



Physiology of Melatonin

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ABSTRACT

The pineal gland has tremendous control over the homeostatic mechanisms of the body. The main hormone produced by the pineal gland, melatonin regulate circadian rhythms, sleep-wake cycles, thermal and immunologic systems, and reproductive capability. Human research has demonstrated that melatonin also plays a role in sleep disturbances, menstrual and reproductive irregularities, psychological and behavioral disorders, and may even serve as a tumor inhibitory gland. It is secreted with a marked circadian rhythm. Many biological effects are produced through the activation of melatonin receptors. It can lower body temperature and acts as a powerful antioxidant. These properties indicate that melatonin can be used therapeutically in circadian rhythm disorders. Melatonin receptors of several subtypes are found in the brain, the retina, the pituitary and elsewhere. The reason for this study is to understand the importance of pineal gland and melatonin on human beings.

Keywords: Pineal gland, melatonin, Physiology.

INTRODUCTION

The hormone "Melatonin" was first discovered by dermatology professor Aaron B. Lerner and colleagues at Yale University, in the year 1958. It was discovered in the hope that a substance from the pineal gland might be useful in treating skin diseases. They isolated the hormone from bovine pineal gland extracts and named it melatonin. In humans, as in other vertebrates, melatonin production takes place primarily in the pineal gland – a major component of the epithalamus.¹

Melatonin has revealed itself as a functionally diverse molecule. It has been found integral to circadian rhythms and sleep regulation in addition to effects on immune function, cell growth, and other endocrine regulation. Although the pineal gland is the main site for synthesis of melatonin, other sites such as the testis, retina, and the gastrointestinal tract contribute, to a lesser extent, to the circulating levels of melatonin. The mechanisms that control its synthesis within the pineal gland have been well characterized and the retinal and biological clock processes that modulate the circadian production of melatonin in the pineal gland are rapidly being unraveled. A feature that characterizes melatonin is the variety of mechanisms it employs to modulate the physiology and molecular biology of cells². Additionally, by virtue of its ability to detoxify free radicals and related oxygen derivatives, melatonin influences the molecular physiology of cells via receptor-independent means. These uncommonly complex processes often make it difficult to determine specifically how melatonin functions to exert its obvious actions. What is apparent, however, is that the actions of melatonin contribute to improved cellular and organism physiology³. In view of this and its virtual absence of toxicity, melatonin may well find applications in human beings.

DISCUSSION

Synthesis

Melatonin, chemically is N-acetyl-5-methoxy tryptamine⁴, and is synthesized from tryptophan via 5-hydroxylation by tryptophan-5-hydroxylase and is converted to 5-hydroxytryptophan, it undergoes decarboxylation by the enzyme aromatic amino acid decarboxylase to 5-hydroxytryptamine (serotonin), serotonin is converted to N-acetyl serotonin (NAT) by N-acetyl transferase and finally O-methylation by hydroxyindole-O-methyltransferase (HIOMT) to melatonin (N-acetyl-5-methoxytryptamine). The cardinal feature of this synthetic pathway is its rhythmicity. The activity of the enzyme NAT in particular increases from 30-fold to 70-fold at night and, in most circumstances, is rate-limiting in melatonin synthesis⁵.

Physiology of melatonin

Melatonin has multiple effects on different type of physiological processes. Melatonin plays an important role in circadian rhythms, sleep wake cycle and reproduction. It also acts as a free radical scavenger as it has an antioxidant property.

CIRCADIAN RHYTHMS

Melatonin is synthesized by the pineal gland during darkness. The activity of the pineal gland is very sensitive to circadian and seasonal variations in the length of the photoperiod, i.e. it provides information about day length⁶. Melatonin acts as the arm of the circadian clock. It is synthesized and released in rhythmic fashion during night under normal environmental conditions. It is controlled by circadian timing system and is also suppressed by light. The primary function of melatonin is to give information concerning the daily cycle of light and darkness to body. The secretion of melatonin at night can



be used for the organization of circadian rhythms. It mainly stabilizes and strengthens the circadian rhythm especially the maintenance of core body temperature and also the sleep wake cycle.

Sleep wake cycle

The waking state is largely controlled by the ascending reticular activating system, (ARAS) located in the diencephalon and the upper brainstem. One division of this projects to thalamic nuclei whereas a second division extends to the lateral hypothalamus all the way to the cerebral cortex. Sleep is controlled by two different regulatory processes: the 'C' circadian system, in charge of sleep induction and arousal, and the 'S' sleep debt homeostatic mechanism⁷. There is evidence that administration of melatonin is able: (i) to induce sleep when the sleep is insufficient; (ii) to inhibit the drive for wakefulness emanating from the circadian pacemaker; and (iii) induce phase shifts in the circadian clock such that the circadian phase of increased sleep propensity occurs at a new, desired time⁸.

Reproduction

Melatonin is one of the key factors that regulate the seasonal variation in gonadal activity. The circadian disturbances related to reproduction are probably due to the seasonal change. Melatonin is considered essential to both spermatogenesis and oogenesis. As mentioned earlier the exposure to bright light, suppresses the concentration of melatonin in circulation, and is hypothesized to be useful in treatment of both male and female infertility in couples³. In women, seasonal variation observed in the concentrations of gonadotropins and gonadal steroids is associated with melatonin synthesis. This hormone may exert an inhibitory effect on the GnRH pulse generator to decrease gonadotropin secretion. Consequently, it has been implicated in the control of the pubertal onset and timing of ovulation. The number of irregular menstrual cycles with an ovulation increases in winter compared to summer⁹. In addition, there is circadian variation in the time of ovulation, occurring usually in the morning during summer and in the evening during winter¹⁰. Hormonal interactions and phases of the cycle are important variables contributing to the fluctuations in melatonin levels during the menstrual cycle.

Anti-oxidant

Although melatonin is involved in the biological clock mechanism, in 1993 it was discovered as a powerful free-radical scavenger and wide-spectrum antioxidant^{11 12}. In many living organisms, this is its only known function. The most interesting fact is that as a powerful antioxidant it can easily cross cell membranes¹³ and the blood-brain barrier¹⁴. This antioxidant is a direct scavenger of radical oxygen and nitrogen species including OH, O₂⁻, and NO¹⁵¹⁶. Melatonin works also with other antioxidants in order to improve the overall effectiveness⁹. It has been proven to be twice as active as vitamin E, believed to be the most

effective lipophilic antioxidant¹⁴. An important characteristic of melatonin that distinguishes it from other classic radical scavengers is that its metabolites are also scavengers in what is referred to as the cascade reaction¹⁷. Melatonin proved to be a better protector against mitochondrial oxidative stress¹⁸.

CONCLUSION

Pineal gland is small only structurally but functionally it is a most important gland releasing a versatile functioning hormone Melatonin¹⁹. Melatonin is not only related to Central Nervous System function but also has strong positive effect in endocrine and reproductive system function. Its pharmacological role in puberty related abnormalities, and role in mechanism of action of pulsatile release of GnRH have been reported²⁰. It is important in cancer therapeutic modalities, sleep disorders, headache, protection from radiation, gall bladder stones, immune system. Studies are continuing on this hormone to unravel more of its physiological functions²¹.

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