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Review acrticle

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MELATONIN AND AGING: PROSPECTS FOR HUMAN TREATMENT

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Human life span, with or without modern medicine is around 85-95 years. All living creatures have their inner clock that measures their daily (circadian) and their seasonal (circannual) time. These time changes are mediated by the alteration of levels of melatonin, an evolutionary ancient hormone, which is produced in many body tissues, including the pineal gland, retina and the gastrointestinal tract (GIT). Light is blocking the production of melatonin in the pineal gland, darkness is stimulating it. So, the diurnal changes of light intensity of melatonin, provide a "daily clock" and the seasonal changes provide a "seasonal clock". Finally, the reduction of melatonin observed with aging, may indicate the presence of an "age clock". Melatonin is a strong antioxidant (often it is called scavenger of free radicals), which protects the body from the effects of noxious compounds. Therefore it was hypothesized that the reduction of melatonin levels with age contributes to the aging process. So far, the only remedy to extend the life span was a 40% reduction in caloric intake, which prolonged the life in mice, rats, dogs and monkeys by 30-50%. A large group of people imitate these experiments performed on animals, but the results of these experiments will not be known for several decades. How is being hungry prolonging the life span? There is a connection between caloric reduction and melatonin levels in GIT. Several experiments indicate that fasting in animals substantially increased their production of GIT melatonin. Therefore, instead of being permanently hungry, a prolongation of human life could be achieved by a replacement melatonin therapy. A daily intake of melatonin before bed time might achieve the same effect as fasting *e.g.* an increase of body melatonin levels, which will protect the individual from the ravages of old age. That includes Parkinson's disease and Alzheimer's disease. There is a large group of people taking melatonin daily who believe that melatonin is the "fountain of youth". Those are the subjects which will one day provide an experimental evidence of the efficacy of melatonin.

Key words: *aging, Alzheimer's disease, fasting, gastrointestinal tract, human, life span, melatonin, pineal, antioxidant*

INTRODUCTION

As long as the human culture exists, people were attempting to prevent aging. The discovery of the "fountain of eternal youth" has been announced many times before, but unfortunately, most methods proposed for slowing down the aging process never worked out. So at this moment, because of lack of other proven methods the main principle of an anti-aging practice should be the implemention of measures, which according to an old Chinese proverb will "prevent the preventable and delay the inevitable" (1). However, how can we slow down the aging process, if at the present time we don't know what is causing it? Research studies indicate that humans have a predetermined life span, which is probably genetically defined (as was recently confirmed) and did not change over the thousand of years of civilization. For most of us the maximum age we can reach is around 85-95 years, even with the most advanced medicine. This is not any longer that the age of Michelangelo, Goethe, Picasso or Newton, the giants of humanity who lived long and productive lives into their eighties without the benefits of modern medicine.

As the number of old people in the population is on the rise (2), more and more studies are being published in gerontological journals such *Gerontology, Journal of Gerontology, Experimental Gerontoloy, Aging, Mechanisms of Aging and Development* and many others. The anatomical and physiological changes occurring during our lifetime are related to reproduction. Changes occurring in women during menopause and in men during andropause indicate not only the reduction of secretion of sex hormones but also a decline in production and secretion of metabolic hormones, such as growth hormone, insulin like growth factor, adrenocorticoid hormones, thyroxine, melatonin, androgens such as dihydroxyepiandrosterone (DHEA) and testosterone, as well as LH, leptin, and prolactin (1, 3-7). The reduction of some of these hormonal secretions is due to a decline in concentrations of sex hormones estrogens and androgens and a replacement therapy became very popular and widely accepted (4). For women, estrogen replacement therapy (ERT) is well established, although it is still a controversial part of gynecological endocrinology. For men, androgen replacement therapy (ART) is still in its infancy and is even more controversial than ERT.

All living creatures have their inner clock, which measures not only their "daily" (circadian) clock but also their "seasonal" (circannual) clock. These time changes are manifested through changes of daylight, both in the circadian as well as in the

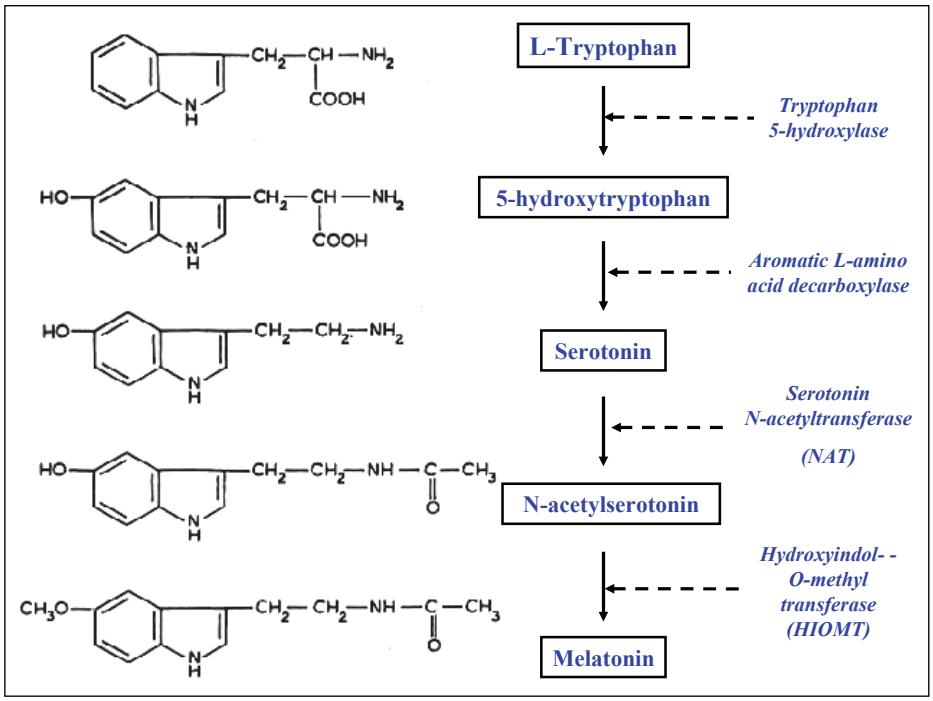

Fig. 1. Synthesis of melatonin in the pineal gland from tryptophan *via* serotonin. (Adapted from Touitou *et al*. 2001).

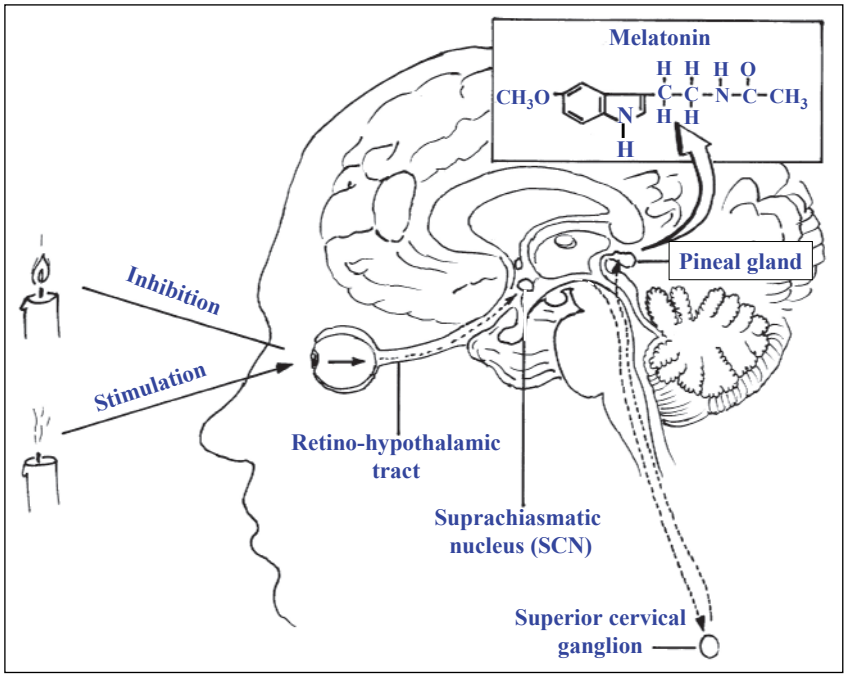

Fig. 2. Inhibition and stimulation of melatonin production in the pineal gland *via* retino-pineal pathway. (Adapted from Konturek *et al*. 2007).

circannual mode and are tied up to the secretion of a hormone called melatonin (8, 9). Melatonin is a derivative of serotonin (10) (*Fig. 1*), which is produced in many body tissues, including the pineal gland, retina and the gastrointestinal tract (GIT) (11). How is melatonin involved in the perception of time? During the day, the intense light blocks the production of melatonin in the pineal; however, during dusk, the decline in the intensity of light is registered in the retina, which then sends the information to the pineal gland (*Fig. 2*) (12). Upon arrival of the signal from the retina, concentrations of pineal-produced melatonin begin to rise in blood and then in all other body tissues. This increase of melatonin levels provides a convenient signal to all body cells about the onset of night. The diurnal changes of light intensity provide the daily clock and the seasonal changes of day length provide the yearly clock. Interestingly, changes in the production of pineal melatonin with age might also provide the "age clock" (4, 10, 12). The pineal gland of newborns is not yet fully functional; infants may relay on the melatonin timing signals received from their mother *via* the breast milk (10, 13). Therefore breast-fed babies have a better sleeping rhythm then babies fed with milk formulas. In children, the nighttime concentration of melatonin increases rapidly with age and peak levels are achieved between 2-4 years. The peak concentrations of melatonin in blood then decline rapidly till puberty when the melatonin plateau signals the onset of sexual maturation (14) (*Fig. 3*). From puberty there is a steady decline till the old age (*Fig. 4*) (2, 9, 15, 16). That decrease of melatonin produced in our bodies is considered to be a predisposing factor in

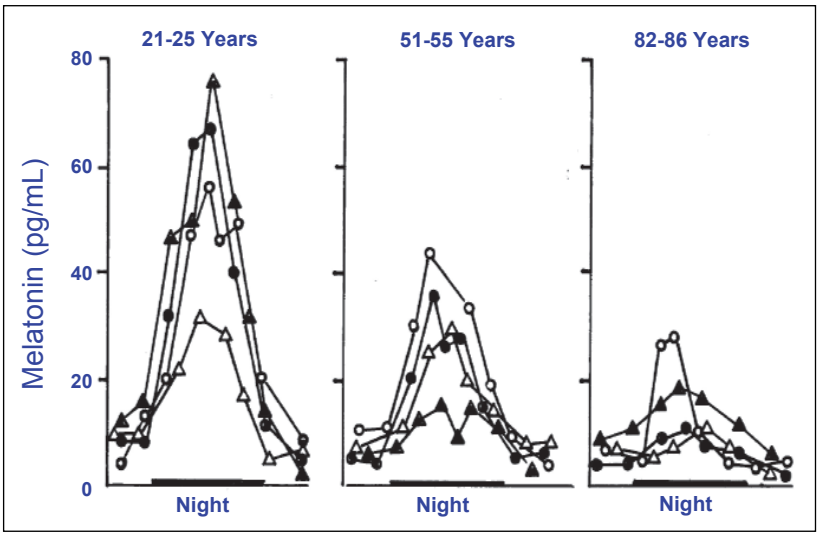

Fig. 3. Diurnal variations of blood melatonin concentrations in various age categories. Note the peak night time levels in the youngest group. (Adapted from Reiter *et al*. 1995).

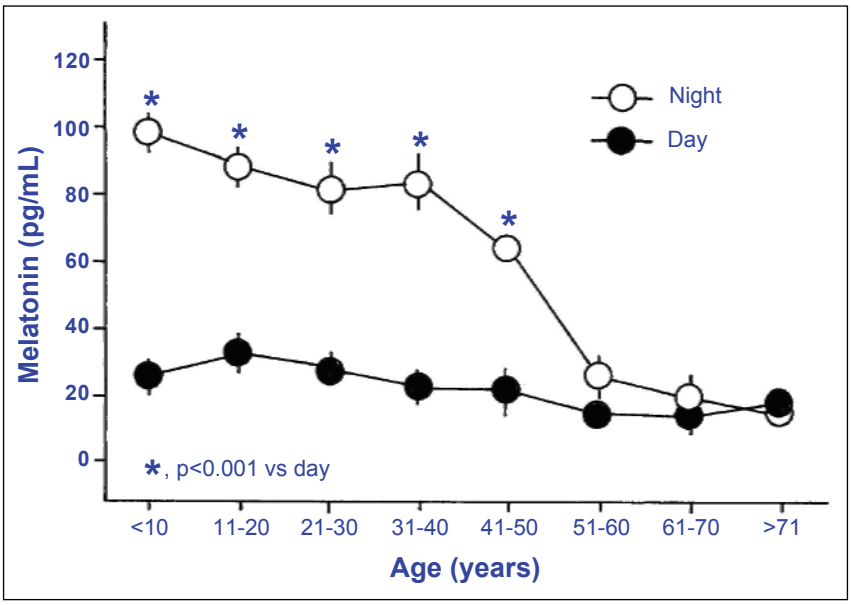

Fig. 4. Day and night time values of melatonin in serum during the aging. Note the decline in melatonin levels in night time samples (made mostly in the pineal gland) whereas no decrease of melatonin was registered in the day time samples (made mostly in the GIT). (Adapted from Benot *et al*. 1998).

neurodegenerative diseases like Alzheimer's disease (17). As I mentioned before, day and night time variation of melatonin in blood indicates the circadian timing. In a young person this daytime/nightime difference in melatonin concentration is very robust, but in a 60 years old person the difference is 80% lower than during puberty and it is almost completely abolished at old age (16). This age-dependent decline (*Fig. 4*) is still controversial, as there are big variations in individual nighttime concentrations of melatonin. It is also not yet resolved whether rhythm alteration is a cause or a consequence of the aging process in humans (5). Because of a strong antioxidant capacity, melatonin may be a safe and effective remedy to slow down aging, extent the life span and counteract age-related disorders (18) such as Alzheimer's and Parkinson's diseases (19).

Melatonin has a strong natural hypnotic effect and the lack of diurnal variation may be related to geriatric insomnia. Sleep disturbances are one of the most common complaints in old people. They not only experience a shift in timing of onset of sleep but also an increased fragmentation. The onset of sleep is associated with the decline in core body temperature. Generally, younger people choose to go to bed shortly after the core body temperature achieves the minimum. Interestingly, melatonin lowers the body temperature and therefore this property may be a part of the melatonin hypnotic mechanism.

What causes the decline of melatonin production in old age is still unknown. It has been speculated, however that this progressive decline of diurnal variation in melatonin concentrations during the lifetime, signals our body to age. Based on this assumption a melatonin replacement therapy has been proposed and is practiced by many people all over the world. Is such a therapy safe and effective? Over the last 35 years I collected around 5000 papers on melatonin, many of them are devoted to the topic of melatonin and aging. In the last 100 years numerous scientific methods to extend life span were tested. Despite all the effort, the only proven remedy against aging is food restriction (3). It was determined, that a chronic 40% reduction in caloric intake beginning at the young age extended the life span of mice, rats, dogs and monkeys by some 30-50%. The undernourished animals matured very slowly, reaching puberty much later than their *ad libitum*-fed counterparts. In addition, whereas old, *ad libitum* fed rats suffered from tumors and cataracts, the chronically undernourished rats appeared to be in good health until a very old age. Interestingly, there is a connection of the antiaging effect of caloric restriction to

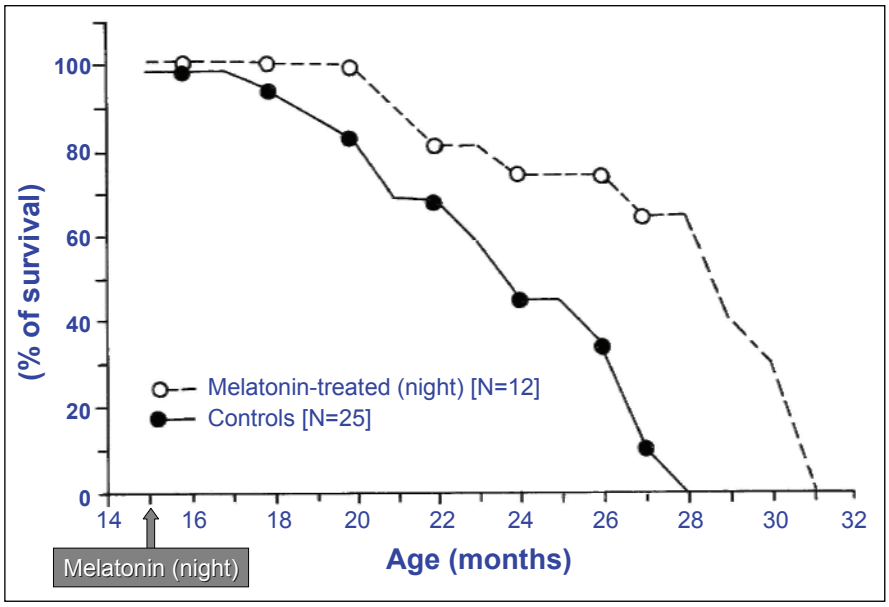

Fig. 5. A three month life extension observed in female mice given daily melatonin in the evening. (Adapted from Pierpaoli and Regelson 1994).

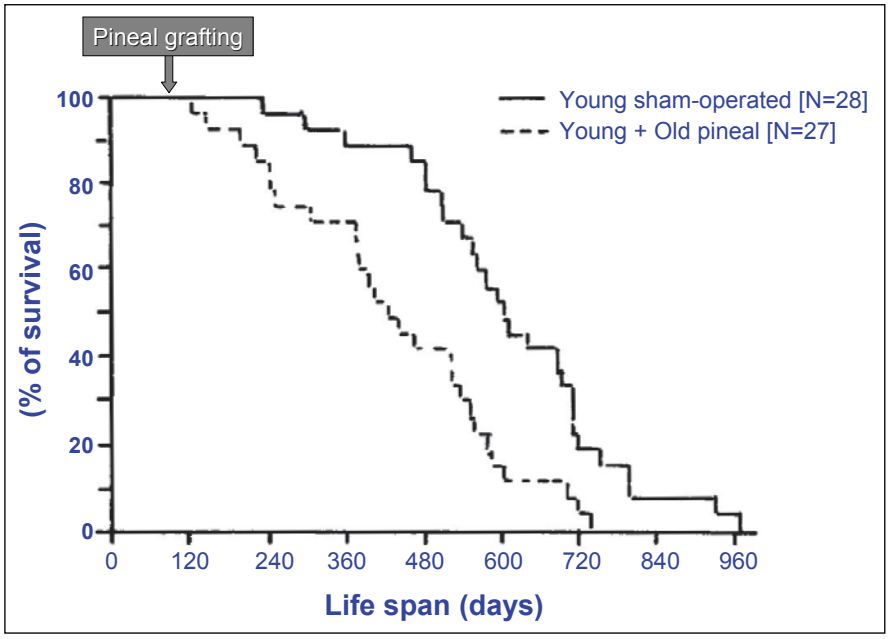

Fig. 6. The grafting of old pineals into the brains of 4 months old male mice caused the early onset of aging. (Adapted from Pierpaoli and Bulian 2001).

melatonin, which was demonstrated in numerous studies. Chronic restriction of food intake preserved the nighttime peak of melatonin secretion, which is mostly lost in old age. (9, 12). The food-restricted rats had nighttime melatonin levels twice as high as their *ad libitum* counterparts (12, 20, 21). In addition, the number of adrenergic receptors in the pineal gland, which are involved in melatonin secretion, was twice as high in food-restricted rats than in controls (22) (*Fig. 5*). In several studies melatonin given in the drinking water significantly extended the life span of male rats and increased their levels of testosterone (23). In elegant, but controversial studies of Pierpaoli group in Switzerland, transplantations of pineal glands from young mice to old animals increased their life span by 42% (*Fig. 6*). Conversely, implanting old pineals into young mice reduced their life span by 29% (24). Chronic nighttime administration of melatonin not only increased the life span of mice but also improved their imunocompetence, increased the weight of their thymus, adrenals and testis and elevated blood concentrations of testosterone and thyroid hormones (25, 26). In another study, injections of melatonin restored immune functions in experimentally immunosupressed or aging rats (27). Melatonin also antagonized the immunosupressive effect of stress in mice (28).

In Russia, scientists established that the extract from the pineal gland called epithalamin increased the life span of mice and rats up to 30-40% and inhibited spontaneous development of tumours. In another study, an administration of melatonin not only increased the life-span of mice but also reduced the incidence of carcinogenesis in the colon, mammary gland and uterine cervix (29, 30). The addition of melatonin to the drinking water of middle-aged rats, which produced nocturnal and diurnal concentration of melatonin equivalent to those observed in young rats, reduced intra-abdominal fat and non-fasted plasma insulin and leptin. In addition it significantly stimulated investigative behavior response, which was restored to the youthful levels. So, these rats not only lived longer but also had more fun, without ever going hungry. Interestingly, no changes in hormonal levels or behavior were observed when melatonin was given to young rats (31).

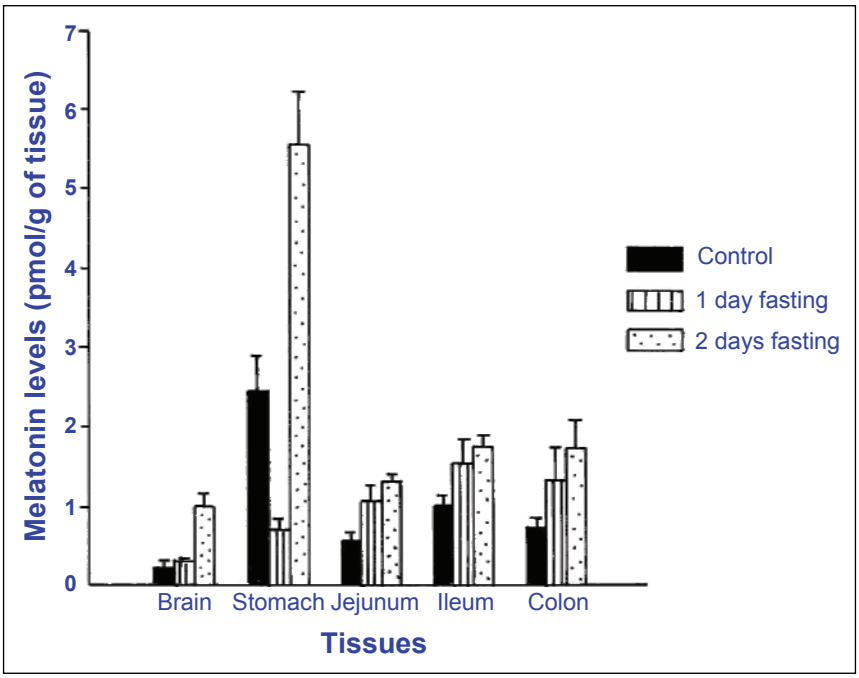

Fig. 7. Melatonin levels in the brain and the various segments of GIT of mice fasting for one or two days. Note the doubling of melatonin levels in fasting mice. (Adapted from Bubenik *et al*. 1992).

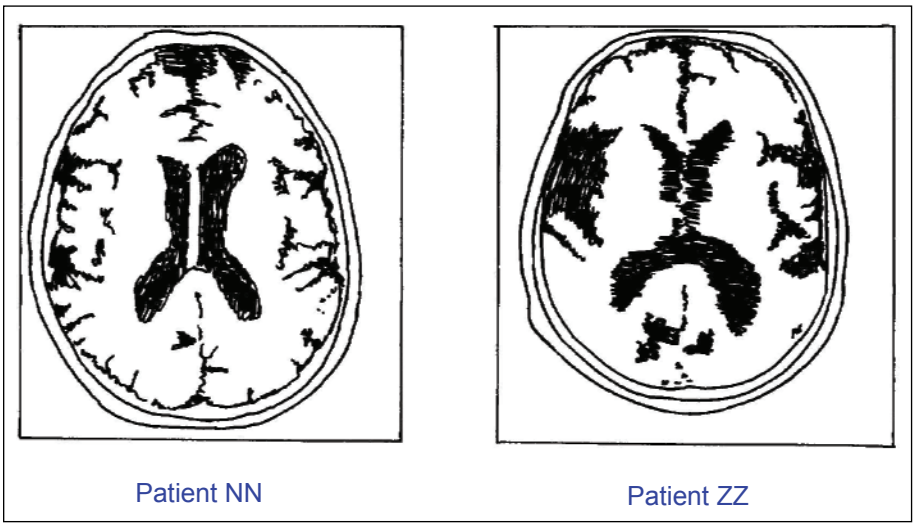

Fig. 8. Comparison of MNR brain recording of monozygotic twins, both of them were suffering from the Alzheimer's disease. The patient on the left (NN) was given melatonin (6 mg/day) for the period of 36 months, whereas patient on the right (ZZ) was given a placebo. Note the bitemporal atrophy and an enlargement of ventricules in the non-treated patient on the right (ZZ). (Adapted from Brusco *et al*. 1998).

So it can be concluded that if you want to live a very long and healthy life you can either be permanently hungry or instead, you can take some melatonin. That at least a part of the effect of food restriction on the life-span extension is probably mediated *via* melatonin produced in the GIT and not *via* the pineal gland was demonstrated by Roky and coworkers (32). Change in food availability altered the diurnal distribution of sleep in rats, but removal of the pineal had no effect on the sleep pattern. This indicated that the hypnotic signal, presumably melatonin, is produced in other tissues than the pineal, perhaps the GIT. In the gut, melatonin secretion is more related to food intake than to the diurnal variation of daylight. The involvement of GIT in the diet-related extension of life span was supported by our study in mice, where 2 days of fasting doubled melatonin concentrations in most gut tissues. Especially high elevation was detected in the stomach tissues (*Fig. 7*) (33).

The GIT tract is a major source of body melatonin, which is probably secreted from the hormone-producing enterochromaffin cells of the GI mucosa (34). Because of the enormous size of the GIT, it is estimated that at any time, this organ contains more than 400x more melatonin than the pineal gland (35). The guts have often been compared to the sewer. The large intestine, especially the colon, which has a vast concentration of melatonin, is full of noxious substances which are the results of terminal metabolic activity. A detoxification of the gut contaminants occurs with the help of powerful antioxidants. One of them is melatonin (9), an ancient scavenger of free radicals. It has not been established yet whether an age-dependant decrease of melatonin, similar to one observed in the pineal gland or serum, also occurs in the gut. However, if such melatonin reduction also occurs in the gut, then such a decrease of melatonin production may facilitate the process of aging. A daily supplementation of melatonin would then bring their serum levels to those observed in younger subjects.

Why should melatonin have such a profound effect on the aging process? There are several possible explanations: as the melatonin rhythm deteriorates with aging, other circadian rhythms are also weakened and crucial rhythms become desynchronized. This desynchronization may significantly contribute to aging and make the organism more susceptible to old age diseases. It has been hypothesized that the duration and

amplitude of nocturnally elevated melatonin, which are reduced at old age, are consequential to the determination of the rate of aging (3, 9). Another prominent theory of aging attributes the rate of aging to accumulated free radicals. As melatonin can significantly protect DNA and other macromolecules against free radical damage (16), melatonin can be a major factor in determining the rate of aging (9). Melatonin is one of the most effective antioxidant (9) effective in scavenging highly toxic hydroxyl radicals (36) and is several times more efficient than vitamin E in neutralizing the peroxyl radicals (9). According to Maestroni and Conti, (37) melatonin is an adaptation hormone that helps to coordinate and synchronize the adaptive responses to environmental variables. Finally, melatonin may be effective in the prevention of neurodegenerative diseases. In animals, given prophylactically melatonin either reduced the beta amyloid toxicity or totally prevented death of cells in the experimental models of Alzheimer disease (38, 39). Melatonin also reduced oxidative damage in several models of Parkinson's disease (*Fig. 8*). In a human study of Brusco and coworkers (40) melatonin was given to one of two of monozygotic twin brothers. After three years of daily melatonin administration, the treated brother exhibited significantly less symptoms of Alzheimer's disease than his non-treated twin. In the most recent study a supplementation with melatonin was found to be effective in mild cognitive impairment, the condition preceding dementia (41). Based on these preliminary experiments it can be speculated that the loss of melatonin in old age may contribute to the incidence or severity of some age-related neurodegenerative diseases (42).

As always in science, not all results of studies are pointing into the same direction. In the most recent article, Anisimov and co-workers reported that melatonin increased both the life-span and the incidence of tumours in female mice (42-44). The authors therefore warned that the use of melatonin as a gerontoprotective agent must be considered with care and more studies are needed before a definite recommendation can be made. Conversely it almost seems logical, that if melatonin extends the life-span more tumours will appear in the melatonin-treated groups, as tumor incidence increases with age.

So far, melatonin has not been officially tested as the "fountain of youth". However, because it cannot be patented, it is sold relatively cheaply in health food stores and pharmacies of many countries, including USA. Because of its reputation as a miracle drug, large number of middle age and old people are taking melatonin daily. That vast group of people may one day provide the so far missing experimental evidence whether the long-term use of melatonin is harmful, had no effect or may increase the life span or improve the health of aging folks of this planet. I would like to have a longer and healthy life, but I hate to be hungry (it gives me pain in the stomach). So after what I learned working for almost 35 years in this field, to be on the safe side, I take melatonin occasionally. If nothing else, it gives me nice dreams.

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Conflict of interests: None declared.

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