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Melatonin, syndrome melatonin dysfunction and its role as a sleep promoting hormone

Zahraa AL-Nafakh, Khamaal AL-Khafaji, Shaimaa Mohammed Ali Jasim
Department of biology, Faculty of Science, University of kufa, Kufa, Iraq.

***Correspondence:**
shimaam.jasim@uokufa.edu.iq
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ABSTRACT

Melatonin is a hormone secreted from the pineal gland at night. Melatonin is related with memory, and its associations with control of body posture and balance. There are neuroprotective, anti-inflammatory, pain-modulating, blood pressure-reducing, retinal, vascular, seasonal reproductive, ovarian physiology, osteoblast differentiation, anti-tumor and antioxidant effects of melatonin. The disorders in which variations in production of endogenous melatonin production were shown are as follows: Sleep disorders, Alzheimer's disease, Parkinson's disease, glaucoma, depression, breast cancer, prostate cancer, hepatoma, melanoma, congestive heart failure, cardiac syndrome X and sepsis, melatonin is able to cross the cell, organelles, and nuclear membranes and directly interact with intracellular molecules in the so-called non–receptor-mediated actions. In addition to that, melatonin also presents receptor-mediated actions that result from the interaction of this hormone with both membrane and nuclear receptors.

Keywords: Melatonin, Circadian rhythms, Hypomelatoninemia, Sleep, Pineal gland.

Introduction

Melatonin is a hormone secreted from the pineal gland at night. Its peak levels in the dark are associated with age as well as various illnesses. Melatonin plays roles in regulating sleep-wake cycle, pubertal development and seasonal adaptation (Pandi-Perumal *et al*., 2008). Melatonin is related with memory, and its associations with control of body posture and balance have been shown (Pandi-Perumal *et al*., 2008). Melatonin regulates memory formation by directly affecting hippocampal neurons (Comai and Gobbi, 2014). Melatonin has antinociceptive, antidepressant, anxiolytic, antineophobic (being afraid of new things) and locomotor activity-regulating effects (Uz *et al.,* 2005). There are neuroprotective, anti-inflammatory, pain-modulating, blood pressure-reducing, retinal, vascular, seasonal reproductive, ovarian physiology, osteoblast differentiation, anti-tumor and antioxidant effects of melatonin (Li DY *et al*., 2013). Dopaminergic system is important for behavior and rewarding and also in cases of drug addiction such as cocaine (Uz *et al.,* 2005). Melatonin inhibits dopamine release (Uz *et al.,* 2005). The increase in melatonin receptor-related cAMP in the mesolimbic dopaminergic system shows that the effect of melatonin may be present in regulation of addictive behavior (Pandi-Perumal *et al*., 2008). It corrects the behavior disorders related to dopamine addiction and alleviates the findings of cocaine abstinence (Uz *et al.,* 2005). Other effects of melatonin are inhibition of dopamine release in hypothalamus and retina (Pandi-Perumal *et al*., 2008). The anti-excitatory effects of melatonin are probably secondary to its antioxidant effect (Bondy and Sharman, 2007). When it is administered in pharmacological doses in children, it leads to reduction in severity and frequency of epileptiform

activity (Fauteck *et al*., 1999). It shows an effect contrary to glutamate, which is an excitatory neurotransmitter, High melatonin level is associated with exercise-related menstrual disorders, oligospermia and delayed puberty (Genell, 2002). Melatonin regulates the secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamic neurons (Dubocovich *et al.,* 2003). GnRH controls the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Melatonin stimulates the secretion of progesterone from granulosa cells (Dubocovich *et al.,* 2003). Melatonin also suppresses the expression of estrogen receptor and estrogen activation (Carlberg, 2000). Neurological disorders which have been reported to be improved by administration of melatonin are as follows: Parkinsonism (Thomas and Mohanakumar, 2004) Alzheimer's disease (Srinivasan *et al.,* 2006), brain edema and traumatic brain injury (Dehghan *et al.,* 2013), alcoholism (Baydas *et al.,* 2005), depression (Weil *et al.,* 2006), cerebral ischemia (Lee *et al*., 2005), hyperhomocysteinuria (Baydas *et al.*,2005), glioma (Martin *et al.,* 2006) and phenylketonuria (Martinez-Cruz *et al.,* 2006). Alzheimer's disease is an age-related progressive neurodegenerative disorder, characterized with loss of cognitive functions, dementia and other neurobiological findings (Comai and Gobbi, 2014; Di Carlo *et al.,* 2012.

The disorders in which variations in production of endogenous melatonin production were shown are as follows: Sleep disorders, Alzheimer's disease, Parkinson's disease, glaucoma, depression, breast cancer, prostate cancer, hepatoma, melanoma, congestive heart failure, cardiac syndrome X and sepsis (Rada and Wiechmann, 2006). Melatonin production is reduced with aging, various cancers, Alzheimer's disease, senile dementia, pineal calcification (Ekmekcioglu, 2006), cardiovascular disorders and hypothalamic hamartoma or craniopharyngioma which lead to precocious puberty in youngsters (Kunz *et al.,* 1999). Other disorders in which melatonin was shown to be reduced are stress, pain, endocrine and metabolic disorders, particularly DM type 2 and acute intermittent porphyria (Lipton *et al.,* 2009).

Melatonin mechanisms of action: As for its amphiphilicity, melatonin is able to cross the cell, organelles, and nuclear membranes and directly interact with intracellular molecules in the so-called non–receptor-mediated actions. In addition to that, melatonin also presents receptor-mediated actions that result from the interaction of this hormone with both membrane and nuclear receptors.

Non–receptor-mediated actions: Melatonin is a well-known effective antioxidant, as it is both a proficient direct free radical scavenger and so are its metabolites (Galano *et al*., 2013) and an activator of a series of scavenging mechanisms such as stimulation of the transcription and activity of antioxidative enzymes (Barlow-Walden *et al.,* 1995, Rodriguez *et al*., 2004) and binding to transition metals that inhibits the formation of the hydroxyl radical (Galano *et al*., 2015). Besides that, melatonin protects lipids, protein, and DNA from oxidative damage (García *et al.,* 2014; Reiter *et al*., 1998), being highly concentrated in the mitochondria. The mechanisms of melatonin antioxidant actions are extensively reviewed elsewhere (Manchester *et al*., 2015; Reiter *et al*., 2016). The antioxidant properties of melatonin are of crucial importance for the mitochondrial functions, a site were free radicals are naturally formed as a result of cellular respiration reviewed in. Indeed, melatonin plays.

critical roles in mitochondrial function besides the antioxidant protection such as regulation of respiratory chain complexes I and IV activities (Martín *et al.*,2000) and protection of mitochondrial DNA from mutations and deletions (Jou *et al.,* 2002). It was recently demonstrated that melatonin is synthetized in mice brain mitochondria and acts through the mitochondrial external membrane melatonin receptor 1 (MT1), preventing cytochrome c leakage and subsequent apoptosis (an action defined as automitocrine) (Suofu *et al*., 2017.

Some of the above-mentioned effects are usually a consequence of melatonin–protein direct interaction. It is also notable that melatonin plays a role in the regulation of the ubiquitin–proteasome system that ultimately controls protein degradation. Melatonin was reported to inhibit Ca^{2+}/calmodulin-dependent protein kinase II activity and autophosphorylation by a direct interaction with Ca^{2+}-activated calmodulin, acting as an antagonist (Benítez-King *et al.,*1996). It has also been suggested that melatonin influences clock genes expression (see "Prospective effects") by acting as a direct proteasome inhibitor(Vriend and Reiter 2015).

Protection against DNA damage is fundamental and melatonin has shown to be efficient in doing so due to its antioxidant properties, once elevated reactive oxygen species (ROS) levels are a major cause of DNA damage. Additional mechanisms include the decrease of ATM (a phosphoinositide 3-kinase–related kinase) expression and of the histone H2AX

phosphorylation, a step involved in the DNA damage response, among others reviewed in (Majidinia *et al.,* 2017) .

Receptor-mediated actions: The discovery, cloning, and characterization of melatonin membrane receptors were performed in the late 1980s and early 1990s (Dubocovich, 1988). MT1 and melatonin receptor 2 (MT2), formerly named Mel1a and Mel1b,, are high-affinity specific G protein–coupled receptors encoded by the *MTNR1A* (human chromosome 4q35.1) and *MTNR1B* (human chromosome 11q21–q22) genes. Human MT_1 is a 350–amino acid protein, and human MT_2 is a 362–amino acid protein with predicted molecular masses of 39,374 and 40,188 Da, respectively, that were found in several areas of the CNS, including the SCN, mediobasal hypothalamus, thalamus, temporal, parietal, and frontal cortex, hippocampus, the preoptic area, basal ganglia, area postrema, retina, cerebellum, and *pars tuberalis* (PT) (reviewed in (Dubocovich *et al*., 2010). Peripheral organs such as adipose tissue (Brydon *et al.,* 2001), kidney (Rew *et al*., 1998), pancreatic islets (Ibolka *et al*., 2018), parotid glands (Isola *et al.*, 2016), adrenal glands, liver), bone, skin, reproductive tract , immune cells (Lopez-Gonzalez *et al.,*1992), and cardiovascular system (CVS) (reviewed in (Slominski *et al*., 2012), among others, also present MT_1 and MT_2 melatonin receptors.

MT_1 and MT_2 melatonin receptors are heterotrimetric G_i/G_o and $G_{q/11}$ protein–coupled receptors that interact with downstream messengers such as adenylyl cyclase, phospholipase A_2, phospholipase C, and calcium and potassium channels, generally decreasing cAMP and cGMP production and/or activating phospholipase C. MT_1 and MT_2 usually dimerize, forming homodimers or heterodimers that keep both melatonin binding sites functional and with the respective selectivity (Ayoub *et al.,* 2002). GPR50 is another G protein–coupled receptor that may dimerize to MT_1, reducing its affinity to melatonin and to melatonin agonists, being a potential regulatory step of this signaling mechanism (Jockers *et al*., 2008).

MT_1 signaling pathways involve, for example, (1) activation of Kir3.1/3.2 potassium ion channels that mediate the inhibition of neuronal firing in the SCN (Nelson *et al.,* 1996). (2) modulation of protein kinase C (PKC) and phospholipase A_2 (McArthur *et al*., 1997) modulation of specific ion channels by MT_1 coupling to $G_{q/11}$ proteins;(3) mitogen-activated protein kinase kinase 1/2–ERK1/2 pathway stimulation in nonneuronal cells(Witt-Enderby *et al.,* 2000) and vasoconstriction (Radio *et al*., 2006).

Complementary MT_2 signaling pathways involve, for example, (1) inhibition of cGMP formation and stimulation of PKC activity in SCN (Hunt et al., 2001); (2) regulation of uterus contractility (Sharkey *et al*., 2009); and (3) vasodilatation (Doolen *et al.,* 1998). It was recently suggested that MT_2 melatonin receptors in the SCN might correspond to a G protein–coupled inwardly rectifying potassium channel .

MT_3 (previously named ML2) is a third characterized mammalian melatonin binding site (not considered a receptor) that is a form of quinone reductase 2, a detoxifying enzyme (Nosjean *et al.,* 2000), and was reported to be involved, for example, in the melatonin-derived increase of chemotherapeutic-induced cytotoxicity and apoptosis in tumor cell lines (Pariente *et al*., 2017).

Melatonin and circadian rhythms: Based on the melatonin well-defined PRC, its immediate and prospective effects, and its strategically timed repetitive daily prescription, this hormone has successfully been clinically used as a chronobiotic agent. It is used to entrain daily rhythms mainly in clinical syndromes involving circadian rhythm disorders, such as the syndromes involving temporary or permanent circadian misalignment as jet lag, the delayed sleep phase disorder, seasonal affective disorder, and others and in clinical disorders causing circadian free running as it occurs in the non–24-hour sleep–wake rhythm disorder, either in totally blind or sighted patients (Emens and Eastman, 2017; Uchiyama and Lockley 2015; Arendt and Skene, 2005).

Importantly, note that melatonin prescription as a chronobiotic agent should rigorously follow the melatonin PRC, taking, in every case, the DLMO as the reference phase to decide the time of melatonin administration in accordance with the desired effect, that is, either phase advance or phase delay (Lewy, 2003). Additionally, the duration of the treatment will depend on the case being a transient one (as it is the case for jet lag) or a longer one (as for the treatment of delayed sleep-phase disorder or non–24-hour sleep–wake rhythm disorder.

Clinical syndromes involving melatonin Dysfunction: Unhealthy low or high hormonal synthesis and actions are classically described in human pathophysiology. Considering melatonin as a hormone, the present section aims to define the syndromes characterized by hypohormonal or

hyperhormonal production and by impaired receptor signaling.

However, as the time domain is one major determinant of melatonin action (duration, daily repetition, immediate and prospective effects, chronobiotic effects, seasonal effects), there are some putative melatonin-related syndromes that are characterized not by hyperproduction or hypoproduction but by the temporal displacement or extension of melatonin's daily profile. Adequate melatonin measurement is a crucial point, and several observations should be made relative to this point. First, it is possible to measure blood levels of melatonin, saliva melatonin, and 6-sulfatoxymelatonin in the urine. Differently from any other hormone measurement, where the biological samples are usually collected during the morning hours, either for blood or saliva melatonin, samples should be collected during the evening and the night, at very low level of illumination, preferably avoiding the blue spectrum of light. Ideally, the patient will be in a dark room or under red light of very low intensity (<50 lux) and have the sample collected every 30 minutes or hour during the evening for DLMO determination (Lewy *et al.,* 2008), one of the best indexes of the internal circadian timing, or, even during the entire evening/night for other purposes. Also note that blood collection should not affect the patients' sleep, as it may lead to flawed internal circadian phase determination. That is why saliva is usually collected at the beginning of the evening and should not be collected during the night. Alternatively, urinary 6-sulfatoxymelatonin excretion is directly proportional to the total amount of melatonin produced in a given night, provided that the patient rests under a low level of environmental illumination. Urine collection from dusk to the first urine excretion in the following morning (e.g., the patient should discard the urine excretion at 1800 hours or 1900 hours and start collecting all of the produced urine until 0600 hours or 0700 hours the next morning) is an excellent index of the total nocturnal production of melatonin. The amount of melatonin produced during the night is directly proportional to the 6-sulfatoxymelatonin excreted load that is calculated as concentration times the total nocturnal urine volume. The ratio between 6-sulfatoxymelatonin and urinary creatinine is usually calculated for the normalization by the patient's renal function.

Hypomelatoninemia: Hypomelatoninemia is defined by decreased melatonin nocturnal peak value or total production when compared with what is expected for the age- and sex-paired population. Putatively, several symptoms may derive from this syndrome that will vary according to the basal underlying pathology: circadian and sleep disorders (insomnia, chronic daytime fatigue or somnolence, delayed sleep onset, non–24-hour sleep–wake syndrome); hypertension; insulin resistance and glucose intolerance; dyslipidemia; obesity; metabolic syndrome; higher risk of type 2 diabetes; higher risk of cancer, mainly breast and prostate cancer; low-quality aging process, such as frailty syndrome, and others. However, differently from other classical hormonal hypofunction syndromes, hypomelatoninemia is usually not found in isolation, as it can be seen below, being either a participant of a complex genetic disease syndrome or associated with several other diseases, the aging process or environmental disruptors. As a result, the full picture of the putative hypomelatoninemia syndrome is rarely seen. More frequently, fragments of it such as sleep disturbances and circadian rhythms disorders are the more prominent clinical hallmarks, and those should not be seen as modest abnormalities but rather as very serious ones with systemic repercussions that interfere with every other aspect of human physiology and behavior, jeopardizing health, quality of life, and even longevity.

Sleep deprivation is a well-known cause of metabolic disorders such as obesity, insulin resistance, diabetes, and metabolic syndrome in both children and adults (Patel and Hu, 2008). A subtle daily decrease of 30 minutes in the night sleep episode, for example, may not be perceived by the patient or by the physician, but it increases insulin resistance and body weight in early diagnosed patients with type 2 diabetes, worsening the metabolic picture (Arora *et al*., 2016).

Sleep disturbances derived from melatonin reduction are clearly seen in pinealectomized patients (pineal surgical removal usually as a consequence of pineal tumors or cysts) (see "Melatonin and sleep"). However, in the case of these patients who present a clinical situation where the unique hypomelatoninemia syndrome is represented, there are no complete, prospective, and embracing studies so far, and the only available ones are restricted to certain aspects of the expected syndrome such as sleep, circadian rhythms, and eventually some hormonal secretion such as GH, cortisol, prolactin, and ACTH disturbances (Májovský *et al*., 2017; Petterborg *et al*., 1991). Alternatively, in aging, some of the typical clinical aspects of the expected hypomelatoninemia syndrome are seen,

such as sleep and circadian disorders, insulin resistance/diabetes, hypertension, obesity, immunodeficiency, and a higher incidence of tumors. Some of these signals and symptoms could be obviated by melatonin replacement therapy, probably indicating the pathophysiological role played by the natural reduction in melatonin production in aging.

Primary hypomelatoninemia: Primary hypomelatoninemia is dependent on factors that directly affect the pineal or its innervation, embryonic formation, or pineal melatonin synthesis as a result of a genetic or innate disease. It might be dependent on pineal agenesis or hypoplasia, sympathetic pineal innervation agenesis, and biochemical defects in pineal melatonin synthesis, as is the case in gene polymorphisms linked to the enzymes involved in the melatonin synthesis pathway (tryptophan hydroxylase, AANAT, or acetylserotonin O-methyltransferase) (Grant *et al.,* 2017; Cox *et al*., 2017). The absence of circulating melatonin that follows surgical pinealectomy should be considered primary hypomelatoninemia as well (Arendt, 2018).

Secondary hypomelatoninemia: Secondary hypomelatoninemia develops as a consequence of a primary event, such as another disease, or as a consequence of environmental factors, including medications (iatrogenic). Examples of diseases and situations causing secondary hypomelatoninemia are: spinal cord cervical transection, resulting in tetraplegia; cervicothoracic sympathectomy, aging, neurodegenerative diseases (Parkinson disease, Huntington disease, Alzheimer's disease, depression), genetic diseases not directly linked to the origin of the pineal gland and its innervation (e.g., sepiapterin reductase deficiency leading to reduced serotonin synthesis and drastic melatonin synthesis reduction without daily rhythm; fatal familial insomnia and Morvan syndrome); hyperglycemia associated with diabetes; obesity; exposure to light at night; use of drugs that reduce melatonin production (e.g., beta-blockers, calcium channel blockers, inhibitors of angiotensin synthesis and action) and shiftwork(Ángeles-Castellanos, *et al*., 2016; Lin *et al*., 2014; Kalliolia *et al*., 2014).

Hypermelatoninemia: Medical syndromes associated with hyperproduction of melatonin are rare, and there are five clinical situations described so far: spontaneous hypothermia hyperhidrosis, hypogonadotrophic hypogonadism, anorexia nervosa, polycystic ovarian syndrome, and Rabson-Mendenhall syndrome (which is a rare genetic disorder that shows pineal hyperplasia associated with a high level of plasma melatonin and urinary 6-sulfatoxymelatonin) (Arendt *et al*., 1992). Finally, the iatrogenic hypermelatoninemia is characterized by high nocturnal values usually associated with extended duration resulting in high morning levels of circulating melatonin, which are determined by inadequate control of prescribed melatonin. The reported symptoms in hypermelatoninemia are diurnal sleepiness, sleep episodes, low body temperature, dizziness, and hypotonia (Dawson & Encel,1993). In the spontaneous hypothermia hyperhidrosis syndrome, associated with high levels of circulating melatonin also during the day (>1000 pg/mL), it is described by an altered level of consciousness, even complete loss, and syncopal attacks with sweating and hypothermia (body temperature 33 to 34°C). These symptoms associated with a high level of melatonin ameliorate with phototherapy and the patients are successfully treated with beta-blockers (Duman *et al*., 2010).

Melatonin and sleep: The association between melatonin and human sleep started to be studied in the early 1970s (Antón-Tay *et al*., 1971). In the early 1990s low doses of melatonin, generating near nocturnal physiological plasma levels, were able to reduce sleep-onset latency and oral temperature, triggering the usual polysomnographic patterns of the nocturnal sleep architecture observed in young people (Dollins *et al*., 1994). By the end of the 1990s it was suggested (Lavie, 1997) that the beginning of nocturnal melatonin production is phase locked to the end of the "forbidden zone" and to the opening of the "sleep gate" (Lavie, 1986) (zones of increased arousal and induced hypnogogic mechanisms, respectively or, as proposed by Moruzzi (Moruzzi, 1969), the respective appetitive and consummatory sleep behavioral stages), thus triggering the nocturnal circadian episode of sleep. This conception attributes to the nocturnal production of melatonin the property of switching the organism from the biological day (in diurnal species: arousal, energy intake and storage, high cortisol, and active interaction with the external environment) to the biological night (in diurnal species: sleep, low temperature, energy consumption, low cortisol) (as defined in (Srinivasan *et al.*, 2009), suggesting that melatonin might promote sleep by regulating the activity–wake/rest–sleep circadian rhythm probably by its actions on melatonin receptors in the SCN.

A randomized clinical trial to study disturbed sleep in a population of adults with developmental brain disorders suggested that the efficacy of melatonin

treatment (irrespective of the dose) was dependent on the beforehand amount of endogenously produced melatonin, being that the exogenous melatonin was more effective as the lower was the individual natural nocturnal production (Laakso *et al*., 2007). Confirming the hypothesis of melatonin regulating sleep by acting on the circadian rhythm, this study showed that melatonin treatment induced an increase in the day-to-night activity ratio (rhythmic amplitude) and a decrease in the fragmentation of the rhythm, increasing its stability, as evaluated by actgraphic records.

The importance of physiological levels of pineal melatonin for human sleep was assessed by studies on pinealectomized patients. Despite some contradictory reports (Krieg *et al*., 2012), these patients presented a disrupted 24-hour circadian rhythm, a reduction of total sleep time, more nighttime awakenings, poor sleep quality, and, in most cases, all symptoms were reverted by melatonin treatment (Lehmann *et al*., 1996).

Experimental studies show that melatonin might affect the sleep mechanism itself, in addition to circadian control. MT_1 and/or MT_2 knockout mice studies showed that the MT_1 melatonin receptor seems to be associated with the incidence of rapid eye movement sleep episodes whereas the MT_2 melatonin receptor was associated with the incidence of nonrapid eye movement episodes (sleep spindles and delta waves) (Comai *et al*., 2013). The association of MT_2 to nonrapid eye movement electroencephalographic patterns was demonstrated to be dependent on melatonin action on MT_2 receptors present in reticular thalamic neurons.

Recent reviews and meta-analysis studies of melatonin or its analogs effects on sleep disorders points to its efficacy in reducing sleep latency, increasing total sleep time, and reducing night awakenings, in addition to improving overall sleep strains).

quality (Xie *et al*., 2015). Melatonin, or its analogs, seems to be effective in managing primary insomnia in elderly people, sleep disorders associated with neurologic disorders and neurodegenerative diseases (autism, attention-deficit hyperactivity disorder, Parkinson disease, Huntington disease, Alzheimer's disease), patients with hypertension taking beta-blocker, and rapid eye movement sleep behavior disorder (Auger *et al*., 2015).

Note that all of the above-mentioned studies are in line with the daily experience in medical practice, where most of the patients report positive results, especially regarding subjective well-being and quality of sleep. Despite that, some guidelines state that the effects of melatonin or its analogs (apart from effects on sleep latency and circadian sleep disorders) are small, of low strength, or insufficient (Wolden-Hanson *et al*., 2000). These guidelines are mainly based on systematic or narrative reviews that are based on the few randomized placebo-controlled clinical trials. Additionaly, as shown below, the dosage of melatonin should be individually adjusted and would vary among patients. In randomized clinical trials, a fixed and determined dose is usually prescribed to everyone in a relatively large population. The chances of odd results are higher because a greater number of individuals may be inappropriately responsive to the determined dose, differently from what would be expected for a small sample study. This would probably reduce the magnitude of the effect of melatonin in the analyzed outcome. However, one should be cautious, and more adequately planned and controlled studies that take into consideration melatonin ways of action and effects, the melatonin PRC, and, above all, individual differences will surely help to better understand the real therapeutic value of melatonin on human sleep.

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