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CHRONOREGULATING AND RHYTHM-STABILIZING ROLE OF MELATONIN IN SEASONAL STRUCTURE OF CIRCADIAN RHYTHMS OF NON-SPECIFIC IMMUNITY INDICES WITH AGING

Abstract. *The effect of melatonin, the pineal gland hormone, on a seasonal structure of non-specific immunity circadian rhythms with aging has been examined. Multidirectional biorhythmic changes of humoral and cellular indices of the non-specific defense have been found. It ensures the most valuable adjustment of the body to cyclic environmental changes. The pineal gland effect is characterized by age features and preserved to extreme old age. The studies with modified lighting are indicative of the possibility to stimulate melatonin-producing function of the pineal gland by means of prolongation of a dark period and intensification of activity of the non-specific immunity system at the elderly age.*

Key words: *chronoregulation, melatonin, pineal gland, density, mineral content, dynamics.*

Introduction. In man and other mammals the pineal gland (PG) or epiphysis plays an important role in synchronization of circadian endocrine activity. The role of PG in neuroendocrine regulation of the body [2] and its direct participation in the development of general adaptation syndrome [1] is also known. The pineal gland is one of the main oscillator to regulate chronobiological processes of the body [3].

In the process of aging circadian and seasonal oscillations of the body vital signs are gradually fading [4], production and secretion of melatonin by the epiphysis decrease, daily oscillations of melatonin level in the blood plasma reduce [9], resulting in the development of various pathological conditions due to increased reactivity of the sympathoadrenal, hypophysial-adrenal and cardio-vascular systems. Restoration of melatonin concentration increases resistance of the cardio-vascular and other systems of the body to the impact of stress factors [5, 10].

A positive effect of the hormone melatonin on the neuroendocrine regulation and its antioxidant action have been described as well [8, 11]. Melatonin reduces activity of the hypothalamic-hypophysial and sympathoadrenal systems, decreases the initial stage of stress development – the anxiety stage, and therefore, preventing development of general adaptation syndrome.

Recent studies are indicative of the role of PG as a constituent of the central biological clock with aging [7], and administration of melatonin in pharmacological doses can prevent development of aging signs [6]. A stimulating action of melatonin on immunostructural homeostasis is evidenced [9]. Seasonal oscillations of certain signs of non-specific immunity are studied [3].

Objective: to investigate the role of melatonin, a hormone of the pineal gland, in alternations of circadian rhythms seasonal structure of non-specific immunity signs with aging, its controlling and rhythm-stabilizing action.

Materials and methods. Our studies were conducted on 160 albino laboratory male rats of two age groups: mature – at the age of 12-15 months and body weight 140-180 g and old ones at the age of 24 months and older with their body weight of 200 g and more. The rats were kept in vivarium at a stable room temperature and artificial light. The light regimen was the following: 12 hours – light and 12 hours darkness. Pseudo-operated rats were also used in the experiment. Together with intact animals they constituted the control group contrary to those animal with epiphysectomy performed on the 15-20th days after PG removal. With the purpose to study circadian rhythms of non-specific immune signs of the body the experiments were conducted on

mature and old male rats. A light period of the day was from 8 a.m. to 8 p.m., and the period of darkness – from 8 p.m. to 6 in the morning. The blood was taken every 6 hours: at 9 a.m., 3 p.m., 9 p.m. and 3 in the morning. To examine seasonal rhythms the experiments were conducted during 2 years in spring (April, May), in summer (July, August), Autumn (October, November), and winter (January, February).

The indices of non-specific immunity were studied in the experiment: activity of the serum complement, concentration of the serum lysozyme, total leukocyte amount, HCT-test, myeloperoxidase activity of neutrophils, glycogen level, phagocytic activity and phagocytic index of polymorphonuclear leukocytes.

Results and discussion. The results of the study are indicative of the complement system rhythm availability and decrease of its level due to epiphysectomy. Circadian rhythm of the serum complement activity depend not only on age and PG available, but the time of the year, especially in spring and summer. The content of serum lysozyme in mature rats decreased after pinealectomy, and in old rats circadian rhythm was leveled. Seasonal rhythm after removal of PG changed: in old rats miniphase was shifted to autumn. Administration of melatonin was associated with growth of lysozyme content in the control groups of mature and old rats, and in mature animals after epiphysectomy – a reduced level of this index.

A considerable role of lysozyme should be mentioned here. Its content increased with aging which is a compensatory mechanism directed to activation of the phagocyte enzymatic activity, first of all lysosomal enzymes, and muromidase in particular, that breaks bacterial walls.

Leukopenia was found both in mature and old rats due to pinealectomy. The staging of circadian rhythm reduced, acrophase and miniphase were shifted. The index of leukocyte amount was not informative concerning the effect of melatonin and changed lightening, although its dynamics and rhythmostasis changed.

HCT-test remained unchanged considerably when animals were kept under conditions of long darkness. Melatonin effect was not found in this case. This index characterizes activation of neutrophil metabolism, first of all, the function of

hexosomonophosphate shunt and free radical synthesis associated with it which is essential for successful implementation of phagocytosis. In our experiments we have found a tendency to alternation of this index with age and disorders of circadian rhythms.

Circadian rhythms of glycogen content in neutrophils of mature rats after epiphysectomy did not differ considerably, and in old ones – they decreased reliably, and acrophase and bathyphase amplitudes leveled. Similar changes were registered in animals with removed PG. Melatonin administration was accompanied by increasing content of glycogen in the mature and old rats after pinealectomy. A low level of glycogen in experimental animals is indicative of insufficient energy supply of neutrophils as the main chain in functioning of the non-specific immune adaptation system to possible oscillations in the activity of non-specific protective system. These findings clearly characterize the processes of body aging.

Myeloperoxidase activity of neutrophils in the peripheral blood provides their bactericidal properties and destruction of hydrogen peroxide. Circadian rhythm of myeloperoxidase activity was characterized by miniphase in the morning in all the three groups of old rats. Low activity of myeloperoxidase was normalized under the influence of melatonin under conditions of usual photoperiod, long darkness and in case of continuous lightening.

The results obtained due to our experimental studies are indicative of the fact that after pinealectomy the indices of glycogen content, level of HCT-test and myeloperoxidase activity change, which is a direct evidence of alternations of phagocytic activity of segmented neutrophilic leukocytes under these conditions. Phagocytic activity in old animals reduced reliably, and removal of PG resulted in disorders of staging of a daily curve, the levels of indices decreased reliably at any period of time. Melatonin administration made reduced indices of phagocytic activity normal both in mature and old rats, and with the gland available the hormone did not affect this index in case of usual photoperiod. In case of PG inhibition under continuous lightening melatonin administration stimulated phagocytic activity both in mature and old control animals. Similar

changes were found in both groups of rats after epiphysectomy. Therefore, in case PG is removed melatonin effects do not depend on photoperiod.

Phagocytic index in mature rats after removal of PG was characterized by disorders of staging of circadian rhythm, shifting of acrophase to morning hours. Reduced rhythmic oscillations were registered as well as reliable decrease of the index in old rats after epiphysectomy. Exogenous melatonin made the level of phagocytic index normal, as it was reduced due to removal of PG and after the impact of continuous lightening. Together with absent effect of continuous darkness and melatonin on the dynamics and rhythmstasis of phagocytic index in all the groups of mature rats, the index increased in the control group of old animals.

Conclusions. Therefore, different directions of biorhythmic changes of the humoral and cellular indices of non-specific immunity found provides the most substantial adaptation of the body to cyclic environmental changes. PG in mammals is directly associated with regulation of circadian rhythms of the non-specific adaptation system of the body. This effect possesses age peculiarities and is kept till old age. A regulating action of the pineal gland on the immunostructural homeostasis is provided by melatonin and other biologically active substances produced by this organ. The studies with changed lightening are indicative of existence of principal possibility to stimulate melatonin-producing function of PG by means of elongation of light period, and as a result, intensification of the activity of the non-specific immune protection system of the body, which is especially important in gerontology and geriatrics, prevention of age changes in old age.

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CONTENT:

Yasnikovska S.M. Peculiarities of pregnancy progress in women with corrected isthmic-cervical incompetence	3
Shkolnikov V.S., Zalevskiy L.L., Zalevska I.V. Structural organization of the cerebellum of 17-18 week human fetuses during intrauterine development	5
Khmara T.V., Okrim I.I., Biriuk I.G., Komar T.V., Khmara A.B. The specialization degree of wood-destroying basidial fungi on trees in samur-davachi lowland forests of azerbaijan	10
Tkachenko P.V. Clinical-morphological prognostic characteristics of prostate cancer	14
Sasina O.S. Psychohygienic aspects of training of disabled adolescents with pathology of the vision (literature review)	19
Banul B.Yu. Development of paramesonephric ducts and their derivatives at the end of embryonic period of human ontogenesis	23
Niankovskiy S.L., Gorodylovska M.I. Heterogeneity of esophagitis in schoolchildren	26
Yevtushenko I.Y, Padalitsa M.A, Goryainova G.V. Age features of cervical arch and height of human renal calyces in mature and elderly ages	32
Vepruk Y., Rohovyy Y., Tovkach Y., Rykhlo I. Characteristic of aluminum salts influence on indexes of ion regulative renal function in mature and immature rats against the background of the pineal gland hyperfunction	35
Zakharchuk O.I., Kryvchanska M.I. Chronoregulating and rhythm-stabilizing role of melatonin in seasonal structure of circadian rhythms of non-specific immunity indices with aging	38
Kachko G.O., Omelchenko E.M., Pedan L.R., Polka O.O. Characteristics of congenital pathology with inherited and multifactorial nature in children of Kyiv region	41
Kosilova S.Y. Metabolic disorders in women depending on menopause duration	44
Kotelban A.V., Godovanets O.I., Burdeniuk I.P. Peculiarities of administration of antiseptic drugs in children suffering from chronic catarrhal gingivitis under conditions of diabetes mellitus	47
Reshetilova N.B., Navarchuk N.M., Popeliuk O.-M.V., Glubochenko O.V., Kulish N.M. Topographic peculiarities of the anterior cerebral vesicle on the 4th week of the embryonic period	51
Fik V.B., Paltov Y.V., Lohash M.V., Kryvko Y.Y. Peculiarities of morphological manifestation of the periodontal tissue in experimental animals against the ground of a short-term effect of opioid analgesic	54
Khomenko V.G. Renal tissue fibrinolysis against the ground of stress and xenobiotics	59
Dudenko V.G., Vdovychenko V.Yu., Kurinnoy V.V. Spatial topography of the diaphragm in the sagittal plane in women	61
Avdieyev Oleksandr, Dziubak Sergii Epidemiological analysis of dental diseases among individuals exposed to unfavourable psychoemotional surroundings	65
Andriets M. M., Andriets V.I. Psychological aspects of physical culture and sport	68
Malanchuk L.M., Kryvytska G.O. Renal tissue fibrinolysis against the ground of stress and xenobiotics	71
Bambuliak A.V., Galagdina A.A., Boychuk O.M. Diagnostics of the frontal sinus development with adjacent structures in the prenatal period of human ontogenesis	73
Kryvetskyi V.V., Narsiya V.I., Kryvetskyi I.V. Blood supply of the cervical region of the vertebral column during the fetal period and in newborns	76
Pavlovych L.B., Bilous I.I. The indicators of stimulation electroneuromyography in patients with diabetic polyneuropathy	80



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