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MELATONIN IN HUMANS

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Melatonin, the hormone of the pineal gland, received a great deal of attention in the last decade because of its availability as over-the-counter drug or food supplement in some countries and suggested role in many vital physiological processes.
Melatonin secretion is not restricted to mammals but is also produced in nonmammalian vertebrates, in some invertebrates, and in many plants, with the same molecular structure. The synthesis of melatonin is strictly controlled by lighting conditions and shows a clear circadian rhythm with low values during the daytime and significant increase at night.
In this survey the basic data on melatonin significance in human physiology and in pathological processes as well as its possible thrapeutic significance are reviewed and discussed.

Key words: *melatonin synthesis; therapeutic implication; circadian rhythm*

INTRODUCTION

Although the pineal gland has been known for more that 2000 years, no further back than 50 years ago there was a common believe that pineal gland is a functionless, rudimentary organ. The situation changed after the discovery of Aaron Lerner and colleagues who in 1958 isolated pineal active substance, named this compound melatonin, and described its chemical structure as *N*-acetyl-5-methoxytryptamine (1, 2). Since then many researchers, including clinicians, become interested in this small, mysterious gland. Interdisciplinary studies conducted in the last four decades, especially after establishment of specific radioimmunoassay for melatonin in late 70's, resulted remarkable

development in research on the role of this hormone in humans, although many functions of pineal gland and melatonin still remains to be elucidated.

BIOSYNTHESIS AND CATABOLISM OF MELATONIN

Melatonin is unique universal substance with the molecular structure unchanged throughout the animal and plant kingdom. It is produced in mammals, including human, mostly in the pineal gland, although several other organs (e.g., retina, extraorbital lacrimal gland, gastrointestinal tract, Harderian gland, bone marrow cells, blood platelets, and possibly other organs as well) may produce the hormone as well (3 - 5). Moreover, secretion of melatonin is not restricted to mammalian species but it is also produced in nonmammalian vertebrates, in some invertebrates, and in many plants (4, 6).

The synthesis of melatonin is presented in *Fig. 1.* The first step in melatonin formation is uptake of the amino acid L-tryptophan from the circulation into the gland. Within the pinealocyte tryptrophan-5-hydroxylase (L-tryptophan, tetrahydropteridine: oxygen oxidoreductase, EC 1.14.16.4) catalyzes L-tryptophan to 5-hydroxytryptophan which is then decarboxylated by L-aromatic amino acid decarboxylase (aromatic L-aminoacid carboxylase, EC 4.1.1.28) to serotonin. The next step, i.e., N-acetylation of serotonin to N-acetylserotonin is completed by arylalkulamine *N*-acetyltransferase (acetyl CoA:aryl-amine N-acetyltransferase, EC 2.3.1.5), the key enzyme in melatonin synthesis. The final step in the pathway is the O-methylation of N-acetylserotonin to melatonin by hydroxyindole-O-methyltransferase (S-adenosyl-L-methionine:N-acetyl-serotonin-O-methyltranferase, EC 2.1.1.4) (4, 7, 8). Once synthesized, melatonin is not stored in pineal cells but is quickly released into the bloodstream (9). Beside the blood melatonin is also present in other body fluids, including saliva, cerebrospinal fluid, bile, semen, amniotic fluid. Mean endogenous melatonin production rates have been calculated to be about 30 μg per day (10). The half-life of melatonin in serum has been calculated by various authors between less than 30 and 60 minutes (4, 6, 11).

Melatonin is metabolized primarily in the liver, and secondarily in the kidney. It undergoes 6-hydroxylation to 6-hydroxymelatonin, followed by sulfate or glucuronide conjugation to 6-hydroxymelatonin sulfate (90%) or 6-hydroxymelatonin glucuronide (10%) (*Fig. 1*). About 5% of serum melatonin content is excreted unmetabolized in urine. Melatonin forms also some minor metabolites, such as cyclic 2-hydroxymelatonin, N-gamma-acetyl-N-2-formyl-5-methoxykynurenamine and N-gamma-acetyl-5-methoxykynurenamine (4, 7).

MELATONIN CIRCADIAN RHYTHM AND ITS REGULATION

The synthesis of melatonin is strictly controlled by lighting conditions. Photosensory information arrives at the pineal via polyneuronal pathway that begins in the retina and involves retinohypothalamic tract, suprachiasmatic nuclei,

paraventricular nuclei, medial forebrain bundle, reticular formation, intermediolateral cell column of the spinal cord, superior cervical ganglia, internal carotid nerve, and nervii conarii (7, 11). Postganglionic sympathetic nerve fibers that ends at the pineal gland releases noradrenalin, which plays crucial role in the control of melatonin synthesis. Noradrenalin binds to pinealocyte β-adrenergic receptors (and partially α-adrenergic receptors), activating adenylate cyclase through GTP-binding protein in the cell membrane, and increase cAMP levels leading to stimulation of the activity of N-acetyltransferase, and subsequently to synthesis of melatonin. Stimulation of α-adrenergic receptors potentates the

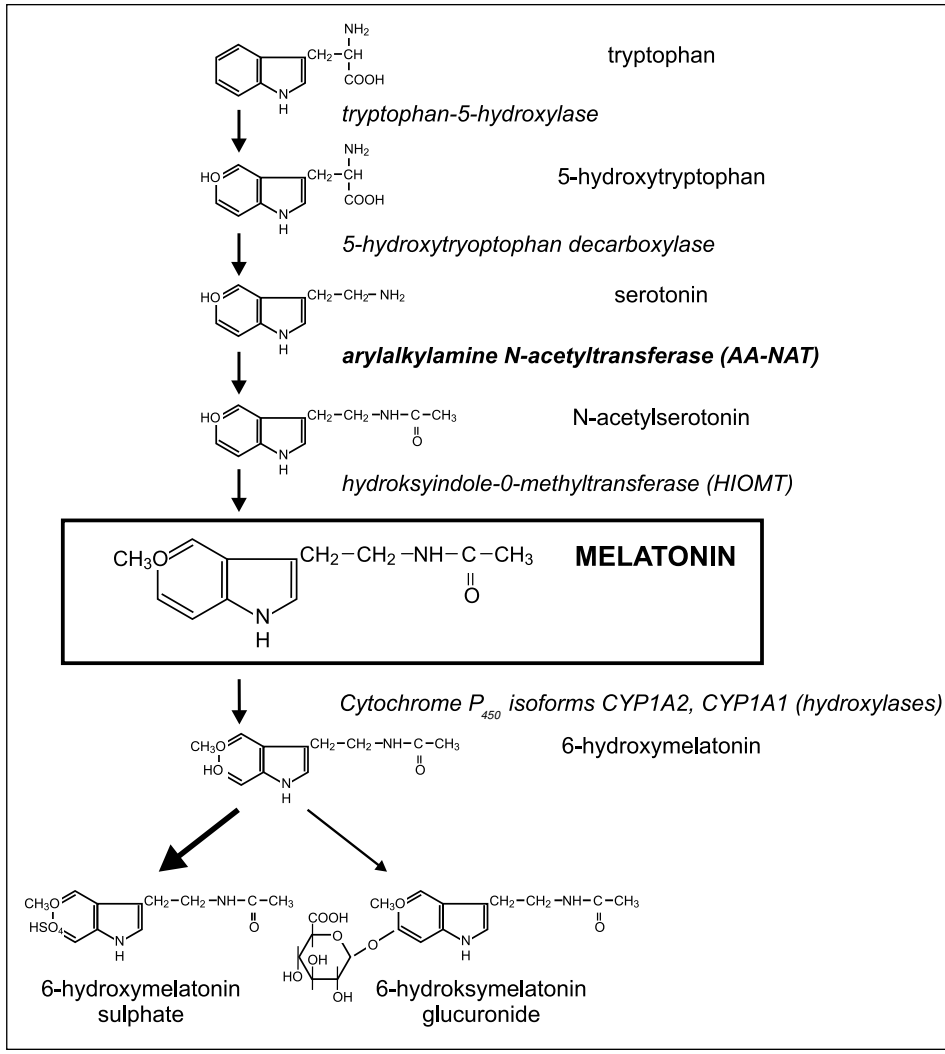

Fig. 1. Synthetic pathway and metabolism of melatonin.

β-stimulation, and in this mechanism participate calcium ions, phosphatidylinositol, diacylglicerol, and protein kinase C (12).

Melatonin has a well-defined circadian rhythm with peak in its production in the pineal gland occurring during the daily dark period (80% of melatonin is synthesized at night) (*Fig. 2*). Melatonin is present in all living organisms from plants, through animal kingdom to humans, and from unicellular algae to man shows this characteristic circadian rhythm.

Rhythm of melatonin synthesis/secretion is generated by the circadian pacemaker (oscillator, biological clock) situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, and synchronized to 24 hours primarily by the light-dark cycle acting via the SCN. During the day serum concentrations of the hormone are low (10-20 pg/ml), significantly increase at night (80-120 pg/ml) with peak between 24:00 and 03:00 h. The onset of secretion is usually around 21:00-22:00 h and the offset at 07:00-09:00 h. Very close relationship to melatonin rhythm shows its major urinary metabolite – 6-sulfatoxymelatonin (7).

The rhythm in melatonin concentrations appears in humans soon after birth, in 6-8 week of life, and seems to be well established in 21-24 week of life (13). Amplitude of the nocturnal peak in melatonin secretion reaches the highest levels between 4th and 7th year of age. There is a drop in melatonin concentrations around maturation, values remain relatively stable until 35-40 years, and thereafter diminish gradually reaching around 70's levels similar to daytime concentrations (7, 11, 14). As a consequence, in advanced age many individuals do not exhibit a day-night differences in melatonin secretion (*Fig. 3*).

Melatonin synthesis is rapidly suppressed in the dark phase by acute exposure to light of sufficient intensity, although there are substantial individual variations

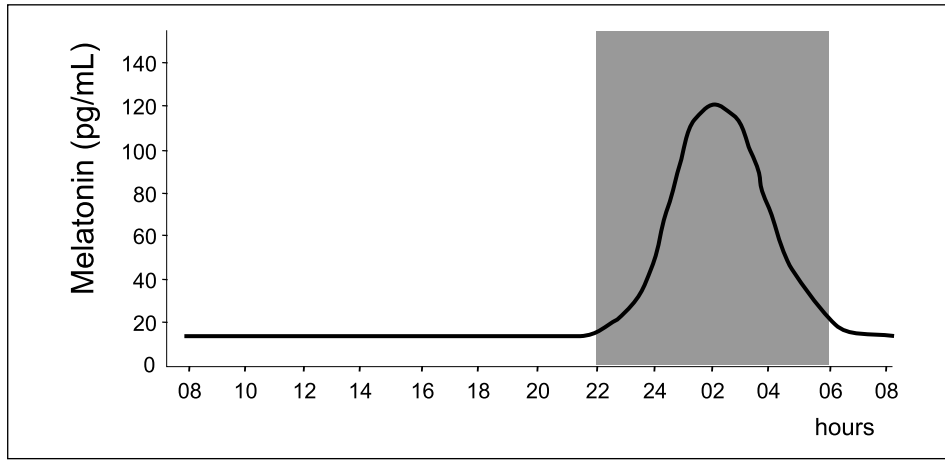

Fig. 2. Circadian profiles of serum melatonin concentrations in humans; gray area = period of darkness.

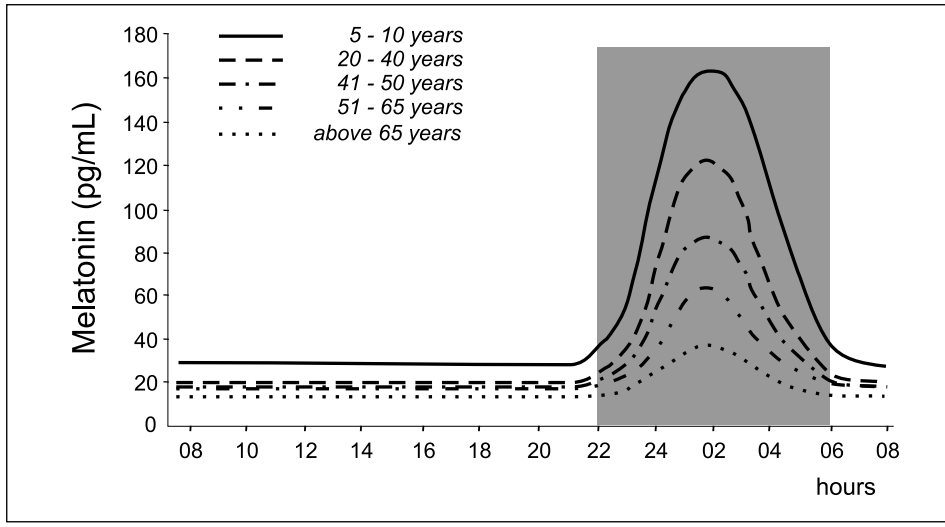

Fig. 3. Circadian profiles of serum melatonin concentrations in humans at various age; gray area = period of darkness.

in human sensitivity to light among individuals that may be both genetically and environmentally determined (7).

The amplitude of nocturnal melatonin secretion is believed to be genetically determined and shows great differences among individuals (15). Thus, some individuals produce significantly less melatonin during lifetime than others. However, the circadian profile of melatonin has been found highly reproducible over a six-week period in the same subject (16).

MELATONIN RECEPTORS

Melatonin acts directly on target tissues through specific binding sites which are situated in the plasma membrane and nucleus of cells. According to the newest classification of nomenclature committee of IUPHAR, the best characterized and the most specific binding sites of melatonin are MT_1 and MT_2 membrane receptors belonging to the G-protein coupled receptor family (17). These receptors show similar high affinity to 2-(^{125}I)-iodomelatonin radioligand but have different molecular structure and chromosomal gene localization. In humans MT_1 receptor is mapped to chromosome 4q35.1 and consists of 350 amino acids (18). The gene for MT_2 receptor is located into chromosome 11q21-22 and cDNA encodes a protein containing 363 amino acids (60% homology to MT_1) (19). Melatonin binding with MT_1 modulates intracellular signal *via* inhibiting adenylate cyclase and stimulating inositol phosphate (20). Activation of MT_2 receptor inhibits formation of two second messengers cAMP and cGMP in cells (21). Third membrane receptor named MT_3 is less known. Recently it has

been shown that its structure is in 95% similar with human quinone reductase 2 and MT_3 receptor participates in the regulation of intraocular pressure (22, 23). In mammals, the high-affinity melatonin receptors are found in the brain, mainly in hypothalamus and also in the pars tuberalis of hypophyseal. The pineal hormone acting through MT_1 and MT_2 receptors regulates the circadian rhythms and seasonal breeding of animals (17). Biological role of human membrane receptors have not been fully recognized. In human brain MT_1 receptors are expressed in the suprachiasmatic nucleus, cerebellum, thalamus, hippocampus and cerebral cortex (24). MT_2 mRNA has been presented in the human cerebellum and hippocampus (19, 25). Among other functions of melatonin, the neuroprotective action of hormone is postulated. It was shown that melatonin levels in Alzheimer's disease (AD) patients are reduced and the *in vitro* study showed that melatonin prevents the human brain cells from amyloid β-induced degeneration (26, 27). Neuroprotective effect of melatonin depends mainly on antioxidant activity. However, the receptor-mediated influence is possible, because MT_1 and MT_2 receptors were found in human hippocampus neurons. Moreover, it was observed that MT_1 expression is higher and MT_2 expression is lower in AD hippocampus (28, 29). MT_1 gene expression and 2-(^{125}I)-iodomelatonin binding were also found in following regions of human fetal brain: hypothalamus, thalamus, leptomeninges, cerebellum and brainstem (30). Melatonin of a pregnant woman easily crossing placenta can influence circadian rhythms of a fetus. Maternal melatonin and locally produced pineal hormone influences also via both membrane MT_1 and MT_2 receptors the function of the human placenta, and among others increases the hCG secretion from the trophoblast cells (31).

Melatonin receptors have been also discovered in several peripheral human tissues, including heart and arteries, kidney, liver, gallbladder, intestines, adipocytes granulosa cells of the ovarian follicle, uterus, breast cells, prostate and skin (32).

As a small lipophilic molecule, melatonin easily crosses cellular membranes and may also perform its biological function through cytoplasmatic and/or nuclear signaling. In 1994 the evidence of genomic action of melatonin via nuclear RZR/ROR receptors has been presented by Becker-Andre *et al*. (33). The RZR/ROR receptors belong to novel subclass of orphan nuclear receptors. They have been cloned simultaneously by two different groups and received the following names: retinoid Z receptor (RZR) and retinoid acid receptor-related orphan receptor (ROR) (34, 35). The RZR/ROR family consists of three subtypes: α, β, and γ. The RZR/ROR receptors are widely expressed in normal tissues (36) and also in some tumor cells such as: colon, prostate and breast cancers (37 - 40).

The antitumor effect of melatonin is connected among others with antiproliferative and proapoptotic activities. The molecular mechanism of these actions still remains unclear, but several investigations have shown that oncostatic effects of melatonin may depend on membrane melatonin receptors and nuclear RZR/ROR receptors.

As a natural antioxidant, the pineal hormone should rather exhibit antiapoptotic properties. Indeed, several experiments involving mainly immune and neuronal cells have revealed the antiapoptotic action of melatonin (41 - 43). Recently, it has been found that melatonin may increase the apoptotis in tumor cells (44). The mechanism by which melatonin can induce apoptosis is unclear. The study conducted in our laboratory has shown that melatonin enhanced apoptosis in murine colonic cancer cells and nuclear RZR/ROR receptors agonist (CGP 52608) exerted a similar proapoptotic effects (45, 46). Moreover, we have found that thiazolidinedione CGP 55644 (an antagonist of nuclear RZR/RORα receptor) given together with melatonin diminishes its antiproliferative properties and blocks the proapoptotic effect of melatonin on colonic cancer cells (47) and completely blocks the inhibitory effects of melatonin on the growth of rat prolactin-secreting tumor (48).

In last years, the relationship between the estrogens and the antitumor action of melatonin has been the object of extensive investigations and the most of these studies have related to the breast cancer. It was shown that hormone's growth-inhibitory effect reveals only in cancer cells having the estrogen receptors (49, 50). Melatonin interferes with estrogen receptor alpha (51). The antiestrogenic action of melatonin has been proposed to explain its oncostatic properties (52).

The investigations over the last years have shown that melatonin can modulate the immune system *via* both membrane and the nuclear receptors. The reduction of melatonin concentration in plasma causes a depression in humoral and cellular immune responses as well as inhibits the cytokines production (53). MT_1 receptors and RZR/RORα receptors were identified in several human immunocompetent cells such as: monocytes, B lymphocytes, natural killer lymphocytes, T helper lymphocytes and cytotoxic T lymphocytes (54). In B lymphocytes melatonin binding to the RZR/RORα receptors down-regulates the expression of gene for 5-lipoxygenase, a important enzyme in allergic and inflammatory diseases like asthma and arthritis (55). The nuclear receptors involve also in cytokines secretion by human peripheral monocytes and cells of leukemia and lymphoma lines (56, 57).

Summing up, the results of many experimental studies strongly support the participation of MT_1 and MT_2 membrane receptors and nuclear RZR/ROR receptors in the action of melatonin. Moreover some evidence indicate that nuclear signaling plays an essential role in immunomodulatory and antitumor effects of pineal hormone.

MELATONIN IN HUMAN PHYSIOLOGY AND PATHOLOGY

Melatonin as an antioxidant

It has been discovered, recently, that melatonin is involved in antioxidative defense system of the organism, designed to protect molecules from damage by toxic oxygen radicals (58-60). Melatonin is a potent free radical scavenger and

antioxidant that scavenges especially highly toxic hydroxyl radicals, and additionally stimulates a number of antioxidative enzymes. Because it is both lipophilic and hydrophilic, easily passes all morphophysiological barriers; enters all cells and may carry out its antioxidant function with equal efficiency in multiple cellular compartments, i.e. in the nucleus, cytosol and membranes (59). Moreover, it is the only antioxidant known to decrease substantially after middle age, and this decrease closely correlates with a decrease in total antioxidant capacity of human serum with age (61).

Question is still open, whether melatonin is efficient free radical scavenger also in physiological concentration or whether the observations made to date are of pharmacological importance only. However, it should be stressed that compared to two well-known scavengers, glutatione and mannitol, melatonin is 4x and 14x more effective, respectively (62). Free radical scavenging ability of melatonin has implications for variety of diseases, including age-associated neurodegenerative diseases and cancer initiation.

Melatonin and sleep and its disorders

There are many data (including those indicating the close relationship between the nocturnal increase of endogenous melatonin and the timing of sleep) suggesting involvement of melatonin in the physiological regulation of sleep (4, 63). Sleep promoting effects of melatonin have been well known since first experiments in early 70s, and is probably a consequence of increasing sleep propensity and of synchronizing effect on the circadian clock (64). The number of reports on melatonin concentrations in sleep disorders is surprisingly low considering its use in the therapy of insomnia. However, it has been demonstrated that the timing of the sleep gate was correlated with the onset of nocturnal melatonin secretion (65). Moreover, in fatal familiar insomnia (disease characterized by loss of sleep due to selective thalamic degeneration) serum melatonin concentrations gradually decrease as the disease progresses with complete rhythm obliteration in the most advanced stage (66).

Nocturnal melatonin concentrations were significantly lower in patients suffering from chronic primary insomnia (67, 68). In major sleep disorders such as narcolepsy, delayed sleep phase syndrome, and Klein Levine syndrome only a small delay in the melatonin rhythm was observed (7). Close association between the evening rise of melatonin levels and the evening increase in sleep propensity suggests a causal relationship (69, 70). Maximum melatonin secretion is also associated with nadir in alertness and performance as well as with maximum sleepiness/fatigue at night (69).

Lavie *et al.* (71) suggest that from the accumulated data it is evident that melatonin characteristics are not those of a typical hypnotic or sedative. Melatonin affects sleep in much more subtle way. The authors propose that the role of melatonin in the induction of sleep does not involve the active induction

of sleep, but rather is mediated by an inhibition of a wakefulness-producing mechanism.

It has been demonstrated in several reports that administration of melatonin has beneficial effects in subjects (especially in advanced age) suffering from insomnia. In most recent reports melatonin was shown to significantly improve subjective and/or objective sleep parameters in some individuals. Its administration reduces sleep latency and/or increases sleep efficacy and total sleep time (64, 72, 73). Such effects are probably the consequence of increasing sleep propensity and of a synchronizing effect on the circadian clock (chronobiotic effect). However, we should keep in mind that melatonin is not a universally effective drug for treatment of insomnia, and it may not be helpful in all patients suffering from insomnia.

It should be noted, however, that although majority of data show that melatonin improve sleep parameters in elderly, in some studies sleep was unaffected by melatonin (see 64, 72 - 76). Moreover, two recent meta-analyses brought about different conclusions. Brzezinski *et al*. (77) concluded that melatonin is effective in increasing sleep efficiency and reducing sleep onset time whereas Buscemi *et al*. (78) failed to document clinically meaningful effects of egzogenous melatonin on sleep quality, efficiency or latency.

Melatonin and circadian rhytms and their disorders

Circadian rhythms play an important role in all living organisms. There are some indications of the relationship between melatonin and some body circadian rhythms. It is well known that in all mammalian species rhythmically produced melatonin (“darkness hormone”) functions as a photoperiodic signal and a circadian mediator, being one of critical components of internal biological clock(s) (79, 80). It is believed that melatonin could act as an endogenous synchronizer able to stabilize or to reinforce rhythms (81).

Wehr *et al.* (82) on the basis of the comparison between melatonin and other circadian rhythms proposed that temporal organization of the human circadian timing system exhibits distinct diurnal and nocturnal states with abrupt switch-like transitions between them. These states and transitions can be conceptualized as “biological day” and “biological night” and “biological dawn” and “biological dusk”. During “biological day” lack of melatonin secretion is accompanied by increasing core body temperature, decreasing sleepiness, decreasing wake EEG theta activity, decreasing REM sleep propensity, decreasing sleep propensity, and decreasing cortisol levels leading to wakefulness. On the contrary, during “biological night” melatonin secretion is accompanied by decreasing core body temperature, increasing sleepiness, increasing wake EEG theta activity, increasing REM sleep propensity, increasing sleep propensity, and increasing cortisol levels, leading to sleep.

There are many data suggesting a role of melatonin in circadian rhythm disorders. The jet-lag effect is perhaps the best clinical indication for melatonin use so far demonstrated (7, 64, 79). Air travelers well know that crossing several time zones during transcontinental flights causes many symptoms, including fatigue, sleepiness, irritability, apathy, digestive upsets, memory lapses, lack of concentration, impaired judgments and decision making, and headache (collectively known as jet-lag) causing distress to an increasing number of travelers. Majority of studies (both controlled and uncontrolled) indicate that melatonin administration is useful for ameliorating jet-lag symptoms (see 7, 64, 79). Moreover, the improvement is greater with the number of time zones, and in an eastwards direction compared to westwards (7).

In many blind people, especially in those with no conscious light perception and free running (non 24-h) rhythms, such circadian rhythm disorders as disrupted rhythms of sleep-wake cycle, core body temperature, cortisol, and melatonin are very common (83). Many blind subjects, have unusual melatonin or 6-sulfatoxymelatonin circadian profiles with the periodicity of the endogenous rhythm varying from 23h50min to 25h00min (84, 85). Melatonin has proven efficacy in phase-shifting of the circadian clock for phase resetting in blind people. It may stabilize sleep onset and sometimes improve quality and duration of sleep (7, 83, 86).

Circadian rhythms are also disturbed in shift workers (especially permanent night shift workers) who often complain of fatigue, sleep disturbances, and gastrointestinal problems (79). Great variability in circadian melatonin profiles, with the onset of the melatonin secretion varying between 21:45 h and 05:05 h, has been demonstrated in night workers (87). Melatonin, when administered at the desired bedtime during a night shift, may improve sleep and increase daytime alertness in shift workers, (7, 79), and therefore, may prove to be a useful strategy for helping real night workers adapt to working night shifts (88).

It seems that melatonin is the effective chronobiotic, i.e. a chemical substance capable of therapeutically re-entraining short-term dissociated or long-term desynchronized circadian rhythms, or prophylactically preventing disruption following environmental insult (89).

Melatonin and immune system

Many data, both from animal and human studies, point to immunomodulatory potential of melatonin (90-93). It has been demonstrated that such parameters of immune reactivity as number of immune cells and their subpopulations, lymphocyte proliferation, blood level of different cytokines, phagocytic index, etc., exhibit well pronounced circadian rhythmicity (94), and these diurnal changes in the immune system function seem to be controlled by or correlated with the pineal melatonin synthesis and secretion (95).

It seems that melatonin may exert a direct influence on the immune system because melatonin receptors (both membrane and putative nuclear) have been discovered in immune organs and cells of humans and various mammalian species (91). Moreover, it was recently reported that cultured human lymphocytes synthesize and release large amount of melatonin which could act, in addition to its endocrine effect, as an intracrine, autocrine, and/or paracrine substance for the local coordination of the immune response (96). Our recent data suggest that endogenous melatonin is an essential part for an accurate response of human lymphocytes through the modulation on interleukin-2/interleukin-2 receptor system (97).

However, the relationship between melatonin and immune system seems to be complex and needs further elucidation.

Melatonin and pituitary hormones

The data on the relationship between melatonin and pituitary hormones are inconsistent. There are some data suggesting the relationship between melatonin and prolactin. The diurnal concentrations of melatonin positively correlate with those of prolactin (98, 99), nocturnal increase, and morning decrease in prolactin levels are proceeded by similar changes in melatonin levels (100), and melatonin administration stimulates prolactin secretion (99, 101). Increased nocturnal serum melatonin concentrations or urinary 6-sulfatoxymelatonin excretion were found in majority of studies in hyperprolactinemic patients compared to their age-matched healthy individuals (102-104). Moreover, administration of 5 mg of melatonin in healthy women resulted in a rapid and prominent prolactin release, similar to that observed at nighttime in patients with hyperprolactinemia (102). However, it does not seem probable that melatonin plays important role in the control of prolactin secretion.

Relationship between melatonin and growth hormone (GH) is poorly understood. Decrease in melatonin concentrations has been observed following stimulation of GH (due to insulin-induced hypoglycemia, arginine infusion, clonidine administration, or growth hormone releasing hormone stimulation) in children (105). Moreover, our recent results showed that melatonin levels were significantly higher in children with GH deficiency in comparison with children with idiopathic short stature, and there was negative correlation between GH peak after stimulation test and nocturnal melatonin concentrations (106). Administration of melatonin caused either enhancement of spontaneous and exercise-induced GH secretion (107, 108), or did not exert any effect (101). However, role of melatonin in mechanisms of regulation of growth hormone secretion seems to be secondary and not important.

There are experimental data suggesting relationship between the pineal gland and hypothalamo-hypophysial-thyroid axis in animals, however, no sufficient data are available on the existence of such relationship in humans (109). Also, no relationship between melatonin and hypothalamic-pituitary-adrenal axis seems to exist (5, 8).

Melatonin and reproductive system

The relationship between the pineal and reproductive system is well established in animals indicating that melatonin regulates the reproduction in sesonally breading animals by its action at various levels of the hypothalamic-pituitary-gonadal axis (110). However, in humans it is more difficult to demonstrate, despite the fact that first association between pineal gland and reproductive system has been suggested in humans already in 19th century. Some studies suggest that melatonin may play a role in physiological development of normal puberty (105, 111). Precocious puberty or delayed puberty is often associated with abnormal melatonin levels (112, 113). Although there are no sufficient data indicating significant role of melatonin in puberty, it seems probable that differences in melatonin concentrations may be responsible for some subtle changes in secretion of gonadotropins or influence the mechanism of pulsatile GnRH secretion, and therefore affects sexual maturation.

Moreover, melatonin may mediate the moderate seasonal fluctuations observed in human reproductive function (4). Elevated concentrations of melatonin were reported in male infertility (114), and in men with hypogonadotropic hypogonadism (115, 116). On the contrary, in men with hypergonadotropic hypogonadism melatonin secretion is decreased, and is normalized following testosterone treatment (117). High nocturnal melatonin concentration was demonstrated also in women with hypothalamic amenorrhea (118, 119). Increase in urinary 6-sulfatoxymelatonin excretion was found also in hyperandrogenic women with polycystic ovary syndrome (120).

Melatonin in various pathologies

Alterations in melatonin concentrations and/or its circadian rhythm were found in various psychiatric disorders, such as major depression, bipolar affective disorder, panic disorder, obsessive compulsive disorder, schizophrenia, eating disorders, cluster headache, most conspicuously in the cluster period diabetic autonomic neuropathy, and in Smith-Magenis syndrome (see 5, 121-123). Lower nocturnal melatonin levels were observed in alcoholic patients as compared with control individuals. Moreover, depressed melatonin concentrations were observed even after long abstinence, suggesting that chronic use of alcohol might permanently alter the pineal ability to produce melatonin (124).

Altered circadian melatonin rhythm was also observed in several other pathologies like: liver cirrhosis, chronic renal failure both with compensated disease and in end-stage renal disease, psoriasis, duodenal ulcer, night-eating syndrome, cardiovascular diseases, and others (see 5).

Melatonin and neurodegenerative diseases

A role for melatonin in neurodegenerative diseases (such as Alzheimer's and Parkinson's diseases) has been recently suggested.

The experimental findings indicate that melatonin may act in a variety of ways to reduce neuronal loss in Alzheimer's disease by altering the process of generation and action of amyloid-β leading to increased cellular survival. Melatonin concentrations decrease in some, but not all, patients suffering from Alzheimer's disease. Decreased nocturnal melatonin levels were found both in preclinical and definite Alzheimer's patients. Many reports demonstrated that melatonin treatment seems to constitute a selection therapy to improve sleep, to ameliorate sundowning, and to slow evolution of cognitive impairment in Alzheimer's patients (see 125, 126).

There are also experimental data that suggest a role of melatonin in another neurodegenerative disorder, Parkinson's disease which is characterized by the progressive deterioration of dopamine-containing neurons in the pars compacta of the substantia nigra in the brain stem due to the oxidation of dopamine (127). There is evidence that melatonin may reduce dopamine auto-oxidation under experimental conditions (128) although its administration did not slow progression of the Parkinson disease (see 125).

Melatonin and neoplastic disease

Although the relationship between the pineal gland, melatonin, and neoplastic disease has been demonstrated in various experimentally-induced animal tumors, and in the majority of studies melatonin has been shown to inhibit development and/or growth of various experimental animal tumors and some human cell lines in vitro its role in human malignancy is not clear (reviewed in 129, 130). Hovewer, depressed nocturnal melatonin concentrations or nocturnal excretion of the main melatonin metabolite – 6-sulfatoxymelatonin were found in various tumor types (breast cancer, prostate cancer, colorectal cancer, endometrial cancer, cervical cancer, lung cancer, and stomach cancer), whereas in other tumor types (Hodgkin's sarcoma, osteosarcoma, ovarian cancer, laryngeal cancer, and urinary bladder cancer) melatonin levels were not changed or showed great variations among individuals (5, 131).

Moreover, some clinical studies performed mainly by Lissoni's group suggest that administration of melatonin (in relatively high doses either alone or in combination with IL-2) is able to favorably influence the course of advanced malignant disease in humans and lead to an improvement in their quality of life (reviewed in 131-133). However, these observations require to be verified by independent and controlled studies.

Melatonin and aging

Rapid increase of the size of the elderly population (over the age 65), both in numbers and as a proportion of the whole raises many social and economic problems because these beneficiaries of health and pension funds are supported by a relatively smaller number of potential contributors in the economically active age, and results also increase in number of people suffering from age-

related diseases (such as atherosclerosis, neoplastic disease, neurodegenerative diseases). Therefore, there is a search for any therapeutic agent improving quality of life of elderly. A role for melatonin as such a compound was recently suggested.

Although many theories relating melatonin to aging have been put forward, the role of this compound in the aging process is not clear. Aging is beyond a doubt mulfifactorial process, and no single element seems to be of basic importance. Although there is not clear evidence indicating that melatonin may delay aging there are some reasons to postulate a role for this compound in the aging process: (i) melatonin participates in many vital life processes, and its secretion falls gradually over the life-span; (ii) diminished melatonin secretion in advanced age may be related to deterioration of many circadian rhythms, as a consequence of a reduced function of suprachiasmatic nucleus; (iii) Melatonin acts as endogenous sleep-inducing agent, and its reduced concentrations may result in lowered sleep efficacy very often associated with advancing age; (iv) melatonin exhibits immunoenhancing properties, and suppressed immunocompetence has been implicated in the acceleration of aging processes; (v) melatonin is a potent free radical scavenger, and free radicals cause damage to vital cellular constituents, accumulating with age which has significance not only for aging per se but also for many age-related diseases (4, 14, 134).

Aging is beyond a doubt mulfifactorial process, and no single element seems to be of basic importance. However, the age-related decline in melatonin secretion may have various consequences including sleep inefficiency, circadian rhythm dysregulation, depressed immune function, reduced antioxidant protection, and possibly others (14). Recent findings of Kunz *et al.* (135) show that exogenous melatonin, when administered at the appropriate time, seems to normalize circadian variation in human physiology, and therefore, melatonin may have impact on general health, especially in the elderly.

Possible therapeutic significance of melatonin

It has been proposed that melatonin may be of some therapeutic significance. Moreover, in some countries (e.g. Argentina, China, Poland, USA) melatonin has become recently available as either an OTC drug or food supplement. There are some widely accepted indications for therapeutic use of melatonin but also perspectives for its broader use (136).

Generally, melatonin has been proven to be useful in circadian rhythm disorders, such as sleep disturbances, jet lag, sleep-wake cycle disturbances in blind people, and shift work. Other possibilities for therapeutic usefulness of melatonin are not definitively proved.

It should be stressed that toxicity of melatonin is remarkably low, and no serious negative side effects of melatonin have been reported, so far (136).

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