Chapter 14

AGE-RELATED CHANGES IN THE RHYTHMICITY OF ENDOCRINE AND IMMUNE SYSTEMS IN NEURODEGENERATIVE DISEASES: THE ROLE OF PINEAL GLAND AND THYMUS

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INTRODUCTION

Circadian (daily) and circannual (seasonal) rhythms play a key role in adaptation of human organism to such fluctuating environmental factors as light and temperature[1]. Circadian rhythms provide fast organism adaptation to the day-night shifts; circannual rhythms control potential possibilities of organism functions and processes of differentiation. In aging there observers disturbances of above rhythms and change of adaptive capacity of organism functions, in particular of the neuroendocrine and immune systems[2]. The pineal gland hormone melatonin plays main role in regulation of circadian and circannual rhythms of human organism functions[3]. The regulator of immune functions of organism is the thymus hormone, thymulin[4]. Many researchers have revealed age-dependent changes in the functioning of pineal gland and thymus and their influence on lifespan

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of people[5]. The age disturbances of the pineal gland and thymus functions coincide with the development of age-related pathology.

This chapter of monograph reviews the published and our own data about circadian and circannual rhythms of the pineal gland melatonin-producing function and the thymus hormone function (thymulin production) in adult healthy people and their connection with changes in the rhythmicity of neuroendocrine and immune system functions both in aging and development of neurodegenerative pathologies.

1. Rhythmicity of pineal gland and thymus functioning in adult human organism and their changes in aging

Melatonin. It's known that the pineal hormone melatonin is the main regulator of circadian and circannual rhythms both in humans and mammals[6]. This hormone closely functioning with the suprachiasmatic nucleus (SCN) of the hypothalamus (endogenic generator of rhythms). In young people melatonin content in dark period and with shortening season photoperiod is increased.

In aging, the nocturnal peak of blood melatonin level was found to be lower in the majority elderly and old subjects versus young people[7]. We also showed disturbances in the circannual blood melatonin rhythms during human aging: in particular, the winter melatonin peak was decreased or shifted to the spring season[8]. It was found the link between the organism

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adaption and lifespan in old subjects and saved circadian rhythmicity of blood melatonin level.

Melatonin effects are largely realized via functions of the hypothalamus-pituitary-endocrine glands axes[9]. The functioning and circadian rhythmicity of the above organs are changed in aging but improved after melatonin treatment[10]. According to our results, there is also a connection between age-associated changes in the circannual rhythms of blood melatonin, adrenocorticotrophic hormone (ACTH) and cortisol contents in people[11]. We observed seasonal rhythm disturbances of blood 0melatonin content as early as at 40 years and outstrip desynchronization of blood ACTH and cortisol content.

So, the age-related pineal gland dysfunction may be the pathogenic factor of desynchronosis of the neuroendocrine system functions in aging, and, as a result, promote development of age-related changes in neurogenesis. Melatonin increases proliferation and differentiation of neural stem cellsin the subventricular zone of the hypothalamus through stimulation of brain growth factors production[12]. It's showed the influence of sex and glucocorticoid hormones on the brain neurogenesis[13].

Thymulin. Rhythmicity of immune system functions is under the influence of the pineal gland[14]. According to our results and data of other researchers,

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the circadian and circannual rhythms in the peripheral blood contents of different T lymphocytes subpopulations, B- and natural killer cells, granulocytes, and some cytokine were observed in healthy young people[15].

At the same time, the functions of immune system are under regulatory control of its central organ – the thymus[16]. The thymus is not only the lymphoid organ, but it also serves as the endocrine organ producing the such hormones as thymic serum factor /thymulin, thymosine, thymopoetin and thymus humoral factor[17]. The highly active hormone thymulin reveals the biological activity of all known thymus hormones[18]. In particular, thymulin influences on the different thymocyte subpopulations activity, the balance of regulatory T cells, proliferation and migration T lymphocytes, etc. Importantly, age-dependent disturbunces of thymus function precede immune system changes in aging. In the opinion of researchers[19], thymus is a pacemarker of lifespan and its coinvolution with pineal gland can determine the aging.

The data of investigators and our own results have shown the similar night peaks of blood thymulin and melatonin content in young people[20]. Besides, we showed seasonal similarities in the rhythms of melatonin and

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thymulin in young people and their changes in aging[21]. Also, the changes of circannual rhythms of immunological indices in aging coincide with seasonal desynchronozis of blood thymulin level. Besides, in our data, the thymus of elderly and old people can increase thymulin production under the influence of melatonin[22]. Moreover, our results demonstrated improvement of thymulin and cortisol levels rhythmicity owing to melatonin administration to the elderly patients with pineal gland dysfunction[23].

Thymulin had reverse effects on functioning of the hypothalamus-pituitary-adrenal and hypothalamus-pituitary-gonad axes[24]. We have shown reverse thymulin influence on the rhythmicity of melatonin production by the pineal gland in young and old organisms[25]. Anti-inflammatory effect of thymulin in the brain tissue (production of proinflammatory cytokines) plays neuroprotective role in the maintenance of neurogenesis[26].

So, the thymulin production is the important part of chronobiological organization of immune system functionig[27]. The circadian and circannual biorhythms of thymulin production depend on the synchronizing role of melatonin. Disturbances of melatonin rhythms lead to the intra-immune desynchronozis through changes of the circadian and circannual rhythms of thymulin production and interactions thymulin with the endocrine glands, both in aging and age-associated pathologies.

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2. Rhythmicity of pineal gland and thymus functioning in neurodegenerative diseases

Alzheimer's disease (AD), Parkinson's disease (PD), brain ischemia and multiple sclerosis (MS) are the widespread neurodegenerative pathologies[28]. The frequency of these neurodegenerative diseases increases worldwide and has great social and economic implications. The progressive neuron loss was shown in AD, PD, brain ischemia and MS. The mechanisms of these diseases development include neuroinflammation along with microglia activation, enhancement of oxidative stress, mitochondrial dysfunction, disturbances in the main regions of brain neurogenesis, etc[29].

Disturbances of the sleep-wake cycle and neuroendocrine-immune system functioning during major neurodegenerative pathologies may be linked with the pineal gland dysfunction. Thymus hormone thymulin has an anti-inflammatory effects on the central nervous system. The development of age-related neurodegenerative pathologies may be associated with intensification or acceleration of age-related disturbances in the immune and neuroendocrine systems functioning.

Alzheimer's disease

More intensive age-related decline of the nocturnal blood melatonin level in AD elderly patients compared to control group are correlated with the development of daily desynchronosis of the blood ACTH and cortisol levels and cognitive dysfunction[30]. It's important that circadian changes of organism functions often occur at early stages of AD and may precede the development of cognitive disturbances.

Pathogenesis of AD may be connected with activation of immune cells[31]. Thus, infiltration of active T lymphocytes and mononuclear phagocytes into injured brain tissues and activation of brain microglia in AD were shown. At the same time, melatonin administration improves disturbed sleep-wake rhythm and produces synchronizing, anti-apoptotic, antioxidant, anti-inflammatory and immunomodulatory effects in such pathology[32].

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Parkinson's disease

PD is characterized by circadian disturbances of the pineal gland functioning. Thus, in patients with PD both the increase of morning blood melatonin content and suppression of nighttime peak of this hormone compared to elderly healthy group was shown[33]. Such blood melatonin level changes coincided with degree of destroy sleep-wake circadian rhythm in PD patients. Also there are circadian disturbances in blood cortisol level[34]. At the same time, clinical researches have shown the slowing of PD development after exogenous melatonin administration that may be linked with its antioxidant, anti-inflammatory and chronobiological properties[35].

Active peripheral immune cells (T lymphocytes, macrophages and neutrophils) infiltrate the brain and damage of dopaminergic neurons[36]. In our study, the degree of immune disturbances in parkinsonism may be linked with the decrease of thymus endocrine function; at the same time, the blood thymulin level was restored after melatonin treatment[37].

Brain ischemia

In the elderly patients with ischemic stroke the nocturnal urinary melatonin content is decreased compared to age control people and is associated with increased blood cortisol content, altered sleep-wake rhythm and decreased of T lymphocytes numbers[38]. Peripheral T lymphocytes may migrate into the injured brain, release pro-inflammatory cytokines, chemokines and cause further injury of the ischemic brain[39]. In cerebral ischemia hormone melatonin treatment reveals antioxidant, anti-apoptotic

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and anti-inflammatory effects[40]. In our experimental brain ischemia, the decreasing blood thymulin and melatonin contents coincided[41].

Multiple sclerosis

In MS patients the decrease of night melatonin content is associated with circadian rhythm sleep-wake disturbances and destroy of daily blood cortisol level rhythmicity[42]. The higher frequency of MS attacts in the spring/summer seasons against winter period is linked with a more marked decrease of the night blood melatonin content in these seasons[43]. Exogenous melatonin improves life quality of the MS patients[44].

It's known that activation of immune system cells leads to damage of myelin and neurons in MS and promotes the development of neuro-inflammation in the brain[45]. At the same time, in MS patients melatonin decreases the formation of pathogenic T helper 17, cytokine interleukin-17 and stimulates formation of protective Tr1 regulatory cells and anti-inflammatory cytokine IL-10[46]. We have shown that exogenous melatonin has neuroprotective, anti-inflammatory, antioxidant, immunomodulatory effects in demyelinating pathology[47]. It is important that exogenous melatonin increases the thymus endocrine function in adult and old organisms with demyelinating pathology and restores the seasonal peak of blood thymulin content in autumn.

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Thus, age-related changes in rhythmicity of neuroendocrine and immune systems functions in patients suffering from neurodegenerative diseases are linked with dysfunction of their central organs, melatonin and thymus hormones (thymulin).

3. Sex differences in neurodegenerative diseases

The gender differences in the frequency and symptomatic of neurodegenerative pathologies was shown[48]. Thus, more men against women are suffering from PD. These gender differences may be link with female neuroendocrine status, in particular estrogen neuroprotective action on neurons of brain. Moreover, estrogens can modulate rhythmicity of organism functions acting via estrogen receptors in SCN and possess neurotrophic influence[49]. In our data, the healthy women revealed less intensive and slower age-associated development of blood melatonin and thymulin rhythmicity disturbances. The latter coincides with less expressive age-related disorders of the rhythmicity of ACTH and cortisol content[50].

CONCLUSIONS

The frequency of neurodegenerative pathologies increases worldwide. Therefore it's importantly to study the new pathogenic factors of their development, in particular the role of pineal gland hormone melatonin and thymus hormone thymulin in the mechanisms of circadian and circannual rhythms disturbances of the neuroendocrine and immune systems functions.

The rhythms of neuroendocrine and immune systems functioning and their central regulators, melatonin and thymulin, are changed in human aging. Age-associated disorders of above indicators becomes more pronounced in the development of neurodegenerative diseases (Alzheimer's and Parkinson's diseases, brain ischemia and multiple sclerosis). Melatonin treatment leads to the inhibition of age-dependent disturbances in the rhythms of neuroendocrine and immune systems and slows the development of above neurodegenerative diseases. The synchronous effect of melatonin on the circadian and circannual rhythms of blood thymulin is the important mechanism of such melatonin positive influence.

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Therefore the pineal gland hormone melatonin seems to be perspective for restoring changed rhythms of neuroendocrine and immune systems functioning in the risk groups with accelerated human aging and in patients suffering from neurodegenerative pathology.

In summing up, we hope that this review point to the supporting of rhythmicity of neuroendocrine-immune interactions during aging and development of neurodegenerative diseases.

SUMMARY

This chapter of monograph reviews the authors and own data about circadian and circannual rhythms of the pineal gland melatonin-producing function and the thymus hormonal function in adult healthy people and their role in the changes of endocrine and immune systems rhythmicity both in aging and neurodegenerative pathologies.

Evidence is provided on the importance of the circadian and circannual rhythms in the adaptation of human neuroendocrine and immune systems functioning to the changing photoperiod and also on the disturbances of above systems rhythmicity in aging. It is emphasized that the pineal hormone melatonin is the main regulator of rhythms of healthy human organism functions and involves thymus hormone thymulin in synchronizing effect on immune system functioning. Moreover, the age-related changes in melatonin rhythmicity lead to the changes in circadian and circannual rhythms of thymulin production, endocrine and immune systems functions. Data is provided that age-dependent changes in the circadian and circannual rhythms of melatonin, thymulin, endocrine and immune systems become more pronounced at the development of age-associated neurodegenerative pathologies, such as Alzheimer's and Parkinson's diseases, brain ischemia and multiple sclerosis. The possibility of improving the rhythmicity of the above-mentioned indicators with exogenous melatonin has also been shown.

The prospects of using melatonin to restore the altered rhythms of endocrine and immune systems both in accelerated human aging with pineal gland and thymus dysfunction, and in patients in neurodegenerative diseases are substantiated.

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