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Review paper

Biological rhythms of the liver

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Abstract

The biological rhythm is a fundamental aspect of an organism, regulating many physiological processes. This study focuses on the analysis of the molecular basis of circadian rhythms and its impact on the functioning of the liver. The regulation of biological rhythms is carried out by the clock system, which consists of the central clock and peripheral clocks. The central clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and is regulated by signals received from the retinal pathway. The SCN regulates the circadian rhythm of the entire body through its indirect influence on the peripheral clocks. In turn, the peripheral clocks can maintain their own rhythm, independent of the SCN, by creating special feedback loops between transcriptional and translational factors. The main protein families involved in these processes are CLOCK, BMAL, PER and CRY. Disorders in the expression of these factors have a significant impact on the functioning of the liver. In such cases lipid metabolism, cholesterol metabolism, bile acid metabolism, alcohol metabolism, and xenobiotic detoxification can be significantly affected. Clock dysfunctions contribute to the pathogenesis of various disorders, including fatty liver disease, liver cirrhosis and different types of cancer. Therefore understanding circadian rhythm can have significant implications for the therapy of many liver diseases, as well as the development of new preventive and treatment strategies.

Key words: biological rhythms, liver, circadian rhythm, metabolism.

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Introduction

Most processes in the human organism show some type of rhythmicity. They are called biological cycles, and evidence of these cyclical changes was described as early as the 1960s [1]. So far, the role of these cycles in the functioning of such organs as the liver, heart, muscles, adipose tissues, brain, or pancreas has been presented [2].

The evolution of all organisms on Earth occurred under the constant influence of cyclically changing conditions of the external environment, such as air temperature and light intensity. It is logical that a large amount of biosphere created internal mechanisms which adjust the organism and its functioning to environmental conditions in the current phase of the astronomical cycle, e.g. time of the day or season of the year. Moreover, together with evolutionary development, these mechanisms prepared the organism for the particular phases of the changing cycle.

Processes in the alimentary tract respond to changes in the external environment. It was proven that lack of exposure to external factors does not cause total disappearance of internal rhythms in the organism [3]. A conclusion was reached that the organism possesses internal mechanisms driving rhythmicity independently of environment influence. The presence of such mechanisms was proven repeatedly and they were called biological clocks.

It was proved that circadian oscillations in the liver, similarly to other systems in the whole organism, are imposed by self-perpetuating systems – biological clocks. It was observed that the clock system construction is hierarchic. An overriding entity, i.e. the central

clock, is located in the hypothalamus, and subordinate clocks, called endogenous clocks, are located inside the single cells. It is assumed that they occur in most body cells but their function is most noticeable in metabolically active organs, e.g. in the liver [4].

The central clock affects peripheral clocks by synchronizing. The occurrence of numerous external factors that influence the length of cycle of the circadian clock was observed and numerous studies have proved the regulating influence of temperature or light on circadian clock oscillation [5].

Suprachiasmatic nucleus central clock

The central clock is identified with the suprachiasmatic nucleus (SCN) of the hypothalamus [6]. The SCN rhythm is imposed by the projection received from the retina pathway. The synchronization involves transfer information about the current time of the day to the central clock. It was found that SCN disorder leads to loss of most circadian rhythms of the body but does not result in impairment of their functions [6].

Suprachiasmatic nucleus neurons generate discharges with frequency depending on the time of the day [6]. It was found that each neuron has its own oscillation scheme. The range of period that can be generated by the neurons of described nuclei is wide, but it seems to be within 20 to 30 hours [4]. It is assumed that the neurons to be synchronized must be connected through paracrine and synaptic systems. The frequency of rhythm corresponds with the Earth's rotation [4].

It was proven that the SCN transfers its rhythmical projection through synaptic connections to the surrounding structures [6]. Excitations from the described nuclei are transmitted to other brain structures, i.e. the hypothalamus, pituitary gland, brainstem reticular formation, forebrain, pineal gland and thalamus. The mentioned centers are extremely important metabolically and are responsible for autonomic regulation, body temperature control, time regulation of sleep and wakefulness as well as time of meal intake [7].

Besides functions mentioned above, the central clock also regulates the activity of peripheral clocks. However, it is not clear how it is possible for the SCN to communicate with its peripheral equivalents that are located in distal regions of the body. There are some studies that indicate that specialized hormonal factors may be responsible for this [5]. Other studies have shown that the SCN connects with preautonomic neurons in the hypothalamus. Thus, it is considered that the central clock can directly influence peripheral clocks in innervated autonomic tissues [8].

Peripheral molecular clocks

Peripheral molecular clocks are situated inside most body organs, in their cells, including the digestive system: the liver, intestines, pancreas, and stomach [7]. It was reported that rhythmical circadian oscillations are visible in the cells of a given organ even if the organ is isolated from the rest of the system [3].

The activity of molecular clocks is based on three transcriptional-translational feedback loops [9]. However, the cycles which will be described in this study are not to be interpreted as entirely separate processes. The mentioned pathways repeatedly interact with each other and in some ways, functionally and structurally, complement each other. Nevertheless, their isolation and definition helps to understand the molecular basis of the cell's circadian rhythms.

The first feedback loop is also called the core loop. The clock core genes are considered the base of a given loop and their expression leads to occurrence of two transcriptional factors: BMAL1 and CLOCK. These proteins dimerize and produce the CLOCK/BMAL1 complex. The created heterodimer moves back to the cellular nucleus, where it binds to the E-box element within the PER gene and CRY promoter. It leads to induction of gene expression and, consequently, to the creation of Per 1 and 2 and Cry 1 and 2 factors. The proteins bind to form a complex which moves to the cellular nucleus, where it interacts with the CLOCK/BMAL1 heterodimer, which inhibits its function. Thus, the factors PER and CRY lead to inhibition of their own transcription and close the feedback loop [10]. PER/CRY complexes must be finally removed to unlock the CLOCK/BMAL1 complex function. It is assumed that casein kinase1 is also engaged in this process, which marks free proteins PER and CRY, respectively, leading to their degradation by ubiquitin [11].

The presence of the second feedback loop, which in a way stabilizes the first one, was also revealed. The CLOCK/BMAL1 heterodimer may be considered as the initial point of the structure. It was shown that it binds to the E-Box in the region of promoters of genes responsible for transcription of certain nuclear receptors connected with retinoic acid receptor: ROR α and Ror γ and REV-ERBα and REV-ERBβ [12]. The remaining factors compete for the binding site in the element of the RORE response in the region of the BMAL1 gene promoter [13]. It appears that binding of ROR protein to this element enhances BMAL1 expression. On the other hand, binding of REV-ERB factor leads to inhibition of expression of this gene [14]. Moreover, it turns out that REV-ERB accumulates faster in the cytoplasm, thus practically at once inhibiting

BMAL1 production. On the other hand, ROR factor accumulates more slowly and induces BMAL1 production with a certain delay [13]. Common action of both transcriptional proteins leads to circadian oscillation of BMAIL1 concentration in the cell.

In the processes of the third feedback loop, transcriptional factors from the family DEC1 and DEC2 play a crucial role. Transcription of these proteins proved to be stimulated by the CLOCK/BMAL1 heterodimer bound to the E-box element on promoters of respective genes. Similarly to factors CRY and PER, DEC1 and DEC2 inhibit gene expression and thus reduce protein production. However, DEC1 and DEC2 do not modify the CLOCK/BMAL1 heterodimer as PER and CRY did. They compete for the binding place in E-box. However, in consequence, apart from suppression of their own gene expression they suppress expression of PER and CRY [15].

There are also other bindings that further stabilize all the mentioned loops. It was proven, for instance, that CLOCK/BMAL1 heterodimer promotes DBP transcription, a member of the leucine lock factor family PAR. The proteins that are produced affect many other genes of the clock through binding to D-box elements in their promoter regions [16]. Increasing attention is also being paid to the study of epigenetic processes and how they affect the operation of molecular clocks [9]. However, the problem requires further research.

The presented feedback loops generate oscillation mainly through the production of rhythmical fluctuations in the concentrations of given proteins in the cell. It was proven that the proteins interact with many other signal pathways at the level of gene expression. They lead in this way to the transfer of rhythmicity of the circadian clock to practically all the aspects of cell metabolism [13]. It was reported that 10-40% of transcripts are produced in a rhythmic manner [3]. Such a significant influence of the molecular clock on the functioning of the cell leads to the risk of developing significant pathologies in the case of impairment of genes responsible for oscillator functioning.

Biological rhythms of the liver

The liver is one of the key organs in the human body. A recent analysis of the genome proved the existence of 7,978 genes in hepatocytes that possess binding sites with CLOCK factors as well as 1629 genes that show rhythmical oscillation resulting from CLOCK factor activity [7].

Carbohydrate metabolism

Glucose enters the interior of the cell thanks to the membrane glucose transporters (GLUT). GLUT gene expression was shown to be subject to circadian regulation, which increases in intensity during the body's active phase and decreases during the inactive phase [3]. Targeted liver cell-mediated damage to one of the core clock genes, Bmal1, was found to lead to reduced GLUT2 expression in the liver, likely leading to more frequent episodes of fasting hypoglycemia, reduced liver glycogen levels, and excessive post-meal glucose fluctuations [17]. Another preclinical study showed that the highest expression of glucose transporters and glucagon receptors takes place in the early evening, when mice eat most. It was also revealed that lifestyle can affect the production of glucose transporters. Mice that were deprived of sleep for two weeks had disturbed mechanisms of gene expression for GLUT2 receptors [18].

Glycogenesis and glycogenolysis are processes that are a significant part of liver metabolism. Concentration of glycogen in the liver shows circadian rhythm with its peak at the end of the active phase. It is assumed that the described rhythm results from the changes in balance between the activities of glycogen phosphorylase enzymes and glycogen synthase 2 (Gys2) [19]. One of the core clock genes, CLOCK, proved to affect glycogen metabolism through rhythmic transcriptional activation of Gys2. This regulation leads to intensified Gys2 expression at meal times [3]. The length of the clock cycles in the case of glycogen metabolism is regulated mainly by the time of taking meals. It is concluded that the day-night rhythm, and thus SCN itself, may have only marginal significance in glycogen metabolism regulation [19].

Another aspect of carbohydrate metabolism in the liver is gluconeogenesis. Mutations in core genes of the clock – CLOCK and BMAL1 – lead to impaired conversion of non-sugar substrates into glucose. It was also shown that mice with a damaged CLOCK gene have impaired conversion of pyruvate to glucose, which directly leads to disturbances of the formation of this sugar in hepatocytes [3]. PGC-1α enzyme is considered a coactivator of gluconeogenesis. It turns out that BMAL1 affects rhythmical expression of the enzyme leading to regulation of the process of glucose production [20]. There are also studies that stress the role of cryptochromes in the regulation of carbohydrate metabolism. It was found that these enzymes can both intensify and inhibit gluconeogenesis processes. Clock proteins may impact the balance between its synthesis and lysis [9].

Lipid metabolism

Lipid metabolism in the liver has a distinct circadian rhythm dependent on signal particles of the molecular clock. The expression of genes of the lipid metabolism pathway is altered in mice with disturbed expression of clock genes [9]. It was proven that a polymorphism in one of the clock genes is associated with a greater likelihood of developing hepatic steatosis [21]. Mice whose regular expression of core genes of the clock PER1 and 2 was blocked showed altered content of particular fractions of lipids in cells and were also characterized by an abnormally shifted phase of the diurnal cycle, in which the acrophase of fat accumulation occurred. However, the mutation of the mentioned genes did not lead to a general increase in lipid content in cells [22].

The sterol regulatory element-binding protein 1 (SREBP1c), which is one of the transcription factors driving lipogenous gene transcription, plays a crucial role in the regulation of lipid synthesis pathways in the liver. The intensity of the protein expression is conditioned by circadian rhythm [3]. It is assumed that SREBP1c is regulated by the factors of the molecular clock, such as ROR and REV-ERB. It was also observed that targeted damage to the REV-ERB 1 and 2 gene resulted in deregulation of lipid metabolism and led to hepatic steatosis in test individuals [21]. Furthermore, overexpression of SREBP1c caused increased levels of liver enzymes (ALT, AST), triglycerides, and free fatty acids in serum, which indirectly can lead to increased risk of liver steatosis [3]. There are other signal particles that influence SREBP1c expression. One of them is DEC1. The damage of this gene leads to liver triglyceride accumulation by increased expression of SREBP1c [21]. The endoplasmic reticulum (ER) is involved in the regular activation of SREBP1c transcription factors. It is assumed that physiological regulation of enzymes in ER is determined by rhythmical activation of the IRE1 α pathway. However, the activity of the pathway is conditioned by circadian clock genes, which explains its influence on lipid metabolism in the liver [23].

However, it is assumed that regulation of lipid metabolism in the liver is much more complicated. There can be indirect participation of lipid metabolism products in controlling the liver clock [9].

Cholesterol metabolism

The processes of cholesterol metabolism in the human organism also show circadian rhythms. Numerous studies concern the enzyme that plays a key role in cholesterol synthesis, i.e. HMG-CoA. Preclinical studies proved that HMG-CoA shows circadian oscillations that persist even when the organism is deprived of food. It was also noted that the time of meal consumption had a significantly greater effect on regulating HMG-CoA activity than changing the day-night cycle [24]. It was observed that the expression of HMG-CoA reductase peaked at times when cholesterol itself was not supplied by the diet. It seems that cholesterol synthesis reaches the highest intensity in the rest phase [25]. In another study, the concentration of lathosterol in blood serum was used as the index of cholesterol synthesis intensity and it was found that the indicative compound reached acrophase at night, between midnight and 4 a.m., which proves that cholesterol is synthesized at greater intensity beyond the active phase of the cycle [26].

Bile acid metabolism

Cholesterol 7α-hydroxylase (CYP7A1) has a key role in the synthesis of bile acids in the liver. This enzyme initiates a series of processes that lead to cholesterol transformation into the bile acids. It was revealed that the changes are closely regulated by nutrient availability and the negative feedback loop of the bile acids themselves. The circadian clock is also involved in the processes of CYP7A1 synthesis regulation and generates rhythmic oscillations of its activity [27]. In human studies it was observed that levels of markers of bile acid synthesis reached the acrophase twice in 24 hours – the first time at 1:00 p.m. and the second one at 9 p.m. [26]. Another study showed that mice with damaged Per1 and Per2 genes of the clock have impaired CYP7A1 expression and thus disturbed synthesis of bile acids [28]. In addition, one of the proteins involved in circadian clock function, albumin D-site-binding protein (DBP), is also thought to activate CYP7A1 expression in a rhythmic manner [29].

Farnesoid X receptor (FXR) and liver receptor homolog (LRH) are nuclear receptors that have an important role in regulation of bile acid synthesis. An excessive amount of bile acids in the liver leads to FXR activation, which in turn intensifies the expression of small heterodimer partner (SHP). Only this protein, through action of LRH, induces suppression of CYP-7A1 transcription. It blocks bile acid synthesis and leads to the establishment of feedback loop activity [30]. It was reported that FXR and SHP transcription is regulated by circadian rhythm [31]. It is assumed that REV-ERBα binds with SHP gene promoter factor inducing inhibition of its expression. This results in the unblocking of CYP7A1 transcription, which indirectly intensifies bile synthesis processes [32].

Xenobiotic metabolism

The liver is involved in carrying out all three phases of detoxification processes. It was confirmed that each phase, to a greater or lesser extent, is regulated by the circadian clock [33].

The first phase of detoxification deals mainly with substrate oxidation, reduction, and hydroxylation [34]. Among other factors, a number of cytochromes P450 are involved in this step [35]. In this phase, xenobiotics bind with nuclear receptors and activate detoxification pathways [9]. Clock genes regulate the expression of those nuclear receptors. The expression of a significant number of P450 cytochromes shows circadian rhythm [7]. The impact of the Bmal1 clock gene on the regulation of cytochrome P450 3a11 expression was confirmed in a study from 2019. The study examined the toxicity of two drugs metabolized by the Cyp3a11 enzyme: aconitine and triptolide. The results showed that the toxicity of these substances displayed a circadian rhythm, with increased toxicity during the day compared to the night. Deletion of Bmal1 led to a reduction in Cyp3a11 activity, resulting in increased toxicity and a weakening of the described rhythmicity [35].

In the phase II of detoxification, xenobiotics are coupled and become hydrophilic. Enzymes of this phase are also produced rhythmically, but their expression does not show one peak in 24 hours and thus the evaluation of oscillation is difficult. However, another study on mice showed that the rhythm of sulfotransferases SULT 1C1 and SULT 1D1, which are the enzymes of this phase, shows peak expression during the phase transition from day to night [34]. Other enzymes in this phase include UDP-glucuronosyltransferases (UGT), and it was confirmed in a study from 2020 that the expression of Ugt1a9 exhibits circadian rhythms, reaching its peak level in mouse liver at ZT6 (zeitgeber time). It has been demonstrated that this rhythmicity is regulated by Rev-erbα, which positively modulates Ugt1a9 by periodically inhibiting the Dec2 factor [36].

In phase III, xenobiotics are excreted to the bile through membrane transporters. This detoxification stage has weak circadian regulation [9]. In a study on mice, particular enzymes showed various expression peaks, but it seems that mostly the peaks were in the daily phase of the cycle [34].

It is assumed that circadian rhythms of detoxification enzymes of phase I and II are generated with the use of a transcription factor PAR bZIP (proline and acidic amino acid-rich basic leucine zipper). Mice with PAR bZIP deficiency have decreased expression of liver enzymes of phases I-III [21]. It is assumed that PAR bZIP proteins influence the circadian regulation of detoxification enzymes by direct regulation of transcription of transmembrane proteins necessary in phase I of detoxification, and indirectly by the effect on the CAR receptor [7]. However, the mechanism of regulation of detoxification rhythm is more complicated, and it hypothesized that the intensity of the described processes may be regulated by changing the magnitude of blood flow through the liver [4].

Impact of alcohol on the biological clock

Numerous studies indicate that chronic exposure of the organism to alcohol disturbs the rhythmicity of the circadian system [37]. It was revealed that in alcoholic liver steatosis, the genes Per 1, 2, 3 as well as Npas 2 and Rev-erbα underwent expression in a non-physiological way [21]. Regular alcohol consumption increases PER1 expression, decreases CRY1 expression and changes the patterns of CRY2 expression. It may have consequences in every aspect of metabolism controlled by the above-mentioned genes [38]. In experimental studies on mice, intoxicated with ethyl alcohol acutely or chronically, it was found that in both groups the rhythms of expression of certain genes was altered, particularly in SREBP pathways that control sterol metabolism. It suggests that alcohol abuse predisposes to cholesterol synthesis disturbances and also to fatty acid biosynthesis impairment [39].

BMAL1 gene damage in mice combined with chronic alcohol administration leads to increased aminotransferase concentration in blood serum and predisposes to liver steatosis. Interestingly, mice that were artificially induced to overexpress the BMAL1 gene seemed to be resistant, to a certain extent, to liver damage due to alcohol intake [40].

Hepatitis

The influence of circadian clock genes on the development of hepatitis was examined mainly *in vitro*. In a culture of hepatocytes infected with HCV, irregular expression of clock genes was observed as well as decreased transcription of PER2 and CRY2 factor genes [21].

Other studies have focused on the influence of the biological clock on sodium taurocholate co-transporting polypeptide (NTCP). The HBV virus utilizes NTCP as a receptor for binding to hepatocytes and entering the cell. Research has shown that REV-ERB directly binds to the NTCP promoter and inhibits its expression. Furthermore, pharmacological activation of REV-ERB using synthetic ligands such as SR9009 reduces NTCP levels on cell surfaces and inhibits HBV entry.

Additionally, other studies mentioned in the same article demonstrated that BMAL1 binds to cccDNA and enhances virus promoter activity, leading to increased production of pre-genomic RNA and viral particles [41].

In a recent study, researchers investigated the role of the biological clock in the development and progression of fulminant hepatitis (FHF). They specifically examined the impact of Rev-erbα on regulation of the NLRP3 inflammasome, a protein complex that activates pro-inflammatory cytokines in macrophages. They demonstrated that Rev-erbα inhibits the expression and activity of NLRP3. Furthermore, it was observed that mice deficient in Rev-erb are more susceptible to FHF induced by lipopolysaccharide (LPS) [42].

Liver fibrosis

In pre-clinical studies in animals with CC14-induced liver fibrosis, decreased mRNA concentrations of the genes BMAL1, CLOCK, ROR, and CRY were observed. It suggests that liver fibrosis may induce disturbances in molecular clock activity and, in consequence, lead to impairment of many different aspects of liver metabolism [21]. In another study, a link between PER2 expression level and hepatotoxicity of carbon tetrachloride was revealed. It turned out that the gene shows protective activity against the development of liver fibrosis, probably by suppression of Ucp2 protein activity (uncoupling protein-2) [43].

The potential mechanism by which circadian factors may influence liver fibrosis was proposed by Chen and others in their article. They suggested that CCl4 can lead to the degradation of Rev-Erbα, which subsequently disrupts mitochondrial fission. This results in the release of mtDNA, activating the cGMP-AMP synthase (cGAS) pathway, leading to the induction of inflammation that exacerbates liver fibrosis. Conversely, overexpression of Rev-Erbα restores the proper functioning of mitochondria and inhibits the cGAS pathway, leading to improved liver function [44].

Influence of circadian clock on neoplasm development

The influence of the circadian clock on regulation of the cell cycle, cell proliferation, and neoplasm suppression has been well documented [21]. While examining molecular processes it was found that the heterodimer CLOCK: BMAL1 controls cellular cycle genes, such as Wee1, c-Myc, and cyclin D1 [45]. Thus, disturbances in the functioning of the liver clock may contribute to genome instability and accelerate cellular proliferation. Hepatocellular carcinoma (HCC) biopsy material showed abnormal clock gene expression. Reduced mRNA levels of PER 1,2,3 and CRY2 genes were observed [46]. However, another study, inhibiting Bmal1/Clock induced apoptosis and cell cycle arrest in the G2/M phase in HCC cells, which may be useful for the development of therapy for this disease [47].

Disturbances of molecular clock genes may be responsible for inducing other types of neoplasm. In biopsies of bile duct cancer, a decrease in BMAL1 and PER1 gene expression was documented [48]. Additionally, in another study, an increased frequency of cholangiocarcinoma development was observed in $Cry1^{-/-}$ $Cry2^{-/-}$ mice exposed to diethylnitrosamine [49].

Other processes that undergo diurnal rhythm

The liver is involved in a series of other processes necessary for regular functioning of the whole body. Many of them are regulated by the circadian clock.

The transformation of inactive thyroid gland hormone T4 to the active form T3 takes place in the liver and the enzyme deiodinase 1, engaged in this process, shows circadian rhythm [9]. Many proteins necessary for proper functioning of the immune system are produced in the liver in a rhythmical way, in accordance with circadian rhythm [27]. The proteins of coagulation and fibrinolysis are also produced in the liver in a cyclic manner, in accordance with circadian oscillations [27].

Conclusions

Circadian rhythmicity is undeniably visible in almost all aspects of liver metabolism. However, despite numerous studies on the topic, the basis of this rhythm and its characteristics have been studied only to a small extent. Moreover, some of the research has produced contradictory and unclear results [7]. The huge number of rhythmic external factors (diurnal changes in temperature, light intensity) and the variety of people's daily habits (time of eating, time of physical activity), as well as the complex dependence of liver metabolism on the rest of the body, make it much more difficult to conduct valuable research. Consequently, it is unclear whether the metabolic rhythmicity in hepatocytes is the result of an indirect or direct effect of the factors mentioned here, or whether it is actually due to the existence of the liver's central clock and endogenous clocks. Despite doubts concerning the source of oscillation, the occurrence of rhythmicity itself has been confirmed many times, so it can be assumed that its existence is

practically certain [4, 7]. Further investigations concerning circadian rhythms are significant and may induce progress in hepatology. Research on this topic has already shed new light on the pathogenesis of many diseases that at present still have an unclear etiology (e.g. steatosis, cirrhosis, HCC, biliary tract cancer) [3, 7]. Moreover, a deeper understanding of the impact of circadian rhythms on the development of liver disease would make it possible to identify the specific behavioral and physiological factors that predispose to them. It could favor the development of certain prophylactic strategies reducing morbidity from certain diseases. In addition, research is already underway to develop drugs that directly target modification of specific molecular clock signaling pathways. Such preparations in theory can modify circadian rhythm, leading to therapeutic benefits.

In recent years, a field of science called chronopharmacology has been developing rapidly. It uses the knowledge from biological rhythm analyses to adjust a form of pharmacotherapy for a given patient. The method involves taking into account the rhythms of drug absorption, metabolism and excretion, but also such factors as gastric acid pH, serum hormone levels, etc. A series of studies confirmed that a certain dose of a drug at a certain time can be toxic, while at another time, it can cause only minor side effects [4]. Recommendations in statin therapy can be used as an example of chronopharmacology. These drugs reduce the activity of HMG-CoA reductase required for the synthesis of low-density lipoproteins. They are administered in the evening as cholesterol synthesis is most intense in the evening [50]. It is important to expand knowledge and continue research on circadian rhythms and pharmacological strategies conditioned for this purpose (chronotherapy), which may be a key component of the medicine of the future.

Disclosure

The authors declare no conflict of interest.

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