

Melatonin & Zinc for Age Management

Yaşlanmanın Kontrolünde Melatonin ve Çinko

Güler ÖZTÜRK^a

^aFizyoloji AD,
Maltepe Üniversitesi Tıp Fakültesi,
İSTANBUL

Yazışma Adresi/Correspondence:
Güler ÖZTÜRK
Maltepe Üniversitesi Tıp Fakültesi,
Fizyoloji AD,
Maltepe 84845 İSTANBUL
gulerturk@yahoo.co.uk
gozturk@maltepe.edu.tr

ABSTRACT Why do we age? Why do some people seem to age faster than others? Aging results from a complex interplay between multiple different mechanisms. Over the years, researchers have put forth several theories of aging. The most widely accepted theories on the mechanism of aging are error theories and program theories. Melatonin is the main neurohormone of the pineal gland. The pineal gland shrinks with age, so melatonin production declines as we age. The pineal gland is directly involved in the aging process. Being a powerful antioxidant, melatonin may act against age-related oxidative damage. Zinc (Zn) is an essential trace element. Zn levels also decrease with age. The pineal gland is involved in Zn metabolism. The effect of melatonin on immune functions is partly attributed to an interaction with Zn. Melatonin and Zn treatment in old mice restored the reduced immunological functions. There is a tight relationship between melatonin and Zn. Melatonin and Zn supplementation may postpone aging.

Key Words: Aging, melatonin, zinc

ÖZET Neden yaşlanırsınız? Niçin bazı insanlarda diğerlerinden daha hızlı bir yaşlanma görülür? Yaşlanma çok farklı mekanizmalar arasındaki karmaşık bir etkileşim sonucu ortaya çıkar. Yıllar boyunca, araştırmacılar yaşlanma ile ilgili çeşitli teoriler ortaya koymuşlardır. Yaşlanma teorileri üzerine en yaygın kabul gören teoriler; hata ve program teorileridir. Melatonin pineal bezin başlıca nörohormonudur. Yaşla birlikte pineal bez küçülür ve bu yüzden de yaşlandıkça melatonin üretimi de azalır. Pineal bez doğrudan yaşlanma sürecine katılmaktadır. Güçlü bir antioksidan olarak, yaşla bağlı oksidatif hasara karşı etkili olabilir. Çinko(Zn) esansiyel bir iz elementtir. Zn düzeyleri de yaşla birlikte azalmaktadır. Pineal bez Zn metabolizmasına katılmaktadır. Melatoninin immün sistem üzerine etkisi kısmen Zn ile etkileşime bağlı olabilir. Yaşlı farelerde melatonin ve Zn tedavisi azalmış olan immünolojik fonksiyonları düzeltmiştir. Melatonin ve Zn arasında sıkı bir ilişki bulunmaktadır. Melatonin ve Zn desteği yaşlanmayı geciktirebilir.

Anahtar Kelimeler: Yaşlanma, melatonin, çinko

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Aging is a universal phenomenon characterized by pathological features such as oxidative stress, alterations in cell metabolism, accumulation of misfolded proteins, and nucleic acid damage. In the brain, aging is associated with progressive neuronal loss, cognitive impairment, and enhanced susceptibility to neurological diseases.¹

Sometimes chronologic age and physiologic age are not the same due to complex interaction of genetics and environment. "Why we age" is no longer a solely philosophical question.² The maximum lifespan is dependent not only on the ge-

netic heterogeneity that characterizes different species, but also variable environmental influences.² Aging is characterized by a progressive deterioration in many physiological functions and metabolic processes, ultimately leading to morbidity and mortality.³ The main theories on the mechanism of aging are error theories and program theories.²

Several researchers are making genuine attempts to test and develop various means of intervention for the prevention and treatment of age-related diseases.⁴ At present, the main anti-aging approaches include supplementation with hormones including growth hormone, dehydro-epiandrosterone (DHEA), estrogen and melatonin, and nutritional supplementation with synthetic and natural antioxidant,⁴ and trace element supplementation such as zinc (Zn).⁵ Although some of these approaches have been shown to have some clinical benefits in the treatment of some age-related disease, but, none of these really modulate the aging process itself.⁴

The aim of this article is to provide a brief introduction to the biological effects of melatonin and Zn and critically review their potential usefulness as anti-aging compounds.

MELATONIN AND AGING

Melatonin (N-acetyl 5-methoxytryptamine) is a hormone synthesized from tryptophan mainly by the pineal gland of mammals.⁶ However, other organs and tissues including retina, Harderian glands, gut, ovary, testes, bone marrow and lens have been reported to produce melatonin.⁷ In addition to these organs and tissues, human lymphoid cells are an important physiological source of melatonin and that this melatonin could be involved in the regulation of the human immune system.⁸ The synthesis and release of melatonin are stimulated by darkness and inhibited by light. The rhythm is generated by a circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus.⁴ The SCN clock is set to the 24-hour-day by the natural light-dark cycle. Light signals through a direct retinal pathway to the SCN. The SCN clock sends circadian signals over a neural pathway to the pineal gland. This drives rhythmic melatonin synthesis. The neural input to the gland is norpinephrine, and the output is melatonin.⁴

Melatonin is known to influence a variety of biological processes including circadian rhythms, neuroendocrine, cardiovascular, and immune functions as well as thermoregulation.⁹ It is also highly potent hydroxyl

radical and peroxy radical scavenger.¹⁰⁻¹² Melatonin is the most important antioxidant. Most antioxidant nutrients have difficulty penetrating cell membranes. However, the lipophilic melatonin diffuses into the cell cytosol and nucleus¹³⁻¹⁵ to protect cytosolic and nuclear macromolecules from free radical cytotoxicity.^{11,14,16} In addition, melatonin is reported to stimulate the activity of various antioxidant enzymes, like superoxide dismutase (SOD) and glutathione peroxidase, but inhibits the pro-oxidant enzyme nitric oxide synthase.¹⁴ Many reports have shown that marked changes in melatonin synthesis and secretion during aging process in both animals and humans.¹⁷⁻¹⁹ The pineal gland and its products are involved in the aging process.²⁰⁻²³ Pineal grafting experiments disclose a dramatic new approach for strategies to postpone aging.²⁴ Pierpaoli suggested that melatonin can exert a more pronounced anti-aging effect if the administrations start rather early in life, so it protects the pineal from aging.²⁵

Night levels of melatonin in mammals and man decline progressively in the course of aging. The effect of evening administration of melatonin is more pronounced.²⁵ Melatonin must be taken late in the evening at bedtime in order to mimic and restore the physiological night peak, which normally declines progressively during the course of aging.^{15,25} Circadian night melatonin seems to produce a resynchronization of the entire neuroendocrine system and will certainly improve metabolic and hormonal functions, including blood pressure, cholesterol levels, thyroid, gonadal and adrenal functions, and immune system.^{15,19,24,25} Melatonin treatment at physiological doses in old mice is able to reconstitute the age-associated immune defects, including thymus involution.²⁶

ZINC AND AGING

Zn is essential trace element and involved in many biological functions in the body.^{27,28} Zn is required as a catalytic component for the enzymes and it is a structural constituent of many proteins, hormones and neuropeptides.²⁹ Zn has a role in cell division and programmed cell death, gene expression, and protein synthesis.²⁸ The first enzyme recognized as a Zn metalloenzyme was carbonic anhydrase as reported by Keilin and Mann in 1940.³⁰ In the early 1960's, only three other enzymes, alcohol dehydrogenase, carboxypeptidase and alkaline phosphatase were known to be Zn metalloenzymes.³⁰ At present, Zn metalloenzymes have been recognized in all classes of enzymes, and more than 300 catalytically ac-

tive Zn metalloproteins have been recognized. Since 1985, more than 2000 Zinc dependent transcription factors involved in gene expression of various proteins have been recognized.³⁰

The NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of O₂⁻ from oxygen by using NADPH as the electron donor. Zn is an inhibitor of this enzyme.³⁰ Superoxide dismutase (SOD), which contains copper and Zn, catalyzes the dismutation of O₂⁻ to H₂O₂. Zinc is also known to induce production of metallothionein which is an excellent scavenger of .OH. It is clear that Zn has multiple roles as an antioxidant.³⁰

Mild zinc deficiency is common in the elderly, but frequently can not be confirmed because there are no conclusive criteria for the definition of Zn status. Low plasma Zn levels are more prevalent in the elderly ill.³¹ Lymphopenia and thymic atrophy, which are early markers of Zn deficiency, are known to be caused by high losses of precursor T and B cells in the bone marrow.^{31,32} Because of this, Zn deficiency is considered a causative factor of immune impairment in the elderly.³¹

Zn has many effects on the immune and nervous system *in vivo* and *in vitro*, and these effects mainly depend on the Zn concentration.³³ Many researchers have reported that immune function decreases after Zn depletion. The requirement for Zn is most likely because of its essential constitutive role in maintaining the conformation or enzymatic activity of many important components of these processes, including enzymes, transcription factors, and signaling molecules.³³

The intracellular mechanisms involved in the regulation Zn homeostasis have been poorly studied in aging.³⁴ It is known that the intake of Zn during aging decreases, thus contributing to cause frailty, general disability and increased incidence of age-related degenerative diseases.³⁴

Severe Zinc deficiency causes selective atrophy of lymphoid organs, thymic hypoplasia, and the absence of germinal centers in lymph nodes.^{35,36} In particular Zn is required for the biological activity of serum thymic factor (facteur thymique serique, FTS).^{26,37,38} ZnFTS (zinc-

bound active form) promotes the development and maintenance of cell-mediated immunity.²⁶ The Zn-unbound form is inactive. Active FTS levels decreased with advancing age. Zn supplementation induces a complete disappearance of the inactive form.³⁹

RELATIONSHIP BETWEEN MELATONIN AND ZINC

Melatonin and Zn are considered beneficial for anti-immunosenescence.⁴⁰ Melatonin and Zn plasma levels decline with advancing age. Melatonin and Zn treatment in old mice restored the reduced immunological functions.⁴⁰ The main target of melatonin is the thymus, which is the central organ of the immune system.⁴¹ Melatonin treatment or pineal graft induced a restoration of the altered Zn turnover in old mice. It has been reported that the pineal gland is involved in Zn metabolism.^{39,40}

Pinealectomy in young mice induced a delay in wound healing, a zinc-dependent process, which can be reversed by melatonin administration.³⁹ It is also shown that tissue Zn levels were changed after pinealectomy in rats.^{39,42} Our previous studies were shown that melatonin treatment changed Zn levels of tissues and serum in rats.⁴³⁻⁴⁵ The effect of melatonin on thymic endocrine activity and peripheral immune functions may be mediated by Zn.⁴⁰

In conclusion, melatonin treatment has a restorative effect on decreased thymus Zn levels with advancing age.⁴³ It is beyond any doubt that exogenous administration of melatonin to aging rodents postpones their aging and/or prolongs their life.^{24,46,47} The pineal may act as an endogenous clock governing aging.²⁴

Many factors were found to affect the individual response to Zn, such as general dietary habits, genotype, gender, drug usage and frailty.⁴⁸ This makes it very difficult to draw a definitive conclusion regarding the possible benefits of Zn supplementation during aging.⁴⁸ Many factors related to the control of zinc homeostasis in aging are still unclear. However, it is clear that Zn is involved in many processes in the body, including aging. Recent results obtained with Zn supplementation in elderly subjects are encouraging.

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