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Age-related circadian disturbances in melatonin causing changes in thymus hormones and glucocorticoids rhythmicity in healthy animals and humans

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ABSTRACT

Circadian rhythms of the organism functions cause its adaptation to changes in environmental lighting. The pineal gland is a key regulator of the circadian rhythms of the immune system. The thymus, its central organ, is the source of some hormones, in particular, the highly active thymic serum factor / thymulin. Therefore, the issues of age-related changes in the circadian intra-immune relationships with thymus involvement and the possibility of melatonin influence not only on the above links but also on the glucocorticoids hormones with adaptive effect require an in-depth analysis.

Discussed are the literature data and our own findings how age-related changes in the circadian rhythms of thymus endocrine and adrenal gland glucocorticoid functions are linked with the melatonin-forming function of the pineal gland in healthy animals of different species (mice, rats, rabbits) and humans. The similar manifestations of the above interactions in healthy animals and humans demonstrate the biological significance of the pineal gland for the supporting circadian rhythms of the thymus and adrenal gland functions in the adult organism. The correlation of age-related changes in circadian rhythmicity of pineal gland in healthy animals and human, on the one hand, with the thymus and adrenal glands, on the other hand, has been demonstrated. In addition, the decrease of age-related disorders in the thymulin and glucocorticoid blood levels under the influence of pineal gland factors (melatonin and peptides) was shown. Thus, (a) the thymus endocrine function does not completely disappear in the old organisms and it responds to the effects of melatonin and peptide factors of the pineal gland and (b) age-related pineal gland desynchronosis has pathogenic significance for the formation of circadian disturbances in the thymus hormones and glucocorticoids.

Keywords: melatonin, thymic serum factor/thymulin, glucocorticoids, circadian rhythm, age, animals, humans

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Introduction:

Circadian rhythms of functions of the body are of great importance for its adaptation to constantly fluctuating environmental conditions, in particular lighting [1]. The pineal gland plays the main role as a regulator of circadian rhythms in the organism [2,3]. It closely interacts with suprachiasmatic nucleus of the hypothalamus [1]. The functioning of the pineal gland is accomplished due to the rhythmic synthesis and secretion of the main hormone melatonin [2,3].

The functions of the immune system are controlled by the pineal gland [4,5]. According to the principle of temporal organization of functions, the biorhythms of separate immune system components are interrelated, on the one hand, and are related with the environmental changes, on the other [9]. Therefore in intra-system interactions, attention of the researchers must be drawn to those interactions which are realized through the central immune system organ – the thymus. The thymus is the source of various subpopulations of the T-lymphocytes and of some hormones [6,7]. In particular, the highly active thymic serum factor (FTS) / thymulin affects proliferation, migration, differentiation and co-operation of the immune competent cells, that is, those processes in the immune system which undergo rhythmic changes.

Age-related changes in the functional state of the thymus in animals and humans outpace the development of dysfunction of the peripheral link of the immune system [5]. In view of this, the issues of age-related changes in the circadian intra-immune relationships with thymus involvement and the possibility of melatonin influence on them require an in-depth analysis. In addition, currently there is interest towards the involvement of the adrenal glands in the influence of the pineal gland factors on the rhythmicity of thymus functioning, since the importance of glucocorticoid hormones for the development of adaptive reactions of the living organism is well known [8]. During aging the functional state of the pineal gland and adrenal glands is disturbed and the immunoendocrine interactions are altered [9-13].

Our work aimed to analyze (***a***) the state of study of the issues of age-related changes in the circadian rhythms of thymus hormones and glucocorticoids in the animals of different species of animals and humans and (***b***) their link with the melatonin-forming dysfunction of the pineal gland.

Age-associated disturbances of the circadian rhythms of the blood thymic hormones and corticosterone levels and their improvement by the pineal gland factors in the intact animals of different species:

Mice. It is known that in the dark period of time the level of thymic hormones thymulin and thymosin-α1 increases in the blood of young intact mice [14,15]. In older mice, the thymulin levels decrease compared to young animals but become higher after melatonin administration [14].

To confirm melatonin role in thymus functioning we modelled changes of the pineal gland function in the CBA mice of different age by surgical light deprivation [16,17]. In addition, melatonin was administered to animals of different ages [5, 16]. It is known that light deprivation results in a significant increase of melatonin content in the pineal gland and blood of animals [2]. According to our data, the level of thymulin increased after light deprivation in the blood of young (3-5 months) and old (22-24 months) male mice by 8-16 and 4 times, respectively, while the corticosterone level decreased by 6 times and 3.2 times, respectively [5,16]. Melatonin administration to the mice of different age results in a more pronounced increase of the blood thymulin level in the young versus old mice as well as restores the impaired sensitivity of the thymus stromal cells of old mice to the inhibiting effect of corticosterone [5,18].

Thus, the circadian rhythm of thymus endocrine function in young mice, which changes with

aging, is associated with the functional state and rhythmicity of the pineal and adrenal glands

Rats. According to Molinero et al. [19], the young male rats demonstrated rhythmic changes in the thymulin blood level during the daytime with the peak values in the night.

According to our data [5], we registered a significant increase of the night thymulin blood level in the adult intact Wistar male rats (6-7 months and 10-12 months) comparing to its daytime level, while in the aged (17-18 months) and old (26-35 months) rats the thymulin blood level decreased mainly at the night period. We have also showed that blood corticosterone concentration in the mature adult rats is significantly lower in the night-time than in the daytime and the 24-hour difference in the values significantly decreases with aging especially in the old rats [5].

Consequently, it is possible to generalize that circadian rhythm of the blood thymulin and corticosterone levels in rats are disturbed with age.

Our experimental results about age-related changes in the thymus endocrine function rhythmicity were similar to the results obtained by Gubina-Vakulyk G. et al [20] regarding the decrease of melatonin concentration in the pineal gland and blood serum of the Wistar rats. In addition, we showed that under the influence of the pineal gland peptide (epithalamine), which increases melatonin amount in the pineal gland of rats of different ages, the thymulin blood levels in the aging and old rats were increased in the day and preferentially at night time [5,21]. Besides, after administration of epithalamine the daily difference in the blood corticosterone concentration increases owing to its decrease at night [5,21]. The literature data indicate the reversible effect of the pineal gland on the aggravated age-related sensitivity of the hypothalamus to the action of external and internal factors [22].

Rabbits. According to our data, the intact mature Chinchilla rabbit-male between 4-5 months and 14-15 months demonstrate a circadian rhythm of the thymulin blood level with maximum values in the night comparing to the daytime [23, 24]. In the mature rabbits aged 14-15 months the 24-hour difference in the levels of thymulin at night and in the morning was maintained. At the age of 24 months, the values of the thymic hormone as their daily differences were significantly reduced.

It is known that the experimental modelling of the photoperiod, in particular, the creation of a regime of constant illumination is an adequate model for studying changes in the melatonin-forming function of the pineal gland [25]. Under such conditions several authors observed the accelerated aging of the pineal gland, development of more age-related changes in numerous functions of the organism and reduced life span expectancy of experimental animals [20, 25-27].

Using the round-the-clock illumination, we observed changes in the endocrine function of the thymus in the young mature rabbits which manifested themselves not only in its activation during the daytime with the development of the circadian desynchronosis in the early period of light exposure (in 1 month), but also gradual inhibition irrespective of the time of the day in the dynamics of a long light load (till the age of 14-15 months) [23, 24]. Noteworthy, ten months after the beginning of light exposure the thymulin level in the rabbits aged 14-15 months decreased at noon and at midnight by 8 and 16 times, respectively, compared with the original values. It is characteristic that in the animals aged 14-15 months the thymulin level was close to the values found in intact rabbits at the age of 24 months. The results indicate acceleration of age-related changes in the circadian rhythm of this thymic hormone in rabbits after prolonged exposure to light.

One of the possible reasons of development of desynchronosis of the thymus endocrine

function in rabbits in conditions of round-the-clock illumination may be the disturbed rhythmicity of its interactions with the melatonin-forming function of the pineal glands, on the one hand, and with the functioning of the adrenal cortex, on the other hand. Thus, Gubina-Vakulyk G. research in the rabbits has revealed the disturbance of the biorhythms of the blood melatonin and corticosterone levels in the conditions of round-the-clock illumination [20].

In summing up, the literature data and the results of our own studies indicate the circadian rhythmicity of thymus endocrine function in young animals of different species (mice, rats, rabbits) with the peak level in the blood thymic hormones in the night-time. The importance of thymulin in the rhythmicity of thymus functioning is emphasized. With age, the circadian rhythmicity of the thymic hormone is disturbed and its circadian relationship with corticosterone also changes. The detected changes in circadian rhythms of the thymus and adrenal glands functions in animals of different species may be associated with age-related desynchronosis of the melatonin-forming function of the pineal gland.

Age-associated changes of the circadian rhythms of the thymic hormones and cortisol blood levels in the healthy human subjects and their improvement after modulation of pineal gland function:

It is known that in the blood of healthy young people the levels of thymulin and melatonin significantly increase in the night [19].

Our task was to investigate age-related changes of the circadian relationships in the blood thymulin, melatonin and cortisol levels in the healthy people [28-31]. It appeared that changes in the blood thymulin and melatonin levels during 24 hours in young healthy men aged 20-29 years were similar, being characterized by simultaneous increase at 21.0 p.m. with a peak at about 1.0 a.m., whereas the concentration of cortisol, on the contrary, was lowest at 21.0 p.m. and highest at about 5 a.m. and 9 a.m. [28-31].

According to our data, in the elderly people the circadian rhythm changes in the thymus endocrine function were ambiguous and consistent with the patterns of the rhythmicity of the pineal gland melatonin-forming function [28-32]. Thus, an increase in the thymulin blood level during the dark period (about 21.0 p.m. or 3.0 a.m.) relative to the morning hours (Group 1) correlated with a more pronounced rise of the blood melatonin level in the night time compared with the subjects (Group 2) in whom thymus activation during the dark period was absent. The cortisol blood concentration in Group 1 was somewhat decreased in the night compared to the morning, while in Group 2 the circadian rhythm of blood cortisol level was monotonous.

Our results about synchronizing effects of administration of the melatonin and pineal gland peptides (epithalamine, epithalon) on the rhythmicity of thymulin and cortisol levels in the blood of elderly people have proved the importance of the pineal gland in maintaining daily body rhythms of the thymus endocrine function and its circadian relationships with the biorhythms of adrenal glands [28,32].

Thus, the analyzed results of studies indicate that the circadian rhythm of the pineal gland melatonin-forming function in young healthy people is important for the maintaining of the thymus endocrine function rhythmicity and its interactions with the glucocorticoid function of the adrenal glands.

In aging the importance of the synchronizing influence of the melatonin and peptides of the pineal gland on the circadian rhythm of the thymus endocrine function remains. At the same time the significance of the pineal gland peptides on the activity and rhythm of the thymus function increases. Positive changes in the glucocorticoid function of the adrenal glands with age play important role in the synchronizing influence of the pineal gland factors on the thymus endocrine function.

Conclusion:

The similar manifestations of the immune endocrine interactions in healthy animals and humans demonstrate the general biological significance of the pineal gland for the circadian rhythms of the functioning of the thymus and adrenal glands in the adult organism. Thymus is an important component of the pineal gland influence on the rhythmicity of the immune system functioning [33-35]. The thymus endocrine function does not completely disappear in the old organism and is capable of responding to the effects of pineal gland melatonin and peptides. The age-related dysfunction of the pineal gland has a pathogenic significance for the formation of age-related violations of the circadian rhythm of the thymus endocrine function, which occurs with participation of the glucocorticoid hormones.

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