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Nutrition Bytes

Title
Melatonin and its Role in Aging and Oxidative Stress

Permalink
https://escholarship.org/uc/item/7223c4f1

Journal
Nutrition Bytes, 2(1)

ISSN
1548-4327

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Publication Date
1996

Peer reviewed

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University of California

In an age where medicine has prolonged life by alleviating illness and disease, desires of longevity have also led many in the search for a treatment to delay the aging process. In recent years, evidence correlating neuronal oxidative stress and the promotion of aging has sparked a keen interest in the antioxidative effects of the pineal derived neurohormone, melatonin. Synthesized in the dark phase of a circadian dark/light photoperiod, melatonin is thought to play an integral role in the body's defense against the toxic effects of free radicals. As endogenous levels of melatonin decrease with advancing age, and along with it the protective effects of the hormone, researchers and clinicians see potential in supplementing the body with therapeutic quantities of melatonin to delay the loss of brain cells.

Pineal Gland and Melatonin Secretion

The hormone N-acetyl-5-methoxytryptamine, or melatonin, is synthesized and secreted by the pineal gland. Melatonin affects a diverse array of neuroendocrine functions mediated by both receptor and non-receptor pathways, including biological rhythms, thyroid, adrenal, sexual, and immunological feedback (1). Sympathetic innervation by the release of norepinephrine, acting on both alpha- and beta-adrenergic receptors, stimulate the conversion of serotonin to melatonin by inducing the rate limiting enzyme N-acetyltransferase via a cAMP dependent pathway (2)

In the receptor mediated pathway, melatonin is thought to be essential in the regulation of the circadian dark/light photoperiod and seasonal responses, serving as the biological clock to the repetitious environmental cycle. Synthesis and release of melatonin is synchronized with the dark/light photoperiod, peaking during the dark phase of the cycle and declining during the light phase. Exogenous physiological levels of melatonin have been shown to shift the dark/light phase curve, lower alertness, and lower body temperature (3). In the non-receptor mediated pathway, melatonin directly enters cells and can function as an antioxidant of oxygen free radicals or interact with calmodulin (4). Direct binding of melatonin to calmodulin antagonizes the calcium ion-calmodulin complex, altering the regulation of various intracellular metabolic pathways (4).

Aging and Oxidative Stress

The degenerative processes associated with aging is a biologically complex and multifaceted phenomena. A current, but putative theory on aging associates the gradual accumulation of oxidative stress in neural tissue to accelerated neurodegenerative changes and age-related diseases (2). Oxidative stress is defined as the cellular damage caused by oxygen free radicals. The two types of oxygen free radicals, the superoxide anion and the hydroxyl radical are naturally produced by-products of aerobic metabolism, the latter being more biologically toxic (5). The reactive nature of free radicals stems from their unpaired valence electron that mediates oxidative toxicity, damaging nucleic acids, membrane lipids, proteins, and carbohydrates. Approximately 5% of cellular oxygen is not used in the production of ATP, but is reduced to reactive free radicals. An estimated 1011 free radicals/cell/day formed, inducing perhaps up to 105 oxidized DNA residues formed/cell/day (4). Furthermore, it is suggested that the progression of brain cell aging occurs when the balance between oxidative stress and antioxidative defense tips towards increased free radical production (4). Neural activity, especially the release of the excitatory neurotransmitter glutamate, generates large quantities free radicals (5). Eventual cell death resulting from the accumulation of oxidative stress leads to the morphological and physiological destruction of neurons. A gradual deterioration of neurological tissue occurs, represented by functional loss, such as slowed reactions, diminished memory, or tremor (5). This progressive degeneration is the price the body pays for utilizing oxygen. Increased free radical generation may also result from the additive exposure to toxins, ultraviolet light, and stress, or from the decrease in the bodies defense systems to reduce oxidative stress, namely free radical scavengers, antioxidative enzymes, or metal chelating agents (5).

The brain as an organ has unique characteristics rendering it especially vulnerable to oxidative stress. Primarily, the brain utilizes a large amount of oxygen, comprising only about 2% of the body's weight, yet using 20% of total inspired oxygen in the resting state, and subsequently is the largest producer of free radicals per gram tissue than any other organ in the body (5). The brain also contains a high concentration of polyunsaturated fatty acids, with unsaturated bonds more prone to oxidative damage by free radicals. In addition, the cerebral spinal fluid contains few antioxidants that bind iron and copper, which otherwise are

free to catalyze free radical formation (5). And finally, as mentioned previously, specific neurotransmitter release leads to increased generation of free radicals.

Melatonin's Protective Effect

Melatonin's potential role in aging lies in its non-receptor mediated interactions as a potent oxygen radical scavenger. Studies have show that endogenous levels of melatonin have oxidative protective effects, with a greater reduction in DNA damage at night, reflecting melatonin's phasic secretion pattern (4). It scavenges both the superoxide anion and the hydroxyl radical, protecting nuclear DNA, proteins, and membrane lipids against free radical damage, as well as stimulating the activity of glutathione peroxidase, putatively the most important antioxidant in the brain (5). The indole's lipo- and hydrophilicity are properties unique to antioxidants and allow for rapid diffusion and accessibility to all subcellular components as well as freely crossing the blood-brain barrier (5). Other antioxidants are confined to particular cellular compartments, such as lipid cell membranes for vitamin E and the cytosol for vitamin C.

As the result of the aging process, non-regenerative neuroendocrine cells of the pineal gland, the pinealocytes, degenerate and may have reduced sympathetic innervation as well. This leads to a concomitant decrease in melatonin production, although studies have shown that caloric restriction helps maintain age-related decline of melatonin production (5). A reduction in circulating melatonin deprives the brain's capacity for antioxidative defense, furthering the rate of cellular damage with advancing age. It is interesting to note however, that melatonin synthesis is lowest during the light cycle, when oxidative stress reaches maximum values (1). However, the physiological significance is not well understood.

Clinical Applications of Melatonin

Clinical interests in melatonin reside in its potential as a therapeutic, as the possibility of delaying the aging process sparks great interest among clinicians, scientists, and the general populace alike (5), along with other clinical uses, such as its potential to resynchronize circadian rhythms for treatment of jet lag after eastward travel (6). In one study, therapeutic doses of melatonin has shown to increase life-span of an animal model by roughly 20% (5). Although this and other studies have yet to provide conclusive evidence of melatonin's efficacy as a therapeutic, its pharmacological characteristics at least do not prohibit its use. Melatonin is non-toxic, readily absorbed gastrointestinally, and has low-protein binding and rapid and extensive distribution after oral ingestion. It also readily crosses the blood-brain barrier (7). Notwithstanding proven efficacy, melatonin can be bought over-the-counter and has already been used as a dietary supplement in hopes of slowing the aging process.

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