JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2007, 58, Suppl 6, 105–113
www.jpp.krakow.pl

M. KARASEK

DOES MELATONIN PLAY A ROLE IN AGING PROCESSES ?

Department of Neuroendocrinology, Chair of Endocrinology, Medical University of Lodz and Department of Endocrinology and Metabolic Diseases; Polish Mother's Memorial Hospital - Research Institute, Lodz, Poland

Increasing number of people in advanced age is one of the most distinctive demographic events of the 21st century which raise many social and medical issues. Therefore, there is a search for any therapeutic agent improving the quality of life of the elderly. Melatonin, the hormone of the pineal gland, received recently a great deal of attention because of its suggested role in aging processes and availability as over-the-counter drug or food supplement in some countries, including Poland. In this survey the basic data on the possible role of melatonin in human aging as well as its possible therapeutic significance are reviewed and discussed.

Key words: *Aging, Immune system, Quality of life, Neurodegenerative diseases*

INTRODUCTION

Melatonin, the hormone of the pineal gland, was discovered in 1958 by Aaron Lerner and colleagues (1) who a year later described also its chemical structure as *N*-acetyl-5-methoxytryptamine (2). This discovery constituted a milestone for further pineal research. Since then the knowledge of the structure and function of the pineal gland has tremendously increased, especially during the last three decades. However, it should be stressed that many functions of the pineal gland and melatonin still remain to be confirmed.

One of the most pronounced consequences of human life is aging. The term 'aging' (or more correctly 'senescence') refers to post-maturational processes leading to diminished homeostasis and increased vulnerability of the organism (3). The worldwide prolongation of the mean life expectancy as well as the drastic

reduction of fertility rate result in a rapid increase of the size of the elderly population (over the age 65), both in numbers and as a proportion of the whole (4). In consequence, increasing number of people in advanced age raises many social and economic problems because these beneficiaries of health and pension funds are supported by a relatively smaller number of potential contributors (*i.e.* those in the economically active age of 18 - 65), and results also in an increase of the 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 the elderly. A role for melatonin as such a compound was recently suggested. Moreover, melatonin which is currently available in some countries (*e.g.* USA, Argentina, and Poland) as a food supplement or over-the-counter drug, is often advertised as a "rejuvenating" agent (5, 6).

In this survey, data on the possible role of melatonin in human aging are briefly discussed.

BIOSYNTHESIS OF MELATONIN, AND ITS CIRCADIAN RHYTHM

Although melatonin is synthesized in mammals, including human, mostly in the pineal gland, it can be produced also in several other organs (*e.g.*, retina, extraorbital lacrimal gland, Harderian gland, gastrointestinal tract, blood platelets, bone marrow cells) (7). Interestingly, secretion of melatonin is not restricted to mammalian species but it is also produced in nonmammalian vertebrates, in some invertebrates, and in many plants (7, 8). It should be stressed that extraordinariness of melatonin lies in the fact that it is a substance with the molecular structure unchanged throughout the animal and plant kingdom.

The biosynthesis of melatonin is initiated by the uptake of the amino acid L-tryptophan from the circulation into the gland. Within the pinealocyte it is catalyzed to 5-hydroxytryptophan which is then decarboxylated to serotonin. The next step, *i.e.*, N-acetylation of serotonin to N-acetylserotonin is completed by arylalkulamine *N*-acetyltransferase, the key enzyme in melatonin synthesis. The final step in the pathway is the O-methylation of N-acetylserotonin to melatonin (6, 9).

Once synthesized, melatonin is not stored in pineal cells but is quickly released into the bloodstream. Beside the blood melatonin is also present in other body fluids, including saliva, cerebrospinal fluid, bile, semen and amniotic fluid (10).

Melatonin is metabolized primarily in the liver by hydroxylation to 6-hydroxymelatonin, followed by sulfate or glucuronide conjugation to 6-hydroxymelatonin sulfate (90%) or 6-hydroxymelatonin glucuronide (10%). About 5% of serum melatonin content is excreted unmetabolized in urine. Melatonin forms also some minor metabolites, such as cyclic 2-

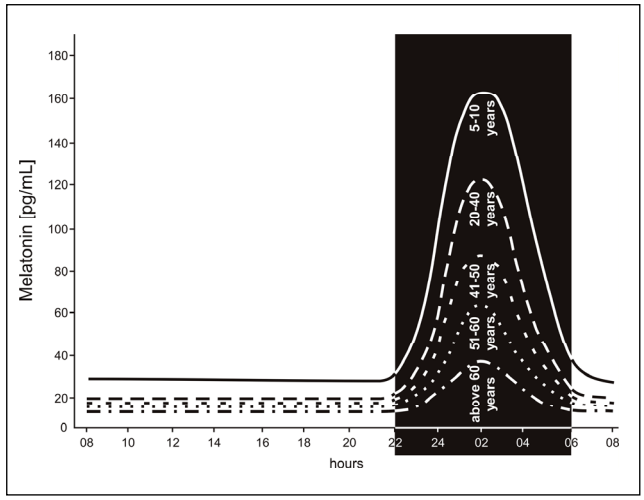

Fig. 1. Circadian profiles of serum melatonin concentrations in humans at various age; black area = period of darkness.

hydroxymelatonin, N-gamma-acetyl-N-2-formyl-5-methoxykynurenamine and N-gamma-acetyl-5-methoxykynurenamine (6, 9).

Melatonin has a well-defined circadian rhythm (*Fig. 1*) which 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 melatonin concentrations are low (10-20 pg/ml), significantly increase at night (80-120 pg/ml) reaching the 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. A very close relationship to the melatonin rhythm shows its major urinary metabolite - 6-sulfatoxymelatonin with peak in its production in the pineal gland occurring during the daily dark period. Melatonin shows this characteristic circadian rhythm in all living organisms from plants, through animal kingdom to humans (6, 9).

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 the 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 (6, 9). The crucial role in the control of melatonin synthesis plays noradrenalin, which is released from postganglionic sympathetic nerve fibers that ends in the pineal gland, and binds to pinealocyte β-adrenergic receptors (and partially α-adrenergic receptors), activating adenylate cyclase, and increases cAMP levels leading to stimulation of the activity of N-acetyltransferase, and subsequently to the synthesis of melatonin (11).

Undoubtedly, the aging process is multifactoral, and no single element seems to be of basic importance. Although many theories relating melatonin to aging have been put forward, the role of this compound in the aging processes is not clear. However, there are several reasons to postulate a role for melatonin in aging (5, 6):

- melatonin participates in many vital life processes and its secretion falls gradually over the life-span;
- melatonin is a potent free radical scavenger, and the proposed link between oxidative stress and aging itself as well as age-related diseases suggest a role for melatonin in these processes;
- reduced concentrations of melatonin in the elderly may be related to lowered sleep efficacy very often associated with advanced age;
- reduced concentrations of melatonin may be related to deterioration of many circadian rhythms very often associated with advanced age.
- melatonin exhibits immunomodulatory properties, and a remodeling of immune system function is an integral part of aging.

Changes in melatonin concentrations during the life-span

The nocturnal rise in melatonin concentrations appears in humans in 6^{th}-8^{th} week of life, and its circadian rhythm seems to be well established in 21^{st}-24^{th} week of life (12). Amplitude of the nocturnal peak in melatonin secretion reaches the highest levels between 4^{th} and 7^{th} 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 (5, 6, 9). As a consequence, in advanced age many individuals do not exhibit a day-night differences in melatonin secretion (*Fig. 1*).

The amplitude of nocturnal melatonin secretion is believed to be genetically determined and shows great differences among individuals (13). 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 (14).

Melatonin and free radicals

Free radicals are reactive molecules which have an unpaired electron and are continuously produced in cells as byproducts of oxidative phosphorylation and fatty acid oxidation. It should be stressed that the free radical theory of aging formulated initially by Harman (15, 16) seems to be recently one of the most compelling explanations for many degenerative changes associated with aging. According to the free radical theory of aging the deterioration of functions in the advanced age is in part related to the damage of subcellular constituents, cells, and organs sustained as a consequence of their persistent bombardment by free radicals. This damage is

a result of disturbance in the prooxidant-antioxidant balance in the organism. Moreover, free radicals are believed to be involved in pathogenesis of large variety of diseases, including age-related diseases (such as Alzheimer's disease, Parkinson's disease, neoplastic disease, atherosclerosis, cataract, *etc.*) (5, 17).

It has been discovered that melatonin is involved in antioxidative defense system of the organism, designed to protect molecules from damage by toxic oxygen radicals. Melatonin is a potent free radical scavenger and antioxidant. It scavenges both hydroxyl radicals and peroxyl radicals, although it is a more efficient direct scavenger of the highly toxic hydroxyl radicals. Additionally, melatonin stimulates a number of antioxidative enzymes, *e.g.* glutathione peroxidase and glutathione reductase (18-21). Melatonin is both lipophylic and hydrophilic and diffuses widely into cellular compartments, thus providing on-site protection against free radical mediated damage to biomolecules. It may carry out its antioxidant function with equal efficiency in multiple cellular compartments, *i.e.* in the nucleus, cytosol, and membranes (20). It should be stressed that melatonin 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 (22).

Melatonin and sleep in advanced age

It is well known that increased frequency of sleep disorders occurs in the advanced age (23). Sleep disturbances affect 40 to 70% of elderly population, including 10 - 25% of the elderly complaining of persistent insomnia. This may influence the subjective and objective general physical health of the elderly, and may be associated with mental health problems including poor life satisfaction or quality of life as well as poor cognitive, psychological, and social functioning (24).

On the contrary, as indicated above, melatonin concentrations significantly decrease in the elderly. According to Cajochen *et al*. (2003) the soporific and chronobiotic properties of melatonin make it an optimal candidate for treating sleep. There are numerous studies in which melatonin was administered in elderly patients suffering from sleep disorders. Although majority of data show that melatonin improved sleep parameters in the elderly, in some studies sleep was unaffected by melatonin (24-30). Melatonin was shown to significantly improve subjective and/or objective sleep parameters (reduces sleep latency and/or increases sleep efficacy and total sleep time) in some individuals (27-29).

Lavie *et al*. (31) 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.

Although melatonin can not be considered as universally effective drug for treatment of sleep disorders, it may be helpful in elderly patients suffering from

insomnia. It should be stressed that melatonin seems to be superior to some other hypnotics because it does not influence psychomotor performance (32).

Melatonin and circadian rhythms in the elderly

Deterioration of many circadian rhythms which play an important role in homeostasis (*e.g.* sleep/wake cycle, the core body temperature, performance, alertness, and secretion of many hormones) is characteristic of advanced age (24), and most probably related to changes in neurons of SCN (33). It is manifested by reduced amplitude of many rhythms, earlier timing of endogenous circadian rhythmicity, disorganization of temporal order, loss of entrainment stability and responsiveness to Zeitgebers (24).

A significant role in timing of the circadian system is attributed to melatonin. In 1989 Armstrong (34) proposed that melatonin is an internal Zeitgeber, and the function of the pineal gland is to adjust the phase and synchronize internal rhythms by the periodic nocturnal release of melatonin. Two years later Armstrong and Redman (35) suggested that melatonin might have beneficial effects in terms of aging just because of its association with circadian timing system. The loss of melatonin in advanced age leads to disturbances in the circadian pacemaker, which causes internal temporal desynchronization inducing a variety of chronopathologies and leads to generalized deterioration of health.

The importance of melatonin in regulation of circadian rhythms is also suggested by studies on its beneficial effects for amelioration of jet-lag symptoms as well as in phase shifting of the circadian clock for phase resetting in blind people (9, 29, 36, 37).

Melatonin and immune system in the elderly

Many alterations in the immune system are observed in the individuals in advanced age, generally viewed as a deterioration of immunity, and termed 'immunosenescence' (38) which have clear clinical consequences, leading to increased incidence of infections, cancers, autoimmune disorders, and chronic inflammatory diseases (39). The age-associated decline in the immune system refers to both humoral and cellular responses, although an overwhelming decrease in T cell functions with aging seems to play the main role (39, 40). Recent reports indicate "remodeling" of structure and function of the immune system rather than its deterioration in aging (40, 41). This remodeling involves several modifications at the level of hematopoiesis, in the compartments of lymphoid organs, and in the peripheral cell populations number and function. As a result, immune parameters measured in old individuals exhibit different values, in comparison with those observed in young counterparts.

Numerous experimental data show that melatonin exerts immunoenhancing action (42-44). Moreover, there are several indications that diurnal changes in the immune system function are controlled by or correlated with the pineal melatonin

synthesis and secretion (45). For example, a circadian rhythm of the thymic hormones thymosin a1 and thymulin was demonstrated to be strictly parallel with that of melatonin content in the pineal gland and in blood (46). It seems that melatonin may exert a direct effect on the immune system because melatonin receptors have been discovered in immune cells (42). 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 (47). 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 (48).

IS THERE A RATIONALE FOR MELATONIN SUPPLEMENTATION IN THE ELDERLY?

It has been proposed that melatonin may be of some therapeutic significance, and in some countries it is available as OTC drug or even food supplement. In Poland melatonin is registered since 2000 as OTC drug for sleep and circadian rhythm disorders. Beside widely accepted indications for therapeutic use of melatonin (*i.e.*, sleep disorders and such circadian clock disturbances as jet-lag and phase-shifting of the circadian clock in blind people), there are also perspectives for its broader use, although other possibilities for therapeutic usefulness of melatonin are not definitively proved (49).

Melatonin is often advertised as an antiaging agent ("fountain of youth"). However, presently available data do not allow us to conclude that melatonin may have a role in extending normal longevity. Although melatonin can not be recognized as a "rejuvenating" agent, some of its actions may be beneficial for the process of aging. Administration of melatonin may improve temporal organization in advanced age. Moreover, it has beneficial effects on sleep as well as on age-related diseases. Although recommendations of melatonin supplementation in elderly should be considered, there is a need for extensive studies on the use of melatonin in order to improve the quality of life in advanced age.

It should be stressed that melatonin treatment seems to be safe because of its remarkable low toxicity and absence of any significant side effects (49). Additionally, melatonin has been shown to reduce the toxicity and increase the efficacy of a large number of drugs whose side effects are well documented (50).

REFERENCES

1. Lerner AB, Case JD, Takahashi Y, Lee TH, Mori N. Isolation of melatonin, pineal factor that lightens melanocytes. *J Am Chem Soc* 1958; 80: 2587.
2. Lerner AB, Case JD, Heinzelman RU. Structure of melatonin. *J Am Chem Soc* 1959; 81: 6084-6085.

3. Troen BR. The biology of ageing. *Mount Sinai J Med* 2003; 70: 3-22.
4. United Nations, Department of Economic and Social Affairs. World Population Ageing: 1950-2050. New York: United Nations, 2001.
5. Karasek M. Melatonin, human aging, and age-related diseases. *Exp Gerontol* 2004; 39: 1723-1729.
6. Karasek M. Role of melatonin in aging. In Aging and Age-Related Diseases: the Basics, M Karasek (ed). Hauppage, NY, Nova Science, 2006, pp. 83-102.
7. Pandi-Perumal SR, Srinivassan V, Maestroni GJM, Cardinali DP, Poeggeler B, Harderland R. Melatonin. Nature's most versatile biological signal? *FEBS J* 2006; 273: 2813-2836.
8. Harderland R, Poeggeler B. Non-vertebrate melatonin. *J Pineal Res* 2003; 34: 233-241.
9. Arendt J. Melatonin and the mammalian pineal gland. London, Chapman & Hall, 1995.
10. Reiter RJ. Melatonin: clinical relevance. *Best Pract Res Clin Endocrinol Metab* 2003; 17: 273-285.
11. Sugden D. Adrenergic mechanisms regulating pineal melatonin synthesis. *Adv Pineal Res* 1991; 5: 33-38.
12. Kennaway DJ, Stamp GE, Goble FC. Development of melatonin production in infants and the impact of prematurity. *J Clin Endocrinol Metab* 1992; 75: 367-369.
13. Bergiannaki JD, Soldatos CR, Paparrigopoulos TJ, Syrengelas M, Stefanis CN. Low and high melatonin excretors among healthy individuals. *J Pineal Res* 1995; 18: 159-164.
14. Selmaoui B, Touitou Y. Reproducibility of the circadian rhythm of serum cortisol and melatonin in healthy subjects: a study of three different cycles over six weeks. *Life Sci* 2003; 73: 3339-3349.
15. Harman, D. Ageing: a theory based on free radical and radiation chemistry. *J Gerontol* 1956; 11: 298-300.
16. Harman D. Free radical theory of aging. *Mutat Res* 1992; 275: 257-266.
17. Harman D. Aging: phenomena and theories. *Ann N Y Acad Sci* 1998, 854, 1-7.
18. Tan DX, Chen LD, Poeggeler B, Manchester LC, Reiter RJ. Melatonin: a potent, endogenous, hydroxyl radical scavenger. *Endocrine J* 1993; 1: 57-60.
19. Reiter RJ. Oxygen radical detoxification processes during aging: The functional importance of melatonin. *Aging Clin Exp Res* 1995; 7: 430-351.
20. Reiter RJ. Oxidative damage in the central nervous system: protection by melatonin. *Progr Neurobiol* 1998; 56: 359-384.
21. Reiter RJ, Tan DX, Allegra M. Melatonin: reducing molecular pathology and dysfunction due to free radicals and associated reactants. *Neuro Endocrinol Lett* 2002; 23(suppl 1): 3-8.
22. Benot S, Goberna R, Reiter RJ, Garcia-Maurino E, Osuna C, Guerrero JM. Physiological levels of melatonin contribute to the antioxidant capacity of human serum. *J Pineal Res* 1999; 27: 59-64.
23. Miles LE, Dement WC. Sleep and aging. *Sleep* 1980; 3: 119-220.
24. Pandi-Perumal SR, Seils LK, Kayumov L et al. Senescence, sleep, and circadian rhythms. *Aging Res Rev* 2002; 1: 559-604.
25. Cajochen C, Kräuchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 2003; 15: 432-437.
26. Skene D, Lockley SW, Arendt J. Use of melatonin in the treatment of phase shift and sleep disorders. *Adv Exp Med Biol* 1999; 467: 79-84.
27. Zisapel N. The use of melatonin for the treatment of insomnia. *Biol Signals Recept* 1999; 9: 84-89.
28. Monti, JM; Cardinali, DP. A critical assessment of the melatonin effect on sleep in humans. *Biol Signals Recept* 2000, 9, 328-339.
29. Cardinali DP, Brusco LI, Lloret SP, Furio AM. Melatonin in sleep disorders and jet-lag. *Neuro Endocrinol Lett* 2002; 23(suppl 1): 9-13.
30. Baskett JJ, Broad JB, Wood PC et al. Does melatonin improve sleep in older people? A randomized crossover trial. *Age Ageing* 2003; 32: 164-170.
31. Lavie P, Haimov I, Shochat T. Melatonin - shutting off the wakefulness system. *Front Horm Res* 1997; 23: 149-160.

32. Paul, MA; Gray, G; Kenny, G; Pigeau, RA. Impact of melatonin, zaleplon, zopoclone, and temazepam on psychomotor performance. *Aviat Space Environ Med* 2003; 74: 1263-1270.
33. Hofman MA, Swaab DF. Neuroplasticity in the human hypothalamus during ageing, In: The Neuroendocrine Immune Network in Ageing, Vol. 4, RH Straub, E Mocchegiani (eds). Amsterdam: Elsevier; 2004; pp. 105-121.
34. Armstrong SM. Melatonin: the internal Zietgeber of mammals? *Pineal Res Rev* 1989; 7: 157-202.
35. Armstrong SM, Redman JR. Melatonin: A chronobiotic with anti-aging properties. *Med Hypotheses* 1991; 4: 300-309.
36. Arendt J, Deacon S. Treatment of circadian rhythm disorders - melatonin. *Chronobiol Int* 1997; 14: 185-204.
37. Skene DJ, Lockley SW, Arendt, J. Melatonin in circadian sleep disorders in the blind. *Biol Signals Recept* 1999; 8: 90-95.
38. Walford RL. The Immunologic Theory of Aging. Copenhagen: Munsksgaard; 1989.
39. Fulop T, Hirokawa K, Mocchegiani E et al. The immune system in the elderly. In Aging and Age-Related Diseases: the Basics, M Karasek (ed). Hauppage, NY, Nova Science, 2006, pp. 173-196.
40. Pawelec G, Barnett Y, Forsey R et al.. T cell immunosenescence. *Front Biosc* 2002; 7: d1056-d1183.
41. Skwarło-Sońta K, Karasek M. Układ odpornościowy, starzenie się a melatonina. *Aktualności Neurologiczne*, 2003; 3: 215-220..
42. Guerrero JM, Reiter RJ. Melatonin-immune system relationships. *Curr Top Med Chem* 2002; 2: 167-179.
43. Maestroni GJM The immunotherapeutic potential of melatonin. *Expert Opin Investig Drugs* 2001; 10: 467-476.
44. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. *Endocrine* 2005; 27: 189-200.
45. Nelson RJ, Drazen DL. Melatonin mediates seasonal changes in immune function. *Ann NY Acad Sci* 2000; 917: 404-415.
46. Molinero P, Soutto M, Benot S, Hmadcha A, Guerrero JM. Melatonin is responsible for the nocturnal increase observed in serum and thymus of thymosin a1 and thymulin concentrations: observations in the rats and humans. *J Neuroimmunol* 2000; 103: 180-188.
47. Carrillo-Vico A, Calvo JR, Abreu P et al. Evidence of melatonin synthesis by human lymphocytes and its physiological significance: possible role as intracrine, autocrine, and/or paracrine substance. *FASEB J* 2004; 18: 537-539.
48. Carrillo-Vico A, Lardone PJ, Fernandez-Santos J et al. Human lymphocyte-synthesized melatonin is involved in the regulation of the IL-2/IL-2 receptor system. *J Clin Endocrinol Metab* 2005; 90: 992-1000.
49. Karasek M, Reiter RJ, Cardinali DP, Pawlikowski M. The future of melatonin as a therapeutic agent. *Neuro Endocrinol Lett* 2002; 23 (suppl 1): 118-121.
50. Reiter RJ, Tan DX, Sainz RM, Mayo JC, Lopez-Burillo S. Melatonin: reducing the toxicity and increasing the efficacy of drugs. *J Pharm Pharmacol* 2002; 54: 1299-1321.

Received: September 12, 2007
Accepted: November 14, 2007

Author's address: Prof. Michal Karasek, M.D., Ph.D., Department of Neuroendocrinology, Chair of Endocrinology, Medical University of Lodz, 92-216 Lodz, Czechoslowacka 8/10, Poland, tel./fax +48 42 675 7613; e-mail: karasek@csk.umed.lodz.pl