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Melatonin in the Care and Control of Human Health

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Abstract

Since first isolation, purification and chemical characterization of melatonin (N-acetyl-5-methoxytryptamine) from the bovine pineal extracts, past six decades have witnessed enormous growth of knowledge on the physiological significance of this tryptophan-derived hormone in the regulation of a wide variety of body functions in different animals as well as in humans. A number of controlled studies have implicated melatonin to diverse physiological functions ranging from aging to aggression, reproduction to scavenging of free-radicals, sleep to stress, and even to several patho-physiological disorders like immune-suppression and cancer. Studies on different human populations have clearly shown that endogenous capacity of melatonin biosynthesis gradually decreases with the progress of age, and that offers an explanation to the increased susceptibility to diseases at older age. The information that forwards a therapeutic role of melatonin as an anti-aging agent is that it is more potent scavenger of free radicals than any other known drugs. Obviously, in consideration to its multiple actions in the body, melatonin appears to be a powerful chronobiotic molecule in the care of human health and cure of several diseases. Recent focus of attention in human is on sleep disturbances, seasonal affective disorder, neuro endocrine disorder and cancer therapy. A brief overview of the literature is presented in order to show recent findings and avenues of research into the use of melatonin.

Introduction

Discovery of melatonin as N-acetyl-5-methoxytryptamine from the extracts of about 2,00,000 bovine pineal glands by a research team led by Lerner [1], a dermatologist, at the Yale University School of Medicine is a major breakthrough in understanding the link between the environment and endocrine system in vertebrates as well as chrono-biology in living system. The term 'melatonin' has been introduced in recognition to the initial findings [2] that administration of bovine pineal extracts to the tadpoles caused the larvae to blanch due to the aggregation of melanin granules within skin cells. Most interesting and exciting information on melatonin is its occurrence in wide range of living system including unicellular organisms, plants, and invertebrates, though existing knowledge on the biosynthesis and functions of melatonin stemmed mostly from the studies on the pineal gland in vertebrates. Nearly past sixty years after the discovery of melatonin witnessed accumulation of enormous amount of data on different aspects of regulatory mechanism involved in the synthesis and release of this indole derivative and its role in the regulation of a large as well as diverse body functions in vertebrates in general and in human in particular. An obvious outcome has been the publication of excellent reviews in recent years [3-8]. This article aims at summarizing the data that contributed to current understanding of physiological role of melatonin in human with emphasis on clinical significance/ application.

Melatonin: A ubiquitously distributed biological molecule

Melatonin is ubiquitously distributed in living system and is suggested to represent one of the most primitive biological signals appeared on earth, and has been identified in a wide variety of organisms including bacteria, unicellular eukaryotes, different plants, as well as in a large number of animals. Recent studies reveal that melatonin is present in different tissues, organs such as Harderian gland, extraorbital lacrimal gland, retina, gastrointestinal (GI) tract and in bile in human and many vertebrates. By order of magnitude, melatonin content of the GI tract is greater than in the pineal gland or in circulation. Melatonin concentration in the bile is about 1000 times higher than its daytime levels in the blood [8].

Biosynthesis, secretion and metabolism

Biosynthesis: In all vertebrates investigated so far, melatonin is primarily synthesized within the pinealocytes of pineal gland during the night regardless of the diurnal or nocturnal locomotor activity of the animals. Biosynthesis of melatonin

from its precursor L-tryptophan is a four-step phenomenon. First, L-tryptophan is taken up from the circulation (blood) into the pinealocyte and is converted to 5-hydroxytryptophan by tryptophan 5-monooxygenase/hydroxylase which is decarboxylated by L-aromatic amino acid decarboxylase to form serotonin. As a result of acetylation (N-acetylation), serotonin is converted to N-acetylserotonin under the influence of serotonin-N-acetyltransferase/ arylalkylamine N-acetyltransferase (AA-NAT). Finally, N-acetylserotonin is methylated by hydroxyindole-O-methyltransferase (HIOMT) to form melatonin. AA-NAT is the rate-limiting enzyme in melatonin synthesis, but serotonin availability is one of the major factors that play an important regulatory role in this process [9].

The magnitude and duration of the nocturnal increase in melatonin synthesis is dependent upon the length of the dark phase of the photoperiodic cycle and it acts as a "clock" and "calendar" for the entrainment of other biological activities [10]. The rhythm of melatonin synthesis is generated by interacting networks of circadian clock genes located in the suprachiasmatic nucleus (SCN) of the hypothalamic part of brain. SCN is considered as the major central rhythm-generating system or "clock" in mammals. The pineal itself is a self-sustaining "clock" in most of the higher vertebrates. The SCN clock is set to a 24-hour day by the natural light-dark cycle via retinal light input which then sends circadian signals over a neural pathway that project from the superior cervical ganglia (SCG) to the pineal and thereby driving rhythmic melatonin synthesis. Specifically, SCN is the major regulatory site of the activity of AA-NAT, which is the penultimate and key enzyme in the synthesis of melatonin from tryptophan [6].

Secretion: The secretion of melatonin is related to the length of night. A single daily light pulse of suitable intensity and duration in otherwise constant darkness is sufficient to phase shift and to synchronize the melatonin rhythm to 24-hours via SCN. There are indications that prolonged duration of the night leads to longer a duration of secretion of melatonin in most animal species. Ocular light serves to entrain/synchronize the rhythm to 24h and to suppress secretion at the beginning and/or the end of the dark phase. The amount of light required to suppress melatonin secretion at night varies from one species to the other, with the time of night, and with the history of previous light exposure [11]. The amplitude of nocturnal melatonin secretion exhibits considerable inter-individual differences and is known to be genetically determined. In human, serum melatonin concentration is low during the day (10-20pg/ml) and is significantly higher at night (80-120pg/ml) with a peak between 24:00h and 03:00h. The onset of secretion usually takes place around 22:00-02:00h and the offset around 07:00-09:00h.

Serum melatonin concentrations in human vary in relation to the stage of development, puberty, menstrual cycle (in females), and age of the individuals. Its peak values in blood may also vary from one individual to the other and depend on their age, sex, and disease. Just after birth, very little melatonin is detectable in body fluids. A robust melatonin rhythm appears around 6 to 8 weeks of age. The serum level of melatonin increases rapidly thereafter and reaches a lifetime peak in between 3-5 years of age. The increment is much greater at night (54-75pg/ml). Subsequently, a steady decrease occurs reaching to a mean adult concentration in mid to late teens with the major decline before puberty, with relatively stable until 35 to 40 years, and final decline in amplitude takes place until low levels (16-40pg/ml) in old age [12,13]. Generally, elderly women show higher melatonin levels than in elderly men. Melatonin level is low in precocious puberty, but higher concentration is detected in delayed puberty and hypothalamic amenorrhea compared to age-matched control and abnormal melatonin secretion in patients with pre-menstrual stress [14].

Metabolism: Melatonin synthesized in the pineal gland is released in the cerebrospinal fluid in the third ventricle via the pineal recess and attains levels up to 20-30 times higher than in blood, but rapidly diminishes with increasing distance from the pineal gland [15]. In the blood, 50-75% of total melatonin binds reversibly to albumin and glyco-proteins. The half-life of melatonin is bi-exponential, with a first distribution half-life of 2 minutes and a second of 20 minutes. The half-life of endogenous melatonin is about 30-60 minutes and exogenous melatonin has even shorter half-life of about 12-48 minutes. More than 90% of circulating melatonin is metabolized primarily in the liver following classical hydroxylation pathway to 6-hydroxy-melatonin, which undergoes further conjugation with either sulphate to form 6-sulphatoxy-melatonin, or glucuronic acid to form 6-hydroxymelatonin glucuronide and is eliminated in the urine. Urinary aMT6s excretion closely reflects the plasma melatonin profile which is thus frequently used for evaluation of melatonin rhythms in humans [16].

Physiological diversity of melatonin in human:

Due to its pleiotropic nature, melatonin is implicated to a wide range of physiological or patho-physiological functions in humans. Most of the studies used pharmacological doses of melatonin (1 micromolar and above), and a few studies confirmed the functions clinically or perfect experimentally physiological doses (below the nanomolar range) of melatonin. Multiple physiological functions of melatonin are known, but only a few of them are emphasized.

Regulation of reproduction: The role of melatonin in the regulation of reproduction is one of the major areas that received serious attention in recent years. Melatonin might be a crucial factor in regulating several activities associated with human reproduction. It may play a role in pubertal development and reproductive functions by regulating the hypothalamus–pituitary–gonadal (HPG) axis, as the blood melatonin levels decrease considerably during childhood and puberty, and gonadotrophin release in the hypothalamus-pituitary gland axis via specific receptors [17]. The study showing melatonin

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concentrations reach a nadir in the preovulatory phase and a peak in the luteal phase [18] suggest its variable effects depending on the menstrual phase. Likewise, higher concentrations of follicular fluid melatonin in larger preovulatory follicles than in smaller immature follicles [19] indicate that follicular fluid from mature follicles may have higher antioxidant capacity than in smaller follicles, implying its role in oocyte maturation. Addition of melatonin in culture media also improves nuclear maturation rate of immature MI oocytes, implantation rate, and an insignificant increase in clinical pregnancy rate with an optimal threshold of 10^{-5}M to 10^{-9}M [20]. Physiologically, oxidative stress in oocytes caused by reactive oxygen species (ROS) must be limited for the production of a good embryo. ROS induces lipid peroxidation of membranes and DNA damage in oocytes and thus accounts for poor oocyte quality. The effects of melatonin treatment have been studied during human pregnancy under a large range of conditions and at different times during gestation. Predominantly, melatonin is used in assisted reproductive technology aiming to improve oocyte quality and pregnancy rates following *in vitro* fertilization (IVF). Melatonin administration, started prior to IVF-cycles and continued during pregnancy, is associated with modestly improved pregnancy outcomes [21]. Polycystic ovarian syndrome (PCOS) is considered as the most common endocrine disorder that affects women. In PCOS, generation of ROS from mononuclear cells and lipid peroxidation products in serum are significantly elevated, and activities of antioxidative enzymes become reduced, that ultimately may contribute to oxidative stress mediated apoptosis in atretic follicles. Melatonin prevents apoptosis by inducing Bcl2 expression and reducing Casp3 activity. As an antioxidant, melatonin may increase insulin-like growth factor-1 and transform growth factor-beta (TGF-β) production, which are antiapoptotic [22]. Thus, normally the increase in follicular melatonin concentration in the growing follicles could be an important factor in avoiding atresia. Ovarian follicles may be rescued from PCOS by melatonin and thus allow a preovulatory follicle to fully develop and provide a healthy oocyte for fertilization. In males, melatonin, besides its effect on the synthesis and secretion of the hypothalamic GnRH and the adenohypophyseal gonadotropins, may directly modulate testicular activity. More precisely, melatonin by binding with its receptors directly regulate testosterone secretion, increase the responsiveness of Sertoli cells to FSH during testicular development and modulates cellular growth, proliferation, and the secretory activity of several testicular cell types. It inhibits local inflammatory processes and the generation of ROS in testis to increase the rate of spermatogenesis and fertility [23].

Synchronization of rhythmic body functions with the environment: In all living organisms, circadian periodicity (for human 24.2h/cycle) in many body functions is an inherited characteristic which appears to be closely related to diurnal preference and the early or late timing of the circadian system in a normal entrained situation. Melatonin, as an endogenous synchronizer, may act in stabilizing rhythms (circadian) of body functions or in reinforcing them [24]. Hence, melatonin is considered as a 'chronobiotic' molecule, or a "neuroendocrine transducer" or "hormone of darkness" or "biological night", which is exclusively involved in signaling the "length of night" or "time of day" and "time of year" in all tissues [10]. Human studies demonstrated that administration of melatonin changes the timing of rhythms by increasing sleepiness, REM sleep propensity, sleep propensity, endogenous melatonin and decreasing core body temperature, which ultimately leads to sleep [24,25]. This phase-shifting effect of melatonin depends on its time of administration. It phase-advances the circadian clock when given during the evening or the first half of night, whereas circadian rhythms during the second half of the night or at early daytime are phase delayed. The magnitude of phase advance or delay depends on the dose of melatonin. Thus a practical definition of melatonin would be 'a substance that adjusts the timing of internal biological rhythms' as chronological pacemaker or "Zeitgeber" (time cue) as calendar function [26]. However, the appropriate Zeitgeber circadian oscillators are found in every organ and indeed in every cell in the body.

Regulation of sleep-wakefulness cycle: Normal sleep is essential for an individual's physical and mental wellbeing. Although there is a variation in sleep requirements amongst individuals, most adults require approximately seven hours on a regular basis for the promotion of optimal health. Two-process model of sleep regulation considers the timing and architecture of sleep to be a consequence of a homeostatic process of rising sleep pressure and the duration of prior wakefulness, that is dissipated during the sleep period and is a function of circadian pacemaker. Over the last decades, two important protocols have been developed to investigate circadian and sleep homeostatic processes in human. A strong relationship is found between sleep and melatonin levels. Both nocturnal melatonin levels and the quality of sleep decline at puberty and in elderly or aged people. The period of sleep tend to become shorter and the quality of sleep poorer with decrease amplitude of the circadian rhythm and waking in a 12h light/12h dark cycle, and some time with phase advancement of circadian rhythm called delayed sleep phase syndrome (DSPS). Cross meridian flights involve disorganization of biological rhythm caused by rapid change of light/dark cues.

Exposure to artificial light at night results in a disruption of the circadian rhythm, which is deleterious to health. In the modern age of technology, watching television or using smartphones an hour or two before bedtime is a regular practice. Low intensity emission of light from LEDs (Light Emiting Diodes) computer screens or televisions, smart phones, and tablets, is capable of acting on the clock, thus leading to a phase delay and slowing of melatonin secretion, which is often associated with insomnia and sleep deprivation to underlie clock desynchronization disorders. This amounts to a type of chronic social 'jet lag' - i.e. a misalignment between the clock and social

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time. The light emitting from an iPad during e-book reading has a higher concentration of blue light than natural light and blue light affects levels of melatonin more than any other wavelength, which inhibits the tendency of normal sleep [27].

Regulation of mental state, behavior and brain functions: The pineal gland through its hormone melatonin promotes homeostatic equilibrium and acts as a "tranquilizing organ" in stabilizing electrical activity of the central nervous system and causes rapid synchronization of the electroencephalogram [28]. The classic endogenous or non-seasonal depression is characterized by insomnia (early morning awakening), appetite suppression, weight loss and advanced onset of nocturnal melatonin release which begins in the spring and persists through the summer or through the winter during the period of light-phase shortening. Similarly, seasonal affective disorder (SAD) is characterized by late sleep, morning hypersomnia, increased appetite, and retarded onset of nocturnal melatonin release which peaks in the fall and spring [28]. Similar phenomena are associated with individuals with low nocturnal melatonin levels and major depressive/ panic disorders. A link between pineal function, melatonin levels and mood disorders in several human populations is strengthened by epidemiologic and chronobiological evidences. Administration of different doses (>1g/day) of melatonin at night in these individuals prolongs the nocturnal melatonin rise and helps in recovering SAD by changing the expression of clock gene and by changing the expression of Per2 gene in bipolar or classic depression. However, the use of large doses of melatonin in morning or early afternoon represents no clear effect, though phototherapy as an adjuvant may accelerate responses to antidepressants among patients with depression. Consistent evidences are available to suggest that melatonin concentrations decrease during the onset of depression, but rise again after remission. Thus melatonin levels may be used as an effective indicator of the diagnosis for depression [29]. Melatonin secretion is a wavelength of light-dependent phenomenon, as exposure to monochromatic light at 460nm produces a 2-fold greater circadian phase delay. Such idea gains support further from the data on brain serotonin and tryptophan levels, which rise after melatonin administration and show direct link with an array of neuropsychiatric phenomenon. So, it seems that appropriate exogenous melatonin administration can restore human neurological disorders with direct impact on general health of elderly people.

Scavenger of free-radicals: Melatonin because of its lipophilic nature crosses all morphological and physical barriers or hematoencephalic barrier (Blood Brain Barrier-BBB, placenta) and reaches all tissues of the body within a very short time. As a result, melatonin exhibits antioxidant effects and performs a very important receptor-independent metabolioc function, i.e., multifaceted scavenger of free radicals [30]. The antioxidant effects of melatonin includ both direct and indirect effects with equal efficiency in multiple sites (nucleus, cytosol, and membranes) of the cell. It detoxifies a variety of free radicals and reactivates oxygen intermediates including the hydroxyl radical/ hydrogen peroxide, peroxy radicals, peroxynitrite anion, singlet oxygen, nitric oxide and lipid peroxidation. Melatonin is a more potent antioxidant than vitamins C and E [31-33]. A long-term oral melatonin administration at 6 mg/ day for two weeks increases plasma antioxidant ferric reducing ability (FRAP assay) and DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging, and decreases thiobarbituric acid reactive substances (TBARS) and DNA damage [32]. The antioxidant property of melatonin is shared by its two major metabolites: N1-acetyl- N2-formyl-5-methoxykynuramine (AFMK) and with considerably higher efficacy, N1-acetyl-5-methoxykynuramine (AMK). The AFMK is produced by enzymatic and non-enzymatic mechanisms, mainly by myeloperoxidase. The potent scavenger, AMK, consumes additional radicals in primary and secondary reactions. Interestingly, AMK interacts not only with reactive oxygen but also with reactive nitrogen species. AMK exerts its effects on electron flux through the respiratory chain and improve ATP synthesis in conjugation with the rise in complex I and IV activities [33]. The broad spectrum antioxidant activity of melatonin also includes an indirect effect by up-regulating several antioxidative enzymes and down-regulating pro-oxidant enzymes in general, and 5- and 12-lipo-oxygenases, superoxide dismutase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydogenase, catalase and nitric oxide (NO) synthases in particular [34]. There are ample evidences that melatonin and its metabolites scavenge endogenous free-radicals play very effective role in different physiological processes and is thus used as therapeutic agents in the regulation of various diseases like cancer, atherosclerosis, neurodegenerative disorders, diabetes, and inflammation [35].

Modulation of immune function: The role of melatonin as an immunomodulator in the regulation of development, differentiation, and functions of lymphoid tissues is known for nearly past three decades. A number of *in vivo* and *in vitro* studies have clearly documented that melatonin plays a fundamental role in the function of both innate and adaptive immune systems. Melatonin is shown to be highly effective in modulating T-cell activation and differentiation, especially for two recently discovered novel subsets of CD4+ T lymphocytes, Th17 and Treg cells, and memory T cells. Mechanistically, the influence of melatonin in T-cell biology is associated with membrane and nuclear receptors as well as receptor-independent pathways, for example, via calcineurin. Several cell signaling pathways, including ERK1/2-C/EBPα, are involved in the regulatory mechanisms of melatonin in T-cell biology [36]. Melatonin by modulating T-cell responses exerts beneficial effects in various inflammatory diseases, such as type-1 diabetes, bronchial asthma, and arthritis. The nocturnal rise in blood melatonin levels in human is associated with increased production of interleukin (IL)-1, (IL)-2, IL-6, IL-12; thymosin 1a, thymulin and tumor necrosis factor-alpha. However, exogenous melatonin has an adverse effect in patients with asthma. The nocturnal

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asthma is associated with elevation and phase delay of serum melatonin peak. Nuclear factor-kappa B (NF-κB) is a critical transcription factor governing the expression of many cytokines that are involved in the pathogenesis of asthma. Melatonin treatment also inhibits the expression of NF-κB, down-regulates the activity of inducible nitric oxide synthase (iNOS) in lung tissue and decreases the production of nitric oxide (NO) in bronchoalveolar lavage fluid (BALF). These data suggest that the inhibitory effect of melatonin probably play a role in decreasing airway hyper responsiveness and airway inflammation in asthma [37]. In adjuvant-induced arthritis, both prophylactic and therapeutic melatonin administrations inhibited inflammatory response. Melatonin acts on immuno competent cells (monocytes, B-lymphocytes, natural killer lymphocytes, T-helper lymphocytes, cytotoxic T lymphocytes) through MT1 and RZR/ROR α orphan nuclear receptor family and enhances cytokine production/secretions, cell proliferation or oncostasis. In B-lymphocytes, melatonin binds to the RZR/ROR α receptors to down-regulate the gene expression of 5-lipoxygenase which is an important enzyme in allergic and inflammatory diseases like asthma and arthritis [38]. Thus melatonin and immune system is linked by complex bidirectional communication. However, the effects of melatonin on the immune response may not always be beneficial. The effects of melatonin in different autoimmune diseases are not clear, even some studies have implicated melatonin in the development of different autoimmune diseases [36]. The precise mechanisms involved in autoimmune diseases are as yet largely unknown and need further study.

Treatment of cancer: The incidence of cancer is increasing worldwide and causing a heavy health burden on society. An effective drug therapy for the treatment of cancer is an important focus of research. Among the compounds tested, melatonin is of great interest because of its efficacy and lack of toxicity. Melatonin is known for its anti-proliferative, oncostatic, and tumor inhibitory effects. Employing melatonin receptors MT1 and MT2 on various types of cancers (breast, lung, metastatic renal cell carcinoma, hepatocellular carcinoma, brain metastases from solid tumors, prostate, ovarian carcinoma, human neuroblastoma cells, bladder carcinoma and erythroleukemia) with tumor growth, and the incidence of metastases, melatonin exerts physiological to pharmacological effects [39,40]. The oncostatic mechanisms of melatonin are related to several hallmarks of cancer, including anti-proliferation, induction of apoptosis, inhibition of invasion and metastasis, anti-angiogenesis, and enhancement of immunomodulation among others. Melatonin by acting on the neuroendocrine reproductive axis may down regulate the expression of estrogen receptor α (ERα), and finally inhibit the binding of estradiol-ER complex to the estrogen response element. Melatonin also shifts forskolin- and estrogen-induced elevation of cyclic adenosine monophosphate (cAMP) levels by 57% and 45% respectively, thereby affecting signal-transduction mechanisms in human breast cancer cells. The relationship between exposure to light during shift and/or nightwork and the occurrence of breast cancer in workers appears to be very significant. It is clearly suggested that the risk of breast cancer is directly proportional with the number of years spent working night shifts for nurses and flight attendants, though in blind women the rate of occurrence is low [41]. Moreover, melatonin treatment showed MT1 / MT2-dependent inhibition of uptake of fatty acids in general, and of linoleic acid in particular, to prevent the formation of its mitogenic metabolite, 13-hydroxyoctadecadienonic acid [42]. At the same time, melatonin inhibits the fatty acid growth-factor uptake by cancer cells, inhibits telomerase activity by reducing telomere length, which causes apoptosis in cancer cells, inhibit endothelin-1 synthesis, an angiogenic factor, which promotes blood vessel growth in tumors, and finally modulates the expression of tumor suppressor gene, TP53 or inhibit transcriptional expression of cyclin D1. Melatonin also reduces the malignancy of pulmonary tissue through the inhibition of cancer cells metastasis and progression. Such influence may be associated with the downregulation of the expression of osteopontin (OPN), myosin light chain kinase (MLCK), phosphorylation of myosin light chain (MLC), and up-regulation of the expression of occludin via the inhibition of c-jun-N-terminal kinases (JNK) signaling pathway [43]. The action at different levels of signaling pathways in a tumor cell collectively suggests melatonin a supportive anticancer drug in the prevention and treatment of cancer. Recently, several studies reported that melatonin treatment attenuates gastrointestinal, cigarette smoke induced lung cancer mainly by inhibiting tissue injury, inflammation, neutrophils counts, expression of proinflammatory cytokines (TNF-α, IL-1β, IL-8, IL-6), and oxidative stress [40,43,44]. Due to low toxicity, this indoleamine is used to enhance the efficacy of drug against cancer cells and reduce the adverse therapeutic side effects. Furthermore, melatonin supplementation helps to protect myeloid progenitor cells from chemotherapy-induced apoptosis [45] and tissue against electromagnetic radiation-induced damages [46]. Collectively, these findings attest to melatonin being a potential anticancer drug and provide an inducement for further work in this area. However, despite accumulation of several convincing data from a large number of laboratory and clinical studies and significant progress in developing the idea of an anti-carcinogenic effect of melatonin, its exact mechanisms of action on cancer remain to be understood properly.

Conclusion

Current literature review reveals that melatonin is a chronobiotic molecule with multi-faceted effects. Melatonin signaling may have resulted from the nonspecific activation of receptors, which evolved to detect other compounds. Later daily rhythm in melatonin may have synchronized all physiological functions. Its efficacy and safety may eventually drive its use in universally effective clinical applications and an adjuvant therapy for future treatment of different diseases as a supportive molecule to act together with other medicine. In some countries (USA, China, Argentina, Poland) melatonin is sold as a dietary

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supplement, not as a drug, in health food and grocery stores/drug stores, though all potential risks and/or advantages of melatonin may not be known. Notably, the melatonin effects have not always been demonstrated clinically using relevant concentrations or under pathological situations. Thus further detailed clinical investigation of the crosstalk and trans-activation of different pathways will help in understanding the mechanisms of action of melatonin as a drug, allowing the design of powerful therapeutic agents for patho-physiological healing. Obviously, continuing researches are steadily uncovering the mystery of this indoleamine, but much more remains to be known before we can conclude a full comprehension of melatonin and its significance in maintaining and increasing the quality of human.

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