Melatonin Deficiency: Its Role in Oncogenesis and Age-related Pathology

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Summary

Melatonin deficiency may be a critical starting point for the degenerative processes leading to cellular pathology and oncogenesis. Relative melatonin deficiency at the cellular level may be induced by pineal gland decline and/or oxidative damage to melatonin receptor sites. Melatonin, as the primary neurohormone regulator, governs cellular metabolic processes via moderation of cellular cGMP and cAMP ratios, which control the production of intracellular antioxidants. Melatonin deficiency results in uncontrolled cAMP synthesis, leading to unregulated oxidative processes and subsequent free radical damage. Free radical induced pathology is a fundamental mediator of metabolic dys-regulation underlying the development of pathological aging symptoms and the development of cancer. Exogenous melatonin has proved to arrest and reverse the consequences of its deficiency.

All processes can be described as the oscillatory balance of two principles. These principles can be fundamentally characterized by two basic forces of nature, homotropy (entropy) and heterotropy (preservation of order). This concept of dualism can be of great importance in the study of biological phenomena. There are two basic divisions of physiological processes; catabolism (homotropy) predominates during the day and is involved with the oxidative processes of energy production and immunity. During the day, energy production and immunity are regulated by hormones and enzymes which are replenished in a circadian fashion. Anabolic processes (heterotropy) predominate at night. Hetero-tropic forces direct organization and synthesis. It is in this phase that tissues are regenerated, hormones, enzymes and anti-oxidants are synthesized and glycogen reserves are restored (Rozencwaig, 1987). Life is dependent upon the coordinated adaptive changes of these two basic metabolic processes aimed at conserving vital constants (e.g., temperature, pH, energy production, repair, cellular antioxidant levels, etc.).

A healthy organism can be described as one which is able to maintain its homeostatic processes when challenged. Every cell in the body and all of the regulatory hormones are modulated by the pineal hormone, melatonin (Reiter, 1984). Melatonin production is rhythmically induced every sunset (its synthesis is inhibited by light) and its level drops off during the day. Melatonin regulates the hypothala-mic-pituitary-gonadal-adrenal axis (Cardinale, 1975).

One of melatonin's most important functions is that of a transducer. A transducer receives energy from one system and transmits it to another, often in a different form. Melatonin transduces information about variations in external stimuli (light, temperature, humidity, pheromones, antigens, magnetism, etc.) and internal messages (psychogenic stimuli, autoantigens, cancer, etc.) into delicately coordinated neuroendocrine changes (Pierpaoli, 1987). Melatonin also regulates the expression of hormone receptors and antibody receptors (Abo, 1980). Melatonin controls oxidative processes via modulation of cellular cGMP and cAMP ratios (Vacas, 1981). Oxidative processes are induced by low cGMP levels and high cAMP levels (Cutler, 1984). Whereas, melatonin induces low cAMP/ cGMP ratios which favour an increase in anabolic restorative processes and antioxidant production. Organisms have developed the means of counteracting the accumulation of cytotoxic by-products of oxidative reactions. These include: intracellular detoxification reactions, protein

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degradation systems and antioxidant synthesis (Rozencwaig, 1987). It is the mean level of antioxidants that governs the function and longevity of the cell and thus the life span potential of the organism (Cutler, 1984).

Melatonin levels in animals and humans show age-dependent declines (Nair, 1986; Rozencwaig, 1987). Reduced melatonin levels result in a decline in protective and restorative processes and subsequently, a diminished responsiveness of the circadian systems to exogenous and endogenous stimuli (Moor-Ede, 1982). A reduced adaptive capacity may initiate the metabolic dysregulation leading to age-related pathology. The subsequent neuroendocrine changes induce the pathological changes observed in the aging organism: arterio-sclerotic changes; free radical damage to membranes, resulting in reduced absorption of nutrients and excretion of waste products; hormonal changes mediated by a dysregulated hypothalamus-pituitary axis; changes in sleep patterns; increased incidence of cancer, etc.

Oral melatonin, administered to animals and humans, restored these adaptive systems (Arzt, 1988; Pierpaoli, 1987). The oncostatic and anti-proliferative effects of melatonin have been well-established (Barni, 1988; Esposti, 1988; Hill, 1988; Regelson, 1987). Treatment with melatonin has been reported to inhibit the growth of specific cancer cells (Tamarkin, 1981) and to inhibit the induction of tumors by carcinogenic agents (Quay, 1980). Both high and low melatonin blood levels have been observed in neoplastic disorders (Lissoni, 1986; Pico, 1979). We suspect that in the early course of neoplastic development, high melatonin blood levels are seen because melatonin can not bind to free-radical damaged receptors. There is a functional melatonin deficiency at the cellular level in spite of high melatonin blood levels. As the cancer progresses, melatonin production may decline due to a lack of regulatory feedback from damaged cells.

Experiments have shown that exogenous melatonin has a therapeutic regulatory effect on the immune system (Maestroni, 1983). Melatonin, administered to mice completely negated the psychogenic stress effects produced by restraint and restored thymus weight. Melatonin was able to counter *in vivo* the suppression of antibody production produced by administration of corticosteriods (Pierpaoli, 1987). Melatonin protected stressed mice from exposure to encephalomyocarditis virus (EMV), a lethal neurotropic murine pathogen (Pierpaoli, 1987). Most of the mice which had been stressed and infected with EMV died, while most of the stressed melatonin-treated mice survived the virus. Exogenous melatonin may be indicated as an immunoprotective agent in conditions of environmental or psychogenic stress which promotes onset and development of infectious diseases, including AIDS. The immunoenhancement, anti-stress, and oncostatic effects of melatonin were blocked by the specific opioid antagonist naltrexone, indicating that melatonin acts via the endogenous opioid system (Maestroni, 1987).

Melatonin has demonstrated remarkable anti-aging effects in mice (Pierpaoli, 1987). Small doses, prolonged their lives by 20%. Not only were the lives of the treated animals extended but Pierpaoli writes, "melatonin exerted an extraordinary positive action on their performance and reversed or delayed the symptoms of age-related debility, disease, and cosmetic decline in a dramatic fashion."

Conclusion:

It is likely that the metabolic dysregulation leading to the development of the pathological symptoms often seen with the aging process and the onset of cancer are often initiated by a decline in melatonin production and/or utilization. These biochemical disorders originate in the disruption of those neuroendocrine adaptive feed-back process which are governed by melatonin. Melatonin's very low toxicity (Wurtman, 1985; Sugden, 1983) and the ample documentation of its therapeutic effects, call for further investigation.

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