Melatonin in Psycho-Neuro-Endocrine-Immunology

Subjects: Others

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Psychoneuroendocrinoimmunology is the area of study of the intimate relationship between immune, physical, emotional, and psychological aspects. This new way of studying the human body and its diseases was initiated in the 19th century's first decades. However, the molecules that participate in the communication between the immune, endocrine, and neurological systems are still being discovered.

Keywords: immunology ; endocrinology ; neurology

1. Introduction

Psychoneuroendocrinoimmunology (PNEI) studies the intimate relationship between immune, physical, emotional, and psychological aspects, states of consciousness, and chemical mediations to demonstrate their psychochemical interdependence. The research of PNEI, initiated in the first decades of the last century, has opened a world of chemical communication between the brain and the endocrine glands that emerged through various scientific figures' work. Many decades later, peptides released from nerve cells that influence hormone production are still being discovered [1][2].

The hypothalamus is a surprising area of the brain since, in a tiny space, equal to 4 mL in volume, compared to a brain volume of 1350–1500 mL, it contains a set of strategic functions for survival and brain activity organism; a close relationship between the hypothalamus and PNEI has been demonstrated, about its inputs and outputs towards the immune system, its relationship with hormonal processes, with stress states, and with psychological processes. The hypothalamic nuclei regulate water metabolism, hunger and satiety, body temperature, circadian rhythms, emotions and behaviors, and memory. The hypothalamus has one main "gate", the median eminence, located at the base of the hypothalamus, in the center of the tuber cinereum. The median eminence supplies the pituitary gland with blood rich in hypothalamic hormones and, at the same time, is outside the blood–brain barrier (BBB); it represents an interface with the general blood circulation. Therefore, it functions not only as an exit door but also as a gateway to the hypothalamus for some essential peripheral hormones, such as leptin. The hypothalamus has at its disposal the platform control of the endocrine system, which is achieved through three different axes [3]:

(1)By direct secretion, passing through the neurohypophysis, of hormones arginine vasopressin and oxytocin, which affect the kidney, the gravid uterus, the postpartum mammary gland, and the brain [3].

(2)Hormones that influence the adenohypophysis to regulate the activity of the gonads, uterus, thyroid, adrenal cortex, liver, and bones [3].

(3)Through hormones and neural connections with the autonomic nervous system, which innervates the pineal gland, pancreas, and adrenal medulla [3][4].

All the hypothalamus hormones have a particular objective but are rarely unique because their function is generally not limited only to the endocrine compartment. For example, thyrotropin-releasing hormone (TRH) has its main activity on pituitary endocrine cells that produce thyroid-stimulating hormone (TSH), but TRH also stimulates the release of prolactin, adrenocorticotropic hormone (ACTH), and growth hormone (GH). Thus, somatostatin not only inhibits growth hormone production but also inhibits TSH. Similarly, dopamine inhibits prolactin, TSH, gonadotropins luteinizing hormone (LH), follicle-stimulating hormone (FSH), and occasionally even GH. To complete the polyhedral characteristics of the hypothalamic platform and its extensive influence on the body, the neurons in the paraventricular nucleus and the arcuate nucleus produce hormones and a myriad of neurotransmitters and neuromodulators [3][5][6].

2. Development of Psychoneuroendocrinoimmunology

Research in recent years has revolutionized the medical and psychological view by contributing a profoundly unitary and psychosomatic understanding of the human being and highlighting the intimate relationship between physical, emotional, and psychological aspects. Candace Pert, a researcher at the National Institute of Mental Health (NIMH), discoverer of endorphins and neuropeptides, maintains that it is no longer possible to separate the physical aspect from the mental, but that: “We must speak of mind-body as a single entity integrated” [7][8].

PNEI is inserted as a link between medicine and psychology, with a mind–body model that includes all the physiological, emotional, psychological, behavioral, and social processes understood as an organic and unitary system: a network of systems biology [1].

The origin of the PNEI traditionally dates back to the studies of Walter Bradford Cannon (1871–1945), an American physiologist and psychologist from Harvard University. This took the concept of “milieu Interieur” (i.e., internal organic environment) developed by Claude Bernard (1813–1878), a French physiologist [7]. His research on the relationships between animals studied the emotional implications of stress conditions: fight or flight and the attitude adopted in these conditions. He also studied the physiological modifications of animals in this condition, highlighting the emotional experience of the animal and developing the so-called thalamic theory [9]. Stress studies were significantly developed by Hans Hugo Bruno Selye (1907–1982), an endocrinologist of Hungarian origin, responsible for the fundamental division into distress (negative stress) and eustress (positive stress) based on the pathophysiological responses of living organisms and the degree of intensity of the applied stressor [9][10]. Although these studies have had a significant impact on what will be the foundations of the PNEI, it is necessary to remember that the experimental models of stress used were excessively forced and far from the simple concept of stress: Selye demonstrated the hypertrophy of the adrenal glands of rats subjected to highly harsh treatments (electric shocks, cold, heat, drowning, etc.) in response to massive activation of the hypothalamic-pituitary-adrenal axis, and demonstrated how various harmful agents (stress factors) induced both adrenal hypertrophy such as thymic atrophy. This pathophysiological change took the name of general adaptation syndrome and included a higher incidence of gastric ulcers.

The official birth of the PNEI has a precise date of 1981. The first edition of Psychoneuroimmunology was published by Robert Ader (Ph.D. in Psychology at Cornell University); Ader is considered the father of this discipline, and being a young researcher, in 1975, he demonstrated that the psyche is capable of influencing the immune system. Ader and his colleague, immunologist Nicholas Cohen, showed that if mice were given an immunosuppressive drug along with apple juice, they would suffer from the drug’s effects as soon as they tasted the liquid, even in the absence of the drug. Researcher’s beliefs at the time viewed the immune system as entirely autonomous [7]. It was not a single study that started this discipline. Despite the convergence of several studies that confirmed the interactions between the brain and the immune system, the reaction of the biomedical community, especially immunologists, also regarding other studies by other researchers, such as David Felton and Hugo Besedovsky, on the neuroendocrine regulation of the immune system, was quite adverse. However, the immune system was thought to work autonomously, and there was no way to explain the mechanics of the brain’s influence on it [7].

3. Role of Melatonin in the Neuroendocrine and Immune Systems

Melatonin (MLT) is an ancient molecule traced back to the origin of life. One of the main functions of MLT is to function as a free radical scavenger cone; other functions include the regulation of sleep cycles, the modulation of circadian cycles, enhancement of immunity, and as an oncostatic agent, regulating circadian rhythm, immune and metabolism regulation, antioxidant, anti-aging, and anti-tumor effects [11], prevent cell death, reduce inflammation [12], block calcium channels [13] [14], restore autophagy [15] and mitophagy [16], among others [17]. MLT is an indolamine produced in the pineal gland, generated and released in a circadian manner [18]. In humans, the level of MLT increases at dusk, with a higher peak between 2 and 4 am, descending in the second part of the night [18]. In humans and animals, the embryo and fetus depend on maternal MLT, as g. pineal matures and fully develops after birth. MLT crosses all physiological barriers, including the placental barrier, without experiencing any structural or functional modification, and this neurohormone is involved in the placental function itself [18][19]. In humans, the hypothalamic suprachiasmatic nucleus (SCN) expresses receptors to MLT in the fetus and adults. Maternal MLT enters the transplacental fetal circulation by providing photoperiodic information to the fetus [18][19]. MLT concentrations are increased in the maternal circulation during pregnancy, with a peak at the end of pregnancy [19]. The development of fetal sleep patterns in late pregnancy is due to MLT functioning as a regulatory factor, a typical sleep pattern intimately related to neurodevelopment, and providing strong evidence that MLT is involved in fetal neuroprotection [18].

In lower vertebrates, MLT secretion begins early, during embryonic development. The human fetus or newborn does not produce its MLT; it depends on the hormone supplied by the mother via the placenta or milk. Circadian functions in full-term newborn children (MLT secretion, sleep-wake rhythms, body temperature rhythms) do not exhibit circadian variation until 9-12 weeks of postnatal life [18]. At least two types of membrane receptors have been described as MLT, Mel1, and Mel2. Of the MT1 type, there are three subtypes Mel1a, Mel1b, and Mel1c. Mel1a and Mel1b are referred to as MT1 and MT2. The Mel1c receptor subtype is not expressed in mammals [18]. MLT receptors have been identified in embryos and fetuses in the nervous system and peripheral organs, especially in cells of the endocrine system [18]. MLT has been associated with the reproduction process in vertebrates, particularly in seasonal breeding [20].

MLT has been associated with the reproduction process in vertebrates, particularly in seasonal breeding [20]. MLT can regulate several of the reproductive cycles in humans; the pulsatile release of GnRH and the increase in the pulse rate of gonadotrophins are observed to be higher at night during puberty [20], and the elevation in the monthly secretion of LH and FSH by ovulation occurs mainly during the last hours of the dark phase [20][21]. MT1 receptor mRNA has been found in pituitary *pars tuberalis* in rats, as well as the expression of this same receptor in the *pars distalis* in the gonadotrophic fraction [21]. In the anterior pituitary gland, the MLT mediates the effects of the photoperiod, acting mainly on two types of secretory cells, lactotrophs, which secrete prolactin, and gonadotrophs, which secrete two gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [21].

The neuroendocrine and immune systems are closely interrelated; products secreted by the neuroendocrine system can affect the immune system and vice versa [22]. At the level of the immune system, MLT shows contradictory effects, and it can exert both inflammatory and anti-inflammatory effects. Proinflammatory effects related to increased resistance of the organism to pathogens have been reported, as well as anti-inflammatory effects in cases of sepsis, cerebral ischemia-reperfusion, and certain neurodegenerative diseases [22]. MLT has been shown to have five family receptors in mammals, two of them are membrane receptors (MT1 and MT2), and the remaining three are nuclear receptors, ROR-α, ROR-β, and ROR-γ [22][23]. The MT1 receptor is expressed in lymphoid tissue and actively participates in the regulation of the inflammatory response. In contrast, the nuclear receptors ROR-α and ROR-γ play a predominant role in the expression of cytokines such as IL-17A, IL-17F, and IL-23R, as well as the chemokines CCL20 and CCR6 [22]. MLT receptors and their synthases have been reported to be expressed by macrophages. They regulate the cellular differentiation pathways of these cells, which is directly related to the immunoregulatory effect of MLT on macrophages in diseases such as cancer and rheumatoid arthritis [22]. So, MLT is a ubiquitous hormone with pleiotropic effects on the function of immune cells.

The pineal gland is directly involved in innate and adaptive immune responses, the expression of MHC-II in antigen-presenting cells or APCs (macrophages and dendritic cells), as well as in peritoneal macrophages is increased after MLT supplementation; it has been suggested that this neurohormone can prevent age-related changes in the immune system [22][23]. MLT has been reported to play an anti-inflammatory role in innate immune activation, inhibit the de-acetylation of NF-κ B by sirtuin1, inhibit NF-κ B activity in the septic mouse, reduce the proinflammatory response mediated by this same transcription factor, and restore mitochondrial homeostasis [22]. MLT can inhibit the p38 pathway, an inflammatory pathway of MAPKs in breast cancer cells while having anti-invasion and anti-metastasis properties [23].

In humans, the pineal gland's functions overlap with the functions of melatonin [24]. MLT has been considered neuroprotective against various neurodegenerative and immune diseases due to its wide range of biological functions. Major depressive disorder is a common, chronic, and severe life-threatening disorder that could frequently present in neurodegenerative diseases such as Parkinson's or Alzheimer's [15][25][26]. Pathophysiology is characterized by increased oxidative stress and increased levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β, stimulating astrocytes and microglial cells, leading to the development of depressive symptoms [15]. The MLT could act as an antidepressant via MLT receptor MT2 and regulate FOX03A signaling on astrocytes and microglial cells [15], as well as ameliorated oxidative stress [27][28], neuroinflammation [29], and autophagy deficits [15].

MLT is known to have protective effects on cognitive impairment in neurodegenerative diseases such as Alzheimer's. Due to restored mitophagy by improving mitophagosome-lysosome fusion via Mcoln1 and ameliorated mitochondrial functions, attenuated amyloid β pathology [16][30][31]. Additionally, it regulates the mTOR expression in the hippocampus while affecting the downstream proinflammatory cytokines [32]. MLT ameliorated oxidative stress-mediated c-Jun N-terminal kinase (JNK) activation, enhanced Akt/extracellular signal-regulated kinase (ERK)/cAMP response element binding protein (CREB) signaling, decreased the levels of apoptotic markers, and increased neuronal survival, promoted cell survival, proliferation, and memory processes [33].

It has been described as a pivotal role for the IL-17 cytokine family in human inflammatory or autoimmune diseases and neurodegenerative diseases [34]. Stimulation of Th17 cells with IL-1β and IL-23 induces local tissue inflammation, mainly

mediated by type-17 signature cytokines such as IL-17, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [35]. Th17 cells promote neuroinflammation and activation of microglia and astrocytes, actions that contribute to neuronal damage [36] and the development of neuronal diseases. MLT regulates the differentiation of T cells producing IL-17 and induces the synthesis of IL-17A by intact T cells but has little effect on activated cells. Additionally, the high concentration decreased the intracellular expression of IL-17A. So, MLT had a dose-dependent effect [37][38]. Thus, the result of the regulation of all of these molecular mechanisms by MLT is improving cognitive function and ameliorating the pathophysiology of neuronal diseases.

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