

REVIEW ARTICLE

Melatonin: Pharmacology, Functions and Therapeutic Benefits

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Abstract: Background: Melatonin synchronizes central but also peripheral oscillators (fetal adrenal gland, pancreas, liver, kidney, heart, lung, fat, gut, etc.), allowing temporal organization of biological functions through circadian rhythms (24-hour cycles) in relation to periodic environmental changes and therefore adaptation of the individual to his/her internal and external environment. Measures of melatonin are considered the best peripheral indices of human circadian timing based on an internal 24-hour clock.

Methods: First, the pharmacology of melatonin (biosynthesis and circadian rhythms, pharmacokinetics and mechanisms of action) is described, allowing a better understanding of the short and long term effects of melatonin following its immediate or prolonged release. Then, research related to the physiological effects of melatonin is reviewed.

Results: The physiological effects of melatonin are various and include detoxification of free radicals and antioxidant actions, bone formation and protection, reproduction, and cardiovascular, immune or body mass regulation. Also, protective and therapeutic effects of melatonin are reported, especially with regard to brain or gastrointestinal protection, psychiatric disorders, cardiovascular diseases and oncostatic effects.

Conclusion: This review highlights the high number and diversity of major melatonin effects and opens important perspectives for measuring melatonin as a biomarker (biomarker of early identification of certain disorders and also biomarker of their follow-up) and using melatonin with clinical preventive and therapeutic applications in newborns, children and adults based on its physiological regulatory effects.

Keywords: Adaptation to external and internal environment, biological clocks, biomarker, clinical application, central and peripheral oscillators, melatonin, prevention and treatment, sleep-wake rhythm, synchronizer.

1. INTRODUCTION

Melatonin or 5 methoxy-*N*-acetyltryptamine (Fig. 1) was discovered and isolated from bovine pineal in 1958 by Aaron Lerner [1]. Melatonin is the main hormone secreted by the pineal gland. Extrapineal sources of melatonin were reported in the retina, bone marrow cells, platelets, skin, lymphocytes, Harderian gland, cerebellum, and especially in the gastrointestinal tract of vertebrate species [2-9]. Indeed, melatonin is present but can also be synthesized in the enterochromaffin cells; the release of gastrointestinal melatonin into the circulation seems to follow the periodicity

of food intake, particularly tryptophan intake [2, 10]. It is noteworthy that the concentration of melatonin in the gastrointestinal tract surpasses blood levels by 10-100 times and there is at least 400 times more melatonin in the gastrointestinal tract than in the pineal gland [2]. Melatonin in the gastrointestinal tract of newborn and infant mammals is of maternal origin given that melatonin penetrates easily the placenta and is after secreted into the mother's milk [11-13]. It has even been suggested that melatonin is involved in the production of mekonium [2]. Melatonin in human breast milk follows a circadian rhythm in both preterm and term milk, with high levels during the night and undetectable levels during the day [14, 15]. No correlation was found between gestational age and concentration of melatonin. It is noteworthy that bottle milk composition does not contain melatonin in powder formula. Also, human colostrum, during the first 4 or 5 days after birth, contains immune –

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competent cells (colostral mononuclear cells) which are able to synthesize melatonin in an autocrine manner [16].

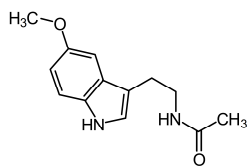


Fig. (1). Melatonin chemical structure (*N*-acetyl-5-methoxytryptamine).

Melatonin is mainly synthesized by the pinealocytes from the amino acid tryptophan, which is hydroxylated (by the tryptophan-5-hydroxylase) in 5-hydroxytryptophan, then decarboxylated (by the 5-hydroxytryptophan decarboxylase) in serotonin. Two enzymes, found mainly in the pineal gland, transform serotonin to melatonin [17, 18]: serotonin is first acetylated to form *N*-acetylserotonin by arylalkylamine-*N*-acetyltransferase (AA-NAT, also called “Timezyme”, is the rate-limiting enzyme for melatonin synthesis), and then *N*-acetylserotonin is methylated by acetylserotonin-*O*-methyltransferase (ASMT, also called hydroxyindole-*O*-methyltransferase or HIOMT) to form melatonin (Fig. 2). Both AA-NAT and ASMT activities are controlled by noradrenergic and neuropeptidergic projections to the pineal gland [19]. Norepinephrine, also called noradrenaline, activates adenylate cyclase which in turn promotes the melatonin biosynthesis enzymes, especially AA-NAT [20]. Once synthesized, melatonin is quickly released into the systemic circulation to reach central and peripheral target tissues.

Melatonin synthesis and secretion is enhanced by darkness and inhibited by light (Fig. 3) [21]. Luminous information is transmitted from the retina to pineal gland through the suprachiasmatic nucleus (SCN) of the hypothalamus. In humans, its secretion starts soon after sundown, reaches a peak in the middle of the night (between 2 and 4 in the morning) and decreases gradually during the second half of the night [22]. Nearly 80% of the melatonin is synthesized at night, with serum concentrations varying between 80 and 120 pg/ml. During daylight hours, serum concentrations are low (10-20 pg/ml) [23].

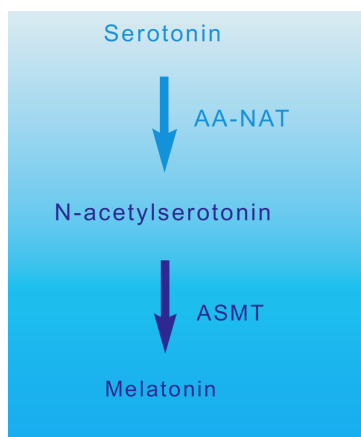


Fig. (2). Melatonin synthesis (AA-NAT: arylalkylamine-*N*-acetyltransferase; ASMT: acetylserotonin-*O*-methyltransferase).

Melatonin (pg/mL)

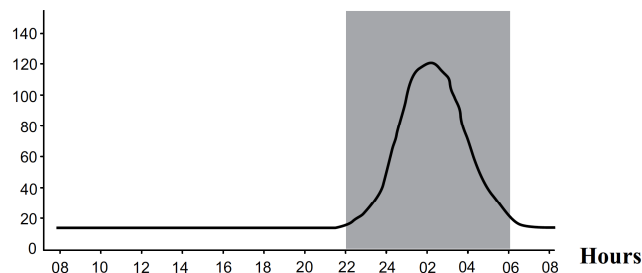


Fig. (3). Circadian profile of melatonin plasma concentrations (in grey is represented the period of darkness).

Serum concentrations of melatonin vary considerably with age, and infants secrete very low levels of melatonin before 3 months of age. Melatonin secretion increases and becomes circadian along with child development: Sadeh [24] reported an association between melatonin secretion and organization of sleep-wake rhythm from 6 months of age. However, more recent studies suggest that melatonin rhythm is set around 3 months of age in typical development, at the same time that infants begin to have more regular sleep-wake cycles associated with nighttime sleep lasting 6-8 h [25]. In 3-years-old children, a stabilization of the sleep-wake rhythm is observed, which corresponds to a regular melatonin secretion rhythm [26]. Nocturnal concentration peaks are the highest between the 4th and 7th years of age [23], and then decline progressively [27].

2. PHARMACOKINETICS

After intravenous administration, melatonin is rapidly distributed (distribution half-life of 0.5 to 5.6 minutes) and eliminated [28]. After oral administration, plasma concentration peak arises within 60 minutes [29]. Plasma concentrations diminution is biphasic, with a half-life of respectively 2 and 20 minutes [30]. Intake of an usual dose (*i.e.*, 1 to 5 mg), allows within the hour after ingestion, melatonin concentrations 10 to 100 times higher than the physiological nocturnal peak to be obtained, with a return to basal concentrations in 4 to 8 hours.

A bioavailability study in four male healthy volunteers [31] showed a plasma melatonin peak varying between 2 and 395 nmol/L and an elimination half-life of 47 ± 3 min (mean \pm SD) after oral administration of a 500 μ g dose. Bioavailability varied from 10 to 56% (mean 33%).

After intravenous or oral administration, melatonin is quickly metabolized, mainly in the liver and secondarily in the kidney. However, after intravenous administration, the hepatic bio-degradation is less important due to the absence of hepatic first pass. It 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. The principal metabolite, the 6-sulfatoxy-melatonin (6-SM), is inactive, and its urinary excretion reflects melatonin plasma concentrations [32]. Plasma levels

can be also measured directly or indirectly assessed through salivary measures. A reverse relation between bioavailability of melatonin and the 6-SM concentrations area under the curve has been shown, the low bioavailability being explained by an important hepatic first pass [31].

3. MECHANISMS OF ACTION

Melatonin acts through different molecular pathways. The best characterized pathway is the activation of two types of membrane specific receptors: high affinity ML1 sites and low affinity ML2 sites [33, 34]. The activation of ML1 receptors, which are G protein-coupled receptors [35], leads to an inhibition of the adenylate cyclase in target cells. The activation of ML2 receptors, currently called MT3, leads to phospho-inositides hydrolysis. MT3 is expressed in various brain areas and has been shown to be the enzyme quinone reductase 2 [36]. Two sub-types of the ML1 receptor have been described [37] Mel1a and Mel1b. Mel1a (or MT1) is encoded in human chromosome #4 (4q35.1) and consists of 351 amino acids. Mel1a is widely distributed in the *pars tuberalis* of the anterior pituitary and the SCN of the hypothalamus (which is the anatomic site of the circadian clock), and also in the cortex, thalamus, substantia nigra, nucleus accumbens, amygdala, hippocampus, cerebellum, cornea and retina [38]. Mel1b (or MT2) is encoded in human chromosome #11 (11q21-q22) and consists of 363 amino acids. Mel1b is distributed mainly in the retina and secondarily in the hippocampus, cortex, paraventricular nucleus, and cerebellum [39]. Melatonin has also an intracellular action by binding, on the one hand, to cytosolic calmodulin [40], and on the other hand, to two receptors of the Z retinoid nuclear receptors family [41]. Melatonin receptors have been found in several central but also in peripheral tissues, including heart and arteries, adrenal gland, kidney, lung, liver, gallbladder, small intestine, adipocytes, ovaries, uterus, breast, prostate, and skin [42]. Furthermore, they have also been detected in T and B lymphocytes. Evidence shows that there is a considerable variation in the density and location of the expression of melatonin receptors between species [43]. In a recent review, Liu *et al.* suggest, on the basis of affinity studies showing species-dependent fluctuations *in vivo* ligand selectivity, that there are considerable species differences in melatonin receptor pharmacology [44]. Models of mice with targeted disruption of either Mel1a or Mel1b receptor subtypes, or double mutants have been used, allowing the cellular mechanisms through which melatonin modulates circadian and photoperiodic rhythmicity to be understood [45, 46].

The effects of melatonin depend on the localization and types of melatonin receptors; those effects are described in the next section.

4. EFFECTS OF MELATONIN

4.1. Physiological Effects

Melatonin regulates circadian rhythms such as the sleep-wake rhythm, neuroendocrine rhythms or body temperature cycles through its action on MT1 and MT2 receptors [23, 42-49]. Ingestion of melatonin induces fatigue, sleepiness and a diminution of sleep latency [26]. Disturbed circadian rhythms are associated with sleep disorders and impaired health [50].

For example, children with multiple developmental, neuro-psychiatric and health difficulties often show melatonin deficiency [51]. When circadian rhythms are restored, behavior, mood, development, intellectual function, health, and even seizure control may improve [50, 52]. It should be noted that according to several studies, circadian rhythms are important for typical (normal) neurodevelopment and their absence suppresses neurogenesis in animal models [53-56].

Finally, melatonin may as well be involved in early fetal development, with direct effects on placenta, glial and neuronal development, and could play an ontogenic role in the establishment of diurnal rhythms and synchronization of the fetal biological clock [57-59]. Iwasaki *et al.* [57] investigated the expression of the two enzymes involved in the conversion of serotonin to melatonin (AA-NAT and ASMT) and found that transcripts of these enzymes were present in the first-trimester human placenta. Moreover, they found also that melatonin significantly potentiated hcg secretion at optimal concentrations on cultured human trophoblast cells. These results suggest that melatonin regulates in a paracrine/autocrine way human placental function with a potential role in human reproduction. *In vitro* studies have shown that neural stem/progenitor cells express MT1 receptors, and melatonin induces glial cell-line derived neurotrophic factor (GDNF) expression in neural stem cells, suggesting an early role for melatonin in central nervous system development. Indeed, as indicated previously, melatonin of maternal origin crosses the placenta and can therefore influence fetal development. Studies in humans have repeatedly confirmed that the cycle of melatonin in maternal blood occurs also in fetal circulation [60, 61]. The maturation and synchronization of the fetal circadian system have not been thoroughly studied. However, studies in nonhuman primate fetus have shown that maternal melatonin stimulates growth of the primate fetal adrenal gland and entrains fetal circadian rhythms, including SCN rhythms [62, 63]. Furthermore, in mice, the suppression of melatonin rhythm by maternal exposure to constant light changes the rhythmic expression in fetal clock genes; these changes are reversed when melatonin is injected daily to the mother [64]. These results document that the fetal clock is imprinted by melatonin, which under normal circumstances is of maternal origin. In addition, some studies in humans and nonhuman primates show 24h rhythms in fetal heart rate and respiratory movements during the latter half of pregnancy. Whether the circadian system of the human fetus, particularly in late pregnancy, is under the influence of maternal SCN remains to be better ascertained [65].

Besides the well-known effects of melatonin on the regulation of sleep-wake rhythms, melatonin is considered as an endogenous synchronizer and a chronobiotic molecule, *i.e.* a substance that reinforces oscillations or adjusts the timing of the central biological clock located in the suprachiasmatic nuclei of the hypothalamus to stabilize bodily rhythms [66]. Furthermore, Pevet and Challet [67] view melatonin as both the master clock output and internal time-giver in the complex circadian clocks network: as a major hormonal output, melatonin distributes, through its daily rhythm of secretion, temporal cues to the numerous tissue targets with melatonin receptors, driving circadian rhythms in some tissue structures such as the adenohypophysis

or synchronizing peripheral oscillators such as the fetal adrenal gland but also many other peripheral tissues (pancreas, liver, kidney, heart, lung, fat, gut, *etc.*). Circadian rhythms, and more precisely the circadian clocks network, allow temporal organization of biological functions in relation to periodic environmental changes and therefore reflect adaptation to the environment. Thus, the sleep–wake rhythm associated with biological circadian rhythms can be seen as an adaptation to the day–night cycle. Moreover, the synchronization by melatonin of peripheral oscillators reflects adaptation of the individual to his/her internal and external environment (for example, the synchronized effects of melatonin on cortisol and insulin secretion allow the individual to be fully awake at 8am and able to start the day by eating and getting some energy from food intake). Given the major synchronizing effects of melatonin on central and peripheral oscillators, measures of melatonin are considered the best peripheral indices of human circadian timing [68].

Furthermore, melatonin is involved in blood pressure and autonomic cardiovascular regulation, immune system regulation but also various physiological functions such as retinal functions, detoxification of free radicals and antioxidant actions through its action on MT3 receptors protecting the brain from oxidative stress [12, 38, 68-74]. A through its action on MT3 receptors specific section is developed below on melatonin and brain protection. The antioxidant actions of melatonin protect also the gastrointestinal tract from ulcerations by reducing secretion of hydrochloric acid and the oxidative effects of bile acids on the intestinal epithelium, and by increasing duodenal mucosal secretion of bicarbonate through its action on MT2 receptors (this alkaline secretion is an important mechanism for duodenal protection against gastric acid); melatonin prevents also ulcerations of gastrointestinal tract by increasing microcirculation and fostering epithelial regeneration [2, 66]. Concerning the role of melatonin in immune regulation, melatonin has direct immuno-enhancement effects in animals and humans [75, 76]. Indeed, melatonin stimulates the production of cytokines and more specifically interleukins (IL-2, IL-6, IL-12) [77]. In addition, melatonin enhances T helper immune responses [76, 78]. Furthermore, the melatonin antioxidant actions contribute to its immuno-enhancing effects [77] and have also an indirect effect by reducing nitric oxide formation which facilitates the decrease of the inflammatory response [79]. As suggested by Esquifino *et al.* [80], melatonin might provide a time-related signal to the immune network.

In addition, effects of melatonin on body mass and bone mass regulation have been reported. Melatonin is known for its role in energy expenditure and body mass regulation in mammals by preventing the increase in body fat with age [81-83]. These effects are mediated by MT2 receptors in adipose tissue [84]. Moreover, melatonin increases bone mass by promoting osteoblast cell differentiation and bone formation [85, 86]. In humans, melatonin stimulates bone cell proliferation and Type I collagen synthesis in these cells, and inhibits bone resorption through down-regulation of the RANKL-mediated osteoclast formation and activation [87, 88]. Also, a deficit of melatonin has been found to be associated with animal scoliosis following pinealectomy and human idiopathic scoliosis [89, 90].

Finally, melatonin has physiological effects on reproduction and sexual maturation in mammals through down-regulation of gonadotropin-releasing hormone (GnRH) gene expression in a cyclical pattern over a 24-hour period [91-93]. The rhythmic release of GnRH controls luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. The daily profile of melatonin secretion conveys internal information used for both circadian and seasonal temporal organization [67]. The melatonin rhythmic pattern entrains the reproductive rhythm *via* the influence of photoperiod on LH pulsatile secretion and therefore mediates the seasonal fluctuations of reproduction clearly observed in animals (seasonal breeding as species-specific seasons for reproduction) and moderately observed in humans [94-96].

4.2. Melatonin in Disorders and Therapeutic Effects

Therapeutic effects of melatonin have been reported in several disorders such as certain tumors, cardiovascular diseases or psychiatric disorders. The part concerning melatonin and psychiatric disorders is in particular developed given our past and current work on this topic.

Indeed, oncogenic effects of melatonin have been reported in several tumors (breast cancer, ovarian and endometrial carcinoma, human uveal melanoma, prostate cancer, hepatomas, and intestinal tumors) [97-106]. These oncogenic effects have been attributed to the anti-oxidative role of melatonin given that oxidative stress is involved in the initiation, promotion and progression of carcinogenesis [107, 108]. Also, decreased melatonin levels (measures of blood melatonin or urinary excretion of 6-SM) were reported in patients with cardiovascular diseases [109-112]. Inversely, melatonin treatment reduces blood pressure in patients with hypertension [69, 74, 113].

Concerning psychiatric disorders, secretion disturbances of the pineal gland have been described in child and adult psychiatry, with notably in most studies a decreased nocturnal melatonin secretion observed in major depressive disorder, bipolar disorder, schizophrenia or autism spectrum disorder [114-117].

Also, a phase-shift of melatonin has been reported in major depressive disorder and bipolar disorder, including in particular a delayed melatonin peak secretion [114, 118, 119]. It is noteworthy that increased melatonin levels (measures of blood melatonin and urinary excretion of 6-SM) were found when clinical therapeutic benefits were observed following the use of antidepressants [120-122]. Furthermore, significant improvement of major depressive disorder and anxiety was described following administration of 25mg per day of agomelatine, a MT1/MT2 melatonin agonist and selective antagonist of 5-HT_{2C} receptors [123-125].

Concerning autism spectrum disorder (ASD), abnormalities in the serotonergic system and sleep-wake rhythm disturbances observed in children with ASD suggest altered melatonin secretion in autism [126-128]. Sleep disorders (mostly increased sleep latency, reduced total sleep and nocturnal awakenings with insomnia) are observed in 50-80% of individuals with autism [129]. It is noteworthy that sleep problems are not specific of autism

and are also observed in children with intellectual disability associated or not with autism [128]. However, melatonin measures in children with intellectual disability not associated with autism, such as some children with Down syndrome and Fragile X syndrome, showed respectively normal melatonin production despite delayed nocturnal melatonin peak secretion and increased levels of melatonin [130, 131], whereas decreased nocturnal melatonin secretion was mostly observed in children with autism [128]. We reported in two different large samples of children with autism significant relationships between decreased nocturnal urinary excretion and severity of autistic impairments in social communication [127, 132]. These results suggest that abnormalities in melatonin physiology might contribute not only to sleep problems in autism, but also to biological and psychopathological mechanisms involved in the development of ASD (for example, certain immunological abnormalities found in autism, such as a decrease number of T lymphocytes, might be explained by the hypo-functioning of the melatonin system).

Concerning schizophrenia, as suggested by Morera-Fumero and Abreu-Gonzalez [116], a possible explanation for the “low melatonin syndrome” present in some individuals with schizophrenia may stem from the study of the melatonin-synthesizing enzymes, the AA-NAT and ASMT. Furthermore, according to some authors, MT3 might be involved in the melatonin disturbances observed in schizophrenia [38]. Finally, melatonin secretion was also studied in obsessive compulsive disorder but no abnormalities in melatonin levels were reported.

4.3. Melatonin and Brain Protection

Neurological and neuropsychological disabilities caused by brain injuries are a major public health concern. Thus, reducing deficits after a stroke is a major issue. In this line, a number of recent studies have reported the important role of melatonin in neuroprotection in animal models of stroke [133]. Indeed, melatonin administration after an experimental stroke in animals reduces infarction volume [134, 135]. Such a protective effect can be seen in both gray and white matter [136] and melatonin reduces also inflammatory response [137], cerebral oedema formation [138], and blood-brain barrier permeability [139]. In addition, Kilic *et al.* [140] investigated how sub-acute delivery of melatonin, starting at 24 hours after stroke onset, and continuing for 29 days can influence neuronal survival, endogenous neurogenesis, motor recovery and locomotor activity in mice submitted to an occlusion of the middle cerebral artery during 30 minutes. Furthermore, melatonin improved neuronal survival and enhanced neurogenesis, even when applied one day after stroke. In addition, the authors showed both motor as well as behavioral improvements after melatonin administration. Indeed, the results indicate that cell survival was associated with a long-lasting improvement of motor and coordination deficits as well as with attenuation of hyperactivity and anxiety of the animals as revealed in open field tests. Its neuroprotective activity in animal models of ischemic stroke, as well as its lack of serious toxicity suggests that melatonin could be used for human stroke treatment in the future.

In addition to its protective effect after stroke, experimental data obtained in various independent animal models of brain lesions in neonates support the notion of a neuroprotective effect of melatonin in preterm neonates (see for a review, Biran *et al.*, [141]). In infants, a major source of brain injury is preterm birth, often associated to long-term neurological, cognitive, educational, and social problems. Neurodevelopmental disorders are not only seen in extremely preterm birth [142] but also in late prematurity [143]. A large number of infants who survive very preterm birth develop cerebral palsy [144] with a high occurrence of associated motor, perceptual and cognitive deficiencies in childhood [145, 146]. Nowadays, the most common brain damage observed in preterm children is diffuse white matter damage as well as reduced neural connectivity [147, 148] in the context of infection, inflammation, and hypoxia-ischemia [149]. Although a number of treatments have been tested in preclinical animal models of perinatal brain injury, none of them had been proved to be efficient as a neuroprotector nor translated in clinical practice. Among the molecules proposed, melatonin is a very good candidate, given its effect on brain development, neuroprotection as well as regarding its absence of adverse effects [150]. As discussed by Biran *et al.*, [141], in addition to its good safety profile, melatonin easily crosses the placenta as the blood-brain barriers and blocks oxidative, excitotoxic and inflammatory pathways, all involved in the pathogenesis of perinatal brain damage caused by preterm birth. However, only a few studies have looked at the synthesis of melatonin in preterm and term neonates. These studies point to a reduced urinary concentration of melatonin during the first 3 months after birth in preterm infants (see Biran *et al.* [141] for review and discussion). As these authors discussed, compared with term neonates, preterm neonates show a delayed secretion of melatonin which persists after correction for gestational age up to 8 to 9 months of age. In the absence of maternal melatonin, the appearance of circadian rhythms depends principally on neurological maturation, and very little on the environment [151].

Since, as above-mentioned, melatonin easily crosses the blood-brain and placental barriers, it can be administered antenatally in order to reduce or prevent the impact of brain lesions in preterm neonates. Currently, two therapeutic trials testing the neuroprotective properties of melatonin administration in the immediate prepartum period in very preterm infants are under way in France and in the United Kingdom (see Biran *et al.*, [141] for description). The French trial aims to determine the dose of melatonin to be administered in prepartum by parenteral route to mothers at risk of preterm delivery, to decrease the extent of white matter damage detected by diffusion tensor imaging in infants born preterm. The objective of the English trial is to prove that melatonin is capable of reducing brain injury and white matter disease as defined by magnetic resonance imaging at term. These trials will probably lead to a clinical use of melatonin before preterm birth (in case of at risk mother) or just after birth in preterm neonates in order to prevent neurodevelopmental deficits in these children.

Interestingly, from a functional point of view, abnormalities in melatonin physiology associated with sleep

disorders, and in particular sleep deprivation, are seen to endanger cerebral and more specifically hippocampal integrity, leading to cognitive dysfunction and contributing to the development of mood disorders [152]. The involvement of melatonin in the development of mood disorders was discussed in the previous section.

Finally, based on the brain protective role of melatonin against oxidative stress previously described in this article, there is also increased experimental evidence showing the therapeutic potential of melatonin in neurodegenerative conditions such as Alzheimer disease, Parkinson disease, Huntington's disease and amyotrophic lateral sclerosis (see Polimeni *et al.* [153] for a review). Additional studies and clinical trials are now required both in preterm neonates and aging adults to test the clinical efficacy of melatonin supplementation in such disorders, and to identify the specific therapeutic concentrations needed regarding the subject's age, disease and brain lesion as well as the short and long-term effects of melatonin both on physiological, functional and cognitive outcomes.

5. CONCLUSION AND FUTURE DIRECTIONS

Regular physiological rhythms are important to ensure a stable internal environment by creating continuity from repetition of identical discontinuities. Several studies, based on animal models and human perinatal development, suggest that stable patterns of repeated stimuli in the form of maternal physiological rhythms, involving cross-modal perception such as regular cardiac rhythm, which provides the fetus with auditory and vibratory stimuli, allow the fetus to integrate sensory information facilitating prenatal perceptual learning and to develop a coherent representation of his or her internal and external environment [154-156]. Fluctuations in physiological rhythms (variants), such as variations in the maternal cardiac rhythm and also variations in hormone levels involved in the circadian rhythms that are already present during the fetus life (the fetus' circadian rhythms are the mother's ones), occurring in a background of regular repetition of identical sequences (invariants), may help the fetus to develop the ability to adapt to change in an environment characterized by high regularity. As previously emphasized by Tordjman [156], very early mother-infant relations provide a secure environment based on the repetition of invariants, while at the same time promoting adaptation to change through the presence of variants. It is through the regular repetition of identical sequences of discontinuity, such as circadian rhythms, that a continuum is constructed associated with the development of adaptation to changes. Melatonin plays a major role in the regularity and synchronization of central and peripheral oscillators allowing the development of harmonious internal functioning and adaptation of the internal environment to external environment. As highlighted by Arendt [50], melatonin might be the best peripheral biomarker of human circadian timing. This review shows the high number and diversity of melatonin effects opening important perspectives for measuring melatonin as a biomarker (biomarker of early identification of certain disorders and also biomarker of their follow-up) and using melatonin with therapeutic applications. Given the very large potential clinical applications of

melatonin and its apparent absence of major side effects, it is amazing to see that the role of melatonin in human clinical trials has been mainly confined to sleep problems and focused on just a few disorders [157]. Future studies are required, such as studies of melatonin dose-response relationships, to extend the use of melatonin in clinical practice, prevention and treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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