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The role of Melatonin in reducing Obesity and its safety of use: A Review

Marwa Ibrahim Salman[1], Maryam I. Salman[2*], Hajir SH. Hamad[2]

[1]Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq;
[2]Department of Biology, College of Science, University of Anbar, Ramadi, Iraq;

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ABSTRACT
Melatonin is the chiefly hormone formed via the pineal gland, its endogenous synthesis occur during the dark phase and controlled by the Suprachiasmatic Nucleus SCN, melatonin is a long-established and widely distributed chemical in nature that exhibits a variety of modes of action and functions in almost every living thing regulating the circadian rhythms, sleep and wakefulness cycle, energy metabolism in addition to its ability to regulate the raleasing of many cytokines participate in weight plus appetite control . It has been established that the hormone is participated in the controlling of body weight, food intake, glucose metabolism and energy balance, the important role of melatonin in modifiable adipose tissue, lipid profile, inflammation and oxidative stress opens up great hopes for the treatment of obesity. Since obesity is a serious public health issue which results from the imbalance between the amount of calories eaten and the amount of energy expended and predisposes to various metabolic diseases, so this review has been focused on some physiological function of melatonin , its role in the controlling of energy equilibrium and reducing obesity in addition to the benefits of its supplementation.

Introduction:

Melatonin Ancient chemical melatonin (N-acetyl-5-methoxytryptamine) Fig. 1 is found in every living things, including photosynthetic bacteria, plants, animals, plus humans [1,2,3]. Its name refers to its skin-lightening properties, and it is created and secreted at night by the pineal gland, it was first identified in 1958 via Lerner and Colleagues as per a hormone which encourages the accumulation of melatonin particles in dermal melanophore cells of forges for lighten their skin color.[4,5]. Its secretion was regulated via the circadian cycle in the suprachiasmatic nucleus which found in the hypothalamus and subsequently stimulates the peak secretion of melatonin for the period of the night while its secretion decrease in the day by exposure to sunlight [6,7,8]

In addition to pineal gland, melatonin is also produced from other sites such as the placenta, retina, gut, skin, platelets, red cells, lymphocytes, bone marrow, the thymus and lacrimal glands [9-14]. Meng etal, 2019 indicate that melatonin is created via all mitochondria having cells, where it acts to regulates metabolism, endogenous antioxidant and sirtuins [15]. Melatonin is a greatly active antioxidant act as a free radical scanvenger plus protect DNA from the injury prompted via free radicles, furthermore melatonin has the ability to increase production of antioxidant enzymes such as superoxide, catalase, dismutase and glutathione [16-23].

The primary mediator for optimizing energy balance and body weight control is melatonin, which also integrates the cyclic environment with the circadian control of physiological plus behavioral functions.[24-27]. Melatonin directly affects the architecture and action of the thymus, stimulating the immune system in a

*Corresponding author at: Department of Biology, College of Science, University of Anbar, Ramadi, Iraq;
ORCID: https://orcid.org/0000-0002-5572-5813
;Tel:+9647805593837
E-mail address: i_maryam_15@uoanbar.edu.iq

significant way, and protect the body from bacteria and viruses [28-34]. Melatonin regulates the sleep- wake cycle and improve sleep quality [35-39]. Melatonin also has great potential in many diseases such as schizophrenia [40]، rheumatoid arthritis [41], Alzheimer's disease [42], autoimmune diseases [43], cardiovascular diseases [44], sickle cell anemia [45].There is a physiological reduction in melatonin secretion with aged and the occurrence of several disease such as obesity and diabetes [46-48] ، this reduction in melatonin secretion illuminated environment during night, induce sleep disturbance, insulin resistance, glucose intolerance and circadian disorganization [49]. Animals with advanced age who supplemented with melatonin showed better insulin signaling, weight loss and improvement in physical activity [50].

Melatonin synthesis and Receptors

During the dark phase, melatonin is produced, while light drives down melatonin synthesis, the length of darkness period directly affects the frequency and amount of hormone release by the pineal gland, making the hormone a neuroendocrine mediator of the photoperiod [51]. The Prolonged exposure to artificial light in most cultures has an acute suppressing effect on melatonin concentrations with increasing in lipid concentration, hypertension, plus abdominal obesity[52,53].

Unlike other hormones the secretion of melatonin is not under the control of the feedback mechanisms so the plasma levels of melatonin do not depend on its output, the suprachiasmatic nuclei of the hypothalamus receive photoperiod information from the retina, photoperiod signals then go along polysynaptic pathways to the pineal gland, where they are innervated by sympathetic nerves from the superior cervical ganglia.[54,55] , the exposure even to small light during the night is enough to reduce melatonin levels [56-58].

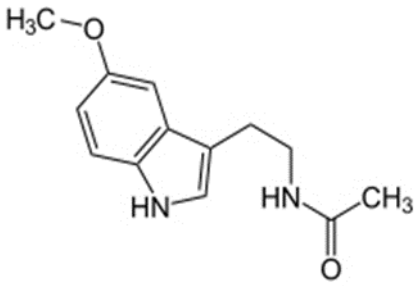

Figure 1: Structure of Melatonin

The primary site of melatonin synthesis in the CNS is the pinealcytes, and the first step in this process is the acceptance of tryptophan, a nutritional amino acid, into the gland. The blood-brain barrier's ability to transport tryptophan into the brain is dependent on the occurrence of extra neutral amino acid that enter to the circulatory system [59].

Tryptophan undergo hydroxylation and changed to 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase enzyme, 5-HTP undergo subsequent decarboxylation to 5-hydroxytryptamine (serotonin) which converted to N-acetylserotonin (NAS) via the enzyme 5-hydroxytryptophan decarboxylase, which is then acetylated by ararylalkylamine N-acetyltransferase (AANAT), which is now O-methylated to melatonin via hydroxyindole-O-methyltransferase.[60,62]. (Fig.2)

Most melatonin was synthesized in pineal gland during the night and transports in a free and albumin-linked manner, the hormone reaches its highest serum concentrations in the night amid 80 to 120 pg/mL, while through the day time its level stays low about 10 pg/mL [63,64].

The melatonin half-life in the serum was vary from below 30 min to 60 min, after oral administration the hormone is quickly absorbed by peak serum concentration happening amid 20 minutes and two hours according to its dosage, melatonin oral administration is metabolized in liver via the cytochrome P450 CYP1A2 enzyme, the hormone suffers a 6-hydroxylation subsequently a sulphate or else glucuronide correlation changes melatonin for 6-hydroxymelatonin sulfate (6-sulfatoxymelatonin), above eight percentage of melatonin is excreted completely in the urine by way of 6-sulfatoxymelatonin, Therefore the quantity of this

metabolite offers a simple evaluation of melatonin excretion [65-69].

Tryptophan

↓ Tryptophan-5-hydroxylase

5-Hydroxytryptophan (5-HTP)

↓ 5-HTP- decarboxylase

5- hydroxytryptamine (5-HT)

(Serotonin)

↓ Arylalkylamine-N-acetyltransferase

N-Acetylserotonin

↓ Hydroxyyindole-O-methyltransferase

Melatonin

Figure:2 Synthesis of melatonin from tryptophan as a precursor.

The two G-protein coupled receptors (GPCR receptors) for melatonin in humans are MT1 and MT2. They have a fifty-five percentage whole homology on the amino acid concentration .[70-74]. Most people believe that melatonin is amphiphilic because it can diffuse through additional membrane gaps and through bilipid cell membranes.[75].

The third melatonin receptor MT3 is a nuclear receptor of retinoic acid family (RZR/ROR) and known as the enzyme quinine reductase2, this enzyme refer to a set of reductases which take part in the defense in contradiction of oxidative stress via stopping electron transfer reactions of quinines, this receptors is found in fish, birds and amphibians [76,77].

Melatonin and Obesity

Obesity is a major health problem affecting wide proportion of people in the world and acts as a thoughtful public health problem in the last century, the World Health Organization showed that about 1.9 billion grown persons above eighteen in age are considered as overweight, from them, above 650 million were fat plus that 3.4 million grown person die every year because of the co-illnesses related diseases [78].

The inequality between food eating and energy expenditure leads to obesity, and extra calories come from the food are deposited as triacylglycerol in white adipose tissue (WAT)[79]. Obesity can cause many additional complication, such as, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, dyslipidemia, concern nervous system pathologies and type 2 diabetes mellitus [80-82].

The scientific public has prepared a great work in the latest years for elucidating the origin plus reasons of obesity genetic, neuroendocrine, epigenetic, environmental, psychological, social in addition to eating disorder and lifestyle effects [83]. The main ways that melatonin establishes an adequate energy balance are via controlling the flow of energy to and from the reserves, as well as by controlling energy expenditure directly by activating brown adipose tissue and taking part in the browning of white adipose tissue. [49].

Melatonin functions as a mediator of energy balance information in organisms by acting by delivering signs to the preoptic part on the hypothalamus, which adjusts the regular points of body temperature in accordance with the metabolic level of the animals[84]. Many animal readings have providing visions into the roles of melatonin on increasing the brown adipose tissue BAT size by the browning of the white adipose tissue [85-90]. Melatonin could effect white plus brown adipose tissue by means of its innervation via the sympathetic nervous system from brain to the fat resulting in modulating of adiposity [62]. BAT has a high metabolic activity and its play a vital role in the controlling of insulin sensitivity, glycemia and lipidemia [91,92].

BAT consumes more molecules of glucose and fatty acids because its burns high numbers of calories for heat production and non-shivering thermogenesis activities [93]. Adipocyte triglyceride lipase, perilipin 1, and hormone sensitive lipase are only a few of the genes and proteins that can be greatly upregulated by melatonin to cause lipolysis of adipocytes [94]. On the other hand many other studies explain the relationship between melatonin and other cytokines involved in obesity for examble, exogenous melatonin could modify the excretion of leptin plus ghrelin the dual important neuropeptides released from adipocytes plus stomach and

took part in the regulating of energy balance, the two main adipokines associated with the etiology of obesity are leptin and adiponectin, which are generated by adipocytes. Unexpectedly, the leptin level was favourably modulated by the oral melatonin administration. Leptin resistance was caused by a lack of melatonin signaling, indicating the critical function melatonin plays in leptin signaling.[95-98].

Some studies on melatonin benefits in weight reduction:

Obese white rabbits Boscat induced by hyperlipidemic diet the administration of melatonin showed distinctive weight loss, improved glycemic control, reducing caloric intake, normalization of blood pressure with a significant reduction of fats which deposits in human's arteries [99] .In pinealectomized rats which develop obesity and type 2 diabetes mellitus the administration of melatonin not only improved high glucose levels but also hindered weight gain [100]. Even in an intact melatonin production from pineal gland the melatonin supplementation reduces body weight in about 25% and the visceral fat size in about 50% in young animals [101]. Daily melatonin supplementation with intake water in mid old rats reduced body weight, intra-abdominal fats plus plasma leptin [98,102], melatonin administration in the intake water for forty three weeks reduced the abdominal fat accumulation in female ICR mice [103], and decrease the adipose deposition when giving for twelve weeks in Sprague Dawley rats [104], in another study the administration of melatonin in the intake water for eight weeks reduced the body weight and serum triglycerides level in the same type of rats [105], in C57BL / 6J mice the administration of melatonin for ten weeks decrease white adipose tissue [106], decrease fat deposition and adipocytes size when giving for ten weeks [107]. The administration of melatonin in diet for seven weeks decrease the body weight, glucose, insulin and leptin levels [108]. Melatonin regulates the body weight via the stimulation of central plus peripheral receptors which caused alterations in the metabolic degree through sympathetic nervous action and changed feeding actions [62].

Melatonin administration increased the basal body temperature in animals models signifying a recognized increase in energy spending more than a decreasing in the energy consumption, the enlargement in the energy spending reliant on the metabolic effect of melatonin on white adipose tissue stimulating browning of these tissue with weight losing and enhancement of glycemic plus lipid metabolism[109-111].

On the other hand several human studies have shown the benefit of melatonin administration in reducing body weight , the daily supplementation of three milligram melatonin for three months increased the brown adipose tissue volume in a small study including four patients who suffering from melatonin deficiency because of radiotherapy or surgical elimination of pineal gland [112]. In a set of postmenopausal eutrophic women who suffering from osteopenia the daily consumption of three milligrams melatonin for twelve months not only improved body composition but also reduced the fat mass of these women with 6.9% [113]. The administration of five milligrams melatonin combined with a balanced diet for twenty four weeks in a group of postmenopausal women significantly reduced the body mass index [114].

Safety administration of melatonin and possible side effect:

In a study of Jahnke et al, a high dose of melatonin equal to 200 mg/ kg/day in pregnant rats in gestational days 6-19 showed no signs of toxicity for both the fetus and the mother [115], another study also showed that high doses of melatonin have no toxic effect besides it did not decrease myometrium action with the progressing of gestation [116].

Readings on humans have also noted the absence of a toxic effect of melatonin even with high doses [117-118], melatonin consumption at a dose of 1-6 mg/day on children plus adolescents suffering with sleep onset insomnia was deemed to be safe [119] , safety information are also appearing from use of this hormone in children with many neurologically syndromes to enhance sleep designs plus learning disabilities [120]. Melatonin supplementation at a dose of 50 mg/day to elderly patients affected by Parkinson's disease showed no significant side effects [121]. In contrast , many other readings have shown side effects for children who use melatonin as a treatment [122-123].

Conclusion:

The hypothesized anti-obesogenic impact of melatonin is partially due to its regulation of the energy balance, which primarily affects the controlling of energy fluidity to plus from the storage as well as in energy expenditure. Yet, Melatonin has been shown to control processes that affect adipose tissue and adipokines, including adipocyte lipolysis, fat accumulation, brown adipose tissue development, beige adipogenesis, plus white adipose tissue browning. These processes, in sequence, influence energy spending.

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دور الميلاتونين في الحد من السمنة وسلامة استخدامه: مراجعة

مروى إبراهيم سلمان [1]، مريم إبراهيم سلمان [2]، هاجر شهاب حمد [2]

[1]قسم التقانة الاحيائية، كلية العلوم، جامعة بغداد / بغداد – العراق

[2] قسم علوم الحياة، كلية العلوم، جامعة الانبار / الرمادي – العراق

i_maryam_15@uoanbar.edu.iq

الخلاصة:

الميلاتونين هو الهرمون الرئيسي الذي تكونه الغدة الصنوبرية، ويحدث تخليقه الداخلي خلال فترة الظلام (في الليل) وتتحكم بتخليقه الانوية فوق الحركية وهو جزيئة معروفة في الطبيعة يظهر آليات متعددة لتنظيم أفعال كل الكائنات الحية أذ ينظم إيقاعات الساعة البيولوجية، دورة النوم واليقظة، واستقلاب الطاقة بالإضافة إلى قدرته على تنظيم إفراز السيتوكينات المختلفة والتي تتحكم بدورها في الوزن والشهية. وقد ثبت أن الهرمون يشارك في تنظيم وزن الجسم وتناول الطعام واستقلاب الجلوكوز وتوازن الطاقة. ان الدور المهم للميلاتونين في تنظيم الأنسجة الدهنية، وصورة الدهون، والالتهابات والإجهاد التأكسدي يفتح آمالًا كبيرة لعلاج السمنة والتي تعتبر مشكلة صحية عامة خطيرة تنتج عن عدم التوازن بين كمية السعرات الحرارية التي يتم تناولها وكمية الطاقة المستهلكة وتؤهب لمختلف أمراض التمثيل الغذائي، لذلك ركزت هذه المراجعة على بعض الوظائف الفسيولوجية للميلاتونين، ودوره في تنظيم توازن الطاقة والحد من السمنة بالإضافة إلى فوائد تناوله كمكمل غذائي وسلامة استخدامه.

الكلمات المفتاحية: ميلاتونين، السمنة، الغدة الصنوبرية، استقلاب الطاقة.