal rhythm of phospholipid phosphatidylserine demarcation of photoreceptor outer segments tip, is not intrinsic to rod photoreceptors but requires activities of the retinal pigment epithelium as well [98]. In line with the circadian cycle of Phospholipid or Phospholipid biosynthesis in vivo and in vitro, levels of serum Phospholipids such as phosphatidylcholines (18:0/18:1) or 1-stearoy1-2-oleoyl-sn-glycero-3-phosphocholine, are typically regulated in mice lacking circadian clock-collected gene PPAR gamma (PPARδ) activity [98]. Serum Phosphatidylcholine (18:0/18:1) can reduce postprandial lipid levels and Phosphatidylcholine can increase FA utilization through muscle PPAR alpha (PPARα) [98]. When mice were fed with a high fat diet, the rhythm of Phosphatidylcholine (18:0/18:1) was diminished. Phosphatidylcholine (1:0/18:1) administration in db/db mice (a model for diabetic dyslipidemia) can improve metabolic homeostasis, suggesting that alterations in diurnal hepatic PPARδ-Phosphatidylcholine (18:0/18:1) signaling affects metabolic disorders, including obesity [99]. Obesity can alter circadian rhythms in multiple tissues. Diet induced obesity altered the rhythm pattern of serum Phosphatidylcholine [99;100]. As a Phospholipid outcome, ceramide, a class of sphingolipids, Jang et al. showed that the ceramide concentration in WT mice showed a strong peak at Zeitgeber Time 9 (ZT9; 9 h after lights-on time) and ZT21 but no rhythmicity in ceramide expression was seen in Per1/Per2 double KO mice [101]. To understand the mechanism of diurnal rhythm of ceramide, they also measure several gene expressions including via sphingomyelinase (SMase), or by ceramide synthase (CerS)-mediated synthesis, both are important for sphingomyelin hydrolysis to ceramide. Jang et al. found that CerS2 expression levels showed a biphasic pattern of expression in WT mice but no rhythmicity in Per1/Per2 double KO mice [102]. While the neutral SMase (nSMase) and acidic SMase (aSMase) mRNA in WT mice were expressed in a circadian variation, the correlation between the expression levels of these SMases with times of day was weak in Per1/Per2 double KO mice [102]. Collectively, this study suggests that both SMases and CerS2 mRNA expression are regulated by the presence of mPer1/mPer2 circadian-clock genes in vivo, and imply that ceramide may play a vital role in circadian rhythms and physiology [102]. However, the molecular mechanism of circadian-clock genes regulating phospholipid metabolism are still unclear and limited.

5. Clinical studies on circadian clocks role in Phospholipid metabolism

Animal research shows a clear involvement of membrane-derived Phospholipid in circadian rhythms. Additionally, 7–20% of metabolites in human blood have been observed showing circadian variation [85;103–106]. Under a series of preclinical studies, the existence of both daily change and seasonal variations, affect the composition of Phospholipids in human cell membranes [12;107;108]. Over 1 year, in 20 healthy subjects, Ruf et al. found that 11 of 13 Phospholipids' FAs content showed significant daily rhythms and were largely synchronous among subjects [108]. This data is supported by several other studies, overall indicating that human physiology is still dominated by geophysical sunrise and sunset, resulting in a strong daily cycle [107;109]. However, seasonal rhythms are less well defined. FA's derived from Phospholipids also play a role as precursors of prostaglandins, thromboxanes, and leukotrienes. A much more likely candidate for such a function of rhythmicity is the interaction between membrane FA's and transmembrane proteins. It is a possible explanation for rhythmic alterations of membrane composition [108]. In particular, a link between sleep deprivation and Phosphatidylcholine is also showed by the result that both the circadian system and plasma lipids display a reciprocal correlation over the day with a subset of Phosphatidylcholine and triglyceride species in plasma being high when sleep deprived in twenty total subjects of young-aged-healthy-ethnic Chinese males [110].

Epidemiological studies comfort the relationship between the circadian system and the regulation of diurnal rhythm of Phospholipids. A marked circadian variation was recorded in plasma total-cholesterol, high-density-lipoprotein–cholesterol, Phospholipid, and total lipid concentration in healthy Indians of different age groups of 162 total subjects [111]. Plasma Phospholipid concentrations were characterized by a circadian rhythm in all age groups. Females had numerically higher values than males. However, the rhythm peak was significantly changed by age, reaching a maximum in middle adulthood and decreasing in the older age group [111;112]. This suggests that the diurnal rhythm of plasma Phospholipids is associated with age, gender, diet and smoking and affects circulating plasma lipid components in healthy Indians. In addition, a 24-hr time series of plasma metabolites has been simultaneously assessed in Type 2 Diabetes, compared with an age and weight-matched control group during a controlled daily routine [113]. Similarly, a total of 100 of 663 metabolites, representing all metabolite categories, showed diurnal rhythmic concentrations that exceeded the bonferroni threshold, showing the peak times of all Phospholipids were clustered during the afternoon-midnight [114;115].

We previously showed that peptide-like drugs H+-peptide cotransporter 1, Pept1, showing diurnal rhythm, could influence the pharmacokinetics of peptide-like drugs [116–118]. Drugs statins, a HMG-CoA reductase inhibitor that is in clinical evaluation for the treatment of Type 2 Diabetes and atherosclerosis, shows beneficial effects on plasma lipids [119–121]. Interestingly, statins was recommended to be administered in the evening [119;121]. However opinions differ on the best time to take statins. Simvastatin was reportedly better in the evening too, but, simvastatin taken in the evening was not better than when it was taken in the morning by a different study group [122–124]. It remains in clinical evaluation for treatment. Lipidomics can be used to examine differences in circadian responses to medications that target lipid pathways, such as statins, and to better characterize the

mode of action of such drugs. So far, there is collecting preclinical and clinical studies overall suggesting a beneficial effect of chronotherapeutics. Beyond circadian-clock's direct Phospholipid role, it has to be noticed that food intake and body weight change because of circadian clock pathway regulation might provide a particular potential for secondy improvement of Phospholipid treatment.

6. Conclusion

The circadian clock system has, over the last twenty years, been researched act involved in a number of metabolic functions that go well over their primary classification as a regulator affecting wakeup/sleep and food intake. Along with circadian clocks regulation in Phospholipid metabolism; various studies evaluated the therapeutic effect of Phospholipid modulation. The circadian clock correlating to Phospholipids might offer a potential treatment for atherosclerosis and obesity associated with pathological atherosclerosis. Circadian clock altering of molecular time will be of chronotherapeutic value to reduce metabolic disorders, impaired immune function, and accelerated aging, and to improve Phospholipid metabolism and cardiovascular diseases. Importantly, while disordered circadian-clock genes and sleep disorder is known to affect more than 50 million U.S. residents (https://www.ncbi.nlm.nih.gov/books/NBK19961/), it is possible that other physiology function of circadian clock are yet to be understood.

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Abbreviations:

ABCA-1
ATP-binding cassette transporter 1

ABCG5/8
ATP binding cassette subfamily G member 5/8

***ApoE*$^{-/-}$**
Apolipoprotein E knockout

aSMase
Acidic SMase

BMAL1
Aryl hydrocarbon receptor nuclear translocator-like protein 1

CerS
Ceramide synthase

Chkα
Choline Kinase alpha

CLOCK
Circadian Locomoter Output Cycles Protein Kaput

***Clock*$^{\Delta 19/\Delta 19}$ or *Clk*$^{mt/mt}$**
Dominant-negative Clock mutant protein mice

CRY1/2
cryptochrome 1,2

FA
Fatty Acid

GSK-3β
Glycogen synthase kinase 3 beta

HAT
Histone acetyltransferase

HMG-CoA reductase
3-hydroxy-3-methyl-glutaryl-CoA reductase

***Ldlr*$^{-/-}$**
Low density lipoprotein receptor knockout

LDL
Low-density lipoprotein

MTTP
Microsomal triglyceride transfer protein

NPAS2
Neuronal PAS containing protein 2

NPC1L1
NPC1 intracellular cholesterol transporter 1

nSMase
Neutral SMase

PC
Phosphatidylcholine

PC
Phosphatidylcholine

PCSK9
Proprotein convertase subtilisin/kexin type 9

PE

Phosphatidylethanolamine

Period1/2/3
Period genes 1, 2, 3

PPARδ
Peroxisome proliferator-activated receptor delta

Rev-erbα
Nuclear receptor subfamily 1, group D, member 1

RGCs
Retinal ganglion cells

Rorα
RAR related Orphan Receptor A

SCN
Suprachiasmatic nucleus

SHP
Small heterodimer partner

SIRT1
Sirtuin 1

SMase
Sphingomyelinase

UBE3A
HECT-type E3 ligase

USF2
Upstream Transcription Factor 2

VLDL
Very low-density lipoprotein

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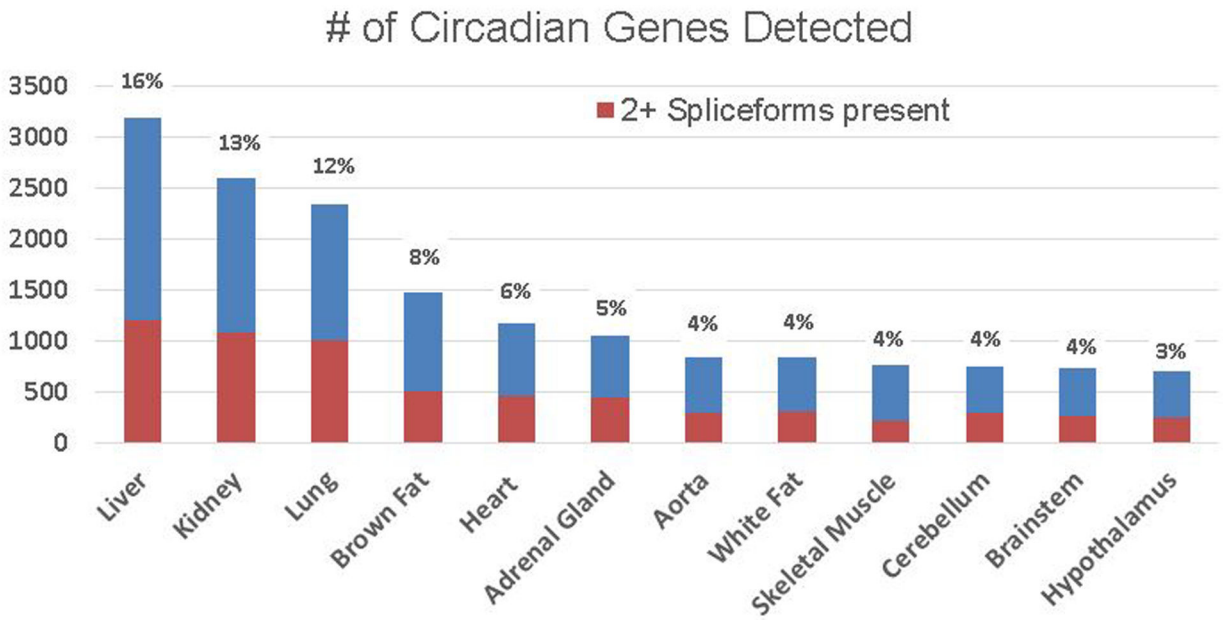

Figure 1. Number of circadian clock genes detected in each organ.

Circadian expression of protein-coding genes in different tissue. Blue marks indicate the number of genes with at least one spliceform detected by RNA-seq. Orange marks indicate the number of genes with at least two spliceforms detected by RNA-seq. Blue numbers to the top of each bar states the percentage of protein-coding genes with rhythmic expression in each organ of Zhang et al. publication. Figure modified according to Zhang et al publication in PNAS[52].

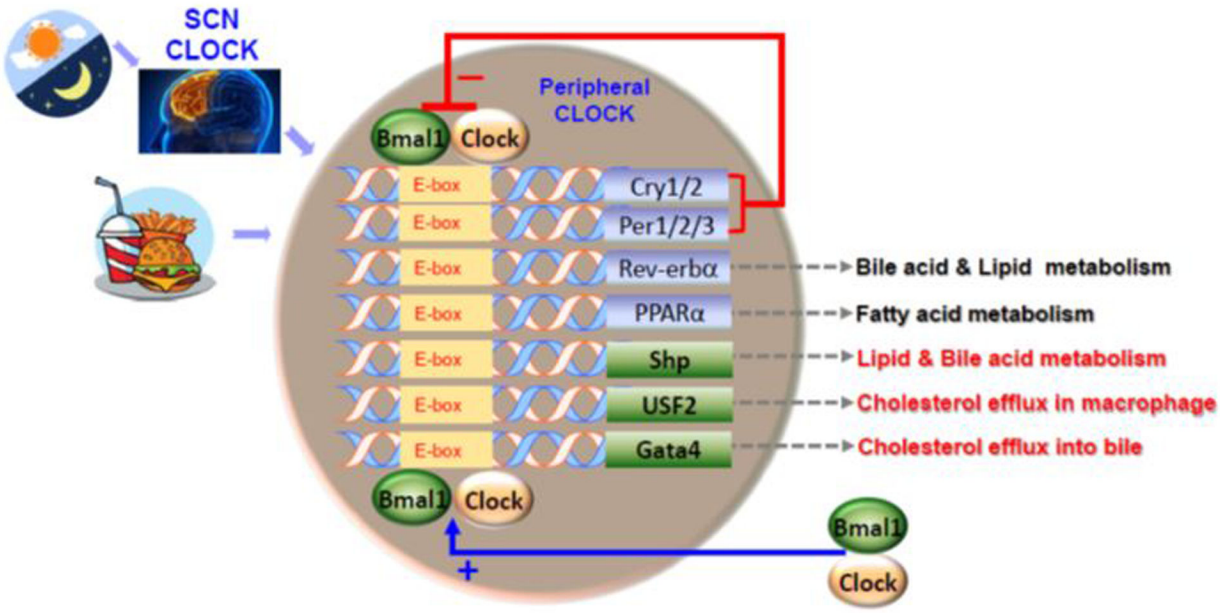

Figure 2. Clock and clock-collected genes regulate metabolic function.

Both light- and food-entrained oscillators appear to affect the expression of circadian-clock genes and clock-collected genes in the peripheral tissue. In SCN and peripheral, Clock :Bmal1 heterodimerize to activate transcription of circadian target genes including the genes of *Per1/2/3 and Cry1/2. Per1/2/3 and Cry1/2* interact and inhibit Bmal1 and Clock. We have shown that Clock and Bmal1 regulate several transcription factors such as Shp, Usf2 and Gata4 regulating the expression of several genes involved in lipid metabolism as well as other pathways that affect metabolism.