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"Melatonergic system; physiology and basic role in disease"

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ABSTRACT

N-acetyl-5-methoxytryptamine (melatonin) is a naturally occurring compound found in animals, plants, and microbes. In animals, regulate the circadian rhythms of several biological functions and also regulates the sleeping and waking cycle as well as related functions within the body. Melatonin maintains an excellent safety profile and it can be especially helpful for those experiencing sleep difficulties due to jet lag, shift work, and insufficient exposure to daytime sunlight. While others are due to its role as a pervasive and powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA. Melatonin in plants has multiple roles including regulation of the photoperiod, in plant defense responses, and as a scavenger of species. And some amphibians and reptiles change the color of their skin is also regulate by melatonin.

KEY WORDS *- Antioxidant, biological functions, photoperiod, regulation,*

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INTRODUCTION

Melatonin also known chemically as N-acetyl-5-methoxytryptamine is a naturally occurring compound found in animals, plants, and microbes. In animals, circulating levels of melatonin vary in a daily cycle, thereby regulating the circadian rhythms of several biological functions. Melatonin is a hormone produced in the pineal gland that regulates the sleeping and waking cycle as well as related functions within the body.[1] Melatonin is related to the mechanism by which some amphibians and reptiles change the color of their skin and, indeed. The light/dark information reaches the suprachiasmatic nuclei(SCN)via retinal photosensitive ganglion cells, intrinsically photosensitive photoreceptor cells, distinct from those involved in image forming (that is, these light sensitive cells are a third type in the retina, in addition to rods and cones). These cells represent approximately 2% of the retinal ganglion cells in humans and express the photo pigment melanopsin the sensitivity of melanopsin fits with that of a vitamin A-based photo pigment.[2] Scientists classify the two types of Melatonin as endogenous, which means "occurring from within" and exogenous, or "occurring from outside of the body." The secretion of endogenous Melatonin is largely dependent on light/dark cycles, so it is inhibited during the day and stimulated at night. Exogenous Melatonin is primarily derived from synthetic origin and typically introduced into the blood stream by way of oral administration.[1]

BIOSYNTHESIS OF MELATONIN

The pineal gland was called the "third eye" by ancient people. It was thought to have mystical powers. This may be why the French philosopher Descartes decided that the pineal gland was the seat of the human soul, the location of what we call the mind. The pineal does contain a complete map of the visual field of the eyes, and it plays several significant roles in human functioning. Also called the pineal body or epiphysis cerebri, the pineal gland is important to this discussion, it is the center for the production of the hormone melatonin. Melatonin is implicated in a wide range of human activities.[3] (fig. no.1)

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ROLE OF MELATONIN

Many animals use the variation in duration of melatonin production each day as a seasonal clock. In animals and humans the profile of melatonin synthesis and secretion is affected by the variable duration of night in summer as compared to winter. The change in duration of secretion thus serves as a biological signal for the organization of day length-dependent (photoperiodic) seasonal functions such as reproduction, the melatonin signal controls the seasonal variation in their sexual physiology, The reproduction of long-day breeders is repressed by melatonin and the reproduction of short-day breeders is stimulated by melatonin. [4] In human It helps regulate other hormones and maintains the body's circadian rhythm. The circadian rhythm is an internal 24-hour "clock" that plays a critical role in when we fall asleep and when we wake up. When it is dark, your body produces more melatonin; when it is light, the production of melatonin drops. Being exposed to bright lights in the evening or too little light during the day can disrupt the body's normal melatonin cycles. For example, jet lag, shift work, and poor vision can disrupt melatonin cycles. Melatonin to attenuate the severity of hypertension, limit myocardial damage, improve the function of the ischemic-reperfused heart, protect the heart from the toxicity of free radical (act as antioxidant). Melatonin is an antioxidant that can easily cross cell membranes and the blood-brain barrier. Melatonin is a direct scavenger of OH, O_2^-, and NO Unlike other antioxidants.[5]

In immune system: - Some studies also suggest that melatonin might be useful fighting infectious disease including viral, such as HIV, and bacterial infections, and potentially in the treatment of cancer. Endogenous melatonin in human lymphocytes has been related to interleukin-2 (IL-2) production and to the expression of IL-2 receptor. This suggests that melatonin is involved in the clonal expansion of antigen-stimulated human T lymphocytes.[6]

Reproductive system: - The release of melatonin, affects reproductive performance in a wide variety of species. The efficacy of exogenous melatonin in modifying particular reproductive functions varies markedly among species, in some species melatonin has antigonadotropic actions, and the responses to it are greater in those species with greater seasonal shifts in gonadal function. Changes in the number of hours of darkness each day, and therefore the number of hours that melatonin is secreted, mediate the link between reproductive activity and the seasons. There is also a report of a man with hypogonadotropic hypogonadism, delayed puberty, and high serum melatonin concentrations in whom gonadotropin secretion increased and pubertal development occurred after a spontaneous decrease in the secretion of melatonin. These findings provide some support for the hypothesis that melatonin has a role in the timing of puberty. Can summarize the effect of melatonin on reproductive systems by saying that it is anti-gonadotropic. In other words, melatonin inhibits the secretion of the gonadotropic hormones luteinizing hormone and follicle stimulating hormone from the anterior pituitary. Much of this inhibitory effect seems due to inhibition of gonadotropin-releasing hormone from the hypothalamus, which is necessary for secretion of the anterior pituitary hormones.[7]

Aging: - A role for melatonin as such a compound was recently suggested. In this survey, data on the possible role of melatonin in human aging and age-related diseases are briefly presented. Undoubtedly the aging process is multi-factorial, and no single factor has been identified which satisfactorily explains the phenomenon. Although many theories relating the pineal gland and its secretory product melatonin to aging have been proposed, the role of this agent in the aging process is still unclear.

However, for several reasons it seems reasonable to postulate a role for melatonin in this process. Melatonin levels decline gradually over the life-span and may be related to lowered sleep efficacy, For example, young children have the highest levels of nighttime melatonin. Researchers believe these levels drop as we age. Some people think lower levels of melatonin may explain why some older adults have sleep problems and tend to go to bed and wake up earlier than when they were younger.[4]

In hyperhomocysteinemia: - Homocystinuria is associated with a syndrome of mental retardation, skeletal and visual problems and arterial as well as venous thrombosis. There are two primary enzymes that, when a defect is present, can result in either homocystinuria or hyperhomocysteinemia. Homocysteine (HCY), a thiol-containing amino acid derived from the metabolism of methionine, is an independent risk factor of cardiovascular disease. HCY is an excitatory amino acid and markedly enhances the vulnerability of neuronal cells to excitotoxic and oxidative injury in vitro and in vivo. HCY induces cell death of astrocytes *in vitro*. Astrocytes are known to play an important role in survival of neurons in the brain and they have been implicated in the regulation of ionic environments, which are required for proper physiological function of neurons. Both chemical and mechanical insults to the brain stimulate astrocyte proliferation with hypertrophy and the formation of glial filaments.[8] This phenomenon is called reactive gliosis and that is responsible for neuronal degeneration and injury. The melatonin has the ability to prevent reactive gliosis both in brain and retina.[8]

In circadian rhythm disorders:-

(1) Cardiac ischemic-reperfusion injury: - Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are considered to be major contributors to cardiac damage during ischemia-reperfusion injury. Thus antioxidant strategies have often been considered in the prevention of ischemia-reperfusion damage. A special interest in this regard is antioxidants that scavenge radicals at the mitochondrial level, which melatonin does. Melatonin has frequently been tested for its ability to arrest cellular and molecular damage associated with a transitory interruption of the blood supply to the heart. These studies have uniformly shown that it is beneficial in reducing cardiac ischemia-reperfusion injury.[9]

(2)Hypertrophic cardiomyopathy:- Hypertrophic cardiomyopathy is a disease that causes a large number of deaths annually and this is Because of hyperthyroid state is associated with increased production of free radicals. Cardiac enlargement, increased generation of lipid hydroperoxides and inhibition of copper/zinc superoxide dismutase, reduction in the glucose transporter GLUT4, down regulation of myocyte enhancer factor-2 (a regulator of GLUT4 expression), and increased B-type natriuretic peptide (a marker of heart failure). Each of these changes was reversed by concurrent administration of melatonin and partially prevented by vitamin E.[9]

(3) Hypertension: - Removal of the pineal gland, a major source of circulating melatonin, causes a gradual, sustained increase in blood pressure. Moreover, melatonin treatment of spontaneously hypertensive rats decreases mean arterial pressure and heart rate, enhances relaxation of mesenteric arteries, and improves baroreflex responses. The circadian rhythm of blood melatonin has a role in the normal daily fluctuation in blood pressure. Blood pressure is greatest during the daytime, when melatonin concentrations are least; these relative values are reversed at night.[9]

In Jet lag: - Each year millions of travelers undertake long distance flights over one or more continents. These multiple time zone flights produce a constellation of symptoms known as jet lag. The

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symptoms which is include in jet lag is reduced alertness, nighttime insomnia, loss of appetite, depressed mood, poor psychomotor coordination and reduced cognitive skills, all symptoms which are closely affected by both the length and direction of travel. The most important jet lag symptoms are due to disruptions to the body's sleep/wake cycle this all the problem related to the dysregulation of melatonin secretion.[10]

Delirium: - Postoperative delirium is a common problem associated with increased morbidity and mortality, prolonged hospital stay, additional tests and consultations and therefore, increased cost. The elderly seem to be at significantly increased risk for this complication. Sleep-wake cycle disruption has been associated with delirium and behavioral changes and sleep deprivation can even result in psychosis. Environmental changes (i.e., hospital stay), medications, and general anesthesia can affect the sleep-wake cycle. Plasma melatonin levels, which play an important role in the regulation of the sleep-wake cycle, are decreased after surgery and in hospitalized patients.[11]

Treatment of Cancer: - Melatonin levels at night are reduced to 50% by exposure to a low-level incandescent bulb for only 39 minutes, and it has been shown that women with the brightest bedrooms have an increased risk for breast cancer. Reduced melatonin production has been proposed as a likely factor in the significantly higher cancer rates in night workers.[4]

(1) Breast Cancer: - Several studies suggest that melatonin levels may be associated with breast cancer risk. For example, women with breast cancer tend to have lower levels of melatonin than those without the disease. Laboratory experiments have found that low levels of melatonin stimulate the growth of certain types of breast cancer cells, while adding melatonin to these cells slows their growth. Preliminary evidence also suggests that melatonin may strengthen the effects of some chemotherapy drugs used to treat breast cancer.[12]

(2) Prostate Cancer: - Studies show that people with prostate cancer have lower melatonin levels than men without the disease. In test tube studies, melatonin blocks the growth of prostate cancer cells. In one small-scale study, melatonin -- combined with conventional medical treatment -- improved survival rates in 9 out of 14 men with metastatic prostate cancer. Interestingly, since meditation may cause melatonin levels to raise it appears to be a valuable addition to the treatment of prostate cancer. More research is needed before doctors can make recommendations in this area.[12]

MECHANISM OF MELATONIN ACTION

Melatonin transduces the effect of photoperiod on the neuroendocrine system. Synthesis of melatonin in the pineal gland is well described, but the location of its target(s) and the mechanism of its action are little known, Sub cellular analysis indicated these binding sites were on plasma membranes, which suggests that melatonin modulates cell functions through intracellular second messengers. The effects of melatonin on second messengers were studied using the neonatal anterior pituitary, in which melatonin is known to inhibit the LHRH-induced release of LH. Studies on the effects of melatonin on second messenger indicated [corrected] that melatonin inhibits accumulation of cAMP and cGMP as well as synthesis of diacylglycerol and release of arachidonic acid.[13]

Redox-sensitive components of melatonin signaling:- In this figure (2) Proposed effects of melatonin on mitochondrial damage and ROS production under physiological or stress-related conditions. Under physiological conditions (right),melatonin can transiently stimulate the production of low amounts of ROS, either through the engagement of its receptors or by the low-affinity

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interaction with signaling effectors such as calmodulin. In this context, ROS are believed to act as second messengers and signaling molecules to sustain the transcription of genes that are involved in the anabolic and survival-promoting effects of this hormone. During cell stress sustained by environmental stressors, accelerated metabolism, or aging (left), melatonin is expected to protect cells by preventing mitochondrial injury and thus preserving membrane potential and the energy-producing function (ATP levels) of mitochondria (bottom box). In this way, melatonin appears to limit the amount of ROS that escape from these organelles to maintain them within levels compatible with optimal control of homeostatic processes.[23] This has important effects in the control of redox-sensitive signaling proteins and is proposed as a main factor in sustaining negative feedback on mitochondrial ROS and apoptotic signals *via* Bcl-2 and possibly other redox sensitive elements that loop on mitochondria. In the presence of a sustained flux of ROS, it is not excluded that pharmacological melatonin could act also *via* direct antioxidant effects to scavenge reactive species, thus preventing their cellular toxicity. Several H2O2 generating enzymes that are, however counterbalanced by the presence of catalase (enzyme). H2O2 is considered the best candidate to play a role in cell signaling in that it is a long-living species that can reach protein targets and specifically and reversibly react with their redox-sensitive epitopes.[13]

In this figure (3) Components in the intrinsic pathway of apoptosis and their interaction with melatonin signaling.Cell stresses generate signals that may in turn stimulate death processes through well-defined signals and mechanisms of execution. The intrinsic (or mitochondrial) pathway of apoptosis is a codified process that integrates signals from the membrane to mitochondria to activate a caspase-dependent execution phase that brings the cell to die by apoptosis. Melatonin and its signaling effects can interfere with this apoptotic pathway at different levels, thus preventing the apoptotic cell death. Control of ROS flux (Fig. 1 and bottom part of commitment box) and transcriptional events are involved in the antiapoptotic effect of melatonin. In this context, melatonin is well demonstrated to act as enhancer of cell GSH and its enzymatic machinery that sustain detoxification reactions and antiapoptotic pathways. Other transcriptional effects mediated by redox-sensitive transcription factors such as NF B, AP-1, and Nrf2 are responsible of the differential control of pro- and antiapoptotic genes in response to exogenous stimuli and melatonin. Further antiapoptotic signals can be generated by the regulatory role that melatonin has on the idiosyncratic signaling of MAPKs, with ERK-MAPK acting as a prosurvival component to counteract proapoptotic effects by stress-related MAPKs. And in the text are clearly involved in the control of apoptosis and stress-mediated events and include Bcl2/Bax, glutathione and its enzymes, and Trx, which together with ASK-1 or through GSTp may loop back to mitochondrial signaling *via* p66Shr and MAPKs.[14]

CONCLUSION

Melatonin is a hormone produced in the pineal gland that regulates the sleeping and waking cycle as well as related functions within the body. In animals, circulating levels of melatonin vary in a daily cycle, thereby regulating the circadian rhythms of several biological functions. And it is also powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA. Melatonin in plants has multiple roles including regulation of the photoperiod, in plant defense responses, and as a scavenger of reactive oxygen species. Melatonin is secreted in darkness in both day-active (diurnal) and night-active (nocturnal) animals. Melatonin has been studied for the treatment of cancer, immune disorders, cardiovascular diseases, depression, seasonal affective disorder (SAD), circadian rhythm sleep disorders and sexual dysfunction.

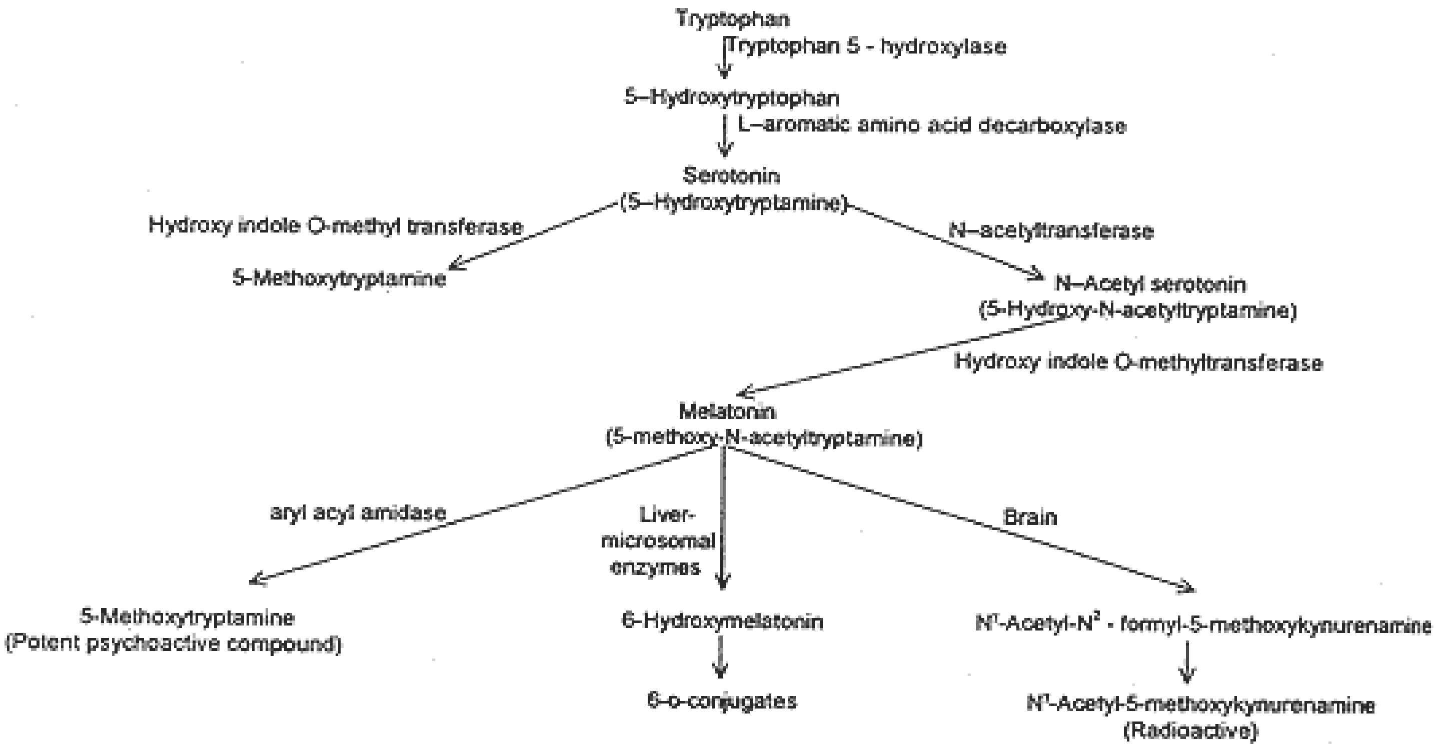

Figure:1 biosynthesis of melatonin

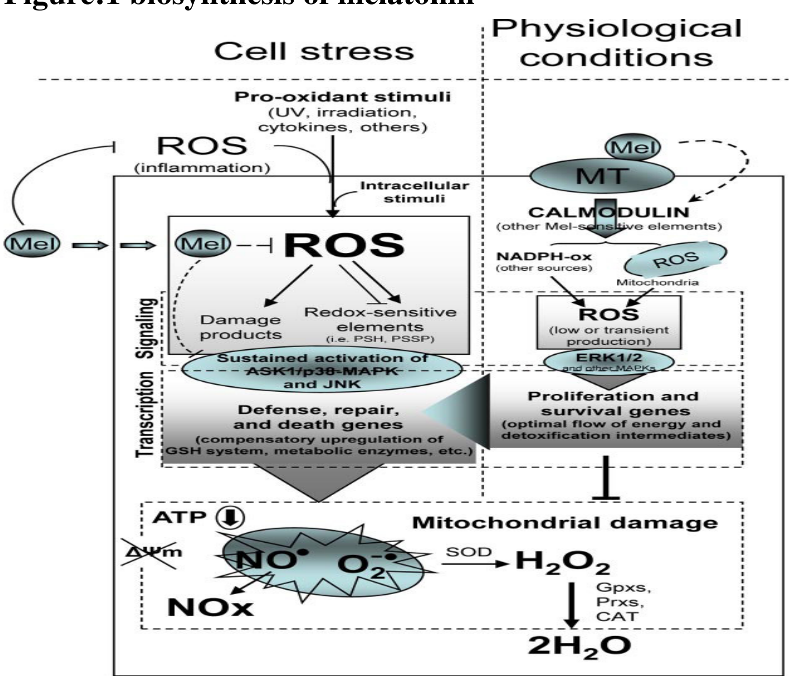

Figure: 2 Melatonin signaling in cell stress condition

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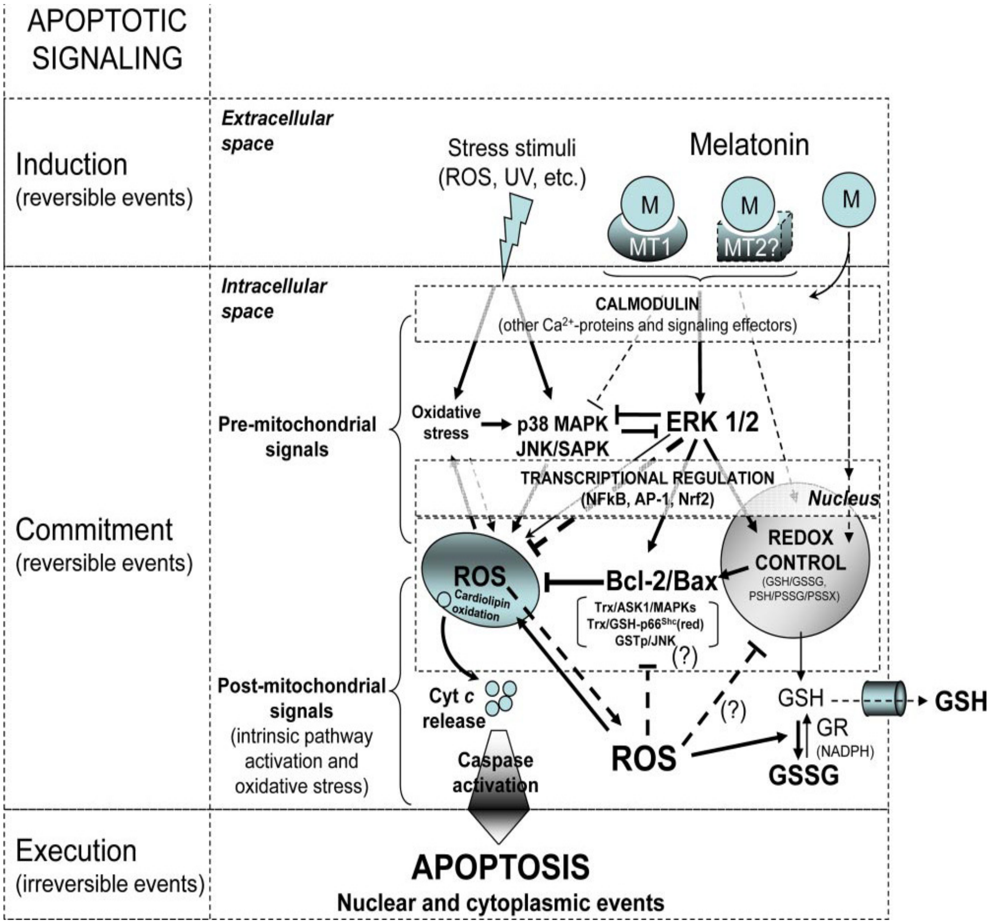

Figure: 3 Melatonin signaling in apoptosis process

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