

Bibliography for Melatonin

Bartsch C, Bartsch H, Schmidt A, Ilg S, Bichler KH, Fluchter SH. 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* 1992;209:153-167.

Becker-Andre M, et al. Pineal gland hormone melatonin binds and activates an orphan of the nuclear receptor superfamily. *J Bio Chem* 1994; 269:28531-28534.

Bellipanni G, DI Marzo F, Blasi F, DI Marzo A. Effects of melatonin in perimenopausal and menopausal women: our personal experience. *Ann N Y Acad Sci.* 2005 Dec;1057:393-402.

The purpose of this clinical trial on possible effects of nocturnal MEL administration in perimenopausal women was to find if MEL by itself modifies levels of hormones and produces changes of any kind, independently of age (42-62 years of age) and the stage of the menstrual cycle. It is accepted that a close link exists between the pineal gland, MEL, and human reproduction and that a relationship exists between adenohypophyseal and steroid hormones and MEL during the ovarian cycle, perimenopause, and menopause. Subjects took a daily dose of 3 mg synthetic melatonin or a placebo for 6 months. Levels of melatonin were determined from five daily saliva samples taken at fixed times. Hormone levels were determined from blood samples three times over the 6-month period. Our results indicate that a cause-effect relationship between the decline of nocturnal levels of MEL and onset of menopause may exist. The follow up controls show that MEL abrogates hormonal, menopause-related neurovegetative disturbances and restores menstrual cyclicity and fertility in perimenopausal or menopausal women. At present we assert that the six-month treatment with MEL produced a remarkable and highly significant improvement of thyroid function, positive changes of gonadotropins towards more juvenile levels, and abrogation of menopause-related depression.

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Coon SL, Roseboom PH, Baler R, et al. Pineal serotonin N-acetyltransferase: expression cloning and molecular analysis. *Science* 1995;270:1681-1683.

Crespo D, Fernandez-Viadero C, Verduga R, Ovejero V, Cos S. J Interaction between melatonin and estradiol on morphological and morphometric features of MCF-7 human breast cancer cells. *Pineal Res.* 1994 May;16(4):215-22.

Melatonin has been shown to have a direct inhibitory effect on the proliferation of estrogen-responsive MCF-7 human breast cancer cells, involving an interaction with estradiol. The anti-proliferative effect of melatonin is reversed by the addition of estradiol to the culture. In the present study, we examined whether inhibition by melatonin and subsequent estrogen rescue of MCF-7 cells are correlated with morphological and morphometric changes in these cells. After 4 days of exposure to melatonin, MCF-7 cells showed significantly smaller cell and nuclear sizes than other groups. These morphometric results were closely related to the ultrastructural features observed in these cells. While control and estradiol-treated cells showed increased tumor characteristics, melatonin-treated cells presented greater differentiation, in keeping with their epithelial origin (presence of cytokeratin filament bundles, conspicuous rough endoplasmic reticulum, and Golgi cisternae together with the presence of prominent nucleoli at the nuclear level). Additionally, some melatonin-treated cells displayed degenerative features (mitochondrial swelling with disruption of cristae, cytoplasmic vacuolation, nuclear chromatin disgregation and cell lysis). The addition of estradiol to cells previously incubated with melatonin reversed the changes induced by the latter and these cells showed

the same ultrastructural features as the control cells. Our results support the notion that melatonin exerts its antitumor effect through a cell-cycle-specific mechanism by delaying the entry of MCF-7 cells into mitosis. This allows the tumor cells to achieve greater differentiation. The fact that the morphometric and morphological effects induced by melatonin are counteracted by estrogens suggests a cell-cycle acceleration induced by estradiol.

Ferrari E, Cravello L, Falvo F, Barili L, Solerte SB, Fioravanti M, Magri F. Neuroendocrine features in extreme longevity. *Exp Gerontol.* 2008 Feb;43(2):88-94.

*In order to evaluate the effects of some neuro-endocrine changes during aging we have studied adrenal, thyroid and pineal secretion in young, healthy old and centenarians. The number of subjects in each hormone group varied. The following parameters were evaluated: serum levels of cortisol, dehydroepiandrosterone-sulfate (DHEAS), free triiodothyronine (FT3), thyroxine (FT4), reverse triiodothyronine (rT3) and thyroid-stimulating hormone (TSH). Urinary 6-hydroxymelatonin sulfate (aMT6s) and free cortisol were measured twice daily. Centenarians exhibited significantly lower TSH levels together with slightly higher rT3 levels than old controls. These changes could be due to reduced 5'-deiodinase activity occurring also in absence of substantial changes of the nutritional pattern. Morning serum cortisol levels were found to be similar in the 3 age groups, whereas the decline of serum DHEAS levels was well evident also after the ninth decade of life. **The cortisol/DHEAS molar ratio, which usually increases with age and considered to be an expression of a neurotoxic pattern of the steroidal milieu in the central nervous system, did not show any further increase in centenarians.** The urinary free cortisol and aMT6s excretion declined with age; however only in centenarians and in young controls aMT6s excretion was significantly higher at night than during the day. **These findings suggest that the circadian rhythm of melatonin secretion is maintained in centenarians and, based on the limitations of this study, could be considered one factor in successful aging.** PMID: 17764865*

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Lesnikov V Piepaoli W Pineal cross-transplantation (old-to-young and vice versa) as evidence for an endogenous "aging clock" *Ann N Y Acad Sci* 1994; 719: 456-460.

Pineal glands were cross transplanted between old and young mice. The young gland transplanted into old mice produced a significant delay in aging and death, whereas the old gland transplanted into young mice produced a remarkable acceleration of aging and death. The differences amounted to one-fourth the usual life span of the mouse. The pineal gland appears to be a kind of "aging clock".

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Lissoni P, Meragalli S, Fossati V et al. A randomized study of low dose subcutaneous interleukin-2 plus melatonin vs. chemotherapy for advanced non-small cell lung cancer. *Tumori* 1994; 80:464-67.

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Melatonin reduces prostate cancer cell growth leading to neuroendocrine differentiation via a receptor and PKA independent mechanism. *The Prostate* 2005 63:29-43

Melatonin reduced the number of human cancer cells in vitro and increased the cells' tendency to differentiate into neuroendocrine cells. It worked on androgen sensitive and insensitive cells. It worked in the presence of androgen also. Melatonin's effects were thought to be both receptor-mediated and due to direct scavenging and anti-oxidant effects. Many anti-oxidants have been shown to help prevent prostate cancer including vitamin E.

Molls TM, Spriggs LL, Hill SM. Modulation of estrogen receptor mRNA expression by melatonin in MCF-7 human breast cancer cells. *Mol Endocrinol* 1994;8:1G81-1G90.

Ortiz GG, Sanchez-Ruiz Y, Tan DX, Reiter RJ, Benitez-King G, BeasZarate C. Melatonin, vitamin E, and estrogen reduce damage induced by kainic acid in the hippocampus: potassium-stimulated GABA release. *J Pineal Res* 2001 Aug;31(1): G2-7.

Pierpaoli W, Bulian D, Dall'Ara A. Circadian melatonin and young-to-old grafting postpone aging and maintain juvenile conditions of reproductive functions in mice and rats. *Exp Gerontology* in press; Abstract: Third Int. Symp. of Neurobiology and Neuroendocrinology of Aging, 1996.

Reiter RJ. The role of the neurohormone melatonin as a buffer against macromolecular oxidative damage. *Neurochem Int* 1995;27:453-460.

Melatonin is phylogenetically a very old molecule. This may be due to its free-radical scavenging ability—especially the hydroxyl radical (-OH). It may be produced in all aerobic organisms and it seems to have evolved coincident with aerobic metabolism to prevent oxidative attack by oxygen-centered radicals. It is highly lipophilic and enters into all cells easily where it appears to concentrate in the nucleus. It is a better free radical scavenger than mannitol or glutathione. Unlike exogenous anti-oxidants which can become toxic at some dose, melatonin appears to have no toxicity. It has been given in amounts of 300mg/day for 5 years with no untoward effects. It has been shown to counteract safrrole-induced liver damage in rats by 20% during sleep when melatonin levels are higher, by 60% in a low dose, and 99% at a high dose. Since many human diseases have free-radical damage as their basis, and since melatonin production decreases with age, melatonin supplementation could become very important in the prevention and treatment of disease in humans.

Reiter RJ. Oxygen radical detoxification processes during aging: the functional importance of melatonin. *Aging (Milano)*. 1995 Oct;7(5):340-51.

That free radical destruction of macromolecules is a basis of aging and age-related diseases has considerable experimental support. Melatonin, a hormone produced in organisms as diverse as algae and humans, is believed to have evolved coincident with aerobic metabolism. In all organisms melatonin is produced primarily during the daily period of darkness, with only small amounts being synthesized during

the day. In mammals including man, melatonin is produced by and secreted from the pineal gland during the night; however, the night-time production of melatonin falls markedly with aging such that in senescent animals a night-time melatonin rise is barely measurable. This may be significant in terms of aging in the light of recent observations which show that melatonin is a highly efficient free radical scavenger and antioxidant both in vitro and in vivo. In vitro, melatonin has been shown to directly scavenge both the hydroxyl and peroxy radical, and it does so more efficiently than other known antioxidants. Furthermore, melatonin greatly potentiates the efficiency of previously-discovered endogenous and exogenous antioxidants. In vivo, both physiological and pharmacological levels of melatonin reportedly counteract the devastatingly destructive actions of free radical generating chemicals. For example, melatonin effectively combats DNA damage in rats given massive doses of the chemical carcinogen safrole, and the indole overcomes much of the genomic damage inflicted by ionizing radiation. Also, lipid peroxidation induced by either paraquat, bacterial lipopolysaccharide or H₂O₂ is highly significantly reduced by concurrent melatonin administration. Finally, cataracts produced in newborn rats by the depletion of the endogenous antioxidant glutathione are prevented by melatonin. These findings provide evidence that melatonin is operative in the cell nucleus, in the aqueous cytosol and in lipid-rich cellular membranes as an antioxidant. Considering this, the loss of this potent antioxidant during aging may be consequential in terms of cellular and organismal aging as well as the onset of age-related diseases. These experimental results from a variety of sources suggest that a more determined approach to the study of melatonin as an anti-aging factor is warranted.

Rommel T, Demisch L. Influence of chronic beta-adrenoreceptor blocker treatment on melatonin secretion and sleep quality in patients with essential hypertension. *J Neural Transm Gen Sect.* 1994;95(1):39-48.

The nocturnal production of melatonin synthesis has been associated with circadian mechanisms of the organization of sleep. It is well known that the synthesis of melatonin is under the control of pineal beta 1-adrenoreceptors. In this study the effect of ten weeks treatment with the beta-adrenoreceptor (beta-AR) blockers propranolol and rizadolol on melatonin synthesis and on sleep quality was examined in 42 patients suffering from essential hypertension. Before and after 6 and 10 weeks of beta-AR-blocker administration urinary sulfatoxymelatonin excretion rates were measured and sleep factors were evaluated by using a standardized sleep inventory consisting of self-rating sleepiness scales. After 6 and 10 weeks of treatment, a significant about 50 percent reduction of sulfatoxymelatonin was measured. No relationship between these reductions and changes in sleep factors was found. The results indicate that a reduced nightly amplitude of melatonin has minor significance for the organization of physiological sleep. Furthermore, it is suggested that pineal mechanisms beside the beta 1-adrenergic receptor transduction system serve to maintain the melatonin signal to a considerable extent during a chronic beta 1-AR blockade.

Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev.* 2004 Jun;13(6):936-43

OBJECTIVE: Light exposure during night work suppresses melatonin production, and night work has been associated with an increased cancer risk. There is little information, however, about the interrelationships of night work, urinary melatonin levels, and levels of plasma steroid hormones in women. **METHOD:** We examined the reproducibility of morning urinary measurements of 6-sulfatoxymelatonin over a 3-year period in 80 premenopausal women. We assessed correlations between average urinary melatonin and plasma steroid hormone levels and evaluated potential associations between night work and hormone levels, using current and long-term shift work information from two large, prospective cohorts, the Nurses' Health Study cohorts. **RESULTS:** The intraclass correlation for creatinine-adjusted 6-sulfatoxymelatonin was 0.72 (95% confidence interval, 0.65, 0.82). We found significantly increased levels of estradiol after longer durations of night work (geometric mean levels of estradiol, 8.8 pg/mL for women who never worked night shifts versus 10.1 pg/mL for women who worked 15 or more years of night shifts; *P* for trend = 0.03). **We observed a significant inverse association**

between increasing number of nights worked within the 2 weeks preceding urine collection and urinary melatonin levels ($r = -0.30$, $P = 0.008$), but no association of recent night work with estradiol ($r = 0.10$, $P = 0.41$). CONCLUSION: A single morning urinary melatonin measurement is a reasonable marker for long-term melatonin levels among premenopausal women. Women who work on rotating night shifts seem to experience changes in hormone levels that may be associated with the increased cancer risk observed among night-shift workers.

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