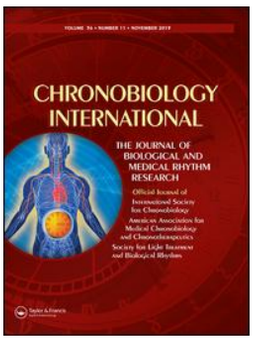

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Circadian rhythms and bile acid homeostasis: a comprehensive review

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ABSTRACT

Circadian rhythms are prominent in nearly all living organisms and regulated by an endogenous central circadian clock that synchronizes physiological and behavioral processes to the external environment. The circadian clock is driven by the transcriptional-translational negative feedback loop that plays important role in the control of liver function and metabolism. As crucial signaling molecules, bile acids participate in regulating the metabolisms of glucose, lipids, energy, medications, and bile acids themselves. Bile acid synthesis, as well as bile acid-activated key enzymes and nuclear receptors involved in bile acid regulation, also displays distinct circadian variations. Circadian deregulation, such as the consequence of circadian clock disruption, restricted feeding and sleep disruption, can disrupt bile acid homeostasis, resulting in cholestatic and metabolic diseases. This review addresses the circadian rhythms in bile acid synthesis and transport and potential consequences of abnormal disrupted circadian rhythm of bile acid homeostasis.

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Introduction

Physiological and behavioral processes of most living organisms, including prokaryotes, fungi, plants and mammals, exhibit rhythmicity with a period of approximately 24 h and in synchrony with cycles of the external environment. In mammals, circadian rhythms are driven by the central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus that in turn coordinates peripheral clocks of cells, tissues and organs (Ohdo et al. 2010). Almost all biological rhythms are regulated by the circadian clock, such as the sleep-wake cycle, body temperature, blood pressure, heart rate and energy metabolism (Griffett and Burris 2013). The circadian properties of organisms play vital roles in maintaining homeostasis and responding to the changes in environmental conditions.

Circadian rhythmicity is also crucial for the regulation of metabolic pathways to maintain the physiological homeostasis in the liver. Approximately 10% of genes within the liver transcriptome is rhythmically expressed (Panda et al. 2002). Many metabolic pathways of the liver, including those involved in the regulation of glucose, lipid, cholesterol and nutrient homeostasis, together with bile acid synthesis and metabolism, show obvious circadian variation that are influenced by the feeding time and light-dark cycle (Adamovich et al. 2014; Bass and Takahashi 2010; Ferrell and Chiang 2015a; Froy 2013).

About 30 years ago, circadian rhythms of bile acid concentration and synthesis were reported (Duane et al. 1979; Edwards et al. 1972; Gielen et al. 1975). The key enzymes of bile acid synthesis also display distinct 24-h variation in their expression and activity (Chiang et al. 1990; Lavery and Schibler 1993; Noshiro et al. 1990). Moreover, bile acid-related nuclear receptors (NRs) show circadian variation and rhythmically regulate genes involved in bile acid synthesis and metabolism (Bookout et al. 2006; Zhang et al. 2011). Recently, bile acids have been recognized as signaling molecules that regulate various processes in the metabolism of glucose, lipids, bile acids, medication and energy substrates as well as immune response through activation of intracellular ligand-activated NRs, such as farnesoid X receptor (FXR) and cell surface G protein-coupled receptors (e.g. G-protein-coupled receptor TGR5) (Li and Chiang

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2014; Stanimirov et al. 2015). Therefore, 24-h variation of bile acids may influence the regulation of glucose, lipid and energy metabolism in mammals. Disruption of circadian rhythm may result in the dysregulation of bile acid homeostasis that serves to accelerate the progression of diabetes, obesity as well as cholestasis, nonalcoholic fatty liver and metabolic diseases (Froy 2012; Rajani and Jia 2018; Shetty et al. 2018; Shi et al. 2013). This review summarizes the evolving roles of circadian rhythms in the regulation of bile acid homeostasis, thus providing a new perspective for understanding the circadian rhythm-driven mechanisms underlying the pathogenesis and development of liver and metabolic diseases.

Bile acid homeostasis

Bile acids, as amphipathic molecules, are synthesized by the enzymatic oxidation of cholesterol in the liver. They function as detergents to facilitate digestion and absorption of fatty acids, monoacylglycerols, dietary lipids and fat-soluble vitamins (Hofmann 2009). In general, bile acids are synthesized in hepatocytes, stored in the gallbladder, secreted into the intestine, reabsorbed in the distal ileum and transported back to the liver through portal blood for re-secretion into the bile. This process is termed the enterohepatic circulation of bile acids. The self-regulation mechanism of bile acids protects against hepatic bile acid accumulation and bile acid cytotoxicity, thereby playing a major role in liver physiology and pathology.

Bile acid synthesis

In humans, the bile acid pool is composed of primary bile acids, including cholic acid (CA) and chenodeoxycholic acid (CDCA), and secondary bile acids, including deoxycholic acid (DCA) and lithocholic acid (LCA) (Li and Apte 2015; Li and Chiang 2014). Primary bile acids are synthesized from cholesterol via two major pathways in hepatocytes, i.e. the classic pathway and alternative pathway (Figure 1). In humans, the classic pathway is responsible for about 90% of total bile acid production in the liver, generating CA and CDCA, which is considered the major bile acid biosynthetic pathway. Cholesterol 7α-hydroxylase (CYP7A1), which is the rate-limiting enzyme in the classic pathway, converts cholesterol into CDCA (Chiang 2009), and microsomal sterol 12α-hydroxylase (CYP8B1) mediates the production of CA. Intermediate 7α-hydroxy-4-cholestene-3-one

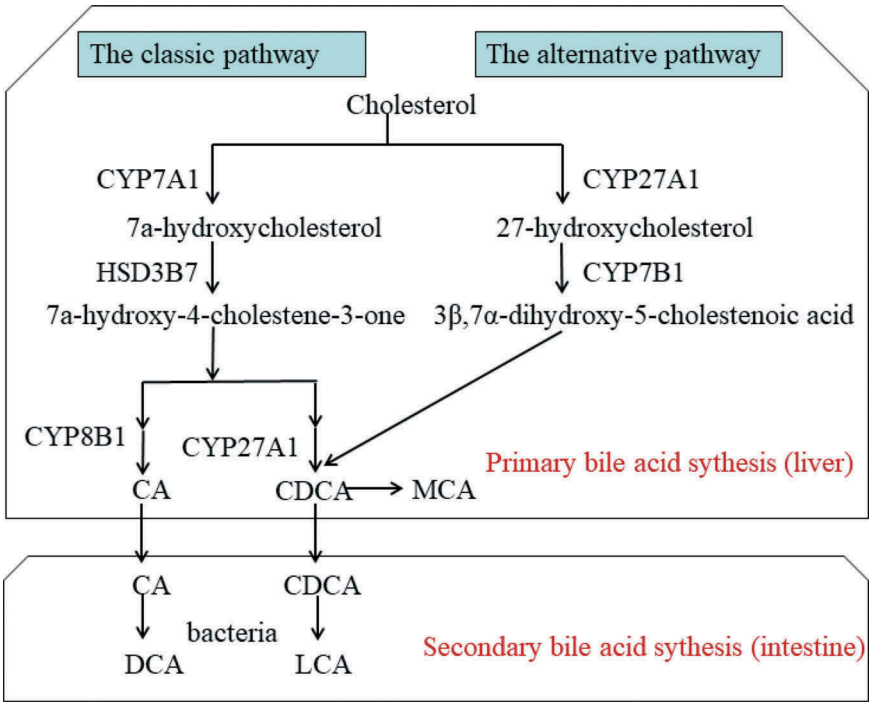

Figure 1. Bile acid synthesis pathways.

(C4) is the common precursor for CA and CDCA and has been used as a surrogate serum marker for the rate of bile acid synthesis in humans (Axelson et al. 1988; Honda et al. 2007). In the alternative pathway, mitochondrial sterol 27-hydroxylase (CYP27A1) catalyzes the conversion of cholesterol into CDCA, which accounts for less than 10% of bile acid synthesis in humans. In contrast, the alternative pathway may be responsible for the synthesis of about 50% of bile acids in rodents (rat and mouse). Secondary bile acids are produced mainly through the conversion of primary bile acids by gut bacteria.

It should be noted that composition and hydrophobicity of the bile acid pool in rats and mice are significantly different from that of humans. In mice and rats, the majority of liver CDCA is converted to the more hydrophilic α-muricholic acid (α-MCA) and β-MCA. In humans, the highly hydrophobic bile acid pool consists of about 40% of CA, 40% of CDCA, and 20% of DCA. In mice, the highly hydrophilic bile acid pool consists of about 50% CA and 50% α- and β-MCAs. In addition, rats do not possess a gallbladder; thus, bile is secreted directly into the small intestine. These differences in humans and rodents are shown in Table 1.

Hepatic bile acid synthesis is mainly mediated by bile acids based on a negative feedback by repressing the expression of the CYP7A1 gene (Chiang 2009). This enables the liver to efficiently regulate the levels of bile acids and prevent their accumulation, thus maintaining bile acid homeostasis.

Bile acid transport

Bile acid transport across the plasma membrane is an active process that requires high-affinity bile acid transporters in the liver and intestine (Alrefai and Gill 2007) (Figure 2(a)). In the liver, conjugated bile acids are taken up by Na^+-dependent taurocholate transporter (NTCP) (Hagenbuch and Meier 1994; Meier and Stieger 2002), and unconjugated bile acids are mainly taken up via Na^+-independent organic anion transporters (OATPs), including OATP1A2 and OATP1B1 (Trauner and Boyer 2003). Bile acids are excreted into canalicular bile through the ATP-binding cassette transporter bile salt export pump (BSEP) (Childs et al. 1995) and multidrug resistance-associated protein MRP2 (Alrefai and Gill 2007). In the terminal ileum, conjugated bile acids are reabsorbed by apical sodium-dependent bile salt transporter (ASBT) (Shneider et al. 1995) and excreted into the portal circulation by organic solute transporter α and β dimer (OSTα/β) located on the basolateral membrane of enterocytes (Ballatori et al. 2005; Rao et al. 2008). Unconjugated mono- and di-hydroxy bile acids can passively diffuse through enterocytes (Hofmann 2009).

Regulation of bile acid homeostasis

NRs are a group of ligand-activated transcription factors that play an important role in bile acid metabolism (Li and Chiang 2013). NRs, such as FXR, pregnane X receptor (PXR) and vitamin D receptor (VDR), regulate a number of bile acid synthetic and metabolizing enzymes and transporters. Among them, FXR primarily maintains bile acid homeostasis by regulating every aspect of bile acid metabolism, including synthesis, detoxification and enterohepatic recycling (Stanimirov et al. 2015). Until now, few studies have demonstrated the circadian rhythm of PXR and CAR in bile acid homeostasis. Therefore, the key roles of FXR in regulating bile acid homeostasis are now elaborated.

Table 1. The differences in bile acid synthesis and circadian rhythm between humans and rodents.

Bile acid synthesis and circadian rhythm	Human (mainly)	Mouse (mainly)	Rat (mainly)
Biosynthetic pathway	The classic pathway	The alternative pathway	The alternative pathway
Bile acid pool	CA, CDCA, DCA, LCA	CA, α-MCA, β-MCA, DCA, ω-MCA	CA, α-MCA, β-MCA, DCA, ω-MCA
Bile acid pool hydrophobicity	40% CA, 40% CDCA, 20% DCA	50% CA, 50% α- and β-MCAs	50% CA, 50% α- and β-MCAs
Gallbladder	YES	YES	NO
Regulation of bile acid synthesis	FXR/SHP pathway FXR/FGF19 pathway	FXR/SHP pathway FXR/FGF15 pathway	FXR/SHP pathway FXR/FGF15 pathway
Circadian rhythm of bile acid synthesis	Two peaks during the daytime	One peak in the dark phase	One peak in the dark phase

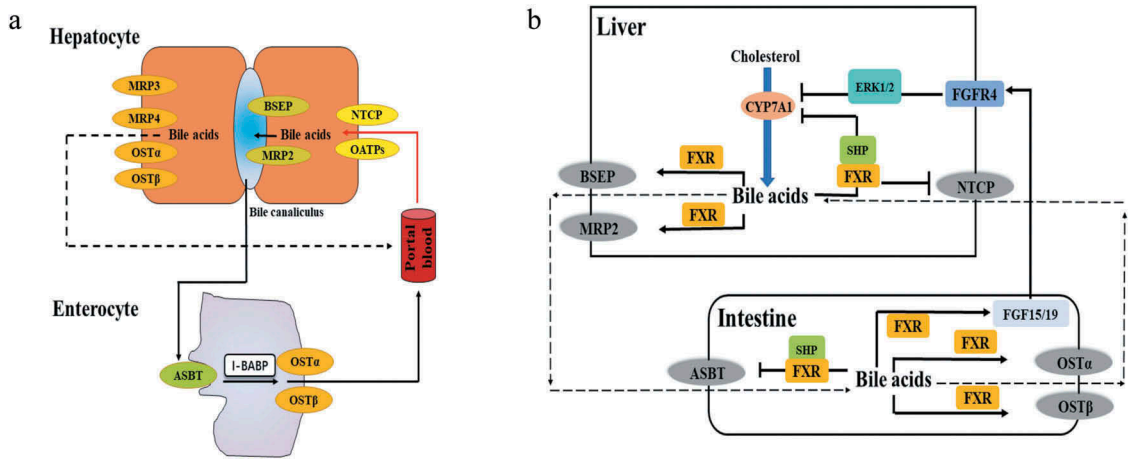

Figure 2. FXR regulation of bile acid synthesis and bile acid transport in the enterohepatic circulation. (a) Bile acid transporters in the hepatocytes and enterocytes; (b) FXR regulation of bile acid synthesis and bile acid transport in the liver and intestine.

Bile acid-activated FXR can repress transcriptional expressions of CYP7A1, CYP8B1, and CYP27A1, and thus predominantly mediate negative feedback regulation of bile acid synthesis (Li and Chiang 2014). It is well-established that bile acids suppress their own synthesis through the FXR-repressed CYP7A1 gene, which is mediated by two pathways (Figure 2(b)). FXR activation by bile acids transcriptionally induces production of small heterodimer partner (SHP) in the liver (Chiang et al. 2000; Goodwin et al. 2000; Lu et al. 2000) and intestinal fibroblast growth factor 15 (FGF15 or human orthologue FGF19) in the intestine (Inagaki et al. 2005; Somm and Jornayvaz 2018; Song et al. 2009), thereby inhibiting CYP7A1 gene and bile acid synthesis. In addition, FXR activation also inhibits hepatic bile acid uptake and promotes biliary bile acid secretion by regulating expressions of multiple bile acid transporters, both in hepatocytes and enterocytes (Li and Chiang 2013; Staudinger et al. 2013) (Figure 2(b)). In hepatocytes, activation of FXR can indirectly repress the expression of NTCP (Denson et al. 2001), and directly promote expression of BSEP (Ananthanarayanan et al. 2001) and MRP2 (Kast et al. 2002). In the intestine, FXR can inhibit expression of ASBT (Li et al. 2005; Neimark et al. 2004), and directly induce expression of OSTα/β (Frankenberg et al. 2006). Therefore, this complex and intertwined network of FXR-activated intestine-to-liver signaling axis prevents the accumulation of potentially toxic bile acids, while maintaining bile acid pool homeostasis (de Aguiar Vallim et al. 2013).

Circadian clocks in mammals

The mammalian circadian rhythm system is composed of a central brain clock and numerous peripheral clocks. In general, the molecular oscillators within the SCN resemble the peripheral ones, the main difference being the manners in which they are synchronized and influenced by various signals (Figure 3(a)). The central clock is mainly entrained by the ambient light-dark cycle, whereas the peripheral clocks are influenced by feeding/fasting cycles and chemical signals from the SCN (Griffett and Burris 2013; Mohawk et al. 2012). The peripheral clock is present in many cells and tissues, such as those of heart, liver and kidney, and affects insulin secretion, lipid metabolism and food absorption (Dallmann et al. 2012; Iurisci et al. 2009). The central clock outputs, such as sleep/wake phases and eating behaviors, affect peripheral clock outputs, such as energy metabolism (Asher and Schibler 2011; Froy 2013). This hierarchical structure of circadian clocks helps synchronize the functions of cells, tissues and organs, presenting a 24 h circadian time organization that is adaptive to environmental changes.

The primary genes of biological clocks are circadian locomotor output cycles kaput (CLOCK), brain and muscle ARNT-like protein-1 (BMAL1), period (PER) and cryptochrome (CRY). At the molecular level, the circadian clock is regulated by a transcriptional-translational negative feedback loop (Ko and Takahashi 2006) (Figure 3(b)).

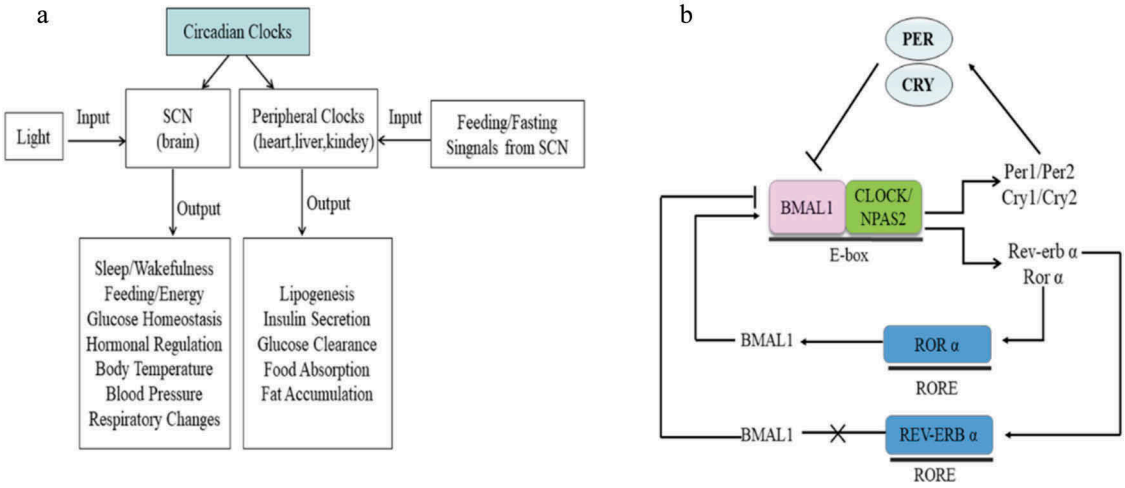

Figure 3. The constitution and mechanism of circadian clock in mammals. (a) Circadian clocks in the central nervous system and in the peripheral tissues; (b) The mechanism of mammalian circadian clock.

CLOCK or NPAS2 interacts with BMAL1 to form heterodimers that bind the DNA E-box elements of the Per and Cry gene promoters to stimulate their transcriptions and protein expressions. When PER and CRY proteins are enriched, PER/CRY complexes in turn inhibit the BMAL1-CLOCK /NPAS2 heterodimers, thereby suppressing activation of the Cry and Per genes and reducing their protein levels (Albrecht 2006). In addition, the BMAL1-CLOCK/NPAS2 heterodimers bind the E-box sequences in the promoters of reverse-erythroblastosis α (REV-ERBα) and retinoic acid receptor-related orphan receptor α (RORα) genes, and regulate circadian expressions of REV-ERBα and RORα (Burris 2008; Crumbley and Burris 2011; Guillaumond et al. 2005). On the contrary, REV-ERBα and RORα bind a ROR response element in the BMAL1 and CLOCK gene promoters to repress their transcriptions. The negative feedback loop, which oscillates with a period of 24 h, significantly participates in maintaining the homeostasis of glucose, lipid and bile acid metabolism (Ferrell and Chiang 2015a).

Circadian rhythm of bile acid homeostasis

Circadian rhythm of bile acid metabolism

The circadian rhythm of bile acid synthesis in humans and rodents has long been known. Twenty-four-hour variation of bile acid levels and key enzyme CYP7A1 differs between humans and rodents. Galman et al. (2005) found that bile acid synthesis in humans had a diurnal rhythm, with two distinct peaks during the daytime, a finding that is consistent with an earlier study by Duane et al. (1983). Kovár et al. (2010) investigated diurnal variation of CYP7A1 activity in healthy subjects. The concentration of C4, a surrogate marker of CYP7A1, underwent evident diurnal variation, showing a peak at ZT6 in most subjects. However, numerous studies conducted in the 1990s demonstrated that CYP7A1 activity in rodents had only one peak, in the dark phase, and was decreased in the middle of the light phase (Falvey et al. 1995; Gilberstadt et al. 1991; Kai et al. 1995; Nakano et al. 1990). Similarly, other studies found that the serum level of total bile acid in mice was maximum at the beginning of the dark phase and lowest in the middle of the light phase (Ma et al. 2009; Zhang et al. 2011). This completely different rhythm pattern between humans and rodents is shown in Table 1, suggesting that species differences exist in the circadian rhythm of bile acid homeostasis.

Recently, it was demonstrated that conjugated and unconjugated bile acids exhibited asynchronous rhythms of enterohepatic circulation in humans: conjugated bile acids were found to peak after food intake, with subsequent FGF19 elevations and reduced bile acid synthesis; however, unconjugated ones were found to peak later at night, and unrelated to FGF19 and bile acid synthesis (Al-Khaifi et al. 2018). This difference

indicates that diurnal variation of bile acid synthesis is influenced by conjugated bile acids, directly and/or via FGF19, presumably due to altered microbial activity in the small intestine.

The circadian rhythm of bile acid synthesis has been extensively studied, although only few studies involving rodents have investigated daily rhythms in bile acid transport (Eggink et al. 2017; Ferrell and Chiang 2015b; Ma et al. 2009; Zhang et al. 2011). Ma et al. (2009) found mRNA expression of NTCP was higher at ZT 14, with the increase in BSEP expression at ZT 2 in control mouse livers. In livers of resin-fed mice, mRNA expression of NTCP was significantly higher in the early evening, and that of BSEP was higher in the early morning; in the ilea, mRNA expressions of ASBT and OSTα showed marked diurnal peaks in the early evening (Zhang et al. 2011).

Meanwhile, circadian expressions of key enzymes and transporters involved in bile acid homeostasis display significant sex differences. Although both male and female mice show the same temporal pattern in the occurrence of peak mRNA levels of CYP7A1, CYP27A1, NTCP, CYP8B1 and BSEP; nonetheless, the temporal pattern of these enzymes and transporters displayed obvious differences between male and female mice. For instance, CYP7A1 mRNA was lowest at ZT23 for male mice and at ZT7 for female mice (Xu et al. 2015). Therefore, sex difference should be cautiously considered in investigating mammalian bile acid homeostasis.

Circadian rhythm of FXR and bile acid homeostasis

As stated above, FXR plays a crucial role in bile acid synthesis and transport. FXR mRNA displays a pronounced circadian peak at ZT7 in both the liver and ileum, and the resin diet markedly increases the level of FXR mRNA, suggesting FXR may be negatively regulated by bile acids (Zhang et al. 2011). In addition, the circadian rhythm of FXR expression also shows sex difference in rodents. In male and female mice, FXR mRNA peak at ZT11, whereas FXR mRNA is minimum at ZT7 and ZT19 for male and female mice, respectively (Xu et al. 2015).

Circadian expression patterns of FXR, SHP and FGF15/19 have been associated with their regulatory effects on bile acid synthesis (Lundasen et al. 2006; Stroeve et al. 2010; Yang et al. 2006; Zhang et al. 2011). In contrast to CYP7A1 mRNA expression, SHP mRNA expression is highest at ZT3 and lowest at ZT15, being consistent with negative regulation of CYP7A1 by the FXR/SHP pathway. Also, intestinal FGF15 mRNA expression shows obvious circadian rhythmicity, with prominent peak at ZT15 and a minor peak at ZT3, which is opposite to the CYP7A1 circadian rhythm found in mice (Stroeve et al. 2010; Zhang et al. 2011). In humans, circulating FGF19 level also exhibits a pronounced diurnal rhythm, with peaks 90–120 min after the postprandial rise in serum bile acid level, which precedes the decline of bile acid synthesis, and its diurnal rhythm is abolished upon fasting (Lundasen et al. 2006). Moreover, transcription factor Kruppel-like factor 15 has recently been identified as the first endogenous negative regulator of circadian FGF15 expression, showing a circadian rhythm that regulates circadian bile acid production (Han et al. 2015; Jeyaraj et al. 2012). In summary, bile acid-activated FXR can regulate the diurnal variation of bile acid synthesis and transport, and thus influence bile acid homeostasis.

Presently, the extent of the contribution, if any, of the biological rhythm of FXR to the regulation of hepatic bile acid homeostasis remains controversial. In FXR-null mice and intestine-specific $FXR^{-/-}$ mice, circadian rhythms of FGF15 and OSTα are undetectable, but the circadian rhythm of CYP7A1 expression does not change in either model (Stroeve et al. 2010; Zhang et al. 2011). Collectively, these findings suggest other pathways, other than FXR, might be involved in the regulation of bile acid homeostasis.

Clock gene and bile acid homeostasis

Several CLOCK-dependent transcription factors, i.e. DBP, REV-ERBα and E4BP4, are involved in maintaining circadian expression of bile acid synthesis (Duez et al. 2008; Lavery and Schibler 1993; Noshiro et al. 2007). DBP, as a PAR (proline and acidic amino acid rich) basic leucine zipper transcription factor, is a key liver CLOCK-controlled

gene. DBP expression follows a stringent circadian rhythm that can stimulate CYP7A1 expression and regulate its 24 periodicity (Lavery and Schibler 1993; Wuarin and Schibler 1990). REV-ERBα is a key player in the circadian regulation of cholesterol and bile acid synthesis; CYP7A1 diurnal expression is dampened in REV-ERBα deficient mice, which strongly indicates REV-ERBα participates in the circadian expression of CYP7A1 (Duez et al. 2008; Le Martelot et al. 2009; Zhang et al. 2018). Furthermore, RORα binds the same response element in the CYP8B1 gene promoter and regulates the circadian variation of CYP8B1 expression, so CYP8B1 mRNA is significantly reduced in the RORα knock-out mouse (Pathak et al. 2013).

Normal circadian clock function is important for the regulation of bile acid homeostasis in the mouse liver. In the liver of Clock mutant mice, not only clock genes, such as Per2 and Bmal1, but also the clock-controlled genes, such as CYP7A1, show a reduced and arrhythmic expression pattern (Kudo et al. 2008). In Per1/2 double knockout mice, Ma et al. (2009) found that key genes in bile acid synthesis and transport, including CYP7A1 and NTCP, no longer undergo circadian expressions. $CLOCK^{\Delta 19}$ mutant and BMAL1-ablated mice exhibit hyperphagia, obesity, hepatic steatosis, impaired glucose tolerance, increased adiposity and adipocyte hypertrophy (Marcheva et al. 2010; Shostak et al. 2013). Additionally, disruption of clock genes can aggravate metabolic diseases, including fatty liver disease, diabetes and obesity (Froy 2012; Maury 2019; Shetty et al. 2018). Therefore, circadian clock disruption can result in dysregulation of bile acid homeostasis and trigger metabolic diseases.

Moreover, it has been noted bile acids are potential chronobiological signals that can affect the molecular clock mechanism. Kim et al. (2015) demonstrated circadian rhythmic fluctuation of bile acid homeostasis is regulated by mixed-lineage leukemia 3 (MLL3) and 4 (MLL4), which function as critical transcriptional coactivators of RORα to regulate hepatic circadian clock genes. Govindarajan et al. (2016) found unconjugated bile acids significantly alter expression levels of circadian clock genes in the ileum and colon as well as the liver, with significant changes in the expression of hepatic regulators of circadian rhythms (including DBP) and associated genes (Per2, Per3 and Cry2). A recent study showed feeding-induced changes in bile acid pool composition may also affect the molecular clock (Eggink et al. 2017). However, the complex interaction between bile acids and the circadian clock requires further investigation.

Life rhythm, bile acid homeostasis and health

Disruptions of circadian rhythms negatively impact human health. Circadian rhythms, which, for example, are disturbed by diets, eating patterns, sleep deprivation, shift work and exposure to artificial light at night, are significantly associated with elevated incidence rates of cardiovascular events, gastrointestinal disorders, cancers and metabolic syndrome (Barger et al. 2017; Codoñer-Franch and Gombert 2018; Potter et al. 2016; Samuelsson et al. 2018).

Circadian regulation of bile acid homeostasis is essential to achieve tight physiological homeostasis. It is well known that restricted feeding and sleep restriction can disrupt the circadian rhythm of bile acid homeostasis, leading to the development of hepatic cholestatic and metabolic diseases. Li et al. (2012) reported restricted feeding rapidly stimulates CYP7A1 expression in mice, whereas fasting strongly reduces CYP7A1 expression and blunts its circadian rhythmicity. The fasting and refeeding protocol impairs bile acid synthesis, contributing to the pathogenesis of diabetes and obesity. Restricting feeding significantly raises hepatic bile acid and aspartate transaminase levels, and it disrupts bile acid homeostasis that mimics cholestatic disease and diabetes (Ma et al. 2009; Sonne et al. 2016). Moreover, time-restricted feeding (TRF) could abolish hepatic Cyp7A1 mRNA expression rhythm and induce the change of plasma bile acid levels and composition, which affect lipid metabolism, resulting in the development of obesity, diabetes and metabolic disorders (Chaix and Zarrinpar 2015; Eggink et al. 2017).

Sleep disruption induces deregulation of lipid accumulation and mobilization, leading to disruption of bile acid homeostasis, and increasing risk for metabolic impairments, including obesity, insulin resistance and metabolic syndrome (Husse et al. 2012). In this regard, a fairly recent

study found sleep disruption, and even short-term circadian disruption, contributes to dyslipidemia by dramatically altering hepatic clock gene expression, bile acid metabolism and lipid homeostasis (Ferrell and Chiang 2015b).

Conclusion

Bile acids have been long recognized as signaling molecules that regulate hepatic lipid, glucose, bile acid and energy metabolisms. Accumulating evidence has demonstrated the circadian rhythm of bile acid synthesis, but that of bile acid transport remains elusive. Circadian disruption can result in the deregulation of bile acid homeostasis, eventually causing cholestatic and metabolic diseases. Our review provides knowledge on the important role of circadian rhythms in bile acid homeostasis. However, the effect of circadian rhythms on the risk of developing liver and metabolic diseases has not been fully explored. Further in-depth studies are needed to investigate the mechanism of circadian rhythms in the pathogenesis (chronopathology) of bile acid-related disease at the molecular level, and development of circadian rhythm-based therapeutic (chronotherapeutic) targets.

Disclosure Statement

The authors declare no conflict of interest.

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