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CIRCADIAN CHRONORHYTHMS OF FREE-RADICAL HOMEOSTASIS, ADRENAL HORMONES AND FACTORS OF HUMORAL IMMUNITY OF WHITE RATS IN NORMAL AND UNDER THE ACTION OF CADMIUM CHLORIDE

Abstract. *In the experiment, the circadian chronorhythms of free radical homeostasis in rat erythrocytes, adrenal hormones in the plasma of their blood and the indicators of humoral immunity in the blood serum were investigated. It was established that as a result of intragastric administration of an aqueous solution of cadmium chloride at a dose of 5 mg / kg for 14 days, desynchronosis occurs in the activity of the pro and antioxidant systems and other studied parameters, which is explained by increased free radical oxidation of lipids and a decrease in the activity of antioxidant enzymes.*
Key words*: circadian chronorrhythms, desynchronoses, blood, free radical homeostasis, adrenal glands, humoral immunity.*

Introduction. At present, it is likely that the prefix "chrono" (chronotherapy, chronopharmacology, chronophysiology, chronoprophylaxis, etc.) should be used for any biomedical area. Knowledge of biological rhythms provides physicians and biologists with an important tool for assessing the functional state of the body and determining the optimal values of physiological functions in a temporal aspect, both for intended and unpredictable actions [1, 2, 3].

Biological rhythms are periodic reproductions of changes in the nature and intensity of biological processes and phenomena. They are inherent in all forms of all living organisms and are noted at all levels of the organization of living matter. In plants, rhythms are manifested, for example, in the daily movement of leaves, petals, autumn leaf fall, and the like. Animal rhythms are clearly expressed in the frequency of motor activity and many other functions (temperature fluctuations, hormone secretion, RNA synthesis, cell division, etc.). Many physiological processes (daily fluctuations in blood pressure and blood clotting parameters, quantitative lymph indices) have a rhythmic character. Biological rhythms are hereditarily fixed and are the most important factor of adaptation and evolution in general [4, 5].

Biological rhythms occur as a reaction to periodic changes in the environment (exogenous rhythms) or are generated by the body itself (endogenous rhythms). The latter arise on the basis of self-regulating processes in living systems (cells, tissues, etc.). External influences have a limited effect on endogenous rhythms, shift the phase of these biological rhythms and change their amplitude [6, 7].

Disruption in the confinement of human biorhythms to periodic changes in the external environment is called desynchronosis. An example is a flight to a different time zone. The consequences of desynchronosis can be exacerbations of chronic diseases, fatigue and decreased performance. Inconsistency of biorhythms (desynchronosis) is, as researches show, the first signal of biological trouble, which can be considered as pre-pathology or pathology. This allows for the early diagnosis of diseases, more effective treatment and prevention [8, 9].

Achievements of biorhythmology are important for the organization of a rational mode of work and rest of a person, especially in extreme conditions (working at night, in polar conditions and in space, flying to other time zones, etc.), when the endogenous biological rhythms are disturbed by cyclic changes in the external environment. Daily rhythms of cell proliferation are taken into account, for example, in cancer clinics when prescribing drugs that act on dividing cells [10].

Medicine and biology now closely approach to the consideration of the processes of the norm and pathology in projection at certain periods of time (during the day, months, seasons, etc.) [11, 12].

An important indicator of the norm and pathology of body functions is the range of their daily fluctuations in the norm. This means that at different times of day, the norm indicator varies in different limits, and, therefore, the same indicator of the function at one time of day will normally have one quantitative characteristic, and another the rest of the time.

Another important indicator is the different sensitivity of the organism to the same physical or chemical effect or to drugs at different times of the day. For example, a higher sensitivity of a person to such well-known antibiotic as penicillin, is registered in the evening and during sleep; dentists know that tooth sensitivity to painful stimuli is maximum at 4 p.m. and minimum in the morning, so they tend to perform the most painful processes in the morning [13].

Preventive medicine is also beginning to take into account the dynamics of biorhythms. For example, doctors have shown that vaccination of children against measles should be carried out only in the first half of the day, since in the second more pronounced negative reactions of the body develop, disrupting the daily regime of physiological functions [14, 15].

For the pathogenesis of many diseases, activation of free radical mechanisms is essential, which is accompanied by an increase in the level of reactive oxygen species in the body [16, 17]. Under normal conditions, the activation of free radical mechanisms is one of the means of reliable protection of the body against various exogenous factors. At the same time, an increased content of free radicals, exceeding the limits of maximum permissible concentrations, adversely affects metabolic processes and may cause the development of pathological changes [18].

It is known that a high content of oxidants causes in the body the activation of lipid peroxidation (LPO) and the accumulation of its products, which can also lead to significant disturbances. In this area, an important role belongs to the mechanisms of protection of cellular structures from the toxic effect of oxidants, antioxidant defense (AOD), which maintains the concentration of reactive oxygen species and peroxidation products at a level safe for the body [19].

At the same time, data on chronorhythmic changes in the parameters of the system of free radical peroxidation both in norm and due to the effect of various stress factors, in particular heavy metal salts, are insufficient.

Due to intensive discharge from industrial enterprises, environmental pollution with cadmium is constantly increasing. As a result, pollution of soil and food products grown on them also increases [20].

Cadmium belongs to highly toxic substances. The main mechanism of cadmium toxic action is the blocking of sulfhydryl groups of enzymes. In addition, the toxic effect of cadmium is associated with its physiological antagonism to zinc. Cadmium has a high ability to cumulate in the tissues in which it is found both in the ionic form (inorganic compounds) and in the complex with thionin [21].

The formation of free radicals, which occurs under conditions of admission of cadmium compounds in the body, accelerates the process of peroxidation, accompanied by damage to the macromolecules and supramolecular components of the cell, depletion of the body’s antioxidant defense system, changes in nitrogen, carbohydrate metabolism and intensity of bioenergy processes [22, 23].

Recently, the subject of active study has been the participation of adrenal hormones in the body's response to various adverse effects. In particular, daily, seasonal and other chronorhythms of physiological functions in adrenalectomized animals are being studied [24]. At the same time, information about circadian changes in the functioning of the adrenal glands is insufficient [26, 26].

When a person is exposed to harmful environmental factors, the adaptive responses may be disturbed, leading to an immunopathological process [27, 28].

The human immune system, when in contact with various infectious agents (bacteria, viruses), produces protective proteins (antibodies), so-called immunoglobulins, which specifically interact with microorganisms and help blood cells cope with the infection faster.

The largest molecules are class M

immunoglobulins, they are first produced by contact with microorganisms, so they are called immunoglobulins of the primary immune response. The presence of immunoglobulin M (IgM) in the blood indicates an acute stage of the infectious process in the human body. This class of immunoglobulins begins to be produced before birth, but IgM does not penetrate through the placenta because of its size, so the presence of IgM in the cord blood of a newborn indicates prenatal infection [29, 30].

Class G immunoglobulins are produced in the later stages of the disease, as well as in exacerbation of chronic infections. They are smaller in size than IgM; four subclasses of IgG are distinguished. The presence of IgG in the blood indicates the duration of the pathological process. By the way, this class of immunoglobulins penetrates through the placenta, ensuring the immunity of the child in the first months of life (up to 3-6 months). But the baby itself begins to produce antibodies of this class in sufficient quantity closer to the age of one, therefore the presence of immunoglobulins of class G in the infant's blood only indicates the possibility of prenatal infection, since the baby's mother has these antibodies. The child needs further examination to determine his status.

Class A immunoglobulins are predominantly located in the mucous membranes and protect the body at the first stage of contact with the infection; the baby receives these immunoglobulins with the mother's milk. These immunoglobulins provide protection against a wide variety of infections; in the presence of such antibodies in the blood, it is possible to judge the presence or absence of infection and its activity [30, 31].

In view of the above, the study of the influence of heavy metals on the state of the immune system, taking into account the chronobiological aspect, is relevant to contemporary issues of biology and medicine.

The purpose of the study is to determine the structure of circadian chronorhythms of free radical homeostasis, adrenal hormones and the dynamics of daily changes in immunological reactivity in white rats under the conditions of the physiological norm, as well as under the influence of cadmium chloride.

Material and methods. The experiments were conducted on 96 adult white male rats weighing 180-200 g, kept in standard vivarium conditions at a constant temperature and humidity, in the usual light mode, with free access to food and water. The test group of animals was intragastrically administered an aqueous solution of cadmium chloride at a dose of 5 mg / kg for 14 days, and the control group was given tap water.

The rats were killed by decapitation in accordance with the requirements of the European Convention for the Protection of Experimental Animals, under light ether anesthesia at 8 a.m. 12 a.m. 4 p.m. 8 p.m. 12 p.m. and 4 a.m.

The blood was stabilized with heparin, centrifuged for 15 minutes at 3000 r.p.m, the plasma was separated from the formed elements. A suspension of red blood cells was obtained by washing three times with a physiological solution of sodium chloride in a ratio of 1:10.

The state of lipid peroxidation was assessed by the content in erythrocytes of malonic aldehyde (MA) and diene conjugates (DC) [32], and the AOD system was evaluated by the level of catalase [33].

The study of the content of epinephrine and noradrenaline in the blood plasma was performed by enzyme immunoassay using the CatCombi ELISA reagent kit from IBL (Hamburg). The level of corticosterone in the blood plasma of rats was determined by radioimmunoassay method using the Corticosterone RIA reagent kit (for rats and mice) from IBL (Hamburg).

For studies, blood serum was also used, in which the level of immunoglobulins IgA, IgG, IgM was determined by the method [34].

Statistical processing of the results was performed by the method of variation analysis with the definition of Student's criterion.

Results and their discussion. As a result of the research, it was revealed that under normal conditions, the indicators of free radical homeostasis in the erythrocytes of white rats change periodically during the studied part of the day. In particular, the smallest amount of MA was detected at 8 a.m. (36.21±0.913 μmol / l), subsequently the level of this indicator gradually increased, reaching a maximum value at 8 p.m. (51.35±0.102 μmol / l). The acrophase of the DK content was observed at 4 p.m. (2.27±0.008 E_{232} /

ml), the batiphase was observed at 12 a.m. (2.03±0.011 E_{232} / ml).

Catalase activity in erythrocytes of intact rats was the smallest at 8 a.m. (2.04±0.035 µmol/min·ml), slightly increased during the next two time intervals, and at 8 p.m. it became almost equal to the initial value (2.08±0.034 µmol / min·ml).

After daily administration of a solution of cadmium chloride to rats for 14 days, significant changes were recorded in the chronorhythms of those indicators of prooxidant and antioxidant homeostasis, which were studied. Thus, the levels of MA and DC significantly increased in all the studied time intervals, and their chronograms, compared with the control, acquired an antiphase character. In both cases, there was a redistribution of acro - and batiphases.

The MA rhythm mezor grew from 44.21±2.525 to 72.80±3.885 µmol / L (p<0.001), the amplitude of oscillations increased by 23.4% relative to that of intact animals. The average level of DC rhythm also significantly changed (from 2,18±0,037 до 3,66±0,198 E_{232}/ml, p<0,001), its amplitude increased 2.7 times.

All these changes occurred against the background of a decrease in the activity of the enzyme of the AOD catalase system. During the entire study period, the activity of catalase compared with the groups of intact rats was significantly less. The rhythm mezor also significantly decreased in accordance with 2.10±0.018 to 1.39±0.065 µmol / min · ml. The amplitude of chronogram fluctuations grew 5.5 times.

Owing to the conducted research, it was also established that catecholamines and corticosteroids are characterized by daily secretory dynamics, and the phase structure of circadian rhythms of adrenaline and noradrenaline was the same. The peak of catecholamine secretion occurs during the daytime: at 12 a.m., the concentration of adrenaline in the blood plasma was 16.5 ± 0.74 nmol / l, and that of norepinephrine - 55.8 ± 1.03 nmol / l. The batiphase content of these hormones in the blood plasma was observed at 8 p.m., at this time the level of adrenaline was 11.1 ± 0.20 nmol / l, and norepinephrine - 33.8 ± 1.10 nmol / l. The amplitude of secretion of norepinephrine was 43.1 ± 3.17%, adrenaline - 17.5 ± 4.35%.

The data obtained coincide with the literature on the daily rhythms of catecholamine secretion [35, 36], and also correlate with morphometric studies. In the latter, periodic enhancement of metabolic and synthetic processes in the tissue is observed, manifested by an increase in the size of the nuclei, detection of a large number of euchromatin in them, expansion of the nuclear pores, an increase in the number of mitochondria and ribosomes. At this time, a sharp increase in the cytoplasm of the number and size of secretory granules filled with catecholamines was recorded [37, 38].

As a result of our experiments, it has been established that the concentration in the blood plasma of the main hormone of the rat adrenal cortex, corticosterone, also has clear circadian characteristics. But its diurnal dynamics have different characteristics than circadian chronorhythms of catecholamines. Thus, the maximum plasma concentration of control animals was observed in the morning period of the day and at 8 a.m. was equal to 119.2 ± 9.70 nmol / l. The rhythm batiphase occurred at 8 p.m. (42.3 ± 3.84 nmol / l). The amplitude of corticosterone secretion was 43.5 ± 3.17%.

A single intragastric administration to rats of the experimental group of cadmium chloride solution in all studied time intervals led to the activation of the secretory activity of adrenal medulla cells, accompanied by an increase in the release of catecholamines into the blood.

The acrophase concentration of adrenaline in the blood plasma was recorded, as in the group of intact animals, at 12 a.m. (23.4 ± 0.65 nmol / l, p<0.001), the batiphase at 8 p.m. (11.1 ± 0.20 nmol / l, p<0.001). The maximum value of norepinephrine was also recorded at 12 a.m. - 74.7 ± 1.12 nmol / l, p<0.001; the minimum is in the evening hours (28.6 ± 0.88 nmol / l, p<0.01).

The amplitude of the rhythm of adrenaline secretion in rats of the experimental group decreased from 17.5% to 14.6%, and norepinephrine from 43.1% to 38.8%. Although such changes did not have a reliable character, they are evidence of a certain functional depletion of cells responsible for the secretion of catecholamines.

Cadmium poisoning in animals caused an

increase in plasma corticosterone concentration during the day. At the same time, the architectonics of the rhythm of this indicator in rats of the experimental group did not differ from the intact ones - the acrophase accounted for 8 a.m., the batiphase at 8 p.m. At 8 a.m. the concentration of corticosterone in the blood plasma was 184.3 ± 6.33 nmol / l ($p<0.001$). At 8 p.m. this indicator in experimental animals significantly decreased and was 78.2 ± 4.32 nmol / l ($p <0.001$). The amplitude of corticosterone secretion decreased from 43.5% to 32.3%, which indicates the stressful functioning of the corresponding adrenal tissue under conditions of cadmium poisoning.

As a result of the research, it was also found that the indicators of the amount of antibodies that were studied in intact rats periodically change during the day.

Thus, the maximum value of the content of immunoglobulins of classes IgA and IgM in serum was recorded at 12 a.m. (in this time interval it reached 0.58 ± 0.031 and 1.36 ± 0.101 g / l, respectively), and the amount of IgG at 4 p.m. (3.81 ± 0.151 g / l). The batiphases of chronorhythms of antibodies, both IgA and IgG, occurred at 4 a.m. and amounted to 0.47 ± 0.044 and 3.14 ± 0.142 g / l, respectively, and IgM at 12 p.m. (1.18 ± 0.124 g / l).

The mezor of circadian rhythms IgA reached 0.53 ± 0.020 g / l with an amplitude of 10.5%, IgM - 1.29 ± 0.036 g / l (7.3%), IgG - 3.51 ± 0.092 g / l (7 9%).

The dynamic equilibrium of the immune system may be disturbed as a result of the direct or indirect influence of stress factors. Their effects on various parts of the immune system can manifest themselves as immunosuppressive and immunostimulating effects [37, 38].

The reaction of the immune system in response to various stress reactions is often accompanied by an increase in the concentration of immunoglobulins in the plasma (mainly classes G and A) due to their release from the depot. Large surgeries that give a strong stress reaction, on the contrary, lead to a decrease in the levels of immunoglobulins of all classes due to their sorption on cells and damaged tissues. Such shifts disappear relatively quickly [28, 31].

More constant are the changes in the ratio of immunoglobulins during the reaction of the immune system to foreign bodies. When the inflammatory reaction associated with the initial contact of the body with this antigen, in the early stages of inflammation increases the content of IgM, and then the level of IgG increases. Levels of IgG and IgA increase with repeated contact with this antigen, even in the early stages of the development of the inflammatory reaction (29, 30).

It is known that the effect of various forms of stress on rats is accompanied by the occurrence of oxidative stress in the tissues of their organs, a manifestation of which is the accumulation of lipid peroxidation products and carbonylated proteins in them. An important role in the stimulation of free radical oxidation of lipids and proteins in rats when exposed to harmful environmental factors acquire shifts from the activity of first-line enzymes of antioxidant protection, increased sensitivity to the action of prooxidants, as well as changes in the state of redox processes in mitochondria [39].

We have found that cadmium poisoning causes disturbances in the chronorhythm organization of the content of all the studied classes of antibodies with signs of desynchronosis in the studied animals.

In particular, the acrophases of the amount of immunoglobulins IgA and IgM have moved from daytime to nighttime. At 12 p.m. the mentioned indicators were respectively 0.38 ± 0.022 and 0.56 ± 0.088 g / l. The smallest amount of these antibodies was recorded: IgA - at 4 p.m. (0.28 ± 0.041 g / l), IgM - at 8 p.m. (0.35 ± 0.112 g / l).

The average daily levels of these immunity parameters reached the following values: IgA - 0.31 ± 0.022 g / l ($p<0.001$ compared with a group of intact rats), the amplitude of oscillation - 16.3%; IgM - 0.44 ± 0.088 g / l ($p<0.001$), amplitude - 23.4%.

The highest level of IgG in cadmium poisoning was found at 12 p.m. - 3.65 ± 0.112 g / l, the batiphase moved to 12 a.m. and amounted to 2.95 ± 0.092 g / l. The mezor of daily variations in the amount of these antibodies reached 3.19 ± 0.084 g / l ($p<0.05$ compared with the control), the amplitude - 21.8%.

Thus, the analysis of the chronorhythms of rat erythrocyte pro- and antioxidant systems, adrenal hormones in their blood plasma and humoral immunity indices in blood serum under conditions of cadmium intoxication revealed activation of the LPO on the background of AOD deficiency, as well as disruptions of the endocrine and immune status of animals, accompanied by signs of desynchronosis. This gives reason to argue about the imbalance of the above mentioned systems, which leads to a decrease in the adaptive-compensatory capabilities of the organism.

Conclusions. 1. Indicators of the oxidative antioxidant state of white rats, the level of adrenal hormones and the immunological reactivity of the organism under the conditions of the physiological norm have a circadian pattern.

2. The impact on the body of cadmium chloride at a dose of 5 mg / kg disrupts the structure of the chronorhythms of the indicators of the pro-and antioxidant systems of white rats, is a consequence of the adaptive-compensatory and decompensatory reactions of the body to environmentally harmful load.

3. Cadmium poisoning leads to a disruption of the hormonal activity of the adrenal glands and the development of desynchronosis of their activity.

4. Analysis of circadian chronorhythms of rats' immune status indicators revealed an immunosuppressive effect of cadmium chloride, accompanied by signs of desynchronosis.

5. The degree of imbalance in the circadian dynamics of the studied parameters depends on the time of day.

Prospects for further research. The study of circadian chronorhythms of free radical homeostasis, adrenal hormones and indicators of humoral immunity under the influence of other xenobiotics on the body will be continued.

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