زانكۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

The role of melatonin hormone in children's growth

A project submitted to the council of the college of Education at Salahaddin University in Partial Fulfillment of the Requirements for the Degree of B.Sc. at chemistry Department

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Supervisor recommendation

I am the student's supervisor, sakar sallem ahmad .I support that the student has completed all the requirements for submitting the research drawn entitled The role of melatonin hormone in children's growth according to the numbered administrative order 3/1/5/1972 on 9th oct. 2022 in accordance with the instructions of Salahaddin university quality assurance and it is ready for discussion.

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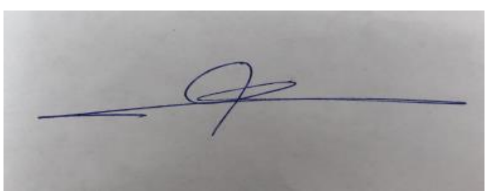

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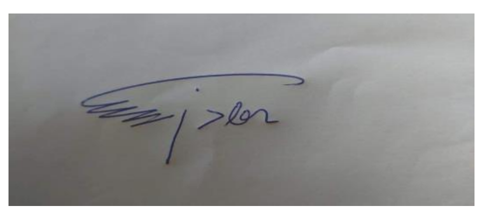

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Dedication

I dedicate it to my family. I would like to thank my mother and father in particular for taking care of me so much and for being so tired for me. I am also grateful to my close friends that they always have my back.

Acknowledgement

I am so thankful to my supervisor a teacher Lutfia , she was helped me a lot and so tired with me , i want to thank her from the bottom of my heart .

Abstract

Melatonin "the light of night" is secreted from the pineal gland principally at night. The hormone is involved in sleep regulation, as well as in a number of other cyclical bodily activities and circadian rhythm in humans. Melatonin is exclusively involved in signalling the 'time of day' and 'time of year' (hence considered to help both clock and calendar functions) to all tissues and is thus considered to be the body's chronological pacemaker or 'Zeitgeber'. melatonin has been widely identified and qualified in various foods from fungi to animals and plants. Eggs and fish are higher melatonin-containing food groups in animal foods, whereas in plant foods, nuts are with the highest content of melatonin. Some kinds of mushrooms, cereals and germinated legumes or seeds are also good dietary sources of melatonin. It has been proved that the melatonin concentration in human serum could significantly increase after the consumption of melatonin containing food. Furthermore, studies show that melatonin exhibits many bioactivities, such as antioxidant activity, anti-inflammatory characteristics, boosting immunity, anticancer activity, cardiovascular protection, anti-diabetic, anti-obese, neuroprotective and anti-aging activity. Administration of melatonin along with Ritalin improves height and weight growth of children. These effects may be attributed to circadian cycle modification, increasing sleep duration and the consequent more growth hormone release during sleep. children have sleep disorders and melatonin secretion disorders, this can cause various physical or mental diseases when they grow up in the future.

Keywords: melatonin; food; bioactivity; antioxidant; sleep ;mechanisms of action ;light ; children growth

1. Introduction

1.1 History

Melatonin is primarily produced by the pineal gland (glandula pinealis). In the 16th century, the French philosopher and scientist, Descartes, described the pineal gland as the seat of the soul. Melatonin itself was only first discovered in 1958 by a dermatologist named Aaron Lerner, Lerner was able to isolate a compound in a bovine pineal gland that had a strong bleaching effect on amphibian skin, which he gave the name melatonin. It was also Lerner who began studying the effect of the hormone on sleep . In the 1960s it was still assumed that the light-dark rhythm was important for mammals, but not for humans. Not until 1981 did Alfred Lewy discover that bright light applied in the night suppressed endogenous melatonin in humans. discovery was a breakthrough for chronobiology and research of melatonin. In the beginning of the 1990s, the hormone received more and more attention as studies showed the effects of melatonin on different bodily processes such as immune modulation, restraining tumor growth, catching of oxygen radicals and the influence on calcium dependent metabolic processes. Subsequently, additional studies are available about melatonin and its multifaceted impact on human health.(I. Chowdhury et al., 2008)

1.2 class of hormone

Hormones can be classified according to their chemical nature, mechanism of action, nature of action, their effects, and stimulation of Endocrine glands.

-Chemical nature: Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm.

-mechanism of action: Melatonin is a derivative of tryptophan. It binds to melatonin receptor type 1A, which then acts on adenylate cylcase and the inhibition of a cAMP signal transduction pathway. Melatonin not only inhibits adenylate cyclase, but it also activates phosphilpase C. This potentiates the release of arachidonate. By binding to melatonin receptors 1 and 2, the downstream signal ling cascades have various effects in the body. The melatonin receptors are G protein-coupled receptors and are expressed in various tissues of the body. There are two subtypes of the receptor in humans, melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2).

-stimulation of Endocrine glands:

Your pineal gland is part of your endocrine system. The full impact of melatonin in humans isn't totally clear, but most research shows it helps to synchronize circadian rhythms in different parts of your body. Circadian rhythms are physical, mental and behavioral changes that follow a 24-hour cycle. It binds to its receptors on the pituitary gland and the ovaries and appears to regulate the release of female reproductive hormones. The pineal gland receives input from postganglionic fibers, leading to the release of noradrenalin and increased production of cyclic AMP, thus activating the enzyme AANAT, mentioned above, which is critical to the production of melatonin.(Litwack, 2017)

1.3 Melatonin

Melatonin, N-acetyl-5-methoxytryptamine (fig. 1), is an indoleamine secreted by the pineal gland with a robust circadian rhythm. Its secretion is stimulated by dark and inhibited by light and the endogenous circadian rhythm is driven by the suprachiasmatic nucleus (SCN). Melatonin entrains the circadian timing system and works as a chronobiotic “a substance that adjusts the timing of internal biological rhythms” . The circadian rhythm is the “internal body clock” that regulates the (roughly) 24-hours cycle of biological processes in animals and plants. The term circadian comes from the Latin circa, meaning “around” and dies, “day”, meaning literally “around a day” .

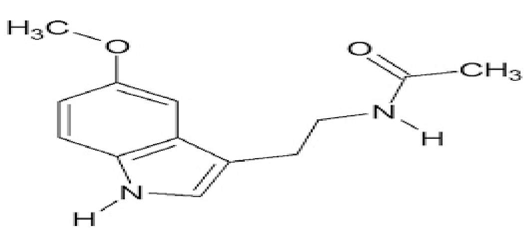

Figure 1. Melatonin, M = 232.283 g/mol[(Römsing, 2010)]

Melatonin, M = 232.283 g/mol Melatonin is both lipid and aqueous soluble which results in that melatonin seems to distribute to all sub cellular compartments, with highest levels of the indoleamine being measured in the nuclei of cells . After release in the circulation it gains access to various fluids, tissues and cellular compartments (saliva, urine, cerebrospinal fluid, preovulatory follicle, semen, amniotic fluid and breast milk). As no pineal storage of melatonin is available, the plasma hormone profile faithfully reflects the pineal activity . The ability of the pineal gland to produce and release melatonin varies greatly with age and between subjects, even though it is very reproducible from one day to another in the same subject . The biosynthesis of melatonin occurs in four steps, starting from the amino acid Tryptophan and the major regulating step in the synthesis is the N-acetyltransferase-mediated conversion of Serotonin to N-acetylserotonin. This step is inhibited by light and stimulated by darkness, creating the 12 marked rhythm which is a distinguishing feature of the pineal output of melatonin (fig. 2). Melatonin is rapidly metabolized in the liver to 6- hydroxyl melatonin, which is conjugated as 60-70% sulphate and 20-30% glucuronide. Circulating plasma melatonin has a relatively short metabolic half-life, 45–60 minutes depending on distribution way i.e. intravenously or orally, with about 90 % being cleared during a single hepatic passage . The 24-h urinary excretion of 6-hydroxymelatonin sulphate highly correlates with plasma melatonin levels and can be used for non-invasive clinical determinations. About 1% melatonin remains unchanged in the urine . Maximum blood plasma concentrations are normally in the low nanomolar range, levels from 50 pmol/l down to 8 pmol/l are normal daytime and from 300 pmol/l down to 50 pmol/l night time . The saliva melatonin concentration is about one-third of that in plasma. In some body fluids, e.g. bile and cerebrospinal fluid (CSF), measured melatonin concentrations are in orders of magnitude greater than in circulation

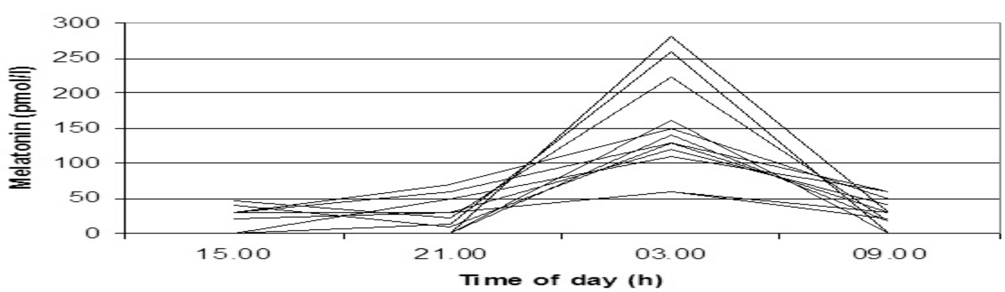

Figure 2. Diurnal saliva melatonin rhythms in 12 volunteers[(Römsing, 2010)]

melatonin levels peak at 60–200 pg/mL between 2 and 4 a.m. and decrease to 0–20 pg/mL during the day (Römsing, 2010)

Figure3 .time melatonin[(Zhu et al., 2021)]

1.3.1 metabolism of melatonin

Tryptophan is the precursor amino acid needed for the production of melatonin. Most foods containing protein usually contain tryptophan, and it is readily available in most people's diets. Tryptophan converts to serotonin and then into melatonin in a multistep process. Along the way, several cofactors needed in this process, including folate , B6, B12, and possibly zinc and magnesium.(Peuhkuri et al., 2012)

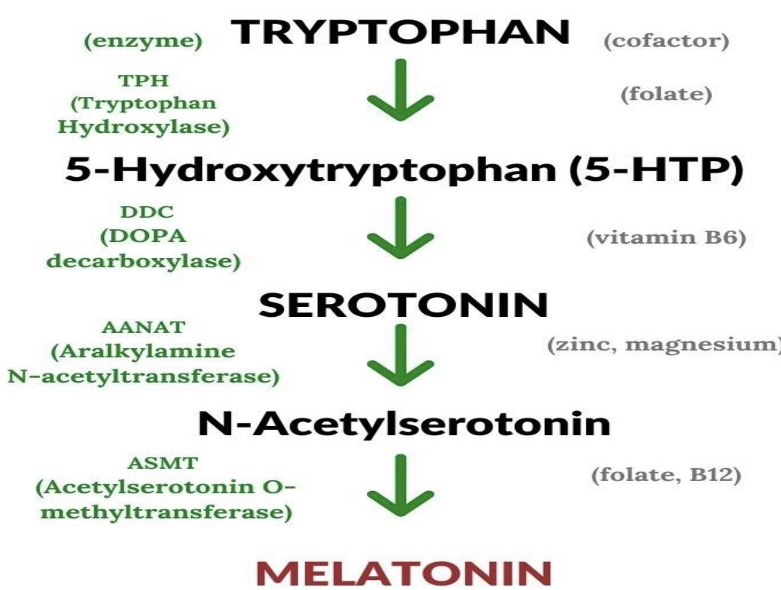

Figure 4. metabolism of tryptophan to melatonin in pineal gland[(Terry et al., 2009)]

1.3.2How is melatonin controlled

In humans and other mammals, the daily rhythm of pineal melatonin production is driven by the 'master' circadian clock. This 'clock' is in a region of the brain called the suprachiasmatic nuclei, which expresses a series of genes termed clock genes that continuously oscillate throughout the day. This is synchronised to the solar day via light input from the eyes . The suprachiasmatic nuclei link to the pineal gland through a complex pathway in the nervous system, passing through different brain areas, into the spinal cord and then finally reaching the pineal gland. During the day, the suprachiasmatic nuclei stops melatonin production by sending inhibitory messages to the pineal gland. At night however, the suprachiasmatic nuclei are less active, and the inhibition exerted during the day is reduced resulting in melatonin production by the pineal gland.(Lee et al., 2022)

1.4Functions of Melatonin Hormone

1. Sleep initiation:It plays an influential role in the regulation of sleep cycles.
2. It plays a role in regulating the female menstruation cycle.
3. Regulation of circadian rhythms :Melatonin hormone has a significant effect on affecting circadian rhythms and integrating photoperiod.
4. This hormone is also helpful for children with developmental disabilities such as ADHD and autism.
5. Measurement of day length :it is often considered to be the body's natural pacemaker, as it plays an instrumental role in signalling time of day and time of year, helping to regulate your body's internal clock
6. Immunomodulation
7. Regulation of mitochondrial functions
8. Anti-inflammatory properties
9. Antioxidant actions
10. Anti excitatory action
11. Vasomotory(Silvestri & Rossi, 2013), (Singh & Jadhav, 2014)
12.

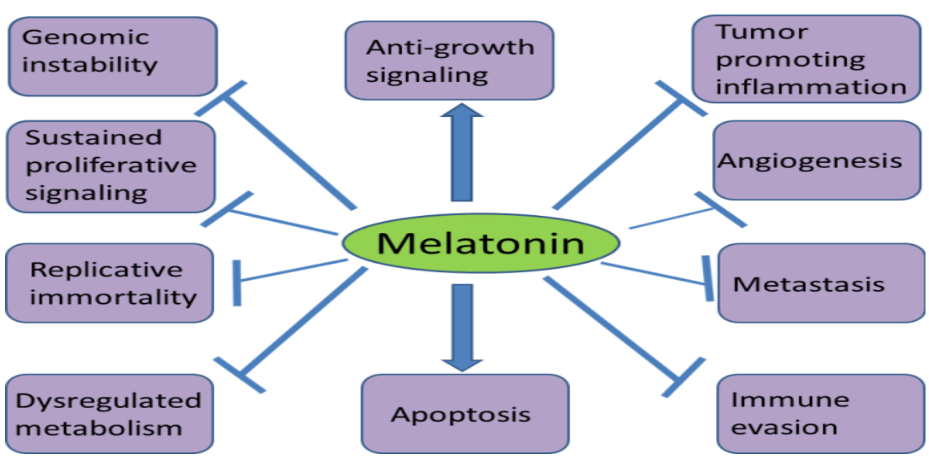

Figure5. Functions of Melatonin[(Talib, 2018)]

1.5Synthesis of melatonin-the role of light

Synthesis of melatonin-the role of light In humans melatonin is produced mainly in the pineal gland and a small portion in the retina. The synthesis and release of melatonin are stimulated by darkness, melatonin is the "chemical expression of darkness" and inhibited by light . Photic information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus of the hypothalamus (SCN) and the sympathetic nervous system . During daylight hours the retinal photoreceptor cells are hyperpolarized and inhibit the release of norepinephrine . With the onset of darkness the photoreceptors release norepinephrine, thereby activating the system, and a number of a1- and b1-adrenergic receptors in the gland increases . The activity of arylalkylamine N-acetyltransferase(), the enzyme that regulates the rate of melatonin synthesis, is increased, initiating the synthesis and release of melatonin. As the synthesis of melatonin increases, the hormone enters the bloodstream through passive diffusion. Environmental lighting does not cause the rhythm but entrains it (alters its timing). Light has two effects on melatonin: day-night light cycles modify the rhythm of its secretion, and brief pulses of light of sufficient intensity and duration abruptly suppress its production . In normal subjects exposure to light inhibits melatonin secretion in a dose-dependent manner. The threshold is 200 to 400 lux (equivalent to ordinary fluorescent light), and maximal inhibition occurs after exposure to intense light (600 lux or higher) for one hour . (Ostrin, 2019)

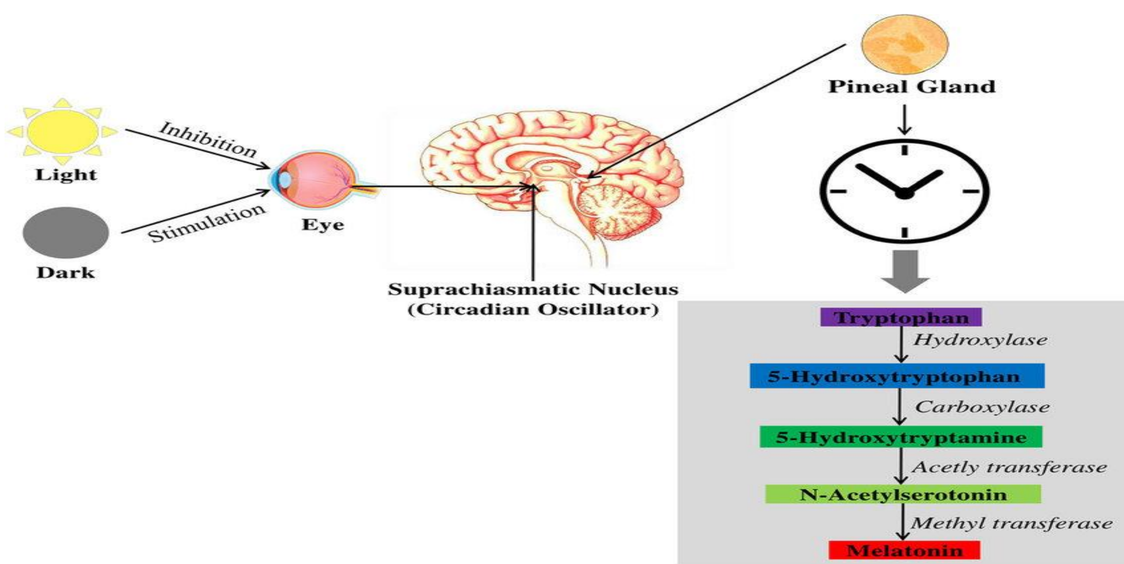

Figure6.Synthesis of melatonin of light[(Hossain et al., 2019)]

1.6How well does melatonin work in children and adolescents

Melatonin has been shown to improve sleep in children and adolescents without psychiatric conditions who have difficulties sleeping, as well as patients with attention-deficit/hyperactivity disorder (AD/HD), autism or developmental delays. In children and adolescents with AD/HD, melatonin may shorten the time it takes to fall asleep by 15 to 30 minutes. Melatonin may also help you stay asleep longer.

This medication may be particularly helpful for patients who experience jetlag from traveling, or who have trouble sleeping from working nightshifts .
Melatonin is only effective if you have low levels of natural melatonin. Before starting treatment with melatonin for sleep, you may wish to try the suggestions below first to see if you have a need for medication. These are suggestions for developing good sleep habits (sleep hygiene). Sometimes, improving sleep hygiene may be all that is needed to improve sleep difficulties. Whenever possible, adding good sleep hygiene
to melatonin therapy increases the chance you will benefit from this medication.

• Avoid caffeine (from tea, coffee or colas) and alcohol, nicotine or other recreational drugs
• Keep a regular sleep/wake schedule everyday; avoid sleeping in or napping during the day
• Avoid stimulating activities before bedtime (e.g. watching television, using the computer, playing video games
or exercising late in the evening)
• Ensure a quiet and comfortable sleep environment (e.g. comfortable temperature, dark room, no pets in bed)
• Doing something relaxing or enjoyable before bedtime (e.g. listening to soothing music or take a warm bath)
• Before bedtime, avoid large meals and exposure to bright lights (e.g. from television or computers)
• Exercise on a regular basis (during the day)
• Use your bedroom only for sleep; remove any clocks from eyesight
• If you do not fall asleep within 30 minutes, get up and go to another room. Come back to bed only when you
start to feel sleepy.(Janjua & Goldman, 2016)

1.7Levels of melatonin

In humans melatonin has diurnal variations. The hormone secretion increases soon after the onset of darkness, peaks in the middle of the night, between 2 and 4 a.m., and gradually falls during the second half of the night . This circadian rhythm of secretion plays an important role in its hormonal activity. In some endocrinopathies like Cushing disease this circadian rhythm of secretion of the hormone is absent. Several diseases such as: Klinefelter's syndrome, Turners syndrome, psoriasis vulgaris, myelomenigocoele, and sarcoidosis have been associated with disrupted melatonin profiles, both in terms of rhythm and magnitude . Seasonal variations There is a seasonal variation in human melatonin, with an earlier phase in summer and increased levels and duration of secretion in winter in high geographical latitudes . Serum melatonin concentrations vary considerably according to age. Infants younger than three months of age secrete very little melatonin. Melatonin secretion increases and becomes circadian in older infants, and the peak nocturnal concentrations are highest (average, 325 pg per milliliter [1400 pmol per liter]) at the age of one to three years, after which they decline gradually 10–15% per decade . In normal young adults, the average daytime and peak night time values are 10 and 60 pg per millilitre (40 and 260 pmol per liter), respectively .(Grivas & Savvidou, 2007)

1.8Melatonin hormone biological clock

Our bodies release chemicals in a 24-hour cycle, nudging us to do certain activities at certain times. Each of these cycles is called a circadian rhythm (see “Circadian Rhythms and Life, One of the most important chemicals involved in this process is melatonin, a hormone that makes us feel drowsy. The amount of melatonin in our bodies starts increasing in the evening and peaks in the middle of the night, letting us know it is time to sleep. It then decreases by morning, allowing us to wake up refreshed.

To maintain our 24-hour sleep schedule, our bodies translate information about time of day into melatonin production. This process starts in the eye’s retina. When the retina is exposed to light, a signal is relayed from the retina to an area of the brain, called the suprachiasmatic nucleus, which plays a role in making us feel sleepy or wide awake.

The suprachiasmatic nucleus sends signals to other parts of the brain that control hormones and body temperature. Then, signals travel from the brain down the spinal cord and back up to the pineal gland, a small pinecone-shaped organ in the brain where melatonin production takes place. During the day, such signals prevent the pineal gland from producing melatonin. But when it is dark outside, these signals are not activated, and the pineal gland is able to produce melatonin . In other words, exposure to light prevents melatonin release, which keeps us awake, and lack of exposure to light causes melatonin release, which tells us to “go to sleep!”

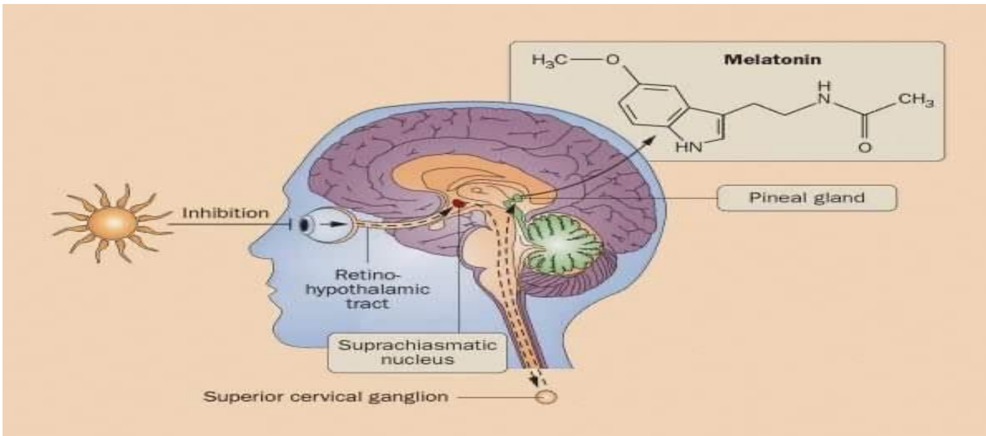

Figure7.Melatonin biological clock [(Terry et al., 2009)]

Light, suprachiasmatic nuclei (SCN), and the pineal/melatonin circuit. Melanopsin in retinal ganglion cells in the eye respond to light (natural or artificially) and transmit signals to the SCN. Then light-induced activation of the SCN prevents the pineal gland from producing melatonin and; conversely, melatonin production and secretion is increased during the dark period.

The light and dark regulation of the biological clock (suprachiasmatic nucleus), pineal melatonin production, and seasonal reproduction in photoperiodic mammals. Specialized photoreceptive cells in the retinas (melanopsin-containing ganglion cells) mediate the effects of light (450-490 nm) on the biological clock and melatonin production.

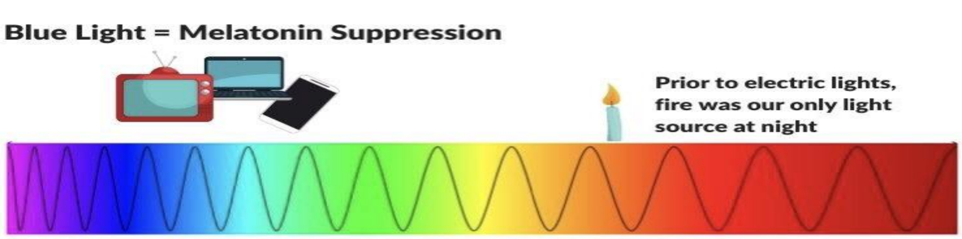

Figure8.light-melatonin[(Ronan, 2007)]

The circuitous neural connections between the eyes and the pineal gland (pinealocyte) are shown. At night, the postganglionic sympathetic neurons ending in the pineal gland release norepinephrine, which activates primarily b-adrenergic receptors to stimulate a cascade of molecular events that culminate in melatonin production and release. Seasonally changing photoperiods alter the duration of elevated nocturnal melatonin production, a signal that provides mammals with the time-ofyear information . This message determines the breeding season of both long-day and short-day breeders. In both cases, the young are characteristically delivered in the spring or early summer. ASMT, acetylserotonin Omethyltransferase; HIOMT, hydroxyindole O-methyltransferase; NAT, alkylamine Nacetyltransferase.(Reiter et al., 2009)

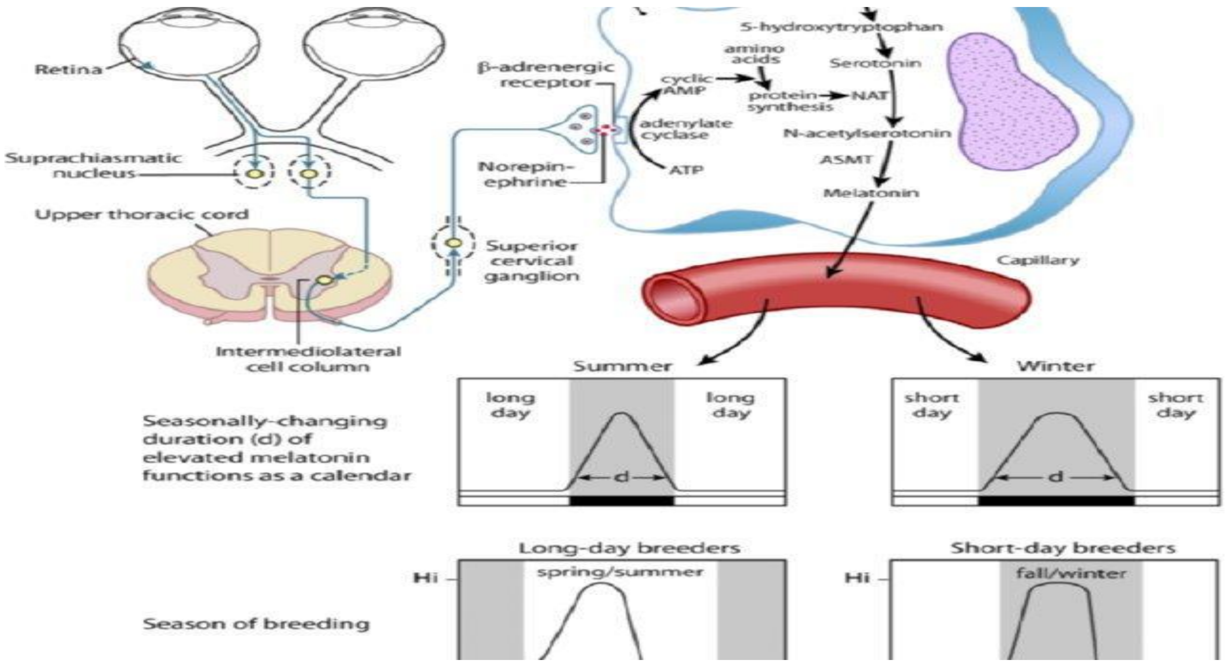

Figure9. biological clock [(Reiter et al., 2009)]

1.9the increase level of melatonin in the body

Many foods are natural sources of melatonin and can assist your body with production. Melatonin is made by animals, plants, and microorganisms. So small amounts of it can be found in certain foods and beverages, such as:
*Animal Foods:
In animal foods, melatonin concentrations were found higher in eggs and fish than those in meat .Melatonin was detected in breast milk of human beings and also in the milk provided by other animals .

Eggs: Among animal foods, eggs are some of the richest sources of the hormone. Plus, they also happen to be highly nutritious, offering protein, iron, and essential vitamins and minerals. Fish: Among animal foods, fish is among the highest in melatonin. One study found that children who ate fish once a week reported sleeping better than those who didn't. Fish is also rich in omega-3s, which may be associated with improved sleep.
Milk: There's a reason you've heard about drinking a glass of warm milk for a restful night. It's because two compounds in milk — tryptophan and melatonin — may help you fall asleep. how much melatonin is in milk depends on the time of day it was collected. At night, melatonin concentrations can be 10x higher. This applies to both cow's milk and breast milk

*Plant Foods: Cereals:
^ Nuts :
When it comes to plant foods, nuts are the richest sources of melatonin. Pistachios and walnuts are especially high in melatonin. As a bonus, pistachios are also high in vitamin B6, which helps convert tryptophan (an essential amino acid) into melatonin.(Meng et al., 2017)

1.10Melatonin and Its Implications for Autism Spectrum Disorder (ASD)

1.10.1Overview of ASD

Autism comprises a series of disorders that vary in severity, intellectual level, and functional disability. The fifth revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) combined specific diagnoses and suggested the single broad ASD diagnosis [. ASD refers to the range of neurodevelopmental disorders accompanying impairments in social interaction ,difficulties in communication, and stereotyped or repetitive behaviors. Because the symptoms of autism vary enormously, the term “autism spectrum disorder” encompasses a single diagnostic category of autism involving numerous conditions . Whereas the older term, autism, described a specific diagnostic category, the newer term, ASD, better explains this disorder by including multiple conditions(Jin et al., 2018) . In this regard, the older term is being replaced by the newer term ASD. Genetic disruption may give rise to synaptic deficits, and ultimately cause ASD. It has been revealed that ASD-related genes are involved in common signal transduction pathways that are responsible for synaptic development and neuronal plasticity .(Jin et al., 2018)

1.10.2 Abnormal Melatonin Secretion and Its Implication in ASD

Melatonin was suggested as a potential therapeutic intervention for FXS with ASD, FXS was the most common form of ASD and seemed to be associated with the loss of fragile X mental retardation (fmr) gene products such as fragile X mental retardation protein (FMRP), leading to diverse physiological and behavioral abnormalities. Additionally, the mutation of this gene disrupts the normal sleep pattern and circadian rhythm. Subsequent alterations of melatonin synthesis and melatonin-dependent pathways may lead to autistic behaviors . Melatonin is a well-known modulator of the regulation of neural plasticity and circadian rhythm . Thus, abnormal melatonin levels may destroy the circadian rhythm, and may even result in autistic behavior. Studies have reported decreased melatonin concentrations in individuals with ASD. Reduced levels of serum melatonin were found in autistic patients . Other studies have demonstrated similar trends. According to Kulman et al . melatonin concentrations in autistic children are lower than those in normal children. They suggested that pineal hypo function in autistic children may be the cause of these reduced melatonin levels. Other researchers have also reported decreased nocturnal melatonin production in autistic individuals . Also, as mentioned above, neurodevelopment mainly occurs during normal sleep. Therefore, children with neurodevelopment disorders including ASD may suffer from pediatric insomnia. For these patients, melatonin may play a beneficial role not only as a neuroprotectant but also as a circadian entrainer . In this context, abnormalities in melatonin concentration are likely to increase the risk of ASD.()

Melatonin is known to freely cross the placental barrier . Even before the maturation of the pineal gland, which is responsible for melatonin secretion, melatonin can be detected in the fetal brain. Melatonin defends against neonatal inflammation and brain injury, evidenced by reduced post-inflammatory unfolded protein response (UPR) and normalization of autophagy following melatonin treatment . Maternal and placental melatonin contribute to fetal neurodevelopment . Thus, abnormalities in maternal melatonin levels may be linked to an augmented risk of fetal neurodevelopmental disorders . Additionally, abnormal maternal melatonin may cause excessive oxidative stress . As the central nervous system consumes a great deal of energy, has few endogenous antioxidants, including catalase and superoxide dismutase, and undergoes vigorous cell differentiation and proliferation, it is highly susceptible to oxidative stress . Therefore, the antioxidant role of melatonin is vital for normal neurodevelopment, especially in the fetus.Thus, mainly as a neuroprotectant, circadian entrainer, and antioxidant, melatonin is thought to protect the fetus from neurodevelopmental disorders and to relieve abnormal oxidative stress, and may reduce the risk of ASD (Figure 10).(Jin et al., 2018)

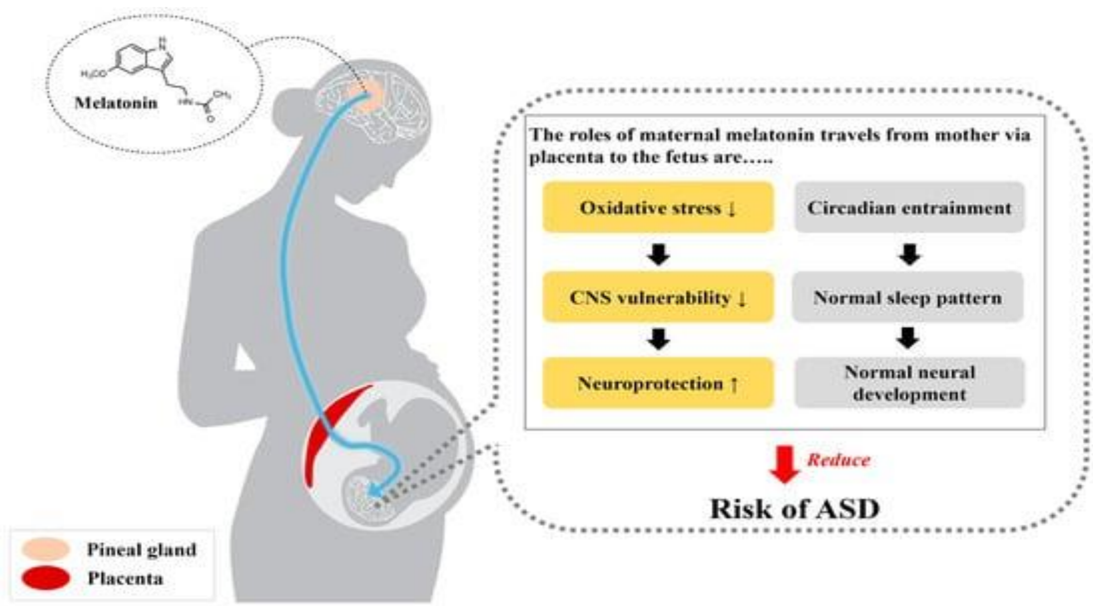

Figure 10. The beneficial roles of maternal melatonin that travels from mother via placenta to the fetus. The functions of melatonin in neuroprotection and circadian entraining may reduce the risk of ASD. Normal melatonin concentrations during pregnancy contribute to neuroprotection and the normal neurodevelopment of the fetus through the inhibition of excessive oxidative stress in the vulnerable central nervous system. Additionally, as adequate melatonin levels maintain the normal sleep pattern and circadian rhythm, normal melatonin secretion may also elicit neurodevelopment.[(Jin et al., 2018)]

1.11 melatonin in clinic

This test helps to determine melatonin levels which are important for accurate diagnosis of endocrine dysfunctions Effectively treating mood and sleep disorders, revealing contributing factors in the pathology of various diseases.

Melatonin levels can be tested with a blood test, urine test or saliva test.

Saliva Sample:

The Melatonin Test requires a saliva sample test requires an evening saliva sample which collected in a vial and sent to pathology Laboratory for testing.

Urine Sample:

Melatonin is measured as MT6s, which is extremely stable urine collected in the bladder overnight, collected and sent in the morning.

The second urine sample is collected 2 hours later, reveals the cortisol increase and rapid fall of the melatonin from night level.

The Third urine sample is collected in the evening when melatonin and cortisol are low.

Fourth, before bed, when the melatonin level is rising and cortisol is lowest.

Blood Sample:

Method: High-Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS)

Sample: Blood

Sample container: Gray top tube

Stability of sample: Room Temperature: 14 days

Refrigerated: 30 day

Frozen: -20 °C: 30 day(Sánchez-Barceló et al., 2011)

1.12 Growth Hormone Regulation by Melatonin

child's body makes HGH (Human Growth Hormone) while he sleeps, which not only helps his body grow but also repairs muscles, tissue, and bone. This hormone helps your child throughout his life, from triggering those rapid growth spurts in early childhood to facilitating development during puberty and beyond.The effects of blinding or constant darkness on growth and growth hormone stores were abolished by pinealectomy—a procedure also found[8] to increase the gain of body weight in otherwise normal rats. Pinealectomy has also been reported to result in increased growth of experimental tumours in rats. The observation of a diurnal fluctuation in the secretion of growth hormone in the rat further suggests that the lighting regime can modify this release. When lighting is reduced, concentrations of the pineal hormone melatonin (N-acetyl-*o*-methylserotonin) are increased because it is synthesized within the pineal gland from serotonin (5-hydroxytryptamine) by the action of the enzymes serotonin-N-acetyltransferase and hydroxyindole-*o*-methyltransferase, both of which exhibit their highest activities in the absence of light(V. S. Chowdhury et al., 2008). The fact that the conditions favouring high melatonin production correlate with those which cause reduced growth (and the other way round) suggests that melatonin has an inhibitory role in growth hormone secretory mechanisms. demonstrated that intraventricular injections of serotonin stimulate secretion of growth hormone in the rat, and they proposed that in this animal secretion of growth hormone is controlled through serotoninergic pathways. Serotonin has also been implicated as the stimulus for secretion of growth hormone after the onset of slow-wave (non-rapid eye movement, NREM) sleep in normal humans.(V. S. Chowdhury et al., 2008)

1.13 the relationship between melatonin and insulin

Insulin regulates blood sugar levels. After eating, blood sugar (i.e. glucose) levels rise. This insulin funnels glucose into cells to be used for immediate energy or stored for later use. Insulin is also a fat storage hormone. If you consume energy in excess of your body's needs (i.e. eating more calories than you burn), insulin promotes the creation of fat cells to store the surplus of glucose.

asleep, your energy needs are at their lowest. Since you're not eating or digesting food while sleeping, your body doesn't need peak levels of insulin to deal with rising blood sugar. And, since you're in a period of fasting during sleep, low levels of insulin at night actually help keep blood sugar levels stable, preventing hypoglycemia, until you eat again the next day.

There is a diurnal rhythm in glucose tolerance in healthy humans, with a decrease in glucose tolerance across the waking day. Such rhythm persists when the influence of the environmental/behavioral cycles are removed, indicating circadian regulation . Melatonin, with the nighttime rise and its inhibitory action on glucose tolerance, can contribute to the nighttime reduction in glucose tolerance in human . Some other generally accepted regulatory pathways include autonomic nerve system , oscillating hormones (e.g. glucocorticoids) and the cell-autonomous peripheral clocks that can influence organ function (e.g., insulin section in pancreatic islets , insulin sensitivity of adipocytes).(Garaulet et al., 2020)

1.13.1 Foods that children should not eat before bedtime

-Sugary Cereal:

sugary cereals (you know them) digest quickly resulting in a spike in sugar. Sugar spikes affect kids much differently than they do adults and this could lead to an entire night of sleep disruption or light sleep , child may experience increased blood sugar levels causing them to do an all-nighter.(Hermes et al., 2022)

- Soda:

Much like sugary cereal soda can create a spike in sugar levels for child resulting in what adults need an energy drink to accomplish. In addition to sugar stimulation the carbonation of a soda can cause stomach pain and discomfort. Soda is recommended as one the foods to avoid at all times, but especially before bed.

-citrus fruits:

child fruit for a late-night snack is beneficial remember that not all fruits are created equal. If you do decide to give child fruit before bedtime, consider a banana or apple with a little peanut butter. These are not only filling but are also nutritious and likely won’t upset child’s stomach.

-Celery

Celery seems like it might be a healthy choice for your kids before bedtime – think ants on a log. celery is a natural diuretic which may cause child to need a late-night potty break when they should be sleeping. (Hermes et al., 2022)

1.14 Melatonin Associated Disorders

melatonin has a pivotal role in regulating body temperature, the sleep/wake cycle , and cardiovascular function, the effect of disrupted secretion rhythms is widespread, manifesting in a variety of physical and psychological disorders .Anxiety, stress, depression

Seasonal affective disorder, Sleep disorders ,Delayed sleep phase syndrome, Immunological disorders, Cardiovascular disease ,Cancer

disorder same name: Schizophrenia ,Multiple sclerosis with major depression, Primary obsessive-compulsive disorder Menie`re's disease, Fibromyalgia ,Migraine ,Critical illness ,Endometrial cancer, Nonsmall cell lung cancer, Acute intermittent porphyria , Diabetes type 2(Hardeland, 2012)

1.15 melatonin hormone excreted from the body after using

undergoes hydroxylation to 6-hydroxymelatonin by the action of the cytochrome P450 enzyme CYP1A2, followed by conjugation with sulfuric acid (90%) or glucuronic acid (10%) and is excreted in the urine. About 5% of serum melatonin is excreted unmetabolized also in urine.(Tordjman et al., 2017)

1.16What Is the Appropriate Dosage of Melatonin?

There is no consensus about the optimal dosage of melatonin, although most experts advise to avoid extremely high dosages. A typical dose in supplements is between 1 and 5 milligrams , but whether this is appropriate for any specific person depends on factors like their age and sleep problems. When melatonin supplements list dosages in micrograms, 1,000 micrograms is equivalent to 1 milligram .Some people experience daytime sleepiness when using melatonin as a sleep aid. If you experience this, it could be that your dosage is too high. It is advisable to start with the lowest dosage possible and work your way up gradually under the supervision of your doctor.

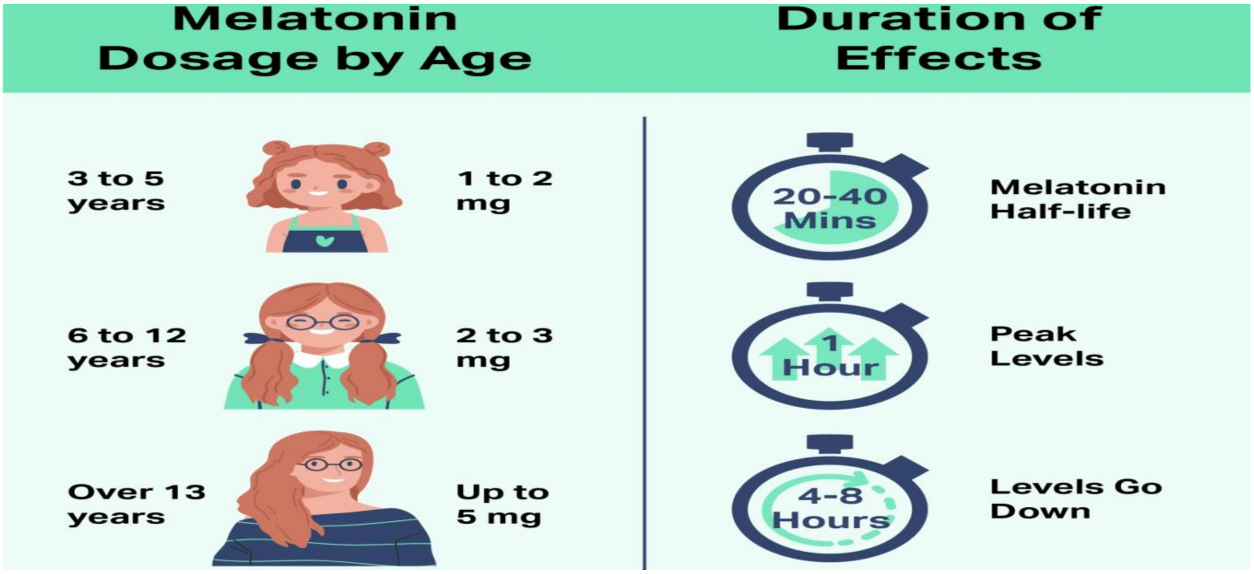

Figure11.dosage by age[(Black et al., 2015)]

Dosages above 5 milligrams are not recommended for children. Typical doses for children start at 1 to 2 milligrams, depending on the diagnosed sleep issue. Young people may respond to smaller doses, and some studies have found benefits to lower doses in adults as well.

Oral supplements can bring the levels of melatonin in the blood to levels much higher than is normally produced by the body. For example, dosages between 1 to 10 milligrams

can raise melatonin concentrations to anywhere from 3 to 60 times typical levels. For this reason, people taking melatonin should use caution before ingesting high doses(Black et al., 2015).

Conclusions

melatonin has a direct effect on the development of children . It is secreted by the pineal gland at night and in the dark. A comfortable and healthy sleep at night is a major factor in both mental and physical development of children. Development hormone and insulin have a direct effect on melatonin hormone. Also, some meals should not be eaten before going to sleep for a more comfortable sleep. Melatonin secretion may be different in disabled children and autistic children. If children have sleep disorders and melatonin secretion disorders, this can cause various physical or mental diseases when they grow up in the future, but this problem can be solved, such children can be given small doses of melatonin with drugs when they are younger, so that their body gets the necessary melatonin, they sleep more comfortably and have a better development.

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