

MELATONIN, FREE RADICALS AND AGING

MELATONİN, SERBEST RADİKALLER VE YAŞLANMA

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Melatonin is the chief hormone of the pineal gland and its actions in organisms are widespread. One of the vital roles of melatonin is to delay aging or inhibit age-related disease processes. Many theories have been advanced to account for the aging process. For example the aging process has been attributed to change immunological function and damage by free radical reactions. Melatonin is being accepted as a very efficient free radical scavenger and antioxidant. Many hypotheses have been put forward that aging is a syndrome of relative melatonin deficiency. Studies have shown that blood melatonin values are significantly diminished in advanced age. However aging process is so complex that further investigations have been required to confirm these hypotheses.

Melatonin pineal bezin ana hormonudur ve organizmadaki etkileri yaygındır. Melatonin'in hayati rollerinden biri yaşlanmayı geciktirmesi veya yaşa bağlı hastalık süreçlerini inhibe etmesidir. Yaşlanma sürecinin sebebini açıklamak için birçok teori geliştirilmiştir. Örneğin, yaşlanma süreci immunolojik fonksiyon değişikliği ve serbest radikal hasarına atfedilmektedir. Melatonin çok etkili bir serbest radikal süpürücü ve antioksidan olarak bilinmektedir. Yaşlanmanın bir relatif melatonin eksikliği sendromu olduğu hakkında birçok hipotez ileri sürülmektedir. Çalışmalar melatonin seviyelerinin ileri yaşta anlamlı olarak azaldığını göstermektedir. Fakat yaşlanma kompleks bir süreçtir, bu nedenle bu hipotezlerin doğrulanması için daha ileri çalışmalara ihtiyaç duyulmaktadır.

Keywords: Melatonin; Free radicals; Aging.

Anahtar sözcükler: Melatonin, Serbest radikaller; Yaşlanma.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine), isolated from thousands of beef pineal gland by Aaron Lerner in 1958 is the chief hormone of the pineal gland. Pined gland is a small endocrin organ located in the brain and synthesizes melatonin from tryptophan (1).

Generally melatonin is produced and secreted into the blood in a circadian manner with maximal production always occurring the dark phase of the light-dark cycle. Melatonin production is stimulated by darkness and inhibited by light. Especially light-dark variation in

melatonin synthesis is the essential factor in the physiological role of pineal (2-4).

The pineal gland has been shown to be related to a wide variety of bodily functions such as reproduction, immunocompetence, oncogenesis, mood and ageing, etc (5).

Biosynthesis

Melatonin is synthesized from tryptophan within the pineal gland via hydroxylation and decarboxylation to

serotonin (5-hydroxytryptamine). Serotonin is converted to melatonin by a two step process. In the first process, "serotonin N-acetyltransferase (SNAT)" acetylates serotonin to N-acetylserotonin. In the second process this product is subsequently methylated by "hydroxyindole-o-methyltransferase (HIOMT)" to melatonin (6, 7).

There is a daily rhythm in the production of melatonin in all mammalian species. It is produced primarily during the daily period of darkness. Characteristically during the darkness period, serotonin level is low, but SNAT activity is high (8).

Major environmental variables such as daily and seasonal changes of light and temperature regulate the daily circadian variations of synthesis and release of the melatonin. Also various physiopathologic states such as aging and cancer affect melatonin rhythms (9, 10)

Age Dependent Changes of Melatonin Levels

Numerous reports suggest that pineal gland, via melatonin, may delay aging itself or inhibit age related disease processes. Therefore melatonin has been classified as an anti-aging hormone and as a juvenile hormone (11, 12).

Aging in mammalian species appears to be the result of normal development and metabolic processes. In fact, aging is clearly characterized by a progressive deterioration of the adaptive capacity of central and peripheral neuroendocrine organs which govern the onset of puberty, sexual maturation, reproductive physiology and possibly aging. In addition, the aging process can be generally defined as a progressive decline and finally the least capacity to cope with the environmental challenges (13-15).

The results of some studies indicated that melatonin levels and its nocturnal

cyclic peaks show age dependent changes. Aging is associated with impaired melatonin production. Studies in hamsters and rats have shown that blood melatonin values were significantly diminished in advanced age (16-19). The chief urinary metabolite of melatonin, 6-hydroxy-melatonin sulfate, shows a gradual age-related decline in humans at 20 and 95 years of age (20-22).

The human pineal body begins to undergo extensive calcification during the second decade of life. It is generally believed that calcification of the pineal body at puberty indicates a loss of function of pineal gland (6, 23).

Aging-free radicals

Many theories have been advanced to account to the aging process and this process has been attributed to molecular cross linking, changes immunological function and damage by free radical reactions (24, 25).

Molecules that serve in biological systems as electron acceptors are referred to as "oxidants" or "free radicals". Free radicals are produced in the body as by-products of normal metabolism and as a result of exposure to radiation and some environmental pollutants (26). Free radicals or reactive oxygen species are chemical constituents that have an unpaired electron in their outer orbital. Electrons in atoms occupy regions of space known as orbital. Each orbital can hold a maximum of two electrons and free radicals contain unpaired electrons. Most biologic molecules are nonradicals, containing only paired electrons. Nonradicals are more stable, but radicals generally are more reactive than nonradicals. (OH) radical is the most reactive radical known to chemistry. It can attack and damage almost every molecule found in

living cells. O^{x2-} is a superoxide radical and it is formed by adding an extra electron onto the oxygen molecule. Superoxide dismutase remove O^{x2-} by converting it into hydrogen peroxide (H_2O_2) and O_2 . Although H_2O_2 is not itself a free radical, it can be quite toxic to cells at high concentration and more importantly, it can be reduced to the hydroxyl radical (27-29).

Aerobic organisms generate oxygen free radicals during oxygen metabolism and they carry chemicals and enzymes that reduce the threat posed by these radicals. Generation of free radicals in vivo also may be the result of exposure to certain chemical agents present in the environment (30, 31).

Oxygen free radicals are very reactive and their reactions are critical for the normal activity of a wide spectrum of biological processes. Reduced intermediates of molecular oxygen, such as superoxide and hydrogen peroxide, are ubiquitous inorganic products of normal aerobic metabolism. Certain cells, such as phagocytes, have evolved to use these intermediates for benefits of the host, but most cells require antioxidant protection against excessive production of these intermediates (29, 32).

A wide variety of oxygen free radicals can be formed in the human body and in food systems. Formation of these radicals is increased during ischemia-hypoxia and subsequent reperfusion/reoxygenation. In lung pathology, conditions such as emphysema, mineral dust toxicity, cigarette smoke toxicity and asthma have been related to oxygen radicals. Inflammatory joint disease, diabetes senil dementia, degenerative eye diseases can sometimes be related to oxygen radicals (33).

Free radicals are toxic molecules which are persistently produced and incessantly attack and damage molecules within cells.

Collectively the process of free radical damage to molecules is referred to as oxidative stress (34). Modern human may be more exposed to oxidative stress. Free radical oxidative stress has been implicated in the pathogenesis of a variety of human diseases, especially the diseases of aging such as cancer and cardiovascular disease (35). There are also other diseases that are related to oxidative stress including the normal process of aging. Oxygen free radicals can be formed in tissues and cells and can damage DNA, proteins, carbohydrates, and lipids. They can also damage genetic material, cause lipid peroxidation in cell membranes and inactivate membrane bound enzymes (36-41). The brain is particularly susceptible to free radical attack. One of the potential major causes of age-related destruction of neuronal tissue is toxic free radicals (42).

Tissues and cells are more susceptible to free radical attacks with age. There is now evidence that even short free radical stresses can speed up the aging of in vitro cultured human fibroblasts. Studies on the origin and evolution of life provided a reasonable explanation for the prominent presence of these unruly class of chemical reactions and these have been implicated by aging. The free radical theory of aging postulates that changes due to aging are caused by free radical reactions (19,43,44).

Antioxidants

Reactive oxygen species are constantly formed in the human body and removed by antioxidant defences. Antioxidants can be defined in various ways. Authors prefer a broader definition-an antioxidant is any substance that, when present at low concentrations compared with those of an oxidizable substrate, delays or

prevents oxidation of that substrate. The term "oxidizable substrate" includes almost everything found in living cells, including proteins, lipids, carbohydrates, and DNA significantly. Antioxidants play important roles in animal and human health by inactivating harmful free radicals produced via normal cellular activity and various stressors, although they are not fully efficient (33, 34, 39, 45).

There are some antioxidants to scavenge or to quench free radicals. Humans are well endowed with antioxidant defences against free radicals. Their effects are prevented by intra- and extracellular antioxidants. These antioxidants are enzyme systems such as superoxide dismutase (SOD), glutathion peroxidase and catalase, macromolecules such as ceruplasmin and transferrin and small molecules such as glutathion, methionin, melatonin and vitamin C and E (46).

One can predict that the life span of an organism may be increased by slowing the rate of initiation of random free radical reactions. In general, tissue levels of antioxidants vary from one tissue to another with age. It is clear, that elderly people suffering from chronic and acute illness have reduced protective antioxidant effect (47,48).

Melatonin-aging

Melatonin has been classified as an anti-aging hormone and as a juvenil hormone. Indeed, this hypothesis has been put forward that aging is secondary to pineal failure. According to this hypothesis, aging is a syndrome of relative melatonin deficiency (11,12,40,49).

The recognized peripheral and central, biochemical, endocrinological, behavioral, pharmacological and clinical actions of melatonin are involved at different levels

of an overall concept of the pathophysiology of aging (34,50).

The antioxidant activities of melatonin have been well documented in tissue homogenate and organisms (33,51-53). More recent studies have shown that melatonin is efficient scavenger of the peroxy and hydroxyl radical and so more efficiently than other known antioxidants. Furthermore, melatonin greatly potentiates the efficiency of previously discovered endogenous and exogenous antioxidants (4,28). The peroxy radical is generated during the oxidation unsaturated lipids and it is sufficiently toxic to propagate lipid peroxidation and causes massive lipid destruction in cell membranes. In-vivo studies have demonstrated that melatonin is remarkable potent is protecting against free radical damage. Thus, DNA damage resulting from either the exposure of animals to the chemical carcinogen safrole or the contact with ionizing radiation is markedly reduced when melatonin is co-administered. Free radicals are drastically attenuated in the presence of melatonin (52).

Melatonin is highly important antioxidant in the brain. It is rapidly taken up by the brain. Vitamin antioxidants (Vit.E, Vit.C) also aid in protecting the brain from oxidative stress by directly scavenging toxic radicals and play a major role in aging brain (54).

In pharmacological doses, melatonin has been found effective in reducing macromolecular damage that is due to a variety of toxic agents (i.e.xenobiotic).

According to some authors, melatonin not only prolongs the life of animals, but also exerts an extraordinary positive action on their performance and reverses or delays the symptoms of age-related debility, diseases and cosmetic decline (7).

Conclusion

Life expectancies at birth in the developed countries are near plateau values. The intrinsic process is now the major risk factor for disease and death in these countries. Many theories have been proposed to account for the inborn aging process. The free radical theory of aging was proposed in 1954. The participation of free radical reactions in the pathogenesis of many diseases is generally accepted. Whether or not these reactions are responsible for aging is still being debated (38).

Despite a realisation that antioxidants will not delay aging in healthy older people, there is increasing scientific interest in the role of free radical oxidants in a number of diseases associated with older age. Free radical damage seems likely to be significant in the pathophysiology of atherosclerosis, ischemia, reperfusion injury, Parkinson disease, cataract, some cancers and rheumatic arthritis. But its doubtful that a single theory will explain all the mechanism of aging (55).

Multiple mechanisms underlie the human aging process but interest continues in the role that free radicals and oxidants may play. The maximum life span is apparently determined largely by the rate of aging of the mitochondria. Antioxidants slow mitochondrial aging without significantly depress in mitochondrial function may increase the maximum life span.

Results of some studies indicate that in old rats the nocturnal rise in pineal melatonin levels may be severely depressed. The mechanism in the age-related reduction in pineal melatonin levels in rats are unknown (56).

The implication of this review is that melatonin may have both direct and indirect beneficial effects in delaying

aging process or it may retard the development of age-related diseases which contribute to a reduced life span.

Generally it is not yet totally clear how and where melatonin intervenes to modulate aging and age related process. So further well-controlled prospective clinical trials of antioxidants are required to establish the efficacy and tolerability of antioxidant therapy in the treatment of human disease and in aging.

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