

Review

## **Low melatonin as a contributor to SARS-CoV-2 disease**

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### **ABSTRACT**

That the pineal gland is a source of melatonin is widely known; however, by comparison, few know of the much larger pool of extrapineal melatonin. That pool is widely distributed in all animals, including those that do not have a pineal gland, e.g., insects. Extrapineal melatonin is not released into the blood but is used locally to function as an antioxidant, anti-inflammatory agent, etc. A major site of action of peripherally-produced melatonin is the mitochondria where it neutralizes reactive oxygen species (ROS) that are generated during oxidative phosphorylation. Its role also includes major actions as an immune modulator reducing overreactions to foreign agents while simultaneously boosting immune processes. During a pandemic such as coronavirus disease 2019 (COVID-19), caused by the virus SARS-CoV-2, melatonin is capable of suppressing the damage inflicted by the cytokine storm. The implications of melatonin in susceptibility and treatment of COVID-19 disease are discussed.

**Key words:** COVID-19, SARS-CoV-2, cytokine storm, coronavirus; melatonin; mitochondria.

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### **1. INTRODUCTION, HISTORICAL PERSPECTIVE**

Melatonin (MT) was identified in the pineal by Aaron Lerner and his coworkers in 1958 while looking for a skin lightening agent (1, 2). Subsequently, the pineal was demonstrated to be an active organ in studies in the seasonally breeding animal, the Syrian hamster. MT became established as the pineal hormone and soon several groups developed sensitive assays to measure MT (3–6) and for its main urinary metabolite, 6-sulfatoxymelatonin (6SM) (7–10), allowing for the study of their levels in animals including humans. In all vertebrates, MT is secreted from the pineal during darkness with its rise typically beginning about two hours prior to twilight at the time of maximal sleep propensity, its peak about the middle of the dark period two hours after

midnight, and virtually no secretion during the day (11). Its secretion during darkness and regulation by the light cycle via the suprachiasmatic nucleus was the prime object of study in several groups of patients and controls for many years (12–16). The regulatory role of light and later of MT on circadian rhythms and their use as chronotherapeutic agents continue to preoccupy those treating circadian rhythm sleep disorders such as advanced and delayed sleep disorder, jet lag, and various insomnias (17–20). This major focus has led to the currently prevailing opinion held by the majority of sleep physicians and the medical field in general that MT exclusively has a role as a hormone, i.e., “the darkness hormone” that regulates circadian rhythms and sleep (21, 22). However, it is now known that many of its actions are non-hormonal and receptor-independent, e.g., it acts as a direct free radical scavenger. Melatonin is now known to be present widely in the body in large quantities, synthesized independently from the pineal and especially present in mitochondria where it is concentrated, synthesized and has a major protective role. These issues will be discussed further below.

## **2. EXTRAPINEAL MT**

Subsequently MT was found to be ubiquitous in tissues. Early hints from the literature, notably the presence of the synthesizing enzyme acetylserotonin O-methyltransferase (ASMT) (previously known as hydroxyindole-O-methyltransferase, HIOMT) in rat pineal, retina and Harderian gland (23, 24) were followed by the identification of MT in isolated enterochromaffin cells by bioassay based on the reasoning that serotonin containing cells might synthesize MT (25, 26), Immunohistochemical (IMHC) studies were promptly done by Bubenik and coworkers who found MT present not only in enterochromaffin cells but surprisingly, also throughout the entire gastrointestinal tract (GIT) from the esophagus to the rectum (27). Around the same time MT was further identified in rat retina, pineal, and Harderian gland by IMHC and radioimmunoassay (RIA) (4, 28, 29), Rat GIT MT showed no diurnal variation and no decrease following pinealectomy (30). GIT MT consistently shows higher levels than in the circulation (31–33) and total GIT MT content in the rat was calculated by Huether and coworkers as exceeding pineal content by some 400 times (34). Based on the foregoing it became readily apparent that GIT MT was not dependent on MT from the pineal and warrants the title “extrapineal”.

Other studies confirmed that pinealectomy did not affect GIT MT although it reduced or abolished serum MT (35–40). Further examination determined that measurable circulating MT following pinealectomy disappears following fasting (48, 49) and it is now known that tryptophan can drive the synthesis of MT in the enterochromaffin cells of the GIT so that measurable MT ends up in the circulation (41–45). Moreover MT itself, as well as tryptophan, are present in a variety of foods suggesting that both may contribute to MT blood levels (46–51). Otherwise, it appears that extrapineal MT rarely enters the circulation.

### **2.1. Location of extrapineal melatonin and its synthesizing enzymes.**

Extrapineal MT has now been documented in numerous tissues including Harderian gland, retina, optic tract, brain, cochlea, airway epithelium, GIT, liver, kidney, thyroid, pancreas, spleen, skin, hair follicles, thymus, carotid body, reproductive tract, endothelial cells, and immune system cells (28,52–59). Moreover synthesizing enzymes, that are identical to those found the pineal gland, have been found widely in many of these tissues by PCR of enzymatic RNA as well as by functionality (57, 60–62). All organs and all body fluids that have been studied contain MT that is

usually present in higher quantities than in blood (58). Of these sites, only the retina has been shown to display circadian rhythms in both MT and synthesizing enzymes that are identical to those in the pineal (36). In mouse and human scalp and hair follicle, in which MT content is 10 folds of higher than serum, levels can be further stimulated another 5 to 10 fold with norepinephrine treatment (54, 63). This activation suggests that extrapineal synthesis of MT may be regulated by local norepinephrine via the same pathway as in the pineal in these tissues, however, alternative pathways are also possible (58).

As such it is evident that extrapineal MT, which is found in so many sites, can act locally, potentially as a scavenger, antioxidant, and immune regulator. In considering that function it should also be noted that MT, a highly amphiphilic molecule, can readily diffuse into tissues from blood or CSF passing readily through cell membranes as well as the blood-brain barrier.

## **2.2. Why should there be two pools of MT?**

Once aware of extrapineal MT investigators rapidly discovered that MT is an ancient molecule. MT is known to be formed in bacteria, and numerous taxa of eukaryotes. This includes various genera in algae (including diatoms) and various plant genera, and invertebrate and vertebrate species (64–67). Being a pleiotropic molecule, MT has a plethora of physiological and cellular functions in plants. This includes, but is not limited to, rooting, germination, growth promotion, photosynthesis, flowering time, leaf senescence, fruit ripening, circadian control, and biomass production. At the cellular level, it acts as a cytoprotective agent against biotic and abiotic stressors. As a potent antioxidant MT controls the ROS and reactive nitrogen species (RNS), which inhibit harmful oxidative molecules. It is only in animals with a pineal gland that MT is secreted into the bloodstream and functions as a hormone

## **2.3. What is the function of tissue MT?**

As MT is so widespread in the body it is important to consider what it does. In the GIT it has been proposed to be protective and also to have a role in propulsion down the GIT(31, 68). A difference in distribution within the GIT in the pig and cow has been suggested to correspond with the requirements for different types of digestion (31). In humans accumulated evidence reviewed in 2010 showed helpful effects of MT as an adjuvant in treating numerous disorders when given in doses and with a timing commonly used to cue circadian rhythms (69). Further to that issue, MT has repeatedly been reported as protective against septic shock in animal models of disease notably against the cytokine storm in bacterial sepsis in C57BL/6 mice (70). In studies in newborns with septic shock, MT added to standard treatment reduced elevated serum levels of lipid peroxidation products [malondialdehyde (MDA) and 4-hydroxylalkenals (4-HDA)] (71). A further study was done in newborns given ventilation for respiratory distress (72). In that study, it was reported that MT reduced the proinflammatory cytokines, interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- $\alpha$ , and improved the clinical outcome. Additional studies have confirmed the beneficial effects of MT in the newborn (73, 74). In one of them, it was shown that MT treatment added to antibiotic treatment caused a significant improvement in clinical condition, complete blood count, and high sensitive C-reactive protein as compared to antibiotics alone (74). As noted recently (75) MT supplementation resulted in decreases in proinflammatory cytokines in several conditions: periodontitis in diabetic patients (76), relapsing-remitting multiple sclerosis (77), inflammation in surgical stress (78), brain ischemia (79) and reperfusion injury (80).

### 3. FUNCTION OF MT, ANIMAL VIRUS STUDIES

MT has been shown to reduce symptoms and reduce mortality in several different virus infections (81) in mice (82–84), mink (85), and rabbits (86). A study of respiratory syncytial virus infection in mice showed that the disease resulted in oxidative stress changes indicated by increasing nitric oxide, malondialdehyde, and hydroxyl radical levels, and decreasing glutathione and superoxide dismutase activities, while in contrast administration of MT significantly reversed all these effects (87). The combination of MT with an indoleamine 2,3-dioxygenase inhibitor was shown to increase the protective effect of a vaccine against human papilloma virus-16 associated tumors in mice (88). In a recent study of influenza A in mice, it was found that MT treatment significantly decreased the expression of TNF- $\alpha$ , IL-6, and interferon- $\gamma$ , while it increased the production of IL-10 and tumor growth factor- $\beta$  (89). MT also significantly inhibited the production of TNF- $\alpha$  in CD8 T cells. Moreover, when MT was given in combination with ribavirin survival was increased significantly over ribavirin treatment alone. Thus, MT is helpful in counteracting the cytokine storm in treated animals.

### 4. WHAT MECHANISMS ARE INVOLVED IN THESE EFFECTS OF MT?

Venegas and coworkers studied the subcellular levels of MT in rat cerebral cortex and liver (37). In both tissues, MT was in the highest concentration in cell membranes followed by mitochondria, nucleus, and cytosol. Pinealectomy caused an increase in levels and as in other studies, no circadian rhythm was found. MT and its metabolite *N*<sup>1</sup>-acetyl-*N*<sup>2</sup>-formyl-5-methoxykynurenine (AFMK) which is formed from MT in mitochondria have been repeatedly been shown to be potent antioxidants, scavenging free radicals especially in mitochondria (90). In a review of mitochondrial function in 2019 Tan and Reiter pointed out that mitochondria synthesize MT in all cells (91). Why is this important? Mitochondria are the essential powerhouses of the body generating energy in the form of ATP via an electron transport chain (92). As this process is the source of the majority of the body's free radicals the presence of MT in the immediate vicinity is highly advantageous as both it and its metabolites along with other processes can neutralize destructive free radicals immediately as they are made. The high mitochondrial concentration of MT is due, not only to its local synthesis but also to the presence of the MT transporter 1/2 (PEPT1/2) that transports MT that has diffused out back into mitochondria (93),

Besides, MT is an immune-modulatory agent acting as either a pro- or anti-inflammatory regulator depending on the context (94). Innate immune cells have a built-in defense against foreign invasion based largely on molecular non-self characteristics by pattern recognition receptors like Toll-like receptors. These cells (particularly macrophages) contain NLRP3 inflammasomes that are activated by such threats (95). However, overreaction of innate defenses will cause cell, tissue, or organ damage. MT can modulate this overreactivity both by suppressing the production of inflammatory cytokines such as IL-1 $\beta$ , iL-6 and TNF $\alpha$  as well as by other mechanisms (94). Simultaneously it can facilitate adaptive immunity-boosting processes in the thymus and other parts of the immune system. MT can delay thymic involution, promote regeneration of thymocytes, promote T-cell activation and promote  $\beta$ -lymphocyte proliferation, some of which may be mediated by sirtuin (SIRT) 1 (94, 96–98). MT decreases with aging may, therefore, have negative effects on vulnerability to infection (98).

## 5. COVID-19 INFECTIONS AND MT

Infections with COVID-19 are often mild, with minimal or no symptoms, but in a minority they are severe with mortality customarily below 5%. In Wuhan where the disease originated usual symptoms included fever, dry cough, myalgia, fatigue, and diarrhea, etc. while in severe cases there was acute lung injury with acute respiratory distress, heart failure, sepsis, and death due to cardiac arrest (99, 100). This evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response lead to a cytokine storm that contributes to COVID-19 pathology (101, 102). No specific treatments for these infections such as a vaccine or an antiviral agent are yet available.

It is known that MT may help to counteract such effects. As one example in human macrophages, it has been established that MT can inhibit Toll-like receptor 9-mediated proinflammatory cytokine production *in vivo* (103). In reviewing possible treatments for the cytokine storm in coronavirus infections several possibilities have been suggested but to date, the best approaches remain to be determined (104, 105). Based on its ability to combat virus disease, limit cytokine storm and prevent excitotoxic effects several reviews have advocated the use of MT as an adjuvant in the treatment of COVID-19 diseases (95, 101, 106, 107) An encouraging case series has very recently been reported (108) and a clinical trial of intravenous melatonin for treatment of COVID-19 was recently approved by the Spanish Agency of Medicines and Medical Devices (109). A helpful effect of dexamethasone as an adjuvant was also reported (110)

## 6. SAFETY OF MT

What about the safety of MT? This issue has recently been thoroughly reviewed (111). In general side effects are minimal and mostly transient. A study of one gram MT orally per day for 30 days reported “drowsiness” as a potential adverse effect, with no statistically significant alteration of various clinical parameters (blood pressure, heart rate, ECG, serum chemistry, urine analysis) (112). In animal studies, huge doses have been given to the extent that the conclusion has been made that the LD50 (lethal dose) may be undefined. The LD50 for the intraperitoneal injection of MT was determined for rats (1168 mg/kg) and mice (1131 mg/kg)(113). But the oral administration LD50 of MT (tested up to 3200 mg/kg in rats) could not be determined for rats nor could that for subcutaneous injection (tested up to 1600 mg/kg in rats and mice). In humans, MT has a high safety profile and in general, is well tolerated.

## 7. LACK OF CLINICAL TRIALS

Why have there never been clinical trials of MT for such diseases? The answer is simple. Since MT, as a natural product, is freely available over the counter no drug company would justify spending the necessary money as there could be no financial return. Unfortunately, the pharmaceutical industry is reluctant to support MT studies because of the lack of protective patents for a natural compound. Hence only with the involvement of governmental or non-profit organizations could such a goal be achieved. At present, the only option for the attending physician interested in the use of MT as a cytoprotective agent is the use of the over-the-counter agent for off label use.



## **8. IMPLICATIONS:**

### **8.1. Susceptibility.**

It is known that there is a huge range of susceptibility to COVID-19 and diverse factors seem to be at work such as pre-existing state of health, genetics, metabolic conditions such as diabetes, previous exposure to similar viruses, age (114), drugs or diseases affecting immune response, etc. However, in many cases, there seems to be no rationale for the illness becoming severe. A major possibility to be considered for susceptibility to COVID-19 is the pre-existing amount of protective MT currently available in the body (115).

### **8.2. Susceptibility, Genetic variability.**

One major factor may be the huge individual differences in circulating MT and urinary 6SM levels that are well documented (116–123). As one example, in an overnight study of MT profiles of eleven volunteers peak nocturnal MT varied between individuals up to six-fold. At the same time, repeated nocturnal profiles in individuals do not differ significantly (124, 125). This variability appears to be largely due to the MT pathway genes (126–129). The most important synthetic enzyme is ASMT, the final enzyme in the synthetic pathway from serotonin, which determines the amount of MT produced (130). The liver enzyme cytochrome P450 1A2 (CYP1A2) is crucial in the metabolism of the majority of MT (131). Several variations in these enzymes have been reported leading to major differences in MT levels that could be directly related to susceptibility to SARS-CoV-2 virus infection (126, 128, 132–134).

### **8.3. Susceptibility, Genetic disorders.**

In addition to these numerous variations in synthetic genes in individuals without any reported disorder, there is a subgroup of patients with autism spectrum disorder (ASD) who have alterations in ASMT resulting in decreased in MT and 6SM levels (135–137); this subgroup may correspond to a similar one that shows alterations in the immune system (138). Several individuals with genetic defects in the serotonin synthetic pathway also have decreased levels of 6SM (139). It may be advisable to keep a close eye on such individuals for signs of the disease.

### **8.4. Susceptibility, Aging.**

Another issue may be the decrease of MT and 6SM levels with age in man (122, 139–145). An extensive review concludes that there is a major drop that is virtually complete by age 35; although the huge variability persists (122), thus reduction in MT may lie at the root of increased susceptibility found in those over that age (121). In the rat MT and its synthetic enzymes are also known to decrease with aging (60, 61, 146, 147).

### **8.5. Susceptibility, Drug treatment.**

An additional factor to be considered is drugs used clinically that can lower MT levels. A prime example is  $\beta$  adrenergic agents such as propranolol and atenolol that are used widely to treat high blood pressure, several types of irregular heart rate, thyrotoxicosis, etc. (148–150). These agents

lower MT levels via blocking  $\beta$ 1 adrenergic receptors. A recent paper hypothesizes that  $\beta$  blockers may be useful in treatment by decreasing ACE2, which may decrease the SARS-CoV-2 virus entry into the host cell (151) although a review suggests only a modestly lower likelihood of a positive test for COVID-19 disease in those on  $\beta$  blockers used to treat hypertension (152). What is not known is how the decrease in melatonin synthesis produced by  $\beta$  blockers might counteract the hypothesized helpful effects. In contrast to  $\beta$  blockers treatments modifying biogenic amines such as desipramine, a relatively selective norepinephrine reuptake inhibitor, brofaromine, a monoamine oxidase inhibitor, and fluvoxamine as well as other drugs suppressing P450 1A2 (CYP1A2), have been shown to increase MT levels in patients (153–156).

### **8.6. Susceptibility, Diet.**

Dietary factors are also important. Inadequate diets are known to be associated with poverty (157–162). This is especially pronounced during the COVID-19 pandemic (163). Moreover, such diets are often deficient in protein containing the amino acid tryptophan, which can lead to low MT as tryptophan is the essential starting molecule for MT synthesis (41, 42, 44, 164, 165).

### **8.7. MT treatment timing.**

The timing of MT doses for body protection should not be confined to the same schedule used for sleep regulation. Adequate doses to ensure the correct sleep timing are necessary. Nevertheless, an adequate supply of MT should be available throughout the day to maintain or elevate tissue melatonin.

### **8.8. MT treatment doses.**

The dose amounts should not be based on the doses used for sleep regulation. Many of the targets for administered MT are located inside various body organs. For example, in mitochondria, the usual source, location, and site of action of MT are within that organelle. But if administered MT is to reach such a site to supplement deficient MT or even enhance it then dosing must be based on reaching the targets. To provide a supply of MT that will reach the targets in adequate quantities, higher doses will undoubtedly be needed as described in detail elsewhere (75, 166). Fortunately, MT has a huge margin of safety (111).

## **9. CONCLUSIONS**

There is now considerable evidence for the protective effects of melatonin due to its antioxidant, scavenging, and immune-modulating effects. The huge range in susceptibility that is largely unexplained by current concepts may well be explained by the correspondingly huge range in protective melatonin amounts present in the body. Numerous factors are known that can produce this variability, some very obvious, such as drugs that alter melatonin levels, others such as genetic variability may be unobvious.

We suggest that the amount of protective melatonin be determined by measurement of overnight 6SM production (little 6SM is produced during the daytime). In practice, this means collecting first-morning urine plus any produced during the nighttime and measuring 6SM concentration corrected by creatinine (123). This determination could be used prospectively (and

retrospectively where possible) in the evaluation of patients to establish which ones have low melatonin and might, therefore, most benefit from melatonin treatment. Those identified as having low 6SM could be monitored, exposure prevented as much as possible, and if they become affected treated with melatonin in addition to usual treatments. It would similarly be important to monitor and potentially treat those patients with ASD and known low melatonin

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## AUTHORSHIP

Following initial conception and draft by GMB, all authors contributed equally in the subsequent preparation of the manuscript. Prior to submission, all authors reviewed and accepted the final version of the manuscript prepared by GMB.

## COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors. No primary data have been reported.

## CONFLICT OF INTERESTS

The authors have read the journal's policy and have the following potential conflicts: SRP is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. This does not alter the authors' adherence to all the journal policies. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might influence the views expressed in this manuscript.

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