Melatonin: a promising drug to ameliorate main human space exploration risks

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Abstract

Melatonin is a small indole molecule synthesized by most cells in the mammalian body. Circulating melatonin secreted by the pineal gland is a circadian signal that regulates main rhythmic physiological processes, including sleep-wake cycle and biological rhythms in cardiovascular function, metabolism, and immune response. Both intracellular and extracellular melatonin have been shown to act as an effective protector for free radicals molecular and tissue injury. During human space exploration crewmembers will be exposed to several risks, including exposure to radiation in the form of high-energy galactic cosmic rays and solar particle events, bone loss and neurological disorders induced by microgravity, and sleep disruption. Due to its important chronobiotic and cytoprotective effect, melatonin treatment could be a potential effective strategy to protect against most space radiation hazards. It has an anti-osteoclastogenic activity and a pro-osteoblastic activity that may reduce bone-loss induced by microgravity. Also, melatonin is potentially effective to prevent neurodegeneration that may result from long term space exploration. Finally, its chronobiotic and hypnotic properties may help to improve sleep and circadian synchronization, decreasing in turn, the risk of fatigue, performance decrements and adverse health outcomes. Melatonin was presumably present from the very beginning of life in Earth and evidence suggests that it could be a helpful partner for our first steps outside the planet.

Melatonin, an ubiquitous molecule

Circulating melatonin (N-acetyl-5-methoxytryptamine) is a small indole molecule synthesized and secreted by the pineal gland. However, almost all cells, tissues and organs in vertebrates have been found to contain melatonin and are capable of its synthesis. Mitochondria were identified as primary sites of its production. Melatonin has been identified in bacteria and eukaryotes (including protists, fungi, plants and animals) and presumably could be present in archaea, thus being considered a universally distributed molecule.[1–3]

Circulating melatonin exhibits a remarkable 24 h rhythm with maximal levels at night. It is controlled by light via a complex pathway that starts in mammals in special photoreceptive retinal ganglion cells that project to the suprachiasmatic nucleus (SCN), the major circadian oscillator. Efferences from the SCN influence, via descending multisynaptic projections originating in the hypothalamic paraventricular nucleus, preganglionic sympathetic neurons that innervate the superior cervical ganglia. The postganglionic sympathetic fibers terminate on the pinealocytes regulating melatonin synthesis by releasing norepinephrine. Once synthetized, melatonin is not stored within the pineal gland but diffuses out into the capillary blood and

cerebrospinal fluid. Melatonin reaches all tissues of the body within a truly short period, with a first distribution half-life of 2 min and a second of 20 min.

Nearly 80% of pineal melatonin is synthesized at night. In humans, its secretion starts soon after sunset, is highest in the middle of the night and decreases gradually during the second half of the night, with serum concentrations changing between 80 and 120 pg/ml. After oral administration, plasma concentration peaks within 60 minutes. The concentration decrease is biphasic (half-lives of respectively 2 and 20 minutes). Within the hour after ingestion, a usual dose of 1 to 5 mg determines 10 to 100 times higher melatonin concentrations than the physiological nocturnal peak. Return to basal concentrations is seen in 4 to 8 hours. After intravenous administration, melatonin is quickly distributed (half-life of 0.5 to 5.6 minutes) and eliminated.[4]

Oral formulations present variability in absorption and metabolism of melatonin.[5] First pass metabolism of melatonin is regulated by a family of cytochrome P450 mono-oxygenases (cytochrome P450s) which hydroxylate melatonin in the C6 position (isoenzymes CYP1A2, CYP1A1 and, to a lesser extent, CYP1B1).[6] Hydroxylated melatonin is conjugated with sulfate to be excreted as 6-sulfatoxymelatonin. The genetic variability of CYP450s might be one of the causes of the large inter-individual and, importantly, gender variability in melatonin pharmacokinetics. The main CYP450 enzyme involved in the hepatic metabolism of melatonin is CYP1A2 and it has higher activity in men.[7]

The metabolism of melatonin in extrahepatic tissues exhibits substantial differences. Tissues of neural origin, including the pineal gland and retina, contain melatonin-deacetylating enzymes, which are either specific melatonin deacetylases or less specific aryl acylamidases. Melatonin can be metabolized nonenzymatically in all cells, and extracellularly, by free radicals and a few other oxidants. It is converted into cyclic 3-hydroxymelatonin when it directly scavenges two hydroxyl radicals.[8] In the brain, a substantial fraction of melatonin is metabolized to kynuramine derivatives. This is of interest as the antioxidant and anti-inflammatory properties of melatonin are shared by these metabolites, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and, with considerably higher efficacy, N^1-acetyl-5-methoxykynuramine.[9]

In as much as melatonin diffuses through biological membranes with ease, it can exert actions in almost every cell in the body. Some of its effects are receptor mediated, while other are receptor independent. The chronobiotic action of melatonin is mediated via the melatonin receptors, which have been identified both in the CNS and in the periphery.[10] MT1 and MT2 receptors all belonging to the superfamily of membrane receptors associated with G proteins (G-protein coupled receptors, GPCR) have been cloned. More recently, another member, GPR50, was included in the melatonin receptor subfamily. GPR50 shows high sequence homology to MT1 and MT2 but does not bind to melatonin or any other known ligand. An interesting feature of these receptors is their capacity to form homo- and heteromers between each other and also with other GPCRs.[11] Due to its liposolubility, melatonin penetrates all

membranes and is associated with cytoplasmic proteins such as calmodulin and tubulin, which causes important changes in the cytoskeleton.[12] Melatonin also accesses the cell nucleus where it may act indirectly via sirtuin-1 activation of the oscillator component RORα.[13]

The cytoprotective activity of melatonin exceeds that mediated via receptors. Almost every cell in the human body contains melatonin, in quantities much higher than those circulating in blood derived from the pineal gland. The mitochondrial capacity to synthesize melatonin is now confirmed, but for reasons that remain unexplained, intracellular melatonin does not get the extracellular space. To modify intracellular melatonin levels, doses much higher than those employed as a chronobiotic are needed.[14,15] Most studies on neuroprotective and anti-inflammatory effects in animals employ pharmacological doses, which clearly exceed the saturation of the receptor.

In both the cytoplasm and the cell nucleus, melatonin has important antioxidant and scavenging effects on free radicals, which are largely independent of receptors.[16] These effects are exerted in three ways: (a) melatonin is a free radical scavenger; (b) melatonin is metabolized to compounds with high antioxidant activity; (c) melatonin is an indirect antioxidant, which stimulates the synthesis of antioxidant enzymes and inhibits that of prooxidant enzymes. Melatonin has a proven superiority to vitamin C and E in protection against oxidative damage and in the elimination of free radicals[17] In addition, melatonin potentiates the effects of other antioxidants, such as vitamin C and Trolox. Several antiapoptotic and cytoprotective effects of melatonin are exerted under conditions of ischemia (unrelated to free radicals) and can be attributed to the stabilizing activity of the mitochondrial membrane.[15]

Melatonin is also an immunological modulator that shows both proinflammatory and anti-inflammatory properties.[18,19] The anti-inflammatory actions are of medicinal interest, since they are observed in high-grade inflammation such as sepsis, ischemia/reperfusion and brain injury, as well as in the low-grade inflammation seen in metabolic syndrome, neurodegenerative disorders and aging. Melatonin has significant anti-inflammatory properties presumably by inhibiting the binding of nuclear factor κB (NF κB) to DNA, thus decreasing the synthesis of proinflammatory cytokines, by inhibiting cyclooxygenase (Cox)[20] in particular Cox- 2,[21] and by suppressing the expression of the inducible gene of nitric oxide synthase.[22] In addition, other pathways of secondary signaling are involved.[19]

The described pharmacokinetic and pharmacodynamic characteristics of melatonin determine an exceptional pleiotropy of actions with absence of major side effects. This implies that the administration of melatonin can readjust numerous physiological functions other than sleep and circadian rhythms, with therapeutic opportunities, among others, in psychiatric, cardiovascular, metabolic and oncologic disorders.[4,23]

Main human space exploration risks

The spaceflight environment, characterized mainly by ionizing radiation, microgravity, and physiological/psychological stressors, presents a significant hazard to spaceflight crews during missions.[24–28] Interestingly, melatonin can be a very useful therapeutic strategy to cope with main human space exploration risks.

Radiation exposure

During human space exploration crewmembers will be exposed to radiation in the form of high-energy galactic cosmic rays and solar particle events. These sources of radiation include protons and high-atomic-number energetic particles, both with a high linear energy transfer (LET) that increases the risk of cellular damage.[29] Through an indirect effect on water, ionizing radiation produces highly reactive free radicals, mainly the hydroxyl radical OH. Free radicals target on DNA molecule, inducing mutations and compromising proliferation. In addition, they interact with unsaturated sites in lipids, causing lipid peroxidation and altering membrane permeability. In turn, this may compromise the central nervous system (including retina damage) and other tissues integrity, induce sterility, heritable genetic damage, or the development of cancer.[30]

As above discussed, melatonin has an important antioxidant effect. First, it increases glutathione levels, stimulates the synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase and down-regulates pro-oxidant enzymes, including 5- and 12-lipo-oxygenases and nitric oxide synthases. The molecule by itself, as well as its secondary and tertiary metabolites, neutralize several oxygen derivatives, with a higher antioxidant capacity than other molecules such as vitamin C, vitamin E, glutathione and NADH. Melatonin also preserves mitochondrial homeostasis, reduces free radical generation and protects mitochondrial ATP. Moreover, the inhibition of pro-apoptosis and upregulation of anti-apoptosis genes, and its effects over inflammatory responses and DNA repair enzymes, may contribute to reduce radiation induced cell damage. [31–33]

Melatonin treatment could be a potential effective strategy to protect against space radiation hazards. For example, it has been shown in high-LET 56Fe particle irradiated mice that melatonin can prevent cerebellum injury and that melatonin metabolite AFMK enhances neurogenesis in hippocampal dentate gyrus. Melatonin treatment also significantly prevented carbon ion irradiation induced mitochondrial dysfunction and apoptosis in mouse brain, and alleviated the carbon induced increase in the percentage of apoptotic cells and elevated oxidative stress in mouse testis.[34] Melatonin has also shown radioprotective effects in erythrocytes, ovary, thyroid and liver of irradiated rodents, as well as in human lymphocites.[30] In humans, a double-blind placebo-controlled study in patients with rectum cancer undergoing radiotherapy examined the radioprotective effects of melatonin (20 mg/day, 5 days a week,

during 28 days) on blood cell counts. Platelet, white blood cells, lymphocyte, and neutrophil reduction (but not erythrocytes) due to radiotherapy was slighter or insignificant in melatonin recipients compared to control.[35]

Microgravity

Microgravity is one of the main hazards in spaceflight environment. It may affect many aspects of human physiology, including shift of body fluids, loss of fluids and electrolytes, bone loss and CNS function.

Bone loss induced by microgravity is currently an important and unresolved health risk for human space exploration. It is associated with changes that weaken the integrity of bone tissue and increases the risk of fracture injuries, incomplete fracture regeneration and renal stone formation. Non-pharmacological countermeasures to this problem include diet supplements and physical exercise, while pharmacological interventions include the use of antiresorptive agents (bisphosphonates and monoclonal antibodies) or anabolic drugs. As these agents are associated with potentially serious adverse effects which limit their use, new drugs like melatonin, with more favorable security profiles, are needed.[36]

Melatonin has an anti-osteoclastogenic activity by downregulating the receptor activator of nuclear factor-kappa beta (RANK), which promotes osteoclast differentiation and activation, and by up-regulating osteoprotegerin, which inhibits osteoclastogenesis and bone resorption. Also, melatonin and its metabolites may scavenge superoxide anions generated by osteoclasts that are involved in the degradative process of bone resorption and increases the production of the osteoclast-inhibiting hormone calcitonin. Concerning anabolic effects, melatonin has a pro-osteoblastic activity by activating the MEK-ERK pathway that promotes pre-osteoblasts proliferation and by upregulating factors involved in cell differentiation via the Wnt/β-catenin signaling pathway.[36]

The first indications that melatonin administration was effective for decreasing bone loss in vivo were obtained in ovariectomized rats.[37–39] In humans, several studies associated the age-related decrease in melatonin production with increased risk of osteoporosis.[40] Regarding double blind studies, a randomized controlled trial conducted in postmenopausal osteopenic women, demonstrated that one year treatment with melatonin increased bone mineral density in the femoral neck in a dose dependent manner (1 mg/day and 3 mg/day), while higher doses (3 mg/day), increased the volumetric bone mineral density in the spine.[41] Another double-blind study that assessed the effects of nightly melatonin supplementation on bone health and quality of life in perimenopausal women for six months, showed that melatonin supplementation was associated with a decreased ratio between type-I collagen crosslinked N-telopeptide NTX (a bone resorption marker) and osteocalcin (a bone formation marker).[42] Finally, Ikegame et al.

reported an inhibitory effect of melatonin on osteoclastic activation by microgravity, using goldfish scales as a bone model of coexisting osteoclasts and osteoblasts. Authors showed that during space flight, microgravity increased gene expression for osteoclast differentiation and activation, stimulated osteoclastic activity and decreased the expression level of mRNA for acetylserotonin O-methyltransferase, a critical enzyme for melatonin synthesis. By contrast, melatonin treatment increased the mRNA expression of calcitonin and decreased the mRNA expression of RANK.[43]

Microgravity has also been linked to neurological disorders, such as learning and memory ability decline, cognitive deficits, visual disturbances, movement/orientation control alteration, nausea, and headaches, and sleep disorders.[44–46] The neurologic sequels could be associated with several factors observed in microgravity. Following ISS missions, it was shown that there is a three times brain ventricular volume increase in astronauts, by comparison with a normal, healthy age- and sex matched control group over the same time interval.[47] In rats subjected to a microgravity paradigm, blood-brain barrier (BBB) dysfunction was documented, including increased oxidative stress levels, proinflammatory cytokine levels and damaged BBB ultrastructure.[48,49] Venous congestion observed in microgravity could impair cerebrospinal fluid (CSF) outflow, affecting waste clearance and leading to accumulation of proteins such as tau protein and amyloid-β.[50,51] In addition, after long-term space missions, brain structures suffer modifications (narrowing of the central sulcus, upward shift of the brain, and narrowing of CSF spaces at the vertex) that could also impair CSF drainage.[50,52]

These changes resemble those that occur during neurodegeneration processes associated with ageing and cognitive impairment. Ventricular expansion has been documented in a range of neurological disorders including mild cognitive impairment (MCI), Alzheimer's disease (AD) and Parkinson's Disease (PD). Ventricular expansion in AD patients with MCI was associated with thinner gray matter in frontal, temporal, and parietal lobes,[53] while PD patients with MCI showed significant lateral ventricular enlargement.[54] Ventricular volume trajectory was associated with presence of infarcts, neurofibrillary tangle and neuritic plaque scores and the presence of APOE ϵ4 allele, but the factors that contribute to brain atrophy in cognitive impairment are not completely determined.[55] On the other hand, alterations of the brain vasculature, the BBB, the blood-CSF barrier and the glymphatic system have been described in AD and PD. These structures are anatomically and functionally interconnected, maintaining brain homeostasis and regulating the movement and exchange of fluid and solutes throughout the brain. The glymphatic system enables the exchange of CSF and interstitial fluid through the parenchyma, facilitating the transport of non-waste compounds and waste clearance. When this complex network is compromised, ischemia, hypoxia, oxidative stress and protein mis-aggregation could lead to neural damage and neurodegenerative disease.[56,57]

Prevention of neurodegenerative disorders associated to microgravity is presently part of the human risk reduction strategy for human space exploration and melatonin merits consideration

in this respect, due to its potential therapeutic applications in MCI, AD and PD. As a cytoprotective molecule, melatonin prevents or reverses inflammatory damage, maintains the normal mitochondrial function, suppresses tau hyperphosphorylation, prevents of dysfunctional oxidatively damaged proteins, and prevents Aβb protein formation and α synuclein assembly. Melatonin also increased removal of toxic proteins by the brain glymphatic system.[58,59] In experimental models of AD and PD, the neurodegeneration observed is prevented by melatonin. Data published from MCI patients consistently showed that melatonin administration improves cognitive performance and sleep quality. A limited number of clinical trials endorse melatonin's potentiality in AD and PD, particularly at an early stage of disease. It must be noted that studies in human usually use up to 10 mg/day doses of melatonin, which are unsuitable to give appropriate comparison with data on neurodegeneration protection derived from animals, which use human equivalent doses up to 150 mg/day, or even more. Given that melatonin is remarkably atoxic and its safety is very high in adults, further studies in humans with higher doses are thus warranted.[58,59]

Sleep disruption

Environmental and operational factors, such as work overload, uncomfortable temperatures, noise (that can average 70 dB), microgravity, radiation exposure, hypercapnia, artificial lighting conditions and multiple sunrises and sunsets (the International Space Station [ISS] orbits the Earth every 1.5 hour) may affect sleep duration, sleep quality and sleep phase, as well as the maintenance of other circadian rhythms.[60] Rather to being exposed to the natural 24-hour day and night cycle of the Earth, astronauts rely on cues from artificial lighting in addition to those from any of the sunrises/sunsets. In space, circadian rhythms and the expression of clock-associated genes are subject to modifications by these changes in light exposure,[60] which leads to the disruption of the sleep-activity cycle,[61–66] temperature rhythm, and feeding.[67,68] In turn, sleep disruption and circadian misalignment is associated with fatigue, decrements in performance, increased risk of errors, incidents and accidents, and adverse health outcomes.[60,69,70]

During space flight, sleep deficiency and the use of sleep-promoting medication are prevalent. It was observed that ISS astronauts obtain a mean of around six hours of sleep (21 astronauts on 13 ISS missions with 3248 in-flight days) and 75% (12 of 16 astronauts) report the use of sleep drugs, mainly zolpidem and zaleplon (Z-type drugs).[71] In 2016, NASA summarized the data of 177 astronauts from seven studies by different researchers and from different years. Findings showed consistently the aforementioned result of about six hours daily sleep time on average during spaceflight.[60] In addition, circadian misalignment (relative to the estimated minimum of circadian temperature) was associated with sleep deficiency and increased medication use.[60,72]

Melatonin has both phase-shifting effects and direct sleep-promoting effects. The molecule can promote sleep initiation via the hypothalamic sleep switch through MT1 receptors located in the SCN. This switch promotes sleep-related neuronal downstream pathways or activates the wake-related ones. The sleep promoting part includes a subset of sleep-active ventrolateral preoptic area (VLPO) neurons, with inhibitory projections to the histaminergic, serotonergic, and noradrenergic components of the arousal system, and use GABA and galanin neurotransmitters. Melatonin also activates VLPO neurons promoting GABAergic function, since it acts on $GABA_A$ receptors to enhance the binding of GABA and on MT1 receptors that are coupled to the stimulation of GABAergic activity. Other routes of melatonin action were also identified in the thalamus where it promotes spindle formation, that characterizes the transition from sleep stage N2 to N3.[73]

Several meta-analyses and consensuses support a therapeutic role of melatonin as a chronobiotic (to promote circadian adaptation) or as a hypnotic (to promote sleep), not only in older adults were reduced endogenous melatonin production is reduced, but also in younger ones.[74–80] Circadian adaptation can be enhanced by exogenous melatonin administration (3 mg) before bed, as recommended by the American Academy of Sleep Medicine for shift-workers.[75] As a hypnotic, a meta-analysis that comprised adults > 18 years demonstrated that melatonin decreases sleep onset latency, increases total sleep time and improves overall sleep quality. The studies included doses that ranged from 0.1 mg to 5 mg; being higher doses associated with higher effects in reducing sleep onset latency and in increasing total sleep, but not in increasing sleep quality.[76] Another metanalysis assessed the efficacy of exogenous melatonin as a treatment for secondary (shift-work, jet-lag) sleep disorders. Participants of the included studies were medical staffs, police, workers after shiftwork, pilots, and travelers after jet-lag. It was shown that melatonin lowers sleep onset latency and increases total sleep time, but with little effect on sleep efficiency.[81]

It must be noted that the effectiveness of melatonin treatment of sleep disorders appears to be higher when endogenous melatonin production is reduced, as occurs during aging.[82] Interestingly, ground based evidence shows that working under artificial light conditions is another situation where a suppression in the release of melatonin is observed,[83] and it is known that prolonged confinement – as seen in space analogues[84] - is associated with a dampening in circadian rhythms.[85,86] Indeed, astronauts coming back from long-term space missions present different health problems, including sleep disturbances, that closely resemble those found in the elderly.[87]

To our best knowledge, only one study assessed the effect of melatonin in humans in space, on shuttle missions STS-90 (Neurolab) and STS-95. Results showed that 0.3 mg of melatonin on alternate nights improved sleep latency but no other sleep parameters[88]. However, doses were below the usually recommended ones. In this regard, most clinical studies assessed the efficacy of melatonin agonists, which have higher binding affinities, longer half-life, and relative higher

potencies than the natural compound. Therefore, studies employing doses of melatonin in the range of 50-100 mg/day (rather than the usual 2-3 mg/day) are warranted to give an give appropriate comparison of the effects of the natural compound.[89]

Conclusion

Although more studies are needed to assess pharmacokinetics and pharmacodynamics and side effects of melatonin in space, it meets various criteria as a promising drug to ameliorate main human space exploration risks. Firstly, even at high doses, it has minimal or null side effects, as it was demonstrated in hundreds of studies along the years. Secondly, it is easily administered by oral route and is a stable compound along time. Finally, not only it can be helpful for reducing main risks of bone loss, neurological disorders, radiation toxicity and circadian rhythm disorders - as described in this chapter -, but it has also the potential for reducing the impact of other adverse outcomes that may arise during space travel, such as spaceflight induced cardiovascular disease, insulin resistance, host-microorganism interactions, or mood disorders.[4,29,87] Overall, it is tempting to entertain that a molecule that is presumably present from the very beginning of life in Earth[2,3] will be a helpful partner for our first steps outside the planet.

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