Chapter 1

Introductory Chapter: Melatonin, the Integrative Molecule within the Human Architecture

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Additional information is available at the end of the chapter

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1. Introduction

In the healthcare scientific environment, nowadays, researchers are inspired by endogenous springs of molecules that can be reinterpreted, better understood, or completely reconsidered in their function and ability to sustain the human organism in maintaining its homeostasis [1].

Melatonin is such a tremendous molecule acting in the center of the integrative molecular mechanisms of the body, based on interlinkages of the regulatory systems: neural, endocrine, immune, and genetic, all embodying the uniqueness of human architecture [1, 2].

The endogenous indole system represented by biomolecules with indole structure such as tryptophan, serotonin, and, above all, melatonin conducts the integration mechanisms of the organisms in the great informational variety of the environment. Melatonin is responsible for coordinating and synchronizing the expression of the most important physiological effects of the biological rhythm, imposes an order of the biochemical systems functionality and, globally, depicts the molecular logic of living [2, 3].

The indole ring is considered by scientists as a "privileged" biological structure [4, 5], due to its outstanding ability to form organic active compounds with different affinities for endogenous receptors, mainly for G protein-coupled receptors [6]. The indole structure is widely found at all levels of the biological systems as an important component of the biomolecules and natural products, such as the alkaloids from ergot, essential tryptophan amino acid, serotonin, neuromediator, and melatonin, the main hormone secreted by the pineal gland. As a consequence of its biological effects, the indole nucleus is present in the structure of many marketed medicines [7–10] or dietary supplements [11–13], as well as in the prototypes of some drugs that are currently under development.

As a constitutive element of proteins, the essential indole amino acid, tryptophan, has the most pronounced hydrophobic character of all the amino acids and forms a specific hydrophobic environment that contributes to the stabilization of the endogenous protein structure, special characteristics regarding membrane fluidity and transmembrane potential [14, 15]. Also, tryptophan is one of the most important indolic endogenous precursors, being involved in the biosynthesis of all endogenous compounds with indole structure: the neurotransmitter serotonin, the pineal hormone melatonin, the neuromodulator and neurotransmitter tryptamine, 5-hydroxytryptophan, and 5-hydroxyindoleacetic acid, as also in the activity of some specific enzymes, cytochrome c peroxidase. Tryptophan depletion is part of the cytotoxic process and antiproliferative cellular mechanism mediated by γ-interferon. Low serum tryptophan concentrations are clinically correlated with the appearance of some pathological infectious, autoimmune, and, not the last, malignant processes [16–18].

Tryptophan is the precursor of serotonin, a neurotransmitter with indole structure, with vast biological effects. Emergence of imbalances in the serotoninergic metabolism determines the etiology and pathological neuropsychiatric and systemic disorders, including the development of serotonin-secreting tumors [19–22]. Thus, a more complete overview of tryptophan and serotonin biochemistry and the precise relationships and interactions of these molecules with other endogenous constituents or structures may contribute to the therapeutic understanding and solving many psychiatric, autoimmune, and neoplastic disorders [23–25].

In particular, melatonin is an indole neurohormone synthesized mainly in the pineal gland, during the night, being also known as the darkness hormone. Melatonin is not exclusively synthesized by the pineal gland; the retina, the skin, and the gastrointestinal tract are only a few other tissues that produce high amounts of melatonin [26].

The direct precursor of melatonin is the serotonin, naturally synthesized in pinealocytes from L-tryptophan. The regulation system of the melatoninergic synthesis is complex, using central and autonomous pathways, so that there are many pathophysiologic situations where the melatonin secretion is deficient. The alteration of the melatoninergic circadian profile [27] is associated with the susceptibility, development, and evolution of a variety of pathologies, the highest incidence of cancer being registered in shift workers, which have a detrimental day-night alternation [28].

On the other hand, small fluctuations in the steady-state levels of the reactive oxygen and nitrogen species concentrations may play a key role in the intracellular signaling, uncontrolled increases of these highly reactive molecules leading to chain reactions mediated by free radicals, which destroy, without discrimination, proteins, lipids, and DNA, resulting, ultimately, in cell death and being the primary or secondary cause of a wide range of diseases [29–35].

Melatonin was closely analyzed, under all biochemical aspects, considering its antioxidant mechanisms, intrinsic or modulatory at the level of antioxidant enzymes or in connected supplementary scavenging processes, and revealing a unique molecular antioxidant cascade. Its effects were interpreted in conjunction with other endogenous structures or assessed in controlled release formulations, aimed to enhance antioxidant processes and endogenous indole modulatory actions [36–38].

This molecule was studied under very different circumstances, from interactions with DNA, in association with other therapeutic agents [39], using different animal models [40–45] and cell lines [46–48]. The current scientific interest focuses on revealing melatonin actions on major physiological process, as pregnancy or aging [49, 50], determining its modulatory abilities on different stages of fetus evolution, on healthy aging mechanisms, and on preventing neurodegeneration, melatonin receptors being highly expressed at the placenta level, the BBB mainly by P-glycoprotein overexpression, mediating the mother-fetus interchanges and restricting the xenobiotic way to the fragile developing organism [51–53].

Melatonin also exerts different effects on the glucose metabolism, considering various targets: it stimulates glucose uptake in muscle cells by phosphorylation of insulin receptor substrate-1 through MT2 signaling, MT2 receptors are expressed in hepatocytes, and melatonin therapy elevates glucose release from the liver [54].

The cardiovascular system physiological, pathophysiological, and molecular endogenous mechanisms are highly influenced by diurnal variations, circadian imbalances affecting gene and protein expression, cardiac remodeling, and promoting ischemia/reperfusion damage [55–64]. Desynchronizations are frequently registered in patients with hypertension, diabetes mellitus, obesity, and metabolic syndrome [65, 66].

Another important research field for melatonin and its derivatives is identifying predictive biomarkers meant to provide extensive control upon pathologic progression and therapy success, markers that are as minimal invasive as possible and readily available [67–72].

Melatonin is the integrative molecule in the in vivo milieu of every living cell, mediating the integration complex mechanisms of the individual entity into the environment, synchronizes its cyclic processes, and depicts the circadian distribution of physiological and behavioral processes.

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