Melatonin

Melatonin is and efficient antioxidant

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We have compared the peroxyl radical scavenger ability of melatonin with that of vitamin E, ascorbic acid (As.A.), reduced glutathione (GSH) and mannitol. All the antioxidants, except mannitol, prevented the lysis of human erythrocytes exposed to an ate-initiator of peroxyl radicals (2,2'azo-bis(2-amidino-propane)dihydrochloride) at 37 degrees C. The percentage of this inhibition of erythrocyte lysis varied with the concentration of antioxidants, but the efficiency was melatonin> vitamin E> As.A.> GSH. Based on the assumption that each molecule of vitamin E scavenges two peroxyl radicals, the scavenging capacity of melatonin was four peroxyl radicals/molecule.

Modulation of cancer endocrine therapy by melatonin: A phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone

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Recent observations have shown that the pineal hormone melatonin (MLT) may modulate oestrogen receptor (ER) expression and inhibit breast cancer cell growth. On this basis, we have evaluated the biological and clinical effects of a concomitant MLT therapy in women with metastatic breast cancer who had progressed in response to tamoxifen (TMX alone. The study included 14 patients with metastasis who did not respond (n = 3) to therapy with TMX alone or progressed after initial stable disease (SD) (n = 11). MLT was given orally at 20 mg day (-1) in the evening, every day starting 7 days before TMX, which was given orally at 20 mg day (-1) at noon. A partial response was achieved in 4/14 (28.5%) patients (median duration 8 months). The treatment was well tolerated in all cases, and no MLT-induced enhancement of TMX toxicity was seen; on the contrary, most patients experienced a relief of anxiety. Mean serum levels of insulin-like growth factor 1 (IGF-I), which is a growth factor for breast cancer, significantly decreased on therapy, and this decline was significantly higher in responders than in patients with SD or progression. This pilot phase II study would suggest that the concomitant administration of the pineal hormone MLT may induce objective tumor regressions in metastatic breast cancer patients refractory to TMX alone.

T-helper-2 lymphocytes as a peripheral target of melatonin

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In the past several years we demonstrated that the pineal neurohormone melatonin has immunoenhancing properties and can counteract the immunodepression that may follow acute stress, drug treatment, and viral diseases or aging. Several laboratories have subsequently confirmed and extended our findings. It soon appeared evident that T-derived cytokines constitute the main mediators of the immunological effect of melatonin. We have recently found a high affinity (Kd: 346 +/- 24pM) binding site for I-125-melatonin on T-helper-type 2 lymphocytes in the bone marrow. Activation of this putative melatonin receptor, with both physiological and pharmacological concentrations of melatonin, resulted in an enhanced production of interleukin-4 (IL4) which in turn acted on bone marrow stromal cells and induced the release of hematopoietic growth factors. This melatonin-cytokine cascade showed the remarkable capacity of rescuing

hematopoietic functions in mice treated with cancer chemotherapeutic compounds without interfering with the anticancer action of these agents. The very low concentration (0.1 nM) at which melatonin is active may well reflect a physiological function of endogenous melatonin. The pineal gland has been, in fact, reported to signal the blood forming system. The evidence of IL4 involvement is relevant to our understanding of many melatonin effects and may be part of a pineal-immune axis involving also Th1 cytokines. The ability of rescuing hematopoiesis against the toxic action of cancer chemotherapeutic compounds and the presence of high-affinity IL4 receptors on human tumors provide a further promising rationale for the clinical use of melatonin.

Impaired nocturnal secretion of melatonin in coronary heart disease

Land 345: 8962 (JUN. 3 7995)

Patients with coronary heart disease have increased nocturnal urinary noradrenaline. Because melatonin suppresses sympathetic activity, we measured serum melatonin concentrations at night (0200 h) in 15 patients with coronary heart disease. Melatonin was significantly lower in the patients than in 10 healthy controls (median 7.8 [interquartile range 6.5 11.81 vs 36.2 [32.2-42.51 pg/mL, p<0.0001). Thus, impaired nocturnal secretion of melatonin is associated with coronary heart disease. Patients disease nocturnal noradrenaline.

The pineal gland and melatonin in relation to aging: A summary of the theories and of the data

Experimental Gerontology 30: 3-4 (May-Aug. 1995)

Within recent years, many investigators have implicated the pineal gland and melatonin in the processes of both aging and age-related diseases. These theories stem from the importance of melatonin in a number of biological functions and the fact that melatonin production in the organism is gradually lost throughout life, such that in very old individuals of any species the circadian melatonin rhythm is barely discernible. In most species, from algae to humans, where it has been investigated, melatonin has been shown to exhibit a strong circadian rhythm in production and secretion, with high levels of the indole always being associated with the dark period of the light:dark cycle. One theory states that when the melatonin rhythm deteriorates during aging, other circadian rhythms are likewise weakened and rhythms become dysynchronized. This dysynchronization is believed to contribute significantly to aging and to render animals more susceptible to age-related diseases. Another theory assumes that the waning melatonin cycle provides an important switch for genetically programmed aging at the cellular level; furthermore, because all cells in the organism are exposed to the same gradually dampening melatonin signal throughout life, all cells age more or less at the same rate. In this theory, it is presumed to be the duration of the nocturnally elevated melatonin (which, like the amplitude, is reduced during aging), which, when coupled to a time-gating signal, is conse quential in determining the rate of aging. Another compelling argument that the reduction in melatonin with age may be contributory to aging and the onset of age-related diseases is based on the recent observations that melatonin is the most potent hydroxyl radical scavenger thus far discovered. A prominent theory of aging attributes the rate of aging to accumulated free radical damage. Inasmuch as melatonin can markedly protect macromolecules, especially DNA, against free radical attack, it could, indeed, be a major factor in determining the rate at which organisms age. Besides its ability to directly scavenge the highly toxic hydroxyl radical, melatonin also promotes the activity of the antioxidative enzyme glutathione peroxidase, thereby further reducing oxidative damage. These actions may be

manifested more obviously in the central nervous system, which is highly susceptible to damage by oxygen-based radicals and, because of its inability to regenerate and its high vulnerability to oxidative attack, its deterioration may be especially important in aging. Thus, if melatonin preferentially affords antioxidant protection to the brain, it could be a major player in delaying aging and age-related diseases. In the few studies where animals have been supplemented with exogenous melatonin throughout life, life span has been increased up to 25%. Besides its protection of the brain, melatonin has been shown to prevent damage by oxidants to DNA in other organs. Again, protecting DNA is particularly important because there are only two copies in each diploid cell, and structurally impaired DNA would not property transcribe, leading to metabolic inefficiency and possibility to death of the cell. Thus, for a number of reasons, maintaining a robust melatonin rhythm by exogenously administering the indole may prove to have a variety of beneficial effects, which collectively could serve to prolong life, postpone aging, and reduce the chances of age-related diseases.

Melatonin stimulates brain glutathione peroxidase activity

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Exogenously administered melatonin causes a 2-fold rise in glutathione peroxidase activity within 30 min. in the brain of the rat. Furthermore, brain glutathione peroxidase activity is higher at night than during the day and is correlated with high night-time tissue melatonin levels. Glutathione peroxidase is thought to be the principal enzyme eliminating peroxides in the brain. This antioxidative enzyme reduces the formation of hydroxyl radicals formed via iron-catalyzed Fenton-type reactions from hydrogen peroxide by reducing this oxidant to water. Since the hydroxyl radical is the most noxious oxygen radial known, induction of brain glutathione peroxidase might be an important mechanism by which melatonin exerts its potent neuroprotective effects.

Sleep-inducing effects of low doses of melatonin ingested in the evening

Clinical Pharmacology & Therapeutics 57:5 (MAY 7995)

We previously observed that low oral doses of melatonin given at noon increase blood melatonin concentrations to those normally occurring nocturnally and facilitate sleep onset, as assessed using an involuntary muscle relaxation test. In this study we examined the induction of polysomnographically recorded sleep by similar doses given later in the evening, close to the times of endogenous melatonin release and habitual sleep onset. Volunteers received the hormone (oral doses of 0.3 or 1.0 mg) or placebo at 6, 8, or 9 PM. Latencies to sleep onset, to stage 2 sleep, and to rapid eye movement (REM) sleep were measured polysomnographically. Either dose given at any of the three time points decreased sleep onset latency and latency to stage 2 sleep. Melatonin did not suppress REM sleep or delay its onset. Most volunteers could clearly distinguish between the effects of melatonin and those of placebo when the hormone was tested at 6 or 8 PM. Neither melatonin dose induced "hangover" effects, as assessed with mood and performance tests administered on the morning after treatment. These data provide new evidence that nocturnal melatonin secretion may be involved in physiologic sleep onset and that exogenous melatonin may be useful in treating insomnia.