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Circadian Rhythms of the Liver and Their Sexual Dimorphism: Current State of the Problem

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Abstract

The rhythmicity of life functioning processes at the cellular, organ, and system levels is one of the fundamental properties of living things. Among the wide range of biorhythms, circadian rhythms are the most important for mammals. In mammals, circadian rhythms coordinate a wide range of physiological processes with constantly changing environmental conditions, primarily with light conditions. Data on the characteristics of the circadian rhythms of the liver (the most important organ for maintaining homeostasis) are limited and sometimes even contradictory. We aim to analyze modern literature investigating the organization of circadian rhythms at the gene, cellular, and organ levels. Over the past decades, it has become known that disruption of the normal circadian rhythm of the liver underlies the development of several pathologies.

This article highlights some aspects of the normal circadian rhythm functioning and the role of circadian dysfunction in the occurrence of specific pathologies. We also focus on the little-explored issue of sex differences in the circadian rhythms of the mammalian liver.

Keywords: liver, circadian rhythm, sex

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Циркадные ритмы печени и их половой диморфизм: современное состояние проблемы

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Резюме

Ритмичность процессов функционирования жизнедеятельности на клеточном, органном и системном уровнях является одним из фундаментальных свойств живого. Среди широкого спектра биоритмов наиболее важными для млекопитающих являются циркадианные (циркадные) ритмы. У млекопитающих циркадные ритмы согласовывают протекание широкого спектра физиологических процессов с постоянно меняющимися условиями окружающей среды, в первую очередь, со световым режимом.

Данные об особенностях циркадных ритмов печени – важнейшего органа поддержания гомеостаза – ограничены, а иногда и вовсе противоречивы. Целью настоящей статьи является анализ современных научных работ, посвященных вопросам организации суточных ритмов на генном, клеточном и органном уровнях. Актуальность данного обзора обусловлена тем, что за последние десятилетия накоплен значительный объем знаний о том, что нарушение нормальной циркадной ритмичности печени лежит в основе развития ряда тяжелых патологий.

В статье освещены некоторые аспекты нормальной циркадной ритмичности функционирования печени и роли нарушения циркадных ритмов в возникновении некоторых патологий. Особое внимание уделено малоизученному вопросу половых различий в суточной ритмичности функционирования печени млекопитающих.

Ключевые слова: печень, циркадный ритм, пол

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Introduction

Homeostasis, organ and system functioning, metabolism, and information processing are all controlled by the biological-structural-temporal discreteness.[1,2] Current research indicates that over 500 distinct functions and processes in the mammalian body are regulated by circadian rhythms (CRs).[3,4] These rhythms differ in amplitude and phase, yet are precisely synchronized with one another as well as with environmental factors, ensuring that body systems function at optimal levels.[5]

The genetic determinants of the mammalian CR complex are well established. However, CRs can also be influenced by both internal and external environmental factors,[6] ensuring the body's ability to adapt to changing conditions. For all living organisms, including humans, the regulation of various physiological rhythms is primarily dependent on the daily light-dark cycle.[7] In cases of adequate adaptation, environmental factors do not significantly impact CRs. However, when adaptation fails, changes in the phase-amplitude characteristics of rhythms can occur, leading to desynchronosis and potentially causing various diseases.[8]

Methods

We thoroughly reviewed articles published in journals recommended by the Higher Attestation Commission under the Ministry of Science and Higher Education of the Russian Federation and publications in PubMed, Scopus, and Web of Science. The studies were assessed for their relevance to our issue of interest and objective in 3 stages: we evaluated titles, abstracts, and full texts. Our team of 2 independent researchers searched publications in databases, including eLibrary, as well as in Google Scholar and ResearchGate.

Discussion

Little is known about gender disparities in the mammalian circadian rhythmicity, which may be attributed to the predominant use of male experimental animals in studies of mammalian CRs.[9] Among the organs that contribute significantly to maintaining homeostasis in mammals, the liver plays a central role. Sexual dimorphism in its structure and functions is well documented, although available data are scant and inconsistent.[10]

Within hepatocytes, as well as other cells, the biological clock at the molecular-genetic level is a complex system. The basic helix-loop-helix ARNT like 1 gene, *BMAL1,* operates in conjunction with the clock circadian regulator gene, *CLOCK*, along with the Period (*PER*) and Cryptochrome (*CRY*) gene families, among other genes.[11] The system is further reinforced by a second negative feedback loop, which is accomplished through the interaction of the REV-ERBα and RORa proteins with the ROR response element (RORE).[12] This additional feedback loop enhances the system's reliability, thereby promoting optimal biological function.

In the absence of external zeitgebers, hepatocytes retain the endogenous CR of expression of clock genes, the *P450* gene, as well as genes affecting lipid metabolism, whereas in complete darkness, the CRs of glucose and lipids disappear, although several other CRs are maintained.[13] Light affects the period and amplitude of the CRs, expression of some genes, and coordination of rhythms.[14]

Extensive research has been conducted concerning the CRs of various processes, such as DNA repair, ribosome biosynthesis, autophagy, and those processes occurring in hepatocytes under endoplasmic reticulum stress.[15] The circadian phases of numerous messenger RNAs in hepatocytes align with the phases of the proteins they encode and their respective biochemical pathways.[16] Interestingly, certain enzymes have also been observed to exhibit circadian rhythmicity through the persistence of their transcripts, suggesting their involvement in regulating the CR of the liver and posttranscriptional mechanisms.[17]

Most liver functions have a CR.[18,19] The expression of genes ensuring liver functioning can be regulated directly by the autonomous circadian system of hepatocytes, rhythmic external signals, or a combination of both.[20] At the same time, the liver functioning has been proven to be highly dependent on the typically synchronized control of its CR by the suprachiasmatic nuclei (SCN) of the hypothalamus and the pineal gland.[21]

The liver maintains blood glucose levels circadian regulation system of which functions by synchronizing the tissue-specific mechanisms of this carbohydrate metabolism. The SCN controls the feeding/fasting rhythm, while peripheral pacemakers initiate temporally coordinated gene expression programs to maintain physiological blood glucose levels.[22]

Studies on the expression of circadian genes in mammals revealed the presence of 2 transcription peaks in hepatocytes, corresponding to the transitions between the states of activity and rest. These genes, at multiple levels, regulate glucose metabolism in hepatocytes by controlling the glucokinase expression.[23] Current research suggests that hepatocyte clock genes play a crucial role in fine-tuning fluctuations in blood glucose levels according to the activity rhythms determined by the SCN. Disruption of the *BMAL1* gene in mouse hepatocytes desynchronizes the CR of glucose,[24] whereas turning off clock genes does not affect the CR of this carbohydrate.[25]

Clock genes in the liver play an essential role in regulating glucose metabolism and perform other vital functions. Cryptochromes regulate gluconeogenesis by interacting with G protein-coupled receptors. This interaction blocks cyclic adenosine monophosphate accumulation and activates the transcription of genes involved in gluconeogenesis. *CRY1* overexpression has been found to reduce blood glucose levels and increase the sensitivity of liver cells to insulin in mice with experimental

diabetes.[26] Cryptochromes also suppress the transcription of genes that encode glucocorticoid receptors and phosphoenolpyruvate carboxykinase, an enzyme that regulates gluconeogenesis.[27] The KLF and KLF15 transcription factor gene families are believed to regulate the rhythmic expression of several enzymes that play a role in nitrogen and amino acid homeostasis. Glucocorticoids influence glucose metabolism by inducing *PER2* expression during hyperglycemia.[28]

The liver plays a crucial role in regulating lipid metabolism by controlling lipoprotein synthesis, lipid uptake and conversion, and de novo fatty acid synthesis and oxidation. Clock genes present in liver cells are significant regulators of lipid metabolism and daily fluctuations in the levels of free fatty acids, cholesterol, triglycerides, and phospholipids.[29] Notably, lipids have been identified as potential regulators of the circadian rhythmicity of the liver.[30] The *CLOCK* gene, along with the timing of food intake, serves as the primary external pacemaker that regulates CRs.[31] Disrupted functioning of this gene has been found to alter the expression of genes that determine lipid metabolism and lead to the accumulation of intermediate products in the liver. Dyslipidemia has been observed in *PER2* knockout mice.[32] Additionally, circadian rhythmicity has been characterized by enzymes and transcription factors that are involved in lipid metabolism and production of bile acids.[33,34]

The primary regulators of all detoxification processes in the liver are proteins specific to this organ, rhythmically activated due to the work of *CLOCK* and *BMAL1*.[35] The circadian rhythmicity of the activity of cytolytic enzymes has been described, although the data are scarce and contradictory.[36]

Disruption of the normal CR of liver functioning is considered one of the leading factors in the development of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and metabolic syndrome.[37-39] Liver clock genes regulate the rhythm of several processes involved in the pathogenesis of NAFLD, such as autophagy, endoplasmic reticulum stress, and oxidative stress, transforming NAFLD into NASH.[40] A number of authors indicate internal desynchronosis as one of the reasons for NASH development.[41]

Disruption of the normal functioning of clock genes in hepatocytes is associated with a number of liver dysfunctions and diseases. Thus, in mice with carbon tetrachloride-induced liver fibrosis, abnormal rhythms of *CRY2* expression were found, and in animals with *PER2* knockout under the same conditions, more pronounced changes in the organ were observed compared with controls.[42] Mice with double knockout of *PER1* and *PER2* are observed to have increased levels of bile acids in the blood serum and the liver and cholestasis.[43] Disruption of the normal functioning of the *PER* family genes in hepatocytes during hepatitis has been described.[44]

Research findings suggest a link between liver CR disorders and cancer incidence. The circadian clock regulates several genes, including cell cycle genes, cell proliferation genes, oncogenes, and tumor suppressor genes.[45] Disturbances in the normal functioning of clock genes are quite common in liver tumors. One such example is the reduced expression of *BMAL1*, which can negatively impact the normal cell cycle progression in hepatocytes. Further investigations are needed to explore the underlying mechanisms and potential therapeutic targets to mitigate the risk of liver cancer associated with CR disruptions.[46-49]

Mice with *PER2* gene mutations, BMAL1$^{+/-}$ mice, as well as mice deficient in both *PER1* and *PER2* or *CRY1* and *CRY2* have shown an increased susceptibility to spontaneous and radiation-induced carcinogenesis compared with wild-type mice.[50] Furthermore, in mice with experimental latitudinal desynchronosis, the development of diethylnitrosamine-induced liver cancer is accelerated.[51] Moreover, abnormal expression of core clock genes has been observed in both human[52] and mouse[53,54] hepatocellular carcinoma biopsy tissue samples.

Hepatocyte proliferation mechanisms have been extensively described.[55] The Bmal1-Clock/Wee1/Cdc2 pathway is believed to regulate the CR of hepatocyte mitosis.[56] Disruption of regular *PER2* expression has been found to increase the number of polyploid hepatocytes in rodents.[57]

In recent years, the role of clock genes in regulating the CR of apoptosis has been established.[58] Additionally, Ca^{2+} and melatonin have also been implicated in the regulation of hepatocyte apoptosis.[59] The *CRY* mutation activates p53-independent apoptotic pathways in hepatocytes, while the *CLOCK* gene and neuronal PAS domain protein 2 gene, *NPAS2*, promote cell proliferation and inhibit mitochondrial apoptosis.[60]

While there has been extensive research on the CRs of hepatocytes in animals,[61] there are still several unclear aspects regarding the structure of these rhythms. Daily liver autophagy rhythms, synchronized with metabolic rhythms, have been well described.[62] Notably, circadian rhythmicity in hepatocyte size has been observed in rodents with a natural feeding/fasting cycle, when the timing of food consumption aligns with their nocturnal activity.[63] Daily fluctuations in liver, hepatocyte, and nuclear size are influenced not only by circadian dynamics of protein content but also by changes in the osmotic pressure of the extracellular environment. Other researchers propose that F-actin plays a significant role in the circadian dynamics of hepatocyte size.[64] It has also been suggested that the primary pacemaker dictating hepatocyte size is not the timing of feeding but rather the SCN of the hypothalamus, which regulates feeding behavior.[65]

Sexual Dimorphism of Liver Functions and Their Daily Rhythm

Due to the complexity of gender differences in the circadian rhythmicity of mammals, only a limited number of studies focus on this issue. Female subjects are often excluded from studies due to their reproductive cycles and hormone fluctuations, which may affect results.[66] Traditionally, studies on mammalian CRs predominantly use male experimental animals or mixed groups, with only about 20% of studies involving females.[67,68] Nevertheless, a few publications have explored the sexual characteristics of the liver circulatory system and its impact on other organs and tissues.

Notable gender differences have been observed in the liver structure. Female rats, for instance, have higher hepatocellularity and a larger proportion of binuclear hepatocytes, contributing to higher regenerative abilities.[69] Limited clinical evidence suggests similar findings in humans.[70]

Several liver functions show gender-specific differences: for instance, sex-specific production of liver proteins (eg, vitellogenin, *α2*-microglobulin), bile acids, xenobiotic transporters, and cytochrome P450 enzymes involved in sex steroid metabolism.[71] The female liver is characterized by a highly efficient metabolic phenotype and increased biogenesis, which are crucial for successful pregnancy;[72] the male liver, on the other hand, exhibits a higher prevalence of severe NASH and fibrosis compared with women.[73] Sexual dimorphism in energy metabolism has been described in both humans and laboratory animals.[74]

Sexual dimorphism of the liver is believed to be influenced by the pulsatile secretion of growth hormone in males and its constant secretion in females, as well as by androgens and estrogens.[75] Studies have shown that male mice lacking the *CRY1* and *CRY2* genes exhibit a near absence of gender-specific liver product expression, which can be restored with pulsatile administration of somatotropic hormone.[76] Furthermore, disruptions in the CRs of carbohydrate metabolism have been observed in women with different types of obesity.[77] Sex differences in the CR of carbohydrate metabolism include decreased glucose tolerance in men compared with women in the morning.[78]

Sex differences in the CR expression of clock genes have been noted in hepatocytes of mice.[79] Both male and female mammals exhibit CRs in lipid and glycogen metabolism in the liver, but gender differences in mesor, acrophase, and rhythm amplitude have been observed in mice.[80] KLF10, a *CLOCK*-regulated transcription factor in the liver, influences gene expression in glycolysis and gluconeogenesis. Loss of KLF10 in male mice leads to postprandial hyperglycemia, while female mice maintain normoglycemia.[81] Peroxisome proliferator-activated nuclear receptors, which play an essential role in hepatic lipid and glucose metabolism and initiation of the inflammatory response, display sexual dimorphism in CRs.[10] In mice with induced obesity, females exhibit more pronounced changes in the daily dynamics of lipid metabolism and *BMAL1* expression.[82] Sexual dimorphism has also been observed in the expression of genes involved in the liver's antioxidant system.[83] Additionally, sex differences have been identified in the characteristics of desynchronosis during experimental hepatitis.[36]

Conclusions

The CRs of the liver are endogenous and genetically determined, yet highly adaptable to external zeitgebers, with photoperiod and food intake being the most significant. Sexual dimorphism in liver functions, particularly in the CR of organ processes under normal and pathological conditions, remains an issue of interest that requires further exploration. A deeper understanding of the nuances of sexual dimorphism in the liver may help identify appropriate therapeutic targets and improve risk stratification for patients undergoing treatment for liver diseases. Hence, it is imperative to investigate the causes of sexual dimorphism in liver functions and the nature of CR processes occurring in the organ. Such studies may aid in unraveling the complex biological mechanisms underlying liver functions and pathologies and may lead to the development of more effective treatment strategies.

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Авторы заявляют об отсутствии конфликта интересов.