PharmacologyOnLine
Archives • 2021 • vol.3 • 1990-2001

CIRCADIAN BIORITHMS OF THE BODY AND THE ROLE OF THE LIVER AS THEIR PERIPHERAL OSCILLATOR

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Abstract

Biorhythm is one of the laws of the organism, which is characterized by the presence of cyclic oscillations, which ensures the adaptation of the organism to the rhythmic changes of the external and internal environment. That is, biorhythms are the basis of adaptation of the organism to environmental factors and ensure its vital functions. The most important practical value and the most detailed among the biorhythms of the body study circadian rhythms. The liver creates a single metabolic and energy pool of the body for the metabolism of proteins, fats, carbohydrates. Therefore, in turn, the metabolism of proteins, fats, carbohydrates, enzymes, vitamins; regulation of water, mineral and pigment metabolism; activity of excretory and detoxification processes are characterized by circadian dependence of the course. All diseases of the body are accompanied by a violation of the architecture of its circadian rhythm, ie the phenomenon of desynchrony, starting from the cellular level and ending at the highest body level. Knowledge of the functional state of biorhythms of a healthy organism and their changes (desynchrony) in liver pathology is the key to targeted correction of dysregulatory disorders in diseases and optimization of this organ of pharmacotherapy.

Keywords: *biorhythm, cyclic oscillations, circadian rhythms, liver,*

Biorhythm is one of the laws of the organism, which is characterized by the presence of cyclic oscillations, which ensures the adaptation of the organism to the rhythmic changes of the external and internal environment. That is, biorhythms are the basis of adaptation of the organism to environmental factors and ensure its vital functions [1, 2, 3, 4]. The most important practical value and the most detailed among the biorhythms of the body study circadian rhythms [3, 4, 5, 6]. The daily dependence of functional activity is characteristic of the central and peripheral nervous systems, endocrine, cardiovascular, respiratory, excretory systems, gastrointestinal tract, as well as the activity of metabolism and detoxification of xenobiotics in the liver [3, 7, 8, 9, 10 , 11].

In the process of evolutionary development of a living organism, circadian rhythms have gained leading importance, as biological change of day and night is an integral part of life processes and most clearly reproduces the body's adaptation to environmental conditions [12, 13, 14, 15, 16, 17]. A common characteristic of all circadian rhythms is the autonomy of oscillations, which can be synchronized with environmental factors [18, 19, 20, 21]. Circadian rhythm has a double structure with endogenous (circadian rhythm of physiological functions) and exogenous component (any influence of the environment). Endogenous rhythm allows living systems to "predict" changes in conditions and pre-adapt to them [62]. Among exogenous factors, the leading role belongs to the light factor and diet [18, 19, 20].

Clear structure and synchronicity of circadian rhythms of different processes with each other forms a single circadian system [65, 63]. This system provides temporal coordination of body functions and its adaptation over time to external and internal conditions [61]. The central pacemaker of circadian rhythms is the suprachiasmatic nuclei of the hypothalamus. Simultaneously with the central diary of the daily organization, the body has peripheral oscillators: liver, spleen, lymphocytes, gastrointestinal tract, kidneys, heart, lungs and others. The activity of peripheral oscillators is clearly controlled and are synchronized by the main driver of rhythms (suprachiasmatic nuclei of the hypothalamus).

The liver, as an organ with an extremely broad functional and metabolic profile that provides energy homeostasis of the body - plays a leading role among peripheral oscillators [22, 23]. Some scholars believe that this organ, along with the suprachiasmatic nuclei, is key in the organization of circadian rhythms.

The liver creates a single metabolic and energy pool of the body for the metabolism of proteins, fats, carbohydrates [66, 67]. Therefore, in turn, the metabolism of proteins, fats, carbohydrates, enzymes, vitamins; regulation of water, mineral and pigment metabolism; activity of excretory and detoxification processes are characterized by circadian dependence of the course [68, 69].

In protein metabolism, the liver plays a central role in the body, because to ensure a dynamic circadian balance of proteins and amino acids in the body, performs the following functions: synthesis and breakdown of proteins; reamination and deamination of amino acids; formation of urea, glutamine and creatinine. During the day, in addition to providing their own proteins, liver cells supply blood proteins forming: 100% blood albumin, 75-90% α- globulins та 50% β- globulins. Researchers have registered an acrophase of the content of total protein in the serum of people about 8 p.m. and bathyphase 2 a.m., whereas the peak of protein excretion is recorded by 12 p.m. and decreases with the onset of night. In general, individual serum protein levels range from 6.0 to 8.0 g / L. In addition, the liver is the main site of coagulation factors and some coagulation inhibitors - antithrombin and antiplasmin is involved in the synthesis of heparin [62]. A daily drop is registered V i VII coagulation factors in the morning and afternoon with acrophase of both indicators at night. The circadian content of free heparin is characterized by a maximum of about 2 a.m. and a minimum at 5 p.m.

Under physiological conditions, circadian fluctuations in the supply of amino acids to the liver are harmonized with the circadian rhythm of hepatocyte activity. As a result of amino acid metabolism, ammonia is formed, from which urea and ammonium salts are subsequently synthesized [24]. The liver is the only organ whose cells have all the enzymes for urea synthesis, so this process takes place only in this body. The team of authors led by prof. V.P. Pishak established a chronorhythm

of ammonia excretion in rats, characterized by two-phase: the maximum values of excretion of this indicator occurred in the period from 12 a.m. до 4 a.m., miniphase - at 8 p.m. [25].

The liver, along with the kidneys, is involved in the circadian rhythm of creatinine synthesis, which is one of the ways to neutralize ammonia [26]. According to prof. V.P. Pishak in humans acrophase of creatinine secretion occurs in the period between 3 p.m. and 6 p.m. Other researchers [13] found an acrophase of excretion of creatinine, amine nitrogen and 6 amino acids 3 p.m. і 6 p.m., and the other 13 at 9 p.m. і 12 a.m. Uric acid is the end product of purine breakdown, the main part of which is formed in the liver and excreted in the urine [27]. It is established that the chronorhythm of uric acid secretion in humans is synchronous with creatinine excretion with a characteristic peak between 3 p.m. and 6 p.m.

Many scientists note the central role of the liver in the circadian stages of intermediate carbohydrate metabolism, and thus ensure energy homeostasis of the body [29, 30]. It is established that the metabolism of carbohydrates in the body undergoes circadian fluctuations. It is believed that part of the glycolytic system or synergistic with it the enzyme system is assigned the role of generator of the circadian rhythm of carbohydrate metabolism. The dependence of circadian rhythms of carbohydrate metabolism on the functional state of the liver is presented in the sources of scientific literature [31]. Thus, the most important role of the liver in the regulation of circadian blood glucose levels is noted [32, 33]. In humans, the following daily dynamics of glucose levels are registered: acrophase at 6 p.m. і 12 a.m., whereas the bathyphase in the period between 6 a.m. and 12 p.m. In the case of changes in blood glucose levels, the signal from sensitive chemoreceptors in the nerve centers, and then through the autonomic nerve fibers, it is transmitted to the liver, where the release of mediators of the sympathetic nervous system and stimulation β2- та β3- adrenoreceptors, glycogen breakdown is enhanced and glucose is released from the liver into the blood [34]. Thus, through the mechanism of reverse reactions of glycogen synthesis and breakdown, the amount of glucose is regulated in accordance with the needs of the organism.

The concentration of glycogen in the liver is the most studied and presented in the sources of scientific literature as an indicator of carbohydrate metabolism, which is subject to daily fluctuations [35, 36, 37, 38, 39, 40]. According to [38, 39, 40], the nature of rhythmic changes in glycogen concentrations in the liver is largely the same in rodents of different species, lines, sex and age, which were kept in natural light for 12 hours. During the dark period, which for nocturnal animals is a period of vigor (activity), glycogen gradually accumulates in the liver with its subsequent expenditure during the day period of rest. Exceptions to this rule occur (constant glycogen levels during the day or its increase in the light and decrease in the dark period of the day) and may be due to specific features of experiments and / or housing conditions [35, 36, 37].

The liver also undergoes the following processes of lipid metabolism, the activity of which is characterized by circadian dependence: oxidation of triglycerides, formation of ketone bodies, synthesis of triglycerides and phospholipids, synthesis of lipoproteins, cholesterol synthesis [72]. It is established that the change in cholesterol levels has a clear daily dynamics in people with a maximum content of 6 p.m. and periods of minimum level from 12 a.m. to 12 p.m. The participation of the liver in lipid metabolism is closely intertwined with biliary function, as a constant level of cholesterol is maintained as a result of synthesis, catabolism and excretion of excess bile in the intestine [45]. The filling of the gallbladder at rest and its contraction in response to irritation and its dilatation are confirmed by a distinct circadian rhythm. The intensity of bile secretion in the liver of rats in the morning is higher than in the evening by 3-10%, and the total content of bile acids in the evening is higher than in the morning by 10-48%. In the evening, the concentration and total amount of secreted bilirubin is also higher than in the morning by 13-81%, and cholesterol by 13-59%. The level of serum bilirubin also has a daily dynamics: the period of high bilirubin content occurs during the day and evening – 12 p.m. and 6 p.m., while the bathyphase in the early morning hours – 6 a.m.

In hepatocytes significant variations in the position of the acrophase of circadian rhythms of various metabolizing enzymes and cellular

organelles are registered: lysosomes, phagosomes, Golgi apparatus. Individual microsomal enzymes may have two or more peaks of activity during the day. In particular, acrophases of circadian rhythms of activity and content of cytochrome P450 in the liver of males and females are shifted by 6 hours relative to each other [77, 76, 75].

There are direct neurotrophic connections between the central nervous system and the liver. Diurnal fluctuations in the tone of the ANS, closely related to the light-dark cycle and day or night period of vigor of the body and play an important role in coordinating cyclical processes in the body and in particular in the liver [72]. Most scientists [73, 74] found that for the human body and animals with diurnal activity (rabbits, guinea pigs) is characterized by a predominance of the tone of the sympathetic part of the autonomic nervous system in daylight, and parasympathetic during night sleep, while for animals with nocturnal type of activity (rats, mice) on the contrary. Therefore, day or night type of activity of the organism is determined by daily fluctuations in the tone and content of hormones, which is confirmed by the antiphase level of their levels in organisms and the period of secretion depending on the type of activity (Table 1). In particular, the acrophase of glucocorticosteroid secretion in humans is registered between 6 a.m. and 10 a.m., in rabbits between 7 a.m. and 11 p.m., whereas rats and mice in between 9 p.m. та 10 p.m. n humans, two peaks of adrenaline secretion are recorded, which occur in the early morning (6 a.m.) and daytime (12 p.m.) hours. There is also a late night rise in adrenaline secretion, which occurs between 8 p.m. and 11 p.m. Whereas in mice and rats the peak of adrenaline secretion (AF) observed by 6 p.m. with inverted bathyphase between 6 a.m. and 9 a.m. The chronorrhythm of norepinephrine content and excretion is also characterized by the presence of circadian peaks, but in comparison with glucocorticosteroids and adrenaline with less pronounced antiphase between organisms with day and night type of activity (Table 1).

The key components of the body's antioxidant system are the glutathione system and enzymatic antioxidants: superoxide dismutase, catalase, glutathione peroxidase, glutathione transferase. Hepatocytes are the main site of synthesis of glutathione, a key component of the antioxidant defense system, which provides intracellular prooxidant-antioxidant balance of the body [49, 50, 51, 52]. The total amount of biooxidants in the body, and in particular in the liver, creates a "buffer antioxidant system", and the ratio of prooxidants / antioxidants determines the "antioxidant" status of the body. In turn, intracellular "antioxidant status" is a direct reflection of metabolic homeostasis among cellular reactive oxygen species, antioxidant enzymes and metabolites [83]. It is known that there is a relationship between the circadian change in redox oxidative metabolism of the cell and the circadian clock, which is realized through the influence on the expression of genes involved in the biosynthesis of protein complexes of clock photosensitive genes BMAL1-CLOCK [84]. The above is confirmed by the circadian rhythm of biosynthetic activity Nicotinamide adenine dinucleotide, Nicotinamide adenine dinucleotide phosphate and their reduced forms Nicotinamide adenine dinucleotide and Nicotinamide adenine dinucleotide phosphate [85]. The content of nicotinamide adenine dinucleotide phosphate in the cell plays a key role in the glutathione system, as it is necessary for the transition of the oxidized form of glutathione to reduced under the influence of the enzyme glutathione reductase. The restored form of glutathione acts as an "active stabilizer" of the lipid peroxidation system - antioxidant protection and simultaneously with antioxidant enzymes plays a leading role in ensuring "stability of antioxidant balance" of cells and the body as a whole [53]. Nicotinamide adenine dinucleotide phosphate is also required to support the cytochrome P450 monooxygenase system in the synthesis of cholesterol and bile acids in the liver [54]. Circadian rhythm has also been established for the activity of the enzymatic antioxidants superoxide dismutase and catalase in the liver tissue. In a healthy body, the intensity of lipid peroxidation processes is balanced by the antioxidant system, which is subject to rhythmic changes during the day [86]. In particular, the level of TBA-active products increases at night and decreases in the morning and day []. Some scientists explain the existence of this pattern by the fact that at night lipid metabolism is more intense and carbohydrate is reduced. It was also found that fluctuations in the level of TBA-active

products during the day correlate with the activity of superoxide dismutase. At night, the content of TBA-active products increases, the activity of superoxide dismutase. in the blood decreases, and in the daytime on the contrary [54]. The amount of phospholipids at night is reduced and increases only in the afternoon, ie there is a redistribution of the fraction of lipids and phospholipids during the day. The chronogram of phospholipid levels during the day repeats the chronogram of superoxide dismutase activity: at night and in the morning, when superoxide dismutase activity. minimal, and the processes of lipid peroxidation are most active, there is a decrease in the total amount of phospholipids [87].

The above confirms that the state of the antioxidant system of the body undergoes circadian oscillations, which are mainly due to light-dependent factors. An analysis of research suggests that "antioxidant status" is an important link between circadian rhythms and cellular metabolism, and suggests a link between the circadian clock and redox oxidative metabolism in the liver.

Thus, the analysis of scientific literature sources summarizes the presence of circadian rhythm of enzymatic and non-enzymatic activity of the antioxidant defense system, the dependence of metabolic, excretory and detoxification processes in the body and the key role of the liver as a peripheral oscillator and the above processes. Biorhythms, especially circadian rhythms, are considered a universal criterion of homeostasis, and their violation causes desynchrony (imbalance of biorhythms), as an integral component of any disease.

All diseases of the body are accompanied by a violation of the architecture of its circadian rhythm, ie the phenomenon of desynchrony, starting from the cellular level and ending at the highest body level [55, 56]. Desynchrony occurs when the dynamics and structure of the biorhythm is disturbed and deepens as the pathological process grows and is characterized by a triad of features: changes in the rhythm mesor, adjustment of the rhythm amplitude and migration of acrophase and bathyphase periods [57, 58].

Data on the nature of desynchrony in liver disease are very limited. In clinical and experimental hepatology, the diagnosis of indicators that characterize the metabolic, synthetic, excretory and detoxifying functions of the liver has become important. Such main markers are the content of total protein and its fractional composition, total bilirubin, cholesterol, glycogen, alkaline phosphatase, urea, oxidative-prooxidant balance, the definition of which allows to characterize the changes in liver activity in hepatobiliary pathology [62, 78]. Circadian dysregulation (desynchrony) of lipid metabolism, detoxification processes, formation of reactive oxygen species, cell cycle control may contribute to the development and progression of hepatic steatosis, fibrosis and carcinogenesis [88, 89, 93]. Special attention should be paid to the diagnosis of transminase activity (alanine aminotransferase and aspartate aminotransferase), as it reflects the pathogenetic basis of cytolysis syndrome - violation of the integrity of plasma membranes of hepatocytes and their organelle cytolysis syndrome is the most sensitive and informative characteristic of the degree of pathological process in hepatocytes [90]. Diagnosis of the activity of markers of cytolysis is prescribed in the protocols for the treatment of hepatitis of various etiologies, and the degree of increase in transaminases is the basis for assessing the activity of the pathological process in the liver [92]. However, data on the circadian dependence of the growth of alanine aminotransferase and aspartate aminotransferase on the background of different etiologies of hepatitis have not been studied. Simultaneously with the increase in the activity of tramsminases, changes in the prooxidant-antioxidant balance in hepatocytes are of great practical importance. It is well known that the role of activation of free radical oxidation processes in the pathogenesis of hepatitis of various origins, characterized by changes in circadian rhythms of components of the antioxidant defense system of lipid peroxidation (glutathione reductase, glutathione reductase, glutathione peroxidase, total bilirubin and its fractions, products of protein, purine, lipid metabolism [20, 52, 62]. It should also be noted that in diseases of the hepatobiliary system, the imbalance is registered during the excretory and detoxification processes in hepatocytes [64, 85]. That is why today in practical hepatology a list of indicators that are diagnosed and studied in detail in the analysis of certain

diseases of the hepatobiliary system. The ranges and frameworks within which the values of the studied indicators change are established, however, the peculiarities of these changes depending on the time and period of the day in which the sampling for analysis is carried out are absent. The latter is important in the implementation of chronopharmacological approaches in the appointment of drugs, as it is known that the features of therapy will depend on the established pathophysiological changes [90]. It is also known that very often treatment tactics are based on the "desire" to reduce the severity of the pathological rhythm by creating the maximum concentration of the drug in the body until the maximum manifestation of pathology (desynchrony, breakdown) [62]. The above confirms the relevance of the diagnosis in chronodeterministic mode, with the establishment of circadian features of changes in biorhythms, ie the detection of desynchrony. It should also be noted that the leading role in ensuring the functional activity of the liver is played by neurohumoral regulation and, accordingly, desynchrony of autonomic nervous system tone and / or hormone secretion levels in the future is reflected in changes in the activity of this organ [78, 79]. In viral hepatitis B and C, changes in the structure of the circadian rhythm of serotonin are registered. Serotonin levels in children with chronic hepatitis are 3.6 times higher than in healthy children. In inactive chronic hepatitis C there is an ultradian rhythm of oscillations of this mediator, an increase in the size of the mesor and a decrease in the amplitude of the rhythm, acrophase of serotonin is registered at 1 a.m., 7 a.m., 1 p.m. and 8 p.m., and the bathyphase at 4 a.m., 10 a.m., 5 p.m., 11 p.m., whereas, undiscovered differences in serotonin rhythm mesor in active and inactive chronic hepatitis B. It is observed that the amplitude of serotonin rhythm in the active form of chronic hepatitis is much higher than in inactive [70]. At active chronic hepatitis C shift of an acrophase of a rhythm of serotonin with is characteristic from 10 a.m. (in normal) to 7 a.m., and after treatment to 2 a.m. and increasing the amplitude of oscillations by 29.5%. In patients with chronic hepatitis there is a clear increase in the frequency of exacerbations in April and May, which indicates the feasibility of using chronopharmacological principles in the treatment of liver disease [80, 81, 82]. Knowledge of the functional state of biorhythms of a healthy organism and their changes (desynchrony) in liver pathology is the key to targeted correction of dysregulatory disorders in diseases and optimization of this organ of pharmacotherapy.

References

1. Chronobiology and chronomedicine: a guide / S.I. Rapoport and others.; under ed. S.I. Rapoport, V.A. Frolov, L.G. Khetagurova. M.: LLC "Medical Information Agency", 2012. 480 p.
2. Drogovoz S.M., Kononenko A.V. Biorhythms of nervous activity and pharmacocorrection of their disorders. Pharmacology and drug toxicology. 2013. № 1 (32). P. 14–18.
3. Temporal organization of physiological functions in mammals. Participation of brain structures / R.E. Bulyk and others. Bukovynian Medical Bulletin. 2014. №1 (69). P. 144–147.
4. Chernysheva M.P. Circadian oscillators and hormones. Cytology. 2013. № 11. P. 761–777.
5. Hasting M. Neill S. O, Maywood E. S. Circadian clocks: regulators of endocrine and metabolic rhythms. Endocrinnet. 2007. Vol. 195. P. 187–198.
6. Ohdo S. Development of new chronopharmatherapies based on biological rhythm. Yakugaku Zasshi. 2002. Vol 122, № 12. P. 1059–1080.
7. Crosstalk between xenobiotics metabolism and circadian clock / T. Claudela et al. FEBS Letters. 2007. Vol. 581. P. 3626–3633ю
8. Shibata S. Neural regulation of the hepatic circadian rhythm. The Anatomical Record Part A. 2004. № 280. P. 901–909.
9. Circadian disruption and SCN control of energy metabolism / A. Kalsbeek et al. FEBS Letters. 2011. Vol. 585. P. 1412–1426.
10. Goncharova N. D. Goncharova Hypotalamic-pituitary-adrenal axis and antioxidant enzymes: Circadian rhythms, stress, and aging. Frontiers Neuroendocr. 2006. Vol. 27, № 1. P. 52–53.
11. Zmrzljak U. P., Rozman D. Circadian regulation of the hepatic endobiotic and xenobitoic detoxification pathways: The time matters. Chem. Res. 2012. Vol. 25. P. 811–882.
12. Pishak V. P., Bulyk R. E., Vlasova K. V. Molecular genetic markers of temporal organization of physiological functions in mammals (literature review and own data). Bukovynian Medical Bulletin. 2014. № 1 (169). P. 172–177.
13. Пішак В. П. Фотоперіодизм і функціонування репродуктивної системи у людини. Міжнародний ендокринологічний журнал. 2013. № 2 (50). С. 77–80.
14. Ripperger J. A. Mapping of binding regions for the circadian regulators BMAL1 and CLOCK within the mouse REV-ERBa gene. Chronobiology International. 2006. Vol. 23. P. 135–142.
15. Vetter C., Scheer FAJL. Circadian biology: uncoupling human body clocks by food timing. Curr. Biol. 2017. № 13. P. 656–658.
16. Hatori M. Aging and homeostasis. Circadian rhythms and aging. Clin. Calcium. 2017. № 27. P. 955–961.
17. Interaction between circadian rhythms and stress. C. E. Koch et al. Neurobiol. Stress. 2016. № 14. P. 57–67.
18. Van Gelder R. N., Buhr E. D. Ocular photoreception for circadian rhythm entrainment in mammals. Annu. Rev. Vis. Sci. 2016. № 14. P 153–169.
19. Manoogian E.N., Panda S. Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Res. Rev. 2016. № 4. P.1568–1637.
20. Effects of altered photoperiod on circadian clock and lipid metabolism in rats / X. Xiex et al. Chronobiology International. 2017. № 6. P. 1–11.
21. Hood S., Amir S. Neurodegeneration and the circadian clock. Front Aging Neurosci. 2017. № 9. P. 170.
22. Ferrell J. M., Chiang J. L. Circadian rhythms in liver metabolism and disease. Acta Pharmacitica Sinica B. 2015. Vol. 5. P. 113–122.
23. Entrainment of the circadian clock in the liver by feeding clock / K.-A. Stokkan et al. Science. 2001. Vol. 291. P. 490–493.
24. Biochemistry: a textbook / Zahaiko A. L. and others, edited by prof. A.L. Zagayko, prof. K.V. Alexandrova. H.: Fort Publishing House, 2014. 728 p.
25. Neuroendocrine regulation of renal function chronorhythms in mammals / V. P. Pishak and others Chernivtsi: Medical Academy, 2005. 166 p.
26. Semenenko S.B. Features of the structure of chronorhythms of excretory function of the kidneys under conditions of hyperfunction of the pineal gland. Bukovynian Medical Bulletin. 2014. № 2 (70). P. 99–101.
27. Johnson R. J., Lanaspa M. A., Gaucher E. A. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome and cardiorenal disease:

evolutionary considerations. Semin. Nephrol. 2011. Vol. 31, № 5. P. 394–399.
28. Stow L. R., Gumz M. L. The circadian clock in the kidney. J. Am. Soc. Nephrol. 2011. № 22. P. 598–604.
29. Sleep and circadian rhythms: Key components in the regulation of energy metabolism / D. A. Laposkya et al. FEBS Letters. 2008. Vol. 582. P. 142–151.
30. Schmutz I., Albrecht U., Ripperger J. A. The role of clock genes and rhythmicity in the liver. Molecular and Cellular Endocrinology. 2012. Vol. 349. P. 38–44.
31. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1 / J. T. Rodgers et al. Nature. 2005. Vol. 434. P. 113–118.
32. A daily rhythm in glucose tolerance: a role for the suprachiasmatic nucleus / S. E. Fleur et al. Diabetes. 2001. Vol. 50, № 6. P. 1237–1243.
33. Kalsbeek A., Fleur S., Fliers E. Circadian control of glucose metabolism. Molecular Metabolism. 2014. Vol. 3. P. 372–383.
34. Glucocorticoid regulation of the circadian clock modulates glucose homeostasis / A. Y. So et al. Proc Natl. Acad. Sci. U S A. 2009. Vol. 106. P. 17582–17587.
35. Doi R., Oishi K., Ishida N. CLOCK regulates circadian rhythms of hepatic glycogen synthesis through transcriptional activation of Gys2. J. Biol Chem. 2010. Vol. 285. P. 22114–22121.
36. Konovalova L.A., Gubin G.D. Daily biorhythm of the functional state of hepatocytes in monkeys. Chronobiology and chronopathology: abstracts. report. All-Union. the conference. M., 1981. P. 134.
37. Glycogen metabolism and the homeostatic regulation of sleep / J.M. Petit et al. Metab. Brain Dis. 2015. Vol 30, № 1. P. 263–279.
38. Features of changes in circadian rhythms in carbohydrate metabolism of schuras in the minds of paracetamol hepatitis / K.O. KalKo and others Pharmacology and toxicology. 2016. № 3 (49) P. 48–53.
39. PER2 promotes glucose storage to liver glycogen during feeding and acute fasting by inducing Gys2 PTG and GL expression / Fabio Zani et al. Mol Metab. 2013. № 2. P. 292–305.
40. Glycogen repletion in brown adipose tissue upon refeeding is primarily driven by phosphorylation-independent mechanisms / Carmean C. M. et al. PLoS One. 2016. Vol. 11, № 5. P. 148–156.
41. Leavens K. F., Birnbaum M. J. Insulin signaling to hepatic lipid metabolism in health and disease. Crit. Rev. Biochem. Mol. Biol. 2011. Vol. 46. P. 200–215.
42. Rudney H., Sexton R. C. Regulation of cholesterol biosynthesis. Rev. Nutr. 1986. Vol. 6. P. 245–272.
43. Pan X., Zhang Y., Hussain M. M. Diurnal regulation of MTP and plasma triglyceride by CLOCK is mediated by SHP. Cell Metab. 2010. Vol. 12. P. 174–186.
44. Pan X., Hussain M. M. Diurnal regulation of microsomal triglyceride transfer protein and plasma lipid levels. J. Biol. Chem. 2007. Vol. 282. P. 24707–24719.
45. Lorbek G., Lewinska M., Rozman D. Cytochrome P450s in the synthesis of cholesterol and bile acids – from mouse models to human diseases. FEBS J. 2012. Vol. 279, № 9. P. 1516–1533.
46. Regulation of bile acid synthesis by the nuclear receptor Rev-erbalpha / H. Duez et al. Gastroenterology. 2008. Vol. 135. P. 689–689.
47. Davidovich O.V. Chronopharmacological features of the liver reaction to dehydrocholic acid. Chronobiology and chronopathology: abstracts. report all-union scientific practical conference, M.,1981., P. 90.
48. Davydovich O.V. Daily and seasonal characteristics of the liver's reaction to the introduction of bilignost. Pharmacology and toxicology. 1984. № 1. P. 101–104.
49. MYC-driven inhibition of the glutamate-cysteine ligase promotes glutathione depletion in liver cancer / Anderton B. and others . EMBO Rep. 2017. № 4 (18). P. 569–585.
50. Peculiarities of the circadian dynamics of the antioxidant system of lipid peroxidation in rats / K.O. Kalko and others. Clinical pharmacy. 2015. № 4. P. 52–57.
51. Sacco R., Eggenhoffner R., Giacomelli L. Glutathione in the treatment of liver diseases: insights from clinical practice. Minerva Gastroenterol. Dietol. 2016. Vol. 62, № 4. P. 316–324.
52. Oxidative stress response elicited by mitochondrial dysfunction: implication in the pathophysiology of aging / C. H. Wang and

others. Experimental Biology and Medicine. 2013. Vol. 238, № 5. P. 450–460.
53. Clinical and experimental substantiation of the use of superoxide dismutase in medicine: monograph / A. V. Stefanov and others. Kh .: NUPh Publishing House: Golden Pages,2004. 288 p.
54. Regular feeding plays an important role in cholesterol homeostasis through the liver circadian clock / D. Yamajuku and others. Circ Res. 2009. Vol. 105. P. 545–548.
55. Agadzhanyan N.A. Desynchronosis: mechanisms of development from molecular genetic to organismal level. Advances in physiological sciences. 2004. No. 2.P. 57–72.
56. Desynchronosis of protein and purine metabolism in paracetamol hepatitis / K.O. Kalko and others. Pharmacy Bulletin .2016. № 1 (71). P. 91–95.
57. Reid K. J., Zee P. C. Circadian rhythm disorders. Semin. Neurol. 2009. Vol. 29. P. 393–405.
58. Drogovoz S.M., Dmitrenko S.V. Inflammation - desynchronosis and its chronotherapy. Clinical pharmacy. 2013№ 2. P. 40–44.
59. Manifestation of toxic action of paracetamol in female and male rats depending on the circadian rhythms of liver activity / Kalko K. O., Drogovoz S. M., Koyro O. O., Tsubanova N. A., Toziuk O. Yu., Lenha E. L., Bahan S. O., Borysiuk I. Yu. Pharmacologyonline. 2021. Vol. 2. P. 926-942. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A113_Drogovoz.pdf
60. Features of circadian rhythms, indicators of rat liver function under physiological conditions / Kalko K., Drogovoz S., Lukashuk M., Horoshko V., Levkov A., Gerush O., Lenha E. Pharmacologyonline. 2021. Vol. 2. P. 1289-1309. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A143_Kalko.pdf
61. Chronopharmacological study of hepatoprotective activity of the drug «Antral®» / Kalko K. O., Zacharko N. V., Drogovoz S. M., Dehtiarova K. O., Gerush O. V., Toziuk O. Yu., Barus M. Pharmacologyonline. 2021. Vol. 2. P. 1263-1275.
62. Chronopharmacology for a doctor, pharmacist, student: textbook / SM Drogovoz et al.; Ed. prof. SM Drogovoz. H.: "Title", 2016. 376 p.
63. Circadian dependence of paracetamol hepatotoxicity in rats / Kalko K. O., Drogovoz S. M., Pozdnyakova A. Yu., Zakharko N. V. Eksperimental'naya i Klinicheskaya Farmakologiya. 79 (7). Pp. 25-28. http://ekf.folium.ru/index.php/ekf/article/view/1815
64. Kalko K.O. Chronopharmacological study of the of hepatoprotective agents activity .... cand. pharm. Science: 14.03.05 / NUPh. Kh., 2017. 195 p.
65. Chronopharmacological features of hepatoprotectors action in the experiment / Bunyatyan N. D., Kalko K. O, Drogovoz S. M, Kononenko A. V. Bulletin of Experimental Biology and Medicine. 2018. No. 6 Pp. 712-715 DOI: 10.1007 / s10517-018-4258-8.
66. Reinke H, Asher G. Circadian Clock Control of Liver Metabolic Functions. Gastroenterology. 2016 Mar;150(3):574-80. doi: 10.1053/j.gastro.2015.11.043. Epub 2015 Dec 2. PMID: 26657326.
67. Mukherji A., Bailey S.M., Staels B., Baumert T.F. The circadian clock and liver function in health and disease. J Hepatol. 2019 Jul;71(1):200-211. doi: 10.1016/j.jhep.2019.03.020. Epub 2019 Mar 28. PMID: 30930223.
68. Saran A.R., Dave S., Zarrinpar A. Circadian Rhythms in the Pathogenesis and Treatment of Fatty Liver Disease. Gastroenterology. 2020 May;158(7):1948-1966.e1. doi: 10.1053/j.gastro.2020.01.050. Epub 2020 Feb 13. PMID: 32061597; PMCID: PMC7279714.
69. Ji Y., Elkin K., Yip J., Guan L., Han W., Ding Y. From circadian clocks to non-alcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol. 2019 Nov;13(11):1107-1112. doi: 10.1080/17474124.2019.1684899. Epub 2019 Oct 30. PMID: 31645151.
70. Tong X., Yin L. Circadian rhythms in liver physiology and liver diseases. Compr Physiol. 2013 Apr;3(2):917-40. doi: 10.1002/cphy.c120017. PMID: 23720334.
71. Zhou D., Wang Y., Chen L., Jia L, Yuan J, Sun M, Zhang W, Wang P, Zuo J, Xu Z., Luan J. Evolving roles of circadian rhythms in liver homeostasis and pathology. Oncotarget. 2016 Feb 23;7(8):8625-39. doi: 10.18632/oncotarget.7065. PMID: 26843619; PMCID: PMC4890992.

72. Chen R. , Zuo Z. , Li Q , Wang H. , Li N , Zhang H. , Yu X , Liu Z . DHA substitution overcomes high-fat diet-induced disturbance in the circadian rhythm of lipid metabolism. Food Funct. 2020 Apr 1;11(4):3621-3631. doi: 10.1039/c9fo02606a. Epub 2020 Apr 15. PMID: 32292967.
73. Harris B.E., Song R.L., He Y.J., Soong S.J., Diasio R.B. Circadian rhythm of rat liver dihydropyrimidine dehydrogenase. Possible relevance to fluoropyrimidine chemotherapy. Biochem Pharmacol. 1988 Dec 15;37(24):4759-62. doi: 10.1016/0006-2952(88)90349-8. PMID: 3202908.
74. Gnocchi D., Custodero C., Sabbà C., Mazzocca A. Circadian rhythms: a possible new player in non-alcoholic fatty liver disease pathophysiology. J Mol Med (Berl). 2019 June; 97(6):741-759. doi: 10.1007/s00109-019-01780-2. Epub 2019 Apr 5. PMID: 30953079.
75. Zwighaft Z., Reinke H., Asher G. The Liver in the Eyes of a Chronobiologist. J Biol Rhythms. 2016 Apr;31(2):115-24. doi: 10.1177/0748730416633552. Epub 2016 Feb 24. PMID: 26911716.
76. Li. S., Lin J.D. Transcriptional control of circadian metabolic rhythms in the liver. Diabetes Obes Metab. 2015 Sep;17 Suppl 1(0 1):33-8. doi: 10.1111/dom.12520. PMID: 26332966; PMCID: PMC4562072.
77. Yamamuro D., Takahashi M., Nagashima S., Wakabayashi T., Yamazaki H., Takei A., Takei S., Sakai K., Ebihara K., Iwasaki Y., Yada T., Ishibashi S. Peripheral circadian rhythms in the liver and white adipose tissue of mice are attenuated by constant light and restored by time-restricted feeding. PLoS One. 2020 June 12;15(6):e0234439. doi: 10.1371/journal.pone.0234439. PMID: 32530967; PMCID: PMC7292356.
78. Mazzoccoli G., Vinciguerra M., Oben J., Tarquini R., De Cosmo S. Non-alcoholic fatty liver disease: the role of nuclear receptors and circadian rhythmicity. Liver Int. 2014 Sep;34(8):1133-52. doi: 10.1111/liv.12534. Epub 2014 Apr 9. PMID: 24649929.
79. Gachon F. Protéomique circadienne [Circadian proteomics]. Biol Aujourdhui. 2018;212(3-4):55-59. French. doi: 10.1051/jbio/2018025. Epub 2019 Apr 11. PMID: 30973132.
80. Landgraf D., Tsang A.H., Leliavski A., Koch C.E., Barclay J.L., Drucker D.J., Oster H. Oxyntomodulin regulates resetting of the liver circadian clock by food. Elife. 2015 Mar 30;4:e06253. doi: 10.7554/eLife.06253. PMID: 25821984; PMCID: PMC4426666.
81. Westermark P.O., Herzel H. Mechanism for 12 hr rhythm generation by the circadian clock. Cell Rep. 2013 Apr 25;3(4):1228-38. doi: 10.1016/j.celrep.2013.03.013. Epub 2013 Apr 11. PMID: 23583178.
82. Forsyth C.B., Voigt R.M., Burgess H.J., Swanson G.R., Keshavarzian A. Circadian rhythms, alcohol and gut interactions. Alcohol. 2015 Jun;49(4):389-98. doi: 10.1016/j.alcohol.2014.07.021. Epub 2014 Nov 14. PMID: 25499101; PMCID: PMC4431951.
83. Draelos Z.D., Makino E.T., Kadoya K., Nguyen A., Jiang L.I., Mehta R.C. Clinical Benefits of Circadian-based Antioxidant Protection and Repair. J Drugs Dermatol. 2020 Dec 1;19(12):1209-1214. doi: 10.36849/JDD.2020.5355. PMID: 33346522.
84. Xie M., Tang Q., Nie J., Zhang C., Zhou X., Yu S, Sun J., Cheng X., Dong N., Hu Y, Chen L. BMAL1-Downregulation Aggravates Porphyromonas Gingivalis-Induced Atherosclerosis by Encouraging Oxidative Stress. Circ Res. 2020 Mar 13;126(6):e15-e29. doi: 10.1161/CIRCRESAHA.119.315502. Epub 2020 Feb 11. PMID: 32078488.
85. Patel S.A., Velingkaar N.S., Kondratov R.V. Transcriptional control of antioxidant defense by the circadian clock. Antioxid Redox Signal. 2014 Jun 20;20(18):2997-3006. doi: 10.1089/ars.2013.5671. Epub 2014 Jan 3. PMID: 24111970; PMCID: PMC4038985.
86. Singh R., Singh R.K., Masood T., Tripathi A.K., Mahdi A.A., Singh R.K., Schwartzkopff O., Cornelissen G. Circadian time structure of circulating plasma lipid peroxides, antioxidant enzymes and other small molecules in peptic ulcers. Clin Chim Acta. 2015 Dec 7;451(Pt B):222-6. doi: 10.1016/j.cca.2015.09.033. Epub 2015 Oct 3. PMID: 26434551.
87. Plano S.A., Baidanoff F.M., Trebucq L.L., Suarez S.Á., Doctorovich F., Golombek D.A., Chiesa J.J. Redox and Antioxidant Modulation of Circadian Rhythms: Effects of Nitroxyl, N-Acetylcysteine and Glutathione. Molecules. 2021 Apr

26;26(9):2514. doi: 10.3390/molecules26092514. PMID: 33925826; PMCID: PMC8123468.
88. Sabath E., Báez-Ruiz A., Buijs R.M. Non-alcoholic fatty liver disease as a consequence of autonomic imbalance and circadian desynchronization. Obes Rev. 2015 Oct;16(10):871-82. doi: 10.1111/obr.12308. Epub 2015 Jul 27. PMID: 26214605.
89. Shetty A., Hsu J.W., Manka P.P., Syn W.K. Role of the Circadian Clock in the Metabolic Syndrome and Nonalcoholic Fatty Liver Disease. Dig Dis Sci. 2018 Dec;63(12):3187-3206. doi: 10.1007/s10620-018-5242-x. Epub 2018 Aug 18. PMID: 30121811.
90. Cebola I. Liver gene regulatory networks: Contributing factors to nonalcoholic fatty liver disease. Wiley Interdiscip Rev Syst Biol Med. 2020 May;12(3):e1480. doi: 10.1002/wsbm.1480. Epub 2020 Feb 4. PMID: 32020788.
91. Ni Y., Zhao Y., Ma L., Wang Z., Ni L, Hu L, Fu Z. Pharmacological activation of REV-ERBα improves nonalcoholic steatohepatitis by regulating intestinal permeability. Metabolism. 2021 Jan;114:154409. doi: 10.1016/j.metabol.2020.154409. Epub 2020 Oct 21. PMID: 33096076.
92. Maillo C., Martín J., Sebastián D., Hernández-Alvarez M., García-Rocha M., Reina O., Zorzano A., Fernandez M., Méndez R. Circadian- and UPR-dependent control of CPEB4 mediates a translational response to counteract hepatic steatosis under ER stress. Nat Cell Biol. 2017 Feb;19(2):94-105. doi: 10.1038/ncb3461. Epub 2017 Jan 16. PMID: 28092655.
93. Investigation of the hepatoprotective effect of the common cat's foot herb dry extract / Slobodianiuk, L., Budniak, L., Marchyshyn, S., Basaraba, R. Pharmacologyonline. 2020. Vol. 3. P. 310-318.

Table 1. Circadian rhythm of mediators of autonomic nervous system and hormones in organisms with day and night type of activity [29, 30, 89-91]

Type of organism	Glucocorticosteroids		Adrenalin		Norepinephrine	
	AF	B	AF	B	AF	B
Man	6-10*	24-4*	6*, 12*, 20-23*	23-6*	8-14*, 18-22*	22-6*
Rabbits	7-11*	22-2*	8*/**	2*/**	8*/**	2*/**
Rats	21-22*	9-11*	18*	6-9*	18*,22*	14*
Mice	21-22*	8-10*	18*	6-9*	17*, 22-23*	13*

Notes: AF – acrophase of the studied indicator; B – bathyphase of the studied indicator;* the content of the indicator was determined in the blood; ** the content of the indicator was determined in the urine.