

REVIEWS

INFLUENCE OF THE THYMUS AND PINEAL GLAND ON IMMUNITY AND AGING

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ABSTRACT

The thymus and pineal gland (epiphysis) are endocrine glands with pivotal role in the maintenance of normal physiological processes. Their hormonal activity has been the subject of many studies, but on most occasions, each gland has been considered separately. Surveys that identify the link between these two glands, as well as the connection between their hormones, appeared only recently. The growing body of data about the morphology and the functions of the thymus and epiphysis reveals not only the bi-directional links between these glands but also common involutionary mechanisms. The immune activity of the thymus is well-known, and the results indicate that melatonin has significant immunomodulatory potential as well. The hormones of both glands play a role in the antioxidant and antitumor defense of the organism, as well as in the hemostasis processes. Some studies confirm the existence of a functional relationship between the endocrine, immune, and nervous systems and the contribution of thymic and pineal hormones to its establishment. The association between thymus and epiphysis is important not only for the normal immune response but also for the regulation of aging and the occurrence of age-related conditions and diseases.

Keywords: *thymus, pineal gland, immunity, aging*

INTRODUCTION

Among the most important factors responsible for the maintenance of human health is a well-functioning, synchronized circadian system, orchestrated by the epiphysis and its principal hormone—melatonin (1). The onset and development of various pathological processes, including cardiovascular diseases, cancer, neuro-endocrine disorders, diabetes

mellitus, metabolic syndrome, and psychotic disorders are linked to disruption of the “master clock” (1,2,3). Moreover, the desynchronization of the endogenous rhythms and dysfunction of different organs and systems lead to significant health problems in elderly people (4). It is widely known that health, well-being, and life expectancy are highly dependent on the proper functioning of the immune system, where the thymus gland plays the leading role.

A great amount of evidence from both experimental and clinical researches indicates the mutual influences and relationships between the immune, endocrine, and nervous system and their eminent impact on homeostasis. In addition, the correlation between age-related alterations in neuroendocrine control and age-associated conditions and diseases is unquestionable (5). In particular, the co-involution of

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the thymus and pineal gland is considered a very important factor in aging (5,6).

Morphological and Functional Similarities Between Thymus and Pineal Gland

Electronic microscopy data show an intriguing structural similarity of thymic epithelial cells (TECs) and pinealocytes. It has been found that both glands synthesize the same hormones and signal molecules: serotonin, melatonin, pCREB transcription factor, chromogranin A, neuropeptide CGRP and VIP. These findings underline the structural and functional resemblance of pinealocytes and thymic cells, as they are an integral part of the united neuro-immuno-endocrine system. The age-related structural changes of the cells of the pineal gland in people over 60 years are less pronounced, compared to the functional changes that greatly affect the neuro-immuno-endocrine relationship along with the decrease of the synthesis of its main hormone melatonin. The tight interrelation between the two glands is additionally confirmed by findings showing that 20% of the epiphysis consists of lymphoid tissue, namely T-lymphocytes that secrete cytokines, similar to those expressed by the thymus (7).

Analysis of the information about the morphology and functions of the pineal gland and thymus in individuals at a different age shows that in both glands quite similar involutionary mechanisms are involved. Based on the existing data on that matter, along with the related processes, some authors suggest a hypothesis for the functional unity of these organs and their mutual contribution to the maintenance of normal immune and endocrine status during aging (8).

Thymus

The thymus gland consists of cortex and medulla. The cortex is composed mainly of compact lymphoid tissue, typically with a great abundance of lymphocytes (thymocytes). The medulla contains young, developing thymocytes, TECs, macrophages, and dendritic cells. Its cytoarchitecture is evolutionarily preserved in different vertebral species, including humans, along with the main function of the thymus—the immune function (9). A number of studies point out that the thymus is not only the main immune organ but also an endocrine gland. Thymic epithelial cells produce hormone-like peptides (thymu-

lin, thymosins, thymopoetin, thymic humoral factor), which modulate various immune and non-immune responses of the organism, angiogenesis, cell-repairment (10), hemostasis, and coagulation (11). Evidence that thymic hormones influence the pineal synthesis of melatonin is also available (12).

Epiphysis (Pineal Gland)

The epiphysis (glandula pinealis) is composed of two main cell types—parenchyma cells and neuroglia. The pinealocytes secrete the principal hormone—melatonin, along with other polypeptide hormones, which are released into the capillaries and cerebrospinal fluid of the third ventricle (13). In elderly people, x-ray assessment reveals calcifications in large areas of glandula pinealis (acervuli, “brain sand”), which are associated with degenerative changes in the gland (13,14). However, electron microscopy shows not only decreased adrenergic innervation of the pineal gland but also diminished β -adrenergic receptor expression on the pinealocytes with senescence, which explains the lowering of the activity of the gland (15).

In vertebrate species, the epiphysis is a photo-sensitive neuroendocrine organ with various functions: 1) regulation of circadian and seasonal rhythms of the organism (16); 2) regulation of the reproduction; 3) regulation of stress and immune reactions (16,17); 4) antioxidant and antitumor defense; 5) “sun clock of aging” (14). Our previous studies show that the main pineal hormone—melatonin, is involved in hemostasis as well (18).

Influence of the Thymus and Epiphysis on Immunity

Melatonin exerts certain effects on the immune system and its main organ—the thymus, explicitly on the development of the T-lymphocytes (19). Experimental data indicate that the density of specific binding sites for melatonin is greatly dependent on the age of the experimental animals. Melatonin receptors have different localization on immunocompetent cells, not only on the cytoplasmic membrane of the spleen and thymus lymphocytes but also in the nuclei. The melatonin nuclear receptor expression indeed suggests the activation role of the hormone in the production of IL-2 by the mononuclear leukocytes in the blood. Melatonin receptor mRNA is present in CD4+, CD8+, B-lymphocytes, thymus, and

spleen. The high density of melatonin-binding sites in the thymus proves the involvement of the epiphysis in the pineal control of immunity (20). Melatonin has a protective effect on rat thymocytes by modulating the processes of apoptosis and proliferation. The hormone reduces DNA fragmentation and the intensity of oxidative stress. Melatonin directly stimulates activated T-helper cells and NK cells hence linking the factors that affect both the circadian production of melatonin and immunity (21). Some authors assume that the immune response varies according to the circadian rhythms, which also change their characteristics with aging (22). The immunomodulatory effects of melatonin are based not only on its direct and indirect actions on the function of immunocompetent cells but also on the restoration of the time-structure organization of the immune system and immune-endocrine relationships (21).

Removal of the pineal gland in experimental animals causes weight loss, thymus destruction, and serious immune malfunction (23). On the other hand, thymectomy causes disturbances in the biorhythmic activity of various substances, associated with glucocorticoid synthesis (8). The involution of the thymus and epiphysis show significant similarities; there are mutual influences between these glands in terms of regulation of the immunity, so they can be assumed as a functional unit (5,7).

The overlap between some of the functions of the two glands and the understanding that they act together in the regulation of cell growth and differentiation logically leads to the identification of the thymus-pineal axis in the second half of the XX century (24, 25).

Another shared feature of thymus and pineal gland is the secretion of the same cytokines, like TNF- α . The thymic medulla produces TNF- α and, under normal conditions, its biosynthesis is essential for the proper development and regulation of the immune response. Commonly known for its pro-inflammatory properties, TNF- α is also a key player in the thymus-pineal axis, having a certain role in the “switch” between the endocrine and paracrine secretion of melatonin in healthy controls and models of acute inflammation (25). According to Markus et al., TNF- α suppresses melatonin synthesis in rats by downregulation of the expression of a key enzyme (*Aa-nat*). This leads to the conclusion that an inverse

correlation between the concentration of the inflammatory cytokine and the nocturnal melatonin production exists. Some authors consider not only melatonin in particular but also the pineal gland, in general, to participate in the innate immune responses of the organism.

Influence of the Thymus and Epiphysis on Aging

It is well known that the process of aging is linked to desynchronization of the functions of the organism and decreased ability for adaptation to environmental changes (26).

The thymus is largest related to the bodyweight straight after birth. During the first years of life, its mass progressively increases, reaching peak values in puberty, after that the size of the gland decreases and it shrinks. Almost immediately after birth, lipid infiltration of the gland begins and this leads to the so-called physiological involution. It progresses with age, under the influence of various age-related changes in the body—a process called immune senescence (27). This process includes a great number of intrinsic and extrinsic factors and is associated with the age-related changes in the pineal gland.

The age-related changes in the pineal gland are similar to those in the thymus. After the period of initial growth (up to about the 2nd year of life), the pineal size remains relatively constant until the age of 20, after that the weight of the gland progressively decreases, and certain abnormalities in the parenchymal morphology appear. Pineal metabolism is disturbed, the production of peptides and indolamines decreases (28). The circadian rhythm is essential not only for the time organization of the physiological functions of the organism but also for life expectancy. With age, various disruptions appear, including the rhythmical secretion of the hormones, body temperature, sleep, and some behavioral rhythms (14). Melatonin reduction associated with aging is labeled by some authors as the “age clock” (29). The pineal hormone affects genes that control cell cycle, adhesion, and transport. Experiments show that pineal gland extracts increase life expectancy in rats and mice (14). In rats, melatonin inhibits the aggregation of amyloid-beta protein in neurotoxic microaggregations, which are known to cause neuronal death in Alzheimer’s disease (30). The available data is not

sufficient for obtaining a definitive conclusion that melatonin might increase human life expectancy but certainly, some of its effects can improve the organization of the vital processes in senescence (26).

Researches show the mutual impact of thymic peptides on epiphysis and pineal peptides on the thymus. It was found that tissue extracts from both glands along with synthesized peptide analogs can be used in the recovery mechanisms of the organism. These extracts contain cytomedines—biologically active peptides with pronounced geroprotective effects. The cytomedines, namely epithalamin and thymalin, were shown to increase the average life expectancy of experimental animals, presumably on account of their antioxidative, immunomodulating, and oncostatic effects (31).

Pineal peptides (epithalamin, epithalon) exert a stronger geroprotective effect on thymic involution compared with the geroprotective effect of thymus peptides (thymalin, thymogen) on the pineal gland involution. The key mechanism of action of the pineal peptides on thymic dystrophy is immunoendocrine and it is realized via activation of the transcription of various proteins (8).

Studies on the complex processes of aging again underline the mutual interplay between the hormones of the thymus and epiphysis. Senescence also involves the suppression of immune competency and accumulation of free radicals that are important for the onset of many diseases (32,33). Although senescence is a multi-factor process, it is undoubtedly characterized by immunoendocrine and immune deficits. Among the most important is the decreased nocturnal production of the pineal hormone melatonin and decreased production of IL-2 (34).

It was established that the majority of the age-related changes in the organism correspond to the diminished functional activity of immune and endocrine systems. The processes that run in the thymus and pineal gland throughout the whole life are of special importance.

The drop in the humoral and cellular immunity with senescence is linked to the age-related changes in the thymus. Morphological alterations in the cell microenvironment and inadequate synthesis of signal molecules, which in turn influence the functional activity of the immune system and T-lympho-

cyte development and differentiation, are the physiological consequence of the thymic involution.

With aging, certain morphological and functional changes occur in the pineal gland as well. The decrease of the nocturnal secretion of melatonin is of paramount importance and as it is well known, this hormone is responsible for the synchronization of biological rhythms, which is directly linked, to life expectancy and quality.

Some of the referred studies show that human pinealocytes and thymic epithelial cells share similar structural and functional organization as well as complementary age-related deterioration. Analysis of the data published in the scientific literature shows that the close functional interrelations between the thymus and pineal gland determine the existence of the thymus-pineal endocrine axis and its significance for immunity and aging.

CONCLUSION

In the context of the understanding of integrated immune-neuro-endocrine system, whose main purpose is to maintain homeostasis, the review of the published data definitely shows a tight relationship between the thymus and epiphysis. The thymus-pineal endocrine axis plays an important role in the organism under normal as well as pathological conditions. The pineal gland affects the proliferation of immune cells, production of immune mediators, humoral and cellular immunity, mainly by its principal hormone—melatonin. The thymus has the leading role in the execution of many immune functions that are regulated by biorhythms. These two glands form a bi-directional system and establish mutual relations. Thereby the thymus and the pineal gland complete in the maintenance of normal endocrine and immune status from the beginning to the end of life.

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