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Melatonin, human aging, and age-related diseases

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Abstract

The worldwide prolongation of the mean life expectancy has resulted in a rapid increase of the size of the elderly population (over the age of 60), both in numbers and as a proportion of the whole. As a consequence, increasing the number of potential beneficiaries of health and pension funds, mainly those aged 65 and over raises many social and economic problems since they are supported by a relatively smaller number of potential contributors, i.e. those in the economically active ages between 18 and 64. Therefore, there is a search for any therapeutic agent improving quality of life in the elderly. A role for melatonin as such a compound was recently suggested. In this survey, data on the possible role of melatonin in human aging and age-related diseases are briefly presented.

Undoubtedly the aging process is multi-factorial, and no single factor has been identified which satisfactorily explains the phenomenon. Although many theories relating the pineal gland and its secretory product melatonin to aging have been proposed, the role of this agent in the aging process is still unclear. However, for several reasons it seems reasonable to postulate a role for melatonin in this process. Melatonin levels decline gradually over the life-span and may be related to lowered sleep efficacy, very often associated with advancing age, as well as to deterioration of many circadian rhythms. Melatonin exhibits immunomodulatory properties, and a remodeling of immune system function is an integral part of aging. Finally, because melatonin is a potent free radical scavenger, its deficiency may result in reduced antioxidant protection in the elderly which may have significance not only for aging per se but also may contribute to the incidence or severity of some age-related diseases.

Presently available data do not allow us to conclude that melatonin may have a role in extending normal longevity. However, although melatonin cannot be recognized as 'rejuvenating' agent, some of its actions may be beneficial for the aging process. Administration of melatonin may improve temporal organization in advanced age. Moreover, it has beneficial effects on sleep as well as 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.

Keywords: Aging; Melatonin; Age-related diseases; Sleep disorders; Circadian rhythms; Free radicals; Antioxidants

1. Introduction

Population aging was one of the most distinctive demographic events of the 20th century (United Nations, 2001a). The worldwide prolongation of the mean life expectancy has resulted in rapid increase of the size of the elderly population (over the age 60), both in numbers and as a proportion of the whole. In 1950 persons over 60 years of age constituted less than 5% of the world's population (205 million). Today this number increased to 10% of the world's population (606 million) and is expected to reach about 20% of the world population in the next 50 years (2 billion; United Nations, 2001a,b; Schulman and Lunefeld, 2002). Moreover, there is a continuous increase in the number of individuals over the age of 80 (projected from 69 million today to 379 million by 2050) as well as individuals who live beyond the age of 100. Currently only 180,000 centenarians live throughout the world but an increase to 3.2 million is projected in the next 50 years (United Nations, 2001a,b).

Increasing number of potential beneficiaries of health and pension funds, mainly those aged 65 and over raises

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many social and economic issues since these individuals are supported by a relatively smaller number of potential contributors, i.e. those in the economically active ages of 15–64 (United Nations, 2000b). Moreover, an increased number of elderly persons increases the incidence of age-related diseases (e.g. atherosclerosis, neoplastic disease, Alzheimer's and Parkinson's diseases). Therefore there is a search for any therapeutic agent improving the quality of life of the elderly. A role for melatonin as such a compound was recently suggested (Karasek et al., 2002; Reiter et al., 2002a,b). Melatonin, although discovered over 40 years ago, received great attention just in the last decade following the hypothesis suggesting its role in the aging process.

Melatonin is currently available in some countries (e.g. USA, Argentina, and Poland) as a food supplement or an over the counter drug, and is often advertised as a 'rejuvenating' agent. The aim of this survey is to present data on the role of melatonin in aging and age-related diseases.

2. Theories linking melatonin with aging

Although many theories relating melatonin to aging have been put forward, the role of this compound in the aging process is not clear.

Initial reports claiming that melatonin most likely prolonged survival and the youthful character of the animals because of the immunoenhancing actions were published in late 80s and early 90s on the basis of the experiments showing that administration of melatonin in the drinking water at night increased life-span and maintained mice in a more youthful state (Maestroni et al., 1988; Pierpaoli et al., 1991; Pierpaoli and Regelson, 1994). Recently Pierpaoli and Lesnikov (1997) modified their earlier hypothesis and suggested that the pineal gland, through melatonin (or some other signal) monitors and regulates 'self control' and the ability of the immune system to recognize and react against any endo- or exogenic factor. According to this hypothesis, aging is, a result of deterioration of this central role of melatonin.

Rozencweig et al. (1987) and Grad and Rozencweig (1993) hypothesized that 'aging is secondary to pineal failure'. Accordingly then, they viewed aging as a syndrome of a relative melatonin deficiency, and a diminished melatonin:serotonin ratio. As a consequence, aging proceeds because of pro-aging serotonin action.

Advanced age is characterized by 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). Accordingly, because of melatonin's role in circadian activity, Armstrong and Redman (1991) suggested a role for melatonin in aging.

Kloeden et al. (1991, 1993) speculated that there is a centralized clock, localized in the pineal gland, which coordinates gene switching in all cells that age. Thus, the circadian melatonin signal functions as the 'hands' of this clock to inform all cells in the organism, and in consequence the organism as a whole, about the passage of time.

Recent studies (Reiter et al., 1993, 2002; Reiter, 1998) suggest melatonin's decline in advanced age reduces the antioxidant protection against the damage caused by highly toxic free radicals which accumulate with age.

3. Changes in melatonin secretion during life-span

In mammals, melatonin concentrations exhibit a clear circadian rhythm, with low values during the daytime and high values (10–15-fold increase) at night. Such circadian rhythms are present in all living organisms, from unicellular algae to man. In vertebrates, the rhythm, is generated by the circadian pacemaker (oscillator, biological clock) situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, and synchronized to 24 h primarily by the light–dark cycle acting via the SCN. Such rhythms in humans develop around the 6th month of life and reach the highest levels between the 4 and 7th year of age. At puberty there is a drop in melatonin concentrations, and thereafter its plasma concentrations diminish gradually. As a consequence, in many elderly individuals a day–night differences in melatonin secretion are almost absent (Fig. 1; Arendt, 1995; Karasek, 1999). Moreover, there are great variations in the amplitude of the nocturnal concentrations of melatonin among individuals (Bergiannaki et al., 1995) which indicate that some subjects produce significantly less melatonin during lifetime than others, which may have significance in terms of aging.

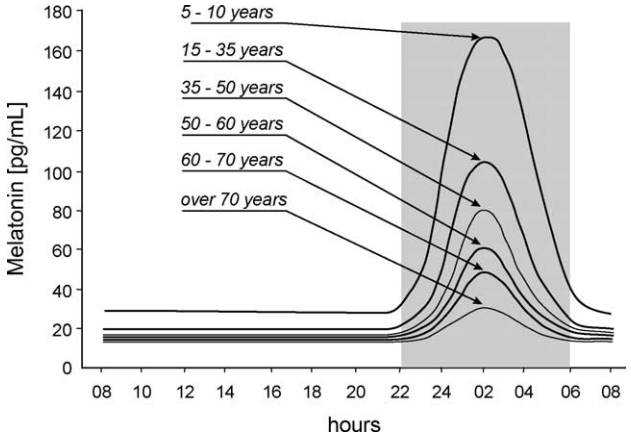

Fig. 1. Circadian profiles of serum melatonin concentrations at various age; gray area—darkness.

4. Possible consequences of age-related decline in melatonin secretion

4.1. Relation of diminished melatonin secretion to circadian rhythm deterioration in the elderly

Many important physiological processes (e.g. sleep/wake cycle, the core body temperature, performance, alertness, and secretion of many hormones), exhibit circadian rhythmicity. Such rhythms play an important role in homeostasis. Advanced age is characterized by deterioration of overt circadian patterns (reduced amplitude of many rhythms, earlier timing of endogenous circadian rhythmicity, disorganization of temporal order, loss of entrainment stability and responsiveness to Zeitgebers). Changes in SCN neurons seem to play a crucial role in age-related deterioration in circadian clock function. There is a desynchronization of overt rhythms that accompanies aging due to a loss of control of these functions by the SCN (Pandi-Perumal et al., 2002).

Armstrong (1989) proposes that melatonin is an internal Zeitgeber. The function of the pineal gland is to adjust the phase and synchronize internal rhythms by the periodic nocturnal release of melatonin. Therefore, Armstrong and Redman (1991) suggest that melatonin might have beneficial effects in terms of aging 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.

4.2. Melatonin and sleep disorders in advanced age

Chronic sleep disturbances are common complaints among the elderly. Between 40 and 70% of older people suffer from the inability to fall asleep, frequent nocturnal awakening, and early awakening. Moreover, 10–25% of the elderly complain of persistent insomnia. These conditions 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 (Van Someren, 2000; Pandi-Perumal et al., 2002).

Interestingly, melatonin secretion during aging inversely correlates with sleep disturbances. Melatonin concentrations significantly decrease in advanced age accompanied by an increased frequency of sleep disorders (Miles and Dement, 1980). Since the early 1970s melatonin was reported to exerts sleep promoting effects (e.g. reduced sleep latency and induction of sleepiness and fatigue). According to Cajochen et al. (2003) the soporific and chronobiotic properties of melatonin make it an optimal candidate for treating sleep disorders. In most studies melatonin (administered in the evening, in doses ranging from 0.3 to 5 mg) improved subjective and/or objective sleep parameters in patients suffering from insomnia (reduced sleep latency, increased total sleep time and sleep efficacy; Zisapel, 1999; Monti and Cardinali, 2000; Cardinali et al., 2002a,b). Although, there are some data showing that melatonin concentrations in elderly suffering from insomnia may be lower than in those without sleep disturbances (Zisapel, 1999), a recent study has not shown such a relationship (Baskett et al., 2001).

4.3. Melatonin and suppressed immunocompetence in advanced age

Suppressed immunocompetence seems to play an important role in the acceleration of aging processes resulting in increased susceptibility to diseases (Ginaldi et al., 1999a,b,c). Several aspects of immune reactivity (e.g. number of immune cells and their subpopulations, proliferation of lymphocytes, blood level of different cytokines, phagocytic index, etc.) exhibit well pronounced circadian rhythmicity (Petrovsky and Harrison, 1997). There are some indications that both diurnal and seasonal changes in the immune system function are controlled by or correlated with pineal melatonin synthesis and secretion (Skwarlo-Sonta, 2002).

Moreover, there are numerous experimental data presented (Gurrero et al., 2001; Maestroni, 2001) showing that melatonin exerts immunoenhancing action, both in animals and in humans.

4.4. Significance of melatonin secretion decline for reduced antioxidant protection in elderly

According to Harman's (1956, 1992) free radical theory of aging, age-related deterioration of function is in part related to damage of subcellular constituents, cells, and organs sustained as a consequence of their persistent bombardment by highly toxic free radicals. These reactive molecules have an unpaired electron and are continuously produced in cells as byproducts of oxidative phosphorylation and fatty acid oxidation. Melatonin is a potent free radical scavenger and antioxidant that scavenges especially highly toxic hydroxyl radicals, and additionally stimulates a number of antioxidative enzymes (Reiter, 1998). Melatonin is both lipophylic and hydrophilic and diffuses widely into cellular compartments, thus providing on-site protection against free radical mediated damage to biomolecules. 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 (Benot et al., 1999). The question of how the balance between the amount of free radical formation and the activity of the antioxidative defense might influence the aging process is still unknown. However, Biesalski (2002) has suggested that such

a balance is not only involved in but even triggers the process of aging of cells and tissues.

4.5. Significance of melatonin in age-related diseases

Age-related diseases are a permanent attribute of aging. Oxidative damage plays an important role in the pathogenesis of neurodegenerative diseases characteristic of aged population (Reiter, 1998; Smith et al., 2000). Therefore, because of melatonin's antioxidant activity its role in many age-related diseases has been suggested. This especially relates to neurodegenerative diseases such as Alzheimer's and Parkinson's because of high vulnerability of the central nervous system to oxidative attack and neoplastic disease.

Alzheimer's disease, having a late life onset (after 50 years of age), and affecting an estimated 15 million people worldwide is the most common cause of progressive cognitive decline in the aged population (Reiter, 1998). Characteristic neuromorphophysiological features of Alzheimer's disease include amyloid-β plaques, neurofibrillary tangles, and extensive neural loss, particularly in the hippocampus and cerebral cortex (Perl, 2000; Chen and Fernandez, 2001; Ghiso and Frangione, 2002). It is believed that neuronal loss is most probably caused by free radicals generated by amyloid-β peptide (in particular by its 25–35 aminoacid residue; Buterfield et al., 1994). There are data indicating that melatonin may reduce the neurotoxicity of the amyloid-β, leading to increased cellular survival (Pappola et al., 1997a,b, 2000; Daniels et al., 1998). Moreover, decreased melatonin concentrations were observed in some, but not all, patients suffering from Alzheimer's disease (Morita et al., 1996; Mishima et al., 1999). Furthermore melatonin treatment seems to improve sleep, ameliorate sundowning, and slow the progression of cognitive impairment in Alzheimer's patients (Brusco et al., 1998; Cardinali et al., 2002a,b). However, a recent multicenter, placebo-controlled trial failed to prove that melatonin has a clinically significant therapeutic effect on objective measures of sleep maintenance, sleep duration, or day–night sleep ratio in patients suffering from Alzheimer's disease, although subjective measures showed some improvement after melatonin treatment (Singer et al., 2003).

Parkinson's disease is characterized by progressive deterioration of dopamine-containing neurons in the pars compacta of the substantia nigra in the brain stem. The loss of these neurons is caused by auto-oxidation of dopamine due to relatively high exposure of these neurons to free radicals (Fahn and Cohen, 1992). Melatonin has been shown to reduce dopamine auto-oxidation (Miller et al., 1996). In experimental animal models of Parkinson's disease, melatonin administration diminished lipid peroxidation that occurred in the striatum, hippocampus and midbrain after injection of 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (Acuna-Castroviejo et al., 1997) and reduced cytotoxicity of 6-hydroxydopamine (Mayo et al., 1998a,b). According to Reiter (1998) these findings suggest the potential utility of melatonin in restraining dopaminergic cell dysfunction and loss in Parkinson's disease.

Aging is also correlated with neoplastic disease. There are data indicating influence of melatonin on tumor development and/or growth with its prevailing oncostatic action (Blask, 1993; Karasek, 1997; Karasek and Pawlikowski, 1999; Pawlikowski et al., 2002b). There are also some data indicating a role of melatonin in human malignancy. Depressed nocturnal melatonin concentrations or nocturnal excretion of the main melatonin metabolite—6-hydroxymelatonin sulfate have been found in some tumors (breast cancer—Bartsch et al., 1981, 1989, 1991, prostate cancer—Bartsch et al., 1983, 1992, colorectal cancer—Khoory and Stemme, 1988, lung cancer, stomach cancer—Kvetnaya et al., 2001, endometrial cancer (Fig. 2A)—Karasek et al., 1996, 2000, and cervical cancer (Fig. 2B)—Karasek et al., unpublished data), whereas in other tumors (laryngeal cancer, urinary bladder—Kvetnaya et al., 2001, ovarian cancer—Karasek et al., 2000, osteosarcoma—Panzer and Viljoen, 1998, and Hodgkin's sarcoma—Lissoni et al., 1986)

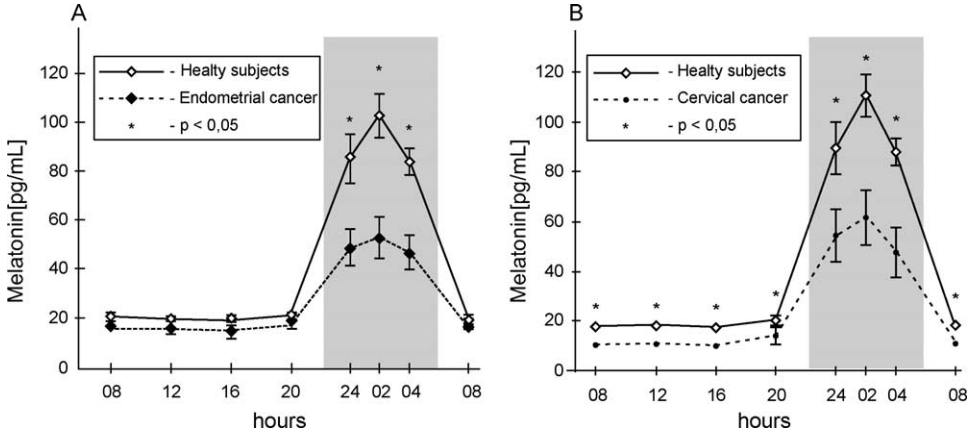

Fig. 2. (A) Circadian profiles of serum melatonin concentrations in women suffering from endometrial cancer (from Karasek et al., 2000, modified; with permission); (B) Circadian profiles of serum melatonin concentrations in women suffering from cervical cancer (Karasek et al., unpublished data); gray area—darkness.

melatonin levels were not changed or showed great variations among individuals. 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) favorably influences the course of advanced malignant disease in humans and leads to an improvement in their quality of life (Lissoni, 2001; Hrushesky, 2001; Bartsch et al., 2002).

In conclusion, melatonin may play some role in age-related diseases which suggests that the loss of this antioxidant with age may contribute to the incidence or severity of some age-associated diseases.

5. Concluding remarks

Aging is a multi-factorial process, and no single element seems to be of fundamental importance. Although, there is no clear evidence indicating that melatonin may delay aging, there are some reasons to postulate a role for this compound in the aging process:

- Melatonin participates in many vital life processes, and its secretion falls gradually over the life-span.
- Diminished melatonin secretion in advanced age may be related to deterioration of many circadian rhythms, as a consequence of a reduced function of the suprachiasmatic nucleus.
- Melatonin acts as endogenous sleep-inducing agent, and its reduced plasma concentration may result in lowered sleep efficacy very often associated with advancing age.
- Melatonin exhibits immunoenhancing properties, and suppressed immunocompetence has been implicated in the acceleration of aging processes.
- Melatonin is a potent free radical scavenger, and since free radicals cause damage to vital cellular constituents, their accumulation with age has significance, not only for aging per se, but also for many age-related diseases.

Current data do not allow us to conclude that melatonin may have a role in extending normal longevity. Although melatonin cannot be recognized as a rejuvenating agent, some of its actions may be beneficial during the aging process. Administration of melatonin may improve temporal organization in advanced age. Moreover, it has beneficial effects on sleep as well as on age-related diseases. It should be stressed that melatonin treatment seems to be safe because of its remarkable low toxicity and absence of any significant side effects (Avery et al., 1998; Seabra et al., 2000; Siegrist et al., 2001; Pawlikowski et al., 2002a; Karasek et al., 2002; Singer et al., 2003). 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 (Reiter et al., 2002a,b).

The generally accepted indications for therapeutic use of melatonin include sleep disorders, and circadian clock disturbances (e.g. jet-lag, phase-shifting of the circadian clock in individual who are blind; Karasek et al., 2002). 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.

References

Acuna-Castroviejo, D., Coto-Montes, A., Monti, M.G., Ortiz, G.G., Reiter, R.J., 1997. Melatonin is protective against MPTP-induced striatal and hyppocampal lesions. Life Sci. 60, PL23–PL29.

Arendt, J., 1995. Melatonin and the Mammalian Pineal Gland. Chapman and Hall, London.

Armstrong, S.M., 1989. Melatonin: the internal Zietgeber of mammals? Pineal Res. Rev. 7, 157–202.

Armstrong, S.M., Redman, J.R., 1991. Melatonin: a chronobiotic with anti-aging properties. Med. Hypotheses 34, 300–309.

Avery, D., Lenz, M., Landis, C., 1998. Guidelines for prescribing melatonin. Ann. Med. 30, 122–130.

Bartsch, C., Bartsch, H., Laumas, K.R., Wetterberg, L., 1981. Urinary melatonin levels in human breast cancer patients. J. Neural Transm. 52, 281–294.

Bartsch, C., Bartsch, H., Flüchter, S.H., Harzmann, R., Attanasio, A., Bichler, K.H., Gupta, D., 1983. Circadian rhythms of serum melatonin, prolactin and growth hormone in patients with benign and malignant tumours of the prostate and in non-tumor controls. Neuroendocrinol. Lett. 5, 377–386.

Bartsch, C., Bartsch, H., Fuchs, U., Lippert, T.H., Bellmann, O., Gupta, D., 1989. Stage-dependent depression of melatonin in patients with primary breast cancer. Cancer 64, 426–433.

Bartsch, C., Bartsch, H., Bellman, O., Lippert, T.H., 1991. Depression of serum melatonin in patients with primary breast cancer is not due to an increased peripheral metabolism. Cancer 67, 1681–1684.

Bartsch, C., Bartsch, H., Schmidt, A., Ilg, S., Bichler, K.H., Flüchter, S.H., 1992. Melatonin and 6-sulfatoxymelatonin circadian rhythms in serum and urine of primary prostate cancer patients: evidence for reduced pineal activity and relevance of urinary determinations. Clin. Chim. Acta 209, 153–176.

Bartsch, C., Bartsch, H., Karasek, M., 2002. Melatonin in clinical oncology. Neuroendocrinol. Lett. 23 (Suppl. 1), 30–38.

Baskett, J.J., Wood, P.C., Broad, J.B., Duncan, J.R., English, J., Arendt, J., 2001. Melatonin in older people with age-related sleep maintenance problems: a comparison with age-matched normal sleepers. Sleep 24, 418–424.

Benot, S., Goberna, R., Reiter, R.J., Garcia-Maurino, E., Osuna, C., Guerrero, J.M., 1999. Physiological levels of melatonin contribute to the antioxidant capacity of human serum. J. Pineal Res. 27, 59–64.

Bergiannaki, J.D., Soldatos, C.R., Paparrigopoulos, T.J., Syrengelas, M., Stefanis, C.N., 1995. Low and high melatonin excretors among healthy individuals. J. Pineal Res. 18, 159–164.

Biesalski, H.K., 2002. Free radical theory of aging. Curr. Opin. Clin. Nutr. Metab. Care 5, 5–10.

Blask, D.E., 1993. Melatonin in oncology, in: Yu, H.S., Reiter, R.J. (Eds.), Melatonin—Biosynthesis, Physiological Effects and Perspectives. CRC Press, Boca Raton, pp. 447–475.

Brusco, L.I., Marquez, M., Cardinali, D.P., 1998. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease. Neuroendocrinol. Lett. 19, 111–115.

Buterfield, D.A., Hersley, K., Harris, M., Mattson, M.P., Carney, J.M., 1994. β-Amyloid peptide free radical fragments initiate

lipoperoxidation in a sequence specific fashion: implications to Alzheimer's disease. Biochem. Biophys. Res. Commun. 2000, 710–715.

Cajochen, C., Kräuchi, K., Wirz-Justice, A., 2003. Role of melatonin in the regulation of human circadian rhythms and sleep. J. Neuroendocrinol. 15, 432–437.

Cardinali, D.P., Brusco, L.I., Liberczuk, C., Furio, A.M., 2002a. The use of melatonin in Anzheimer's disease. Neuroendocrinol. Lett. 23 (Suppl. 1), 20–23.

Cardinali, D.P., Brusco, L.I., Lloret, S.P., Furio, A.M., 2002b. Melatonin in sleep disorders and jet-lag. Neuroendocrinol. Lett. 23 (Suppl. 1), 9–13.

Chen, M., Fernandez, H.L., 2001. Where do Alzheimer's plaques and tangles come from? Aging-induced protein degradation inefficiency. Front. Biosci. 6, e1–e11.

Daniels, W.M.V., van Rensburg, S.J., van Zyl, J.M., Tuljaard, J.J.F., 1998. Melatonin prevents β-amyloid-induced lipid peroxidation. J. Pineal Res. 24, 78–82.

Fahn, S., Cohen, G., 1992. The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. Ann. Neurobiol. 32, 804–812.

Ghiso, J., Frangione, B., 2002. Amyloidosis and Alzheimer's disease. Adv. Drug Deliv. Rev. 54, 1539–1551.

Ginaldi, K., De Martinis, M., D'Ostilio, A., Marini, L., Loreto, M.F., Corso, M.D., Quoglino, D., 1999a. The immune system in the elderly: I. Specific humoral immunity. Immunol. Res. 20, 101–108.

Ginaldi, K., De Martinis, M., D'Ostilio, A., Marini, L., Loreto, M.F., Quoglino, D., 1999b. The immune system in the elderly: II. Specific cellular immunity. Immunol. Res. 20, 109–115.

Ginaldi, K., De Martinis, M., D'Ostilio, A., Marini, L., Loreto, M.F., Martorelli, V., Quoglino, D., 1999c. The immune system in the elderly: III. Innate immunity. Immunol. Res. 20, 117–126.

Grad, B.R., Rozencweig, R., 1993. The role of melatonin and serotonin in aging: update. Psychoneuroendocrinology 18, 283–295.

Gurrero, J.M., Garcia-Maurino, S., Pozo, D., Garcia-Perganeda, A., Carrillo-Vico, A., Molinero, P., Osuna, C., Calvo, J.R., 2001. Mechanisms involved in the immunomodulatory effects of melatonin on the human immune system, In: Bartsch, C., Bartsch, H., Blask, D.E., Cardinali, D.P., Hrushesky, W.J.M., Mecke, D. (Eds.), The Pineal Gland and Cancer. Springer, Berlin, pp. 408–416.

Harman, D., 1956. Ageing: a theory based on free radical and radiation chemistry. J. Gerontol. 11, 298–300.

Harman, D., 1992. Free radical theory of aging. Mutat. Res. 275, 257–266.

Hrushesky, W.J.M., 2001. Melatonin cancer therapy, In: Bartsch, C., Bartsch, H., Blask, D.E., Cardinali, D.P., Hrushesky, W.J.M., Mecke, D. (Eds.), The Pineal Gland and Cancer. Springer, Berlin, pp. 476–508.

Karasek, M., 1997. Relationship between the pineal gland and experimentally-induced malignant tumors. Front. Horm. Res. 23, 99–106.

Karasek, M., 1999. Melatonin in humans: where we are 40 years after its discovery. Neuroendocrinol. Lett. 20, 179–188.

Karasek, M., Pawlikowski, M., 1999. Pineal gland, melatonin and cancer. Neuroendocrinol. Lett. 20, 139–144.

Karasek, M., Dec, W., Kowalski, A.J., Bartsch, H., Bartsch, C., 1996. Serum melatonin circadian profile in women with adenocarcinoma of uterine corpus. Int. J. Thymol. 4 (Suppl. 1), 80–83.

Karasek, M., Kowalski, A.J., Zylinska, K., 2000. Serum melatonin circadian profile in women suffering from the genital tract cancers. Neuroendocrinol. Lett. 21, 109–113.

Karasek, M., Reiter, R.J., Cardinali, D.P., Pawlikowski, M., 2002. Future of melatonin as a therapeutic agent. Neuroendocrinol. Lett. 23 (Suppl. 1), 118–121.

Khoory, R., Stemme, D., 1988. Plasma melatonin levels in patients suffering from colorectal carcinoma. J. Pineal Res. 5, 251–258.

Kloeden, P.E., Rössler, R., Rössler, O.E., 1991. Does centralized clock for aging exist? Gerontology 36, 314–322.

Kloeden, P.E., Rössler, R., Rössler, O.E., 1993. Time-keeping in genetically programmed aging. Exp. Gerontol. 28, 109–118.

Kvetnaya, T.V., Kvetnoy, I.M., Bartsch, H., Bartsch, C., Mecke, D., 2001. Melatonin in patients with cancer of extra-reproductive location, In: Bartsch, C., Bartsch, H., Blask, D.E., Cardinali, D.P., Hrushesky, W.J.M., Mecke, D. (Eds.), The Pineal Gland and Cancer. Springer, Berlin, pp. 177–196.

Lissoni, P., 2001. Efficacy of melatonin in the immunotherapy of cancer using interleukin-2, In: Bartsch, C., Bartsch, H., Blask, D.E., Cardinali, D.P., Hrushesky, W.J.M., Mecke, D. (Eds.), The Pineal Gland and Cancer. Springer, Berlin, pp. 465–475.

Lissoni, P., Viviani, S., Bajetta, E., Buzzoni, R., Barreca, A., Mauri, R., Resentini, M., Morabito, F., Esposti, D., Esposti, G., Fraschini, F., 1986. A clinical study of the pineal gland activity in oncologic patients. Cancer 57, 837–842.

Maestroni, G.J.M., 2001. The immunotherapeutic potential of melatonin. Exp. Opin. Invest. Drugs 10, 467–476.

Maestroni, G.J.M., Conti, A., Pierpaoli, W., 1988. Pineal melatonin, its fundamental immunoregulatory role in aging and cancer. Ann. NY Acad. Sci. 521, 140–147.

Mayo, J.C., Sainz, R.M., Uria, H., Antonin, I., Esteban, M.M., Rodriguez, C., 1998a. Melatonin prevents apoptosis induced by 6-hydroxydopamine in neuronal cells: implications for Parkinson's disease. J. Pineal Res. 24, 179–192.

Mayo, J.C., Sainz, R.M., Uria, H., Antonin, I., Esteban, M.M., Rodriguez, C., 1998b. Inhibition of cell proliferation: a mechanism likely to mediate prevention of neuronal death by melatonin. J. Pineal Res. 25, 12–18.

Miles, L.E., Dement, W.C., 1980. Sleep and aging. Sleep 3, 119–220.

Miller, J.W., Selhub, J., Joseph, J.A., 1996. Oxidative damage caused by free radicals produced during catocholamine autooxidation: protective effects of O-methylation and melatonin. Free Radical Biol. Med. 21, 241–249.

Mishima, K., Tozawa, T., Satoh, K., Matsumoto, Y., Hishikawa, Y., Okawa, M., 1999. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking. Biol. Psychiatr. 15, 417–421.

Monti, J.M., Cardinali, D.P., 2000. A critical assessment of the melatonin effect on sleep in humans. Biol. Signals Recept. 9, 328–339.

Morita, Y., Uchida, K., Okamoto, N., 1996. Melatonin rhythm of Alzheimer patients. Front. Horm. Res. 21, 180–185.

Pandi-Perumal, S.R., Seils, L.K., Kayumov, L., Ralph, M.R., Lowe, A., Moller, H., Swaab, D.F., 2002. Senescence, sleep, and circadian rhythms. Aging Res. Rev. 1, 559–604.

Panzer, A., Viljoen, M., 1998. Urinary 6-sulfatoxymelatonin levels in osteosarcoma: a case–control study. Med. Sci. Res. 26, 43–45.

Pappola, M.A., Sas, M., Omar, R.A., Bick, R.J., Hickson-Bick, D.L.M., Reiter, R.J., 1997a. Melatonin prevents death of neuroblastoma cells exposed to the Alzheimer amyloid peptide. J. Neurosci. 17, 1683–1690.

Pappola, M.A., Sas, M., Omar, R.A., Bick, R.J., Hickson-Bick, D.L.M., Reiter, R.J., Efthimiopoulous, S., Sambamurti, K., Rubakis, N.K., 1997b. Oxidative damage and cell death induced by an amyloid peptide fragment is completely prevented by melatonin, In: Iqbal, K., Winblad, B., Nishimura, T., Takeda, M., Wisniewski, H.M. (Eds.), Alzheimer's Disease: Biology, Diagnosis and Therapeutics. Willey, New York, pp. 741–749.

Pappola, M.A., Chyan, Y.J., Poeggeler, B., Frangione, B., Wilson, G., Ghiso, J., Reiter, R.J., 2000. An assessment of the antioxidant and the antiamyloidogenic properties of melatonin: implications for Alzheimer's disease. J. Neural. Transm. 107, 203–231.

Pawlikowski, M., Kolomecka, M., Wojtczak, A., Karasek, M., 2002a. Effects of six months melatonin treatment on sleep quality and serum concentrations of estradiol, cortisol, dehydroepiandrosterone sulfate, and somatomedin C in elderly women. Neuroendocrinol. Lett. 23 (Suppl. 1), 17–19.

Pawlikowski, M., Winczyk, K., Karasek, M., 2002b. Oncostatic action of melatonin: facts and question marks. Neuroendocrinol. Lett. 23 (Suppl. 1), 24–29.

Perl, D.P., 2000. Neuropathology of Alzheimer's disease and related disorders. Neurol. Clin. 18, 847–864.

Petrovsky, N., Harrison, L.C., 1997. Diurnal rhythmicity of human cytokine production. J. Immunol. 158, 5163–5168.

Pierpaoli, W., Lesnikov, V., 1997. Theoretical considerations on the nature of the pineal 'aging clock'. Gerontology 43, 20–25.

Pierpaoli, W., Regelson, W., 1994. Pineal control of aging: effects of melatonin and pineal grafting in aging mice. Proc. Natl Acad. Sci. USA 91, 787–791.

Pierpaoli, W., Dall'Ara, A., Pedrinis, E., Regelson, W., 1991. The pineal control of aging: the effects of melatonin and pineal grafting on survival of older mice. Ann. NY Acad. Sci. 621, 291–313.

Reiter, R.J., 1998. Oxidative damage in the central nervous system: protection by melatonin. Prog. Neurobiol. 56, 359–384.

Reiter, R.J., Poegeler, B., Tan, D.X., Chen, L.D., Manchester, L.C., Guerrero, J.M., 1993. Antioxidant capacity of melatonin: a novel action not requiring a receptor. Neuroendocrinol. Lett. 15, 103–116.

Reiter, R.J., Tan, D.X., Allegra, M., 2002a. Melatonin: reducing molecular pathology and dysfunction die to free radicals and associated reactants. Neuroendocrinol. Lett. 23 (Suppl. 1), 3–8.

Reiter, R.J., Tan, D.X., Sainz, R.M., Mayo, J.C., Lopez-Burillo, S., 2002b. Melatonin: reducing the toxicity and increasing the efficacy of drugs. J. Pharm. Pharmacol. 54, 1299–1321.

Rozencweig, R., Grad, B.R., Ochoa, J., 1987. The role of melatonin and serotonin in aging. Med. Hypotheses 23, 337–352.

Schulman, C., Lunefeld, B., 2002. The aging male. World J. Urol. 20, 4–10.

Seabra, M.L.V., Bignotto, M., Pinto Jr., L.R., Tufic, C., 2000. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. J. Pineal Res. 29, 193–200.

Siegrist, C., Benedetti, C., Orlando, A., Beltran, J.M., Tuchsherr, L., Noseda, C.J.M., Brusco, L.I., Cardinali, D.P., 2001. Lack of changes in serum prolactin, FSH, TSH, and estradiol after melatonin treatment in doses that improve sleep and reduce benzodiazepine consumption in sleep-disturbed, middle aged, and elderly patients. J. Pineal Res. 30, 34–42.

Singer, C., Tractenbergh, R.E., Kaye, J., Schafer, K., Gamst, A., Grundman, M., Thomas, R., Thal, L.J., 2003. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. Sleep 26, 893–901.

Smith, M.A., Rottkamp, C.A., Nunomura, A., Raina, A.K., Perry, G., 2000. Oxidative stress in Alzheimer's disease. Biochim. Biophys. Acta 1502, 139–144.

Skwarlo-Sonta, K., 2002. Melatonin in immunity: comparative aspects. Neuroendocrinol. Lett. 23 (Suppl. 1), 61–66.

United Nations, 2001a. Department of Economic and Social Affairs. World Population Ageing: 1950–2050. United Nations, New York.

United Nations, 2001b. Population Division, Department of Economic and Social Affairs. World Population Prospects: the 2000 Revision. Highlights. United Nations, New York.

Van Someren, E.J.W., 2000. Circadian and sleep disturbances in the elderly. Exp. Gerontol. 35, 1229–1237.

Zisapel, N., 1999. The use of melatonin for the treatment of insomnia. Biol. Signals Recept. 8, 84–89.