Review

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

Seithikurippu R. Pandi-Perumal[1], Daniel P. Cardinali[2], Russel J. Reiter[3], Gregory M. Brown*[4]

[1]Somnogen Canada Inc., College Street, Toronto, ON, M6H 1C5, Canada.
[2]Faculty of Medical Sciences, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina.
[3]Department of Cell Systems and Anatomy, UT Health San Antonio, San Antonio, Texas USA
[4] Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, ON M5T 1R8, Canada.
*Correspondence: gregory.brown@camh.ca, gbrownpn@gmail.com, Tel: 1-647-801-2941

Running title: Low melatonin and SARS-CoV-2

Received: August 18, 2020; Accepted: September 29, 2020

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, SATS-CoV-2, cytokine storm, coronavirus; melatonin; mitochondria.

---

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 holds 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)-α, 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-α, IL-6, and interferon-γ, while it increased the production of IL-10 and tumor growth factor-ß (89). MT also significantly inhibited the production of TNF-α 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^1-acetyl-N^2-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-1ß. iL-6 and TNFα 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 ß-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 ß 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 ß1 adrenergic receptors. A recent paper hypothesizes that ß 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 ß blockers used to treat hypertension (152). What is not known is how the decrease in melatonin synthesis produced by ß blockers might counteract the hypothesized helpful effects. In contrast to ß 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

ACKNOWLEDGMENT

No funding has been reported for this study.

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.

REFERENCES

1. Lerner AB, Case JD, Heinzelman RV (1959) Structure of Melatonin. *J. Am. Chem. Soc.* **81**: 6084–6085.
2. Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W (1958) Isolation of melatonin, the pineal gland factor that lightens melanocytes. *J. Am. Chem. Soc.* **80**: 2587. doi:10.1021/ja01543a060.
3. Wilkinson M, Arendt J, Bradtke J, DeZiegler D, de Ziegler D (1977) Determination of a dark-induced increase of pineal N-acetyl transferase activity and simultaneous radioimmunoassay of melatonin in pineal, serum and pituitary tissue of the male rat. *J. Endocrinol.* **72**: 243–244. doi:10.1677/joe.0.0720243.
4. Pang SF, Brown GM, Grota LJ, Rodman RL (1977) Radioimmunoassay of melatonin in pineal glands, harderian glands, retinas and sera of rats or chickens. *Neuroendocrinology* **23**: 1–13.

5. Pelham RW, Ralph CL, Campbell IM (1972) Mass spectral identification of melatonin in blood. *Biochem. Biophys. Res. Commun.* **46**: 1236–1241.
6. Harlow HJ, Phillips JA, Ralph CL (1981) Day-night rhythm in plasma melatonin in a mammal lacking a distinct pineal gland, the nine-banded armadillo. *Gen. Comp. Endocrinol.* **45**: 212–218.
7. Brown GM (1992) Day-night rhythm disturbance, pineal function and human disease. *Horm Res* **37** (Suppl 3): 105–111. doi:10.1159/000182410.
8. Cardinali DP, Brusco LI, Lloret SP, Furio AM (2002) Melatonin in sleep disorders and jet-lag. *Neuro.Endocrinol. Lett.* **23** (Suppl 1): 9–13.
9. Deacon S, Arendt J. Adapting to phase shifts (1996) II. Effects of melatonin and conflicting light treatment. *Physiol. Behav.* **59**: 675–682.
10. Bojkowski CJ, Arendt J (1988) Annual changes in 6-sulphatoxymelatonin excretion in man. *Acta Endocrinol. (Copenh)* **117**: 470–476.
11. Rajaratnam SM, Redman JR (1997) Effects of daily melatonin administration on circadian activity rhythms in the diurnal Indian palm squirrel (Funambulus pennanti). *J. Biol. Rhythms* **12**: 339–347.
12. Arendt J (1985) "Assay of melatonin and its metabolites: results in normal and unusual environments," in *Melatonin in humans*, eds. RJ Wurtman, F Waldhauser (Cambridge, Mass: Cbsm), 11–32.
13. Brown GM, Seggie J, Grota LJ (1985) Serum melatonin response to melatonin administration in the Syrian hamster. *Neuroendocrinology* **41**: 31–35. doi:10.1159/000124150.
14. Waldhauser F, Dietzel M. (1985) Daily and annual rhythms in human melatonin secretion: role in puberty control. *Ann. N. Y. Acad. Sci.* **453**: 205–214.
15. Dalery J, Claustrat B, Brun J, Terra JL, Chazot G, de Villard R (1985) Daily profiles of melatonin, cortisol and gonadotropins in 8 adolescents with anorexia nervosa. [French]. *Encephale* **11**: 25–28.
16. Lewy AJ, Sack RL, Singer CM (1985) Melatonin, light and chronobiological disorders. *Ciba Found Symp.* **117**: 231–252.
17. Rajaratnam SM, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birznieks G, Klerman EB (2009) Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* **373**: 482–491.
18. Arendt J, Rajaratnam SMW (2008) Melatonin and its agonists: An update. *Br. J. Psychiatry.* **193**: 267–269. doi:10.1192/bjp.bp.108.050955.
19. Burgess HJ, Emens JS (2016) Circadian-based therapies for circadian rhythm sleep-wake disorders. *Curr. Sleep Med. Reports* **2**: 158–165. doi:10.1007/s40675-016-0052-1
20. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X, Feng Y, Liu W (2017) A review of sleep disorders and melatonin. *Neurol. Res* **39**: 559–565. doi:10.1080/01616412.2017.1315864.
21. MacFarlane JG, Cleghorn JM, Brown GM, Streiner DL (1991) The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. *Biol. Psychiatry* **30**: 371–376. doi:10.1016/0006-3223(91)90293-U.
22. Kayumov L, Zhdanova I V, Shapiro CM (2000) Melatonin, sleep, and circadian rhythm disorders. *Semin. Clin. Neuropsychiatry* **5**: 44–55.
23. Cardinali DP, Rosner JM (1971) Retinal localization of the hydroxyindole-0-methyl transferase (HIOMT) in the rat. *Endocrinology* **89**: 301–303.
24. Cardinali DP, Larin F, Wurtman RJ (1972) Action spectra for effects of light on

hydroxyindole-0-methyl transferases in rat pineal, retina and harderian gland. *Endocrinology* **91**: 877–886.
25. Raikhlin NT, Kvetnoy IM (1976) Melatonin and enterochromaffine cells. *Acta Histochem.* **55**: 19–25.
26. Raikhlin NT, Kvetnoy IM, Tolkachev VN (1975) Melatonin may be synthesised in enterochromaffin cells. *Nature* **255**: 344–345.
27. Bubenik GA, Brown GM, Grota LJ (1977) Immunohistological localization of melatonin in the rat digestive system. *Experientia* **33**: 662–663. doi:10.1007/BF01946561.
28. Bubenik GA, Brown GM, Grota LJ (1976) Immunohistochemical localization of melatonin in the rat Harderian gland. *J. Histochem. Cytochem.* **24**: 1173–1177.
29. Bubenik GA, Brown GM, Uhlir I, Grota LJ (1974 Immunohistological localization of N-acetylindolealkylamines in pineal gland, retina and cerebellum. *Brain Res.* **81**: 233–242. doi:10.1016/0006-8993(74)90938-X.
30. Bubenik GA (1980) Localization of melatonin in the digestive tract of the rat. Effect of maturation, diurnal variation, melatonin treatment and pinealectomy. *Horm. Res.* **12**: 313–323.
31. Bubenik GA, Hacker RR, Brown GM, Bartos L (1999) Melatonin concentrations in the luminal fluid, mucosa, and muscularis of the bovine and porcine gastrointestinal tract. *J. Pineal Res.* **26**: 56–63.
32. Bubenik GA, Ayles HL, Friendship RM, Brown GM, Ball RO (1998) Relationship between melatonin levels in plasma and gastrointestinal tissues and the incidence and severity of gastric ulcers in pigs. *J. Pineal Res.* **24**: 62–66. doi:10.1111/j.1600-079X.1998.tb00367.x.
33. Bubenik GA, Brown GM, Hacker RR, Bartoš L (2000) Melatonin concentrations in the gastrointestinal tissues of bovine fetuses. *Acta Vet. Brno.* **69**: 177–182.
34. Huether G, Poeggeler B, Reimer A, George A (1992) Effect of tryptophan administration on circulating melatonin levels in chicks and rats: Evidence for stimulation of melatonin synthesis and release in the gastrointestinal tract. *Life Sci.* **51**: 945–953. doi:10.1016/0024-3205(92)90402-B.
35. Bubenik GA, Brown GM (1997) Pinealectomy reduces melatonin levels in the serum but not in the gastrointestinal tract of rats. *Biol. Signals* **6**: 40–44. doi:10.1159/000109107.
36. Huether G (1994) Melatonin synthesis in the gastrointestinal tract and the impact of nutritional factors on circulating melatonin. *Ann. N. Y. Acad. Sci.* **719**: 146–158.
37. Venegas C, García JA, Escames G, Ortiz F, López A, Doerrier C, García-Corzo L, López LC, Reiter RJ, Acuña-Castroviejo D (2012) Extrapineal melatonin: Analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **52**: 217–227. doi:10.1111/j.1600-079X.2011.00931.x.
38. Lewy AJ, Tetsuo M, Markey SP, Goodwin FK, Kopin IJ (1980) Pinealectomy abolishes plasma melatonin in the rat. *J. Clin. Endocrinol. Metab.* **50**: 204–205.
39. Ozaki Y, Lynch HJ (1976) Presence of melatonin in plasma and urine or pinealectomized rats. *Endocrinology* **99**: 641–644. doi:10.1210/endo-99-2-641.
40. Lynch HJ, Ozaki Y, Shakal D, Wurtman RJ (1975) Melatonin excretion of man and rats: Effect of time of day, sleep, pinealectomy and food consumption. *Int. J. Biometeorol.* **19**: 267–279. doi:10.1007/BF01451037.
41. Hajak G, Huether G, Blanke J, Blomer M, Freyer C, Poeggeler B, Reimer A, Rodenbeck A, Schulz-Varszegi M, Ruther E (1991) The influence of intravenous L-tryptophan on plasma melatonin and sleep in men. *Pharmacopsychiatry* **24**: 17–20.

42. Fukushige H, Fukuda Y, Tanaka M, Inami K, Wada K, Tsumura Y, Kondo M, Harada T, Wakamura T, Morita T (2014) Effects of tryptophan-rich breakfast and light exposure during the daytime on melatonin secretion at night. *J. Physiol. Anthropol.* **33**: 1–9. doi:10.1186/1880-6805-33-33.
43. Huether G (1993) The contribution of extrapineal sites of melatonin synthesis to circulating melatonin levels in higher vertebrates. *Experientia* **49**: 665–670. doi:10.1007/BF01923948.
44. Wada K, Yata S, Akimitsu O, Krejci M, Noji T, Nakade M, Takeuchi H, Harada T (2013) A tryptophan-rich breakfast and exposure to light with low color temperature at night improve sleep and salivary melatonin level in Japanese students. *J. Circadian. Rhythms* **11**: 1–9. doi:10.1186/1740-3391-11-4.
45. Bubenik GA, Pang SF, Cockshut JR, Smith PS, Grovum LW, Friendship RM, Hacker RR (2000) Circadian variation of portal, arterial and venous blood levels of melatonin in pigs and its relationship to food intake and sleep. *J. Pineal Res.* **28**: 9–15. doi:10.1034/j.1600-079x.2000.280102.x.
46. Hardeland R, Pandi-Perumal S, Poeggeler B (2007) Melatonin in plants–focus on a vertebrate night hormone with cytoprotective properties. *Funct. Plant Sci. Biotechnol.* **1**: 32–45.
47. Dubbels R, Reiter RJ, Klenke E, Goebel A, Schnakenberg E, Ehlers C, Schiwara HW, Schloot W (1995) Melatonin in edible plants identified by radioimmunoassay and by high performance liquid chromatography-mass spectrometry. *J. Pineal Res.* **18**: 28–31.
48. Hattori A, Migitaka H, Iigo M, Itoh M, Yamamoto K, Ohtani-Kaneko R, Hara M, Suzuki T, Reiter R (1995) Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. *Biochem. Mol. Biol. Int.* **35**: 627–634.
49. Johns NP, Johns J, Porasuphatana S, Plaimee P, Sae-Teaw M (2013) Dietary intake of melatonin from tropical fruit altered urinary excretion of 6-sulfatoxymelatonin in healthy volunteers. *J. Agric. Food Chem.* **61**: 913–919. doi:10.1021/jf300359a.
50. Sae-Teaw M, Johns J, Johns NP, Subongkot S (2013) Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers. *J. Pineal Res.* **55**: 58–64. doi:10.1111/jpi.12025.
51. Badria FA. (2002) Melatonin, serotonin, and tryptamine in some Egyptian food and medicinal plants. *J. Med. Food* **5**: 153–157. doi:10.1089/10966200260398189.
52. Bubenik GA, Purtill RA, Brown GM, Grota LJ (1978) Melatonin in the retina and the Harderian gland. Ontogeny, diurnal variations and melatonin treatment. *Exp. Eye Res.* **27**: 323–333. doi:10.1016/0014-4835(78)90166-5.
53. Slominski A, Pisarchik A, Semak I, Sweatman T, Wortsman J, Szczesniewski A, Slugocki G, McNulty J, Kauser S, Tobin DJ, *et al*. (2002) Serotoninergic and melatoninergic systems are fully expressed in human skin. *FASEB J.* **16**: 896–898. doi:10.1096/fj.01-0952fje.
54. Kobayashi H, Kromminga A, Dunlop TW, Tychsen B, Conrad F, Suzuki N, Memezawa A, Bettermann A, Aiba S, Carlberg C, *et al*. (2005) A role of melatonin in neuroectodermal-mesodermal interactions: the hair follicle synthesizes melatonin and expresses functional melatonin receptors. *FASEB J.* **19**: 1710–1712. doi:10.1096/fj.04-2293fje.
55. Naranjo MC, Guerrero JM, Rubio A, Lardone PJ, Carrillo-Vico A, Carrascosa-Salmoral MP, Jiménez-Jorge S, Arellano M V., Leal-Noval SR, Leal M, *et al*. (2007) Melatonin biosynthesis in the thymus of humans and rats. *Cell Mol. Life. Sci.* **64**: 781–790. doi:10.1007/s00018-007-6435-1.

56. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ (2005) A review of the multiple actions of melatonin on the immune system. *Endocrine* **27**: 189–200. doi:10.1385/ENDO:27:2:189.
57. Maldonado MD, Mora-Santos M, Naji L, Carrascosa-Salmoral MP, Naranjo MC, Calvo JR (2010) Evidence of melatonin synthesis and release by mast cells. Possible modulatory role on inflammation. *Pharmacol. Res.* **62**: 282–287. doi:10.1016/j.phrs.2009.11.014.
58. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, Rosales-Corral S, Tan DX, Reiter RJ (2014) Extrapineal melatonin: Sources, regulation, and potential functions. *Cell Mol. Life Sci.* **71**: 2997–3025. doi:10.1007/s00018-014-1579-2.
59. Slominski AT, Hardeland R, Zmijewski MA, Slominski RM, Reiter RJ, Paus R (2018) Melatonin: A cutaneous perspective on its production, metabolism, and functions. *J. Invest. Dermatol.* **138**: 490–499. doi:10.1016/j.jid.2017.10.025.
60. Sanchez-Hidalgo M, de la Lastra CA, Carrascosa-Salmoral MP, Naranjo MC, Gomez-Corvera A, Caballero B, Guerrero JM (2009) Age-related changes in melatonin synthesis in rat extrapineal tissues. *Exp. Gerontol.* **44**: 328–334. doi:10.1016/j.exger.2009.02.002.
61. Popović B, Velimirović M, Stojković T, Brajović G, De Luka SR, Milovanović I, Stefanović S, Nikolić D, Ristić-Djurović JL, Petronijević ND, *et al.* (2018) 111The influence of ageing on the extrapineal melatonin synthetic pathway. *Exp. Gerontol.* **110**: 151–157. doi:10.1016/j.exger.2018.06.010.
62. Stefulj J, Hörtner M, Ghosh M, Schauenstein K, Rinner I, Wölfler A, Semmler J, Liebmann PM (2001) Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. *J. Pineal Res.* **30**: 243–247. doi:10.1034/j.1600-079x.2001.300408.x.
63. Fischer TW. (2009) Einfluss von melatonin auf die physiologie des haares. *Hautarzt* **60**: 962–972. doi:10.1007/s00105-009-1817-y.
64. Hardeland R (2014) Melatonin in plants and other phototrophs: advances and gaps concerning the diversity of functions. *J. Exp. Bot.* **66**: 627–646. doi:10.1093/jxb/eru386.
65. Hardeland R (2016) Melatonin in plants – Diversity of levels and multiplicity of functions. *Front. Plant Sci.* **7**: 1–14. doi:10.3389/fpls.2016.00198.
66. Arnao MB, Hernández-Ruiz J (2019) Melatonin: A new plant hormone and/or a plant master regulator? *Trends Plant Sci.* **24**: 38–48. doi:10.1016/j.tplants.2018.10.010.
67. Hardeland R, Poeggler B (2003) Non-vertebrate melatonin. *J. Pineal Res.* **34**: 233–241.
68. Konturek SJ, Konturek PC, Brzozowski T, Bubenik GA (2007) Role of melatonin in upper gastrointestinal tract. *J. Physiol. Pharmacol.* **58** Suppl 6: 23–52.
69. Sánchez Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ (2010) Clinical uses of melatonin: evaluation of human trials. *Curr. Med. Chem.* **17**: 2070–2095.
70. Xu L, Zhang W, Kwak M, Zhang LJ, Lee PCW, Jin JO (2019) Protective effect of melatonin against polymicrobial sepsis is mediated by the anti-bacterial effect of neutrophils. *Front Immunol*. **10**: 1–11. doi:10.3389/fimmu.2019.01371.
71. Gitto E, Karbownik M, Reiter RJ, Xian Tan DX, Cuzzocrea S, Chiurazzi P, Cordaro S, Corona G, Trimarchi G, Barberi I (2001) Effects of melatonin treatment in septic newborns. *Pediatr. Res.* **50**: 756–760. doi:10.1203/00006450-200112000-00021.
72. Gitto E, Reiter RJ, Sabatino G, Buonocore G, Romeo C, Gitto P, Buggé C, Trimarchi G, Barberi I (2005) Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: Improvement with melatonin treatment. *J. Pineal Res.* **39**: 287–293. doi:10.1111/j.1600-079X.2005.00251.x.

73. El Frargy M, El-Sharkawy H, Attia G (2015) Use of melatonin as an adjuvant therapy in neonatal sepsis. *J. Neonatal. Perinat. Med.* **8**: 227–232.
74. El-Gendy F, El-Hawy M, Hassan MG (2018) Beneficial effect of melatonin in the treatment of neonatal sepsis. *J. Matern. Fetal Neonatal. Med.* **31**: 2299–303.
75. Cardinali DP (2020) High doses of melatonin as a potential therapeutic tool for the neurologic sequels of covid-19 infection. *Melatonin Res.* **3**: 311–317. doi:10.32794/mr11250064.
76. Bazyar H, Gholinezhad H, Moradi L, Salehi P, Abadi F, Ravanbakhsh M, Zare Javid A (2019) The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: a double-blind, placebo-controlled t. *Inflammopharmacology* **27**: 67–76. doi:10.1007/s10787-018-0539-0.
77. Sánchez-López AL, Ortiz GG, Pacheco-Moises FP, Mireles-Ramírez MA, Bitzer-Quintero OK, Delgado-Lara DLC, Ramírez-Jirano LJ, Velázquez-Brizuela IE (2018) Efficacy of melatonin on serum pro-inflammatory cytokines and oxidative stress markers in relapsing remitting multiple sclerosis. *Arch. Med. Res.* **49**: 391–398. doi:10.1016/j.arcmed.2018.12.004.
78. Kücükakin B, Lykkesfeldt J, Nielsen HJ, Reiter RJ, Rosenberg J, Gögenur I (2008) Utility of melatonin to treat surgical stress after major vascular surgery - A safety study. *J. Pineal Res.* **44**: 426–431. doi:10.1111/j.1600-079X.2007.00545.x.
79. Zhao Z, Lu C, Li T, Wang W, Ye W, Zeng R, Ni L, Lai Z, Wang X, Liu C (2018) The protective effect of melatonin on brain ischemia and reperfusion in rats and humans: In vivo assessment and a randomized controlled trial. *J. Pineal Res.* **65**: 1–12. doi:10.1111/jpi.12521.
80. Shafiei E, Bahtoei M, Raj P, Ostovar A, Iranpour D, Akbarzadeh S, Shahryari H, Anvaripour A, Tahmasebi R, Netticadan T, *et al.* (2018) Effects of N-acetyl cysteine and melatonin on early reperfusion injury in patients undergoing coronary artery bypass grafting: A randomized, open-labeled, placebo-controlled trial. *Med. (United States)* **97**: 1–7. doi:10.1097/MD.0000000000011383.
81. Boga JA, Coto-Montes A, Rosales-Corral SA, Tan DX, Reiter RJ (2012) Beneficial actions of melatonin in the management of viral infections: A new use for this "molecular handyman"? *Rev. Med. Virol.* **22**: 323–338. doi:10.1002/rmv.1714.
82. Ben-Nathan D, Maestroni GJM, Lustig S, Conti A (1995) Protective effects of melatonin in mice infected with encephalitis viruses. *Arch. Virol.* **140**: 223–230. doi:10.1007/BF01309858.
83. Bonilla E, Valero-Fuenmayor N, Pons H, Chacín-Bonilla L (1997) Melatonin protects mice infected with Venezuelan equine encephalomyelitis virus. *Cell Mol. Life Sci.* **53**: 430–434. doi:10.1007/s000180050051.
84. Araghi-Niknam M, Lane L, Watson R (1998) Physical inactivity of murine retrovirus infected c57bl/6 mice is prevented by melatonin and dehydroepiandrosterone. *PSEBM* **219**: 144–148.
85. Ellis LGC (1996) Melatonin reduces mortality from Aleutian Disease in mink (Mustela vison). *J. Pineal Res.* **21**: 214–217. doi:10.1111/j.1600-079X.1996.tb00288.x.
86. Tuñõn MJ, Miguel BS, Crespo I, Jorquera F, Santamaría E, Alvarez M, Prieto J, González-Gallego J (2011) Melatonin attenuates apoptotic liver damage in fulminant hepatic failure induced by the rabbit hemorrhagic disease virus. *J. Pineal Res.* **50**: 38–45.

doi:10.1111/j.1600-079X.2010.00807.x.

87. Huang SH, Cao XJ, Liu W, Shi XY, Wei W (2010) Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. *J. Pineal Res.* **48**: 109–116. doi:10.1111/j.1600-079X.2009.00733.x.
88. Moreno ACR, Porchia BFMM, Pagni RL, Souza P da C, Pegoraro R, Rodrigues KB, Barros TB, Aps LR d. MM, de Araújo EF, Calich VLG, *et al.* (2018) The combined use of melatonin and an indoleamine 2,3-dioxygenase-1 inhibitor enhances vaccine-induced protective cellular immunity to HPV16-associated tumors. *Front. Immunol.* **9**: 1914. doi:10.3389/fimmu.2018.01914.
89. Huang SH, Liao CL, Chen SJ, Shi LG, Lin L, Chen YW, Cheng CP, Sytwu HK, Shang ST, Lin GJ (2019) Melatonin possesses an anti-influenza potential through its immune modulatory effect. *J. Funct. Foods* **58**: 189–198. doi:10.1016/j.jff.2019.04.062.
90. Kleszczyński K, Bilska B, Stegemann A, Flis DJ, Ziolkowski W, Pyza E, Luger TA, Reiter RJ, Böhm M, Slominski AT (2018) Melatonin and its metabolites ameliorate UVR-induced mitochondrial oxidative stress human MNT-1 melanoma cells. *IJMS* 19: **3786**: doi:10.3390/ijms19123786.
91. Tan D-X, Reiter RJ (2019) Mitochondria: the birth place, battle ground and the site of melatonin metabolism in cells. *Melatonin Res.* **2**: 44–66. doi:10.32794/mr11250011.
92. Hardeland R (2017) Melatonin and the electron transport chain. *Cell Mol. Life Sci.* **74**: 3883–3896. doi:10.1007/s00018-017-2615-9.
93. Huo X, Wang C, Yu Z, Peng Y, Wang S, Feng S, Zhang S, Tian X, Sun C, Liu K, *et al.* (2017) Human transporters, PEPT1/2, facilitate melatonin transportation into mitochondria of cancer cells: An implication of the therapeutic potential. *J. Pineal Res.* **62**: 1–18. doi:10.1111/jpi.12390.
94. Hardeland R (2018) Melatonin and inflammation—Story of a double-edged blade. *J. Pineal Res.* **65**: 1–23. doi:10.1111/jpi.12525.
95. Tan DX, Hardeland R (2020) Potential utility of melatonin in deadly infectious diseases related to the overreaction of innate immune response and destructive inflammation : focus on COVID-19. *Melatonin Res.* **3**:.120–143. doi:10.32794/mr11250052.
96. Ren W, Liu G, Chen S, Yin J, Wang J, Tan B, Wu G, Bazer FW, Peng Y, Li T, *et al.* (2017) Melatonin signaling in T cells: Functions and applications. *J. Pineal Res.* **62**: 1–15. doi:10.1111/jpi.12394.
97. Majumdar S, Nandi D. (2018) Thymic atrophy: Experimental studies and therapeutic interventions. *Scand J. Immunol.* **87**: 4–14. doi:10.1111/sji.12618.
98. Hardeland R (2019) Aging, melatonin, and the pro-and anti-inflammatory networks. *Int. J. Mol. Sci.* **20**: 1–33. doi:10.3390/ijms20051223.
99. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, *et al.* (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**: 497–506. doi:10.1016/S0140-6736(20)30183-5.
100. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, *et al.* (2020) Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* **5**: 802–810. doi:10.1001/jamacardio.2020.0950.
101. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, Liu C, Reiter RJ (2020) COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci.* **250**: 117583. doi:10.1016/j.lfs.2020.117583.
102. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, Shen B, Gong Z (2020) Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records

in a single medical center, Wuhan, China. *Int. J. Infect. Dis.* **94**: 128–132. doi:10.1016/j.ijid.2020.03.053.
103. Xu X, Wang G, Ai L, Shi J, Zhang J, Chen YX (2018) Melatonin suppresses TLR9-triggered proinflammatory cytokine production in macrophages by inhibiting ERK1/2 and AKT activation. *Sci. Rep*. **8**: 15579. doi:10.1038/s41598-018-34011-8.
104. Channappanavar R, Perlman S (2017) Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopatho.l* **39**: 529–539. doi:10.1007/s00281-017-0629-x.
105. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **395**: 1033–1034. doi:10.1016/S0140-6736(20)30628-0.
106. Shneider A, Kudriavtsev A, Vakhrusheva AV, Kudriavcev A, Vakhrusheva AV (2020) Can melatonin reduce the severity of COVID-19 pandemic? *Int. Rev. Immunol.* **19**: 153–162. doi:doi: 10.1080/08830185.2020.1756284.
107. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F (2020) Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov.* **6**: 1–18. doi:10.1038/s41421-020-0153-3.
108. Castillo RR, Quizon GRA, Juco MJM, E AD, Leon DG De, Punzalan FER, Guingon RBL (2020) Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res.* **3**: 297–310. doi:10.32794/mr11250063.
109. Acuña-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuña-Fernández C (2020) Clinical trial to test the efficacy of melatonin in COVID-19. *J. Pineal Res.* **69**: e12683: doi:10.1111/jpi.12683.
110. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, *et al*. (2020) Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N. Engl. J. Med.* **July**: 1–11. doi:10.1056/NEJMoa2021436.
111. Biancatelli RMLC, Berrill M, Mohammed YH, Marik PE (2020) Melatonin for the treatment of sepsis: The scientific rationale. *J. Thorac. Dis.* **2**: S54–S65. doi:10.21037/jtd.2019.12.85.
112. Nordlund JJ, Lerner AB (1977) The effects of oral melatonin on skin color and on the release of pituitary hormones. *J. Clin. Endocrinol. Metab.* **45**: 768–774.
113. Sugden D (1983) Psychopharmacological effects of melatonin in mouse and rat. *J. Pharmacol. Exp. Ther.* **227**: 587–591.
114. Bonanad C, García-Blas S, Tarazona-Santabalbina F, Sanchis J, Bertomeu-González V, Fácila L, Ariza A, Núñez J, Cordero A (2020) The Effect of age on mortality in patients with COVID-19: A meta-analysis with 611,583 subjects. *J. Am. Med. Dir. Assoc.* **21**: 915–918. doi:10.1016/j.jamda.2020.05.045.
115. Simko F, Reiter RJ (2020) Is melatonin deficiency a unifying pathomechanism of high risk patients with COVID-19? *Life Sci.* **256**: 117902. doi:10.1016/j.lfs.2020.117902.
116. Arato M, Grof E, Grof P, Laszlo I, Brown GM (1984) Reproducibility of the overnight melatonin secretion pattern in healthy men, In *Advances in the Biosciences* (New York: Pergamon Press), 277–282.
117. Bergiannaki JD, Soldatos CR, Paparrigopoulos TJ, Syrengelas M, Stefanis CN 1995) Low and high melatonin excretors among healthy individuals. *J. Pineal Res.* **18**: 159–164.

118. Burgess HJ, Fogg LF (2008) Individual differences in the amount and timing of salivary melatonin secretion. *PLoS One* **3**: e3055. doi:10.1371/journal.pone.0003055.
119. Waller KL, Mortensen EL, Avlund K, Osler M, Fagerlund B, Lauritzen M, Gammeltoft S, Jennum P (2016) Melatonin and cortisol profiles in late midlife and their association with age-related changes in cognition. *Nat. Sci. Sleep* **8**: 47–53. doi:10.2147/NSS.S75946.
120. Knight JA, Thompson S, Raboud JM, Hoffman BR (2005) Light and exercise and melatonin production in women. *Am. J. Epidemiol.* **162**: 1114–1122. doi:10.1093/aje/kwi327.
121. Kennaway DJ, Lushington K, Dawson D, Lack L, Van Den Heuvel C, Rogers N (1999) Urinary 6-sulfatoxymelatonin excretion and aging: New results and a critical review of the literature. *J. Pineal Res.* **27**: 210–220. doi:10.1111/j.1600-079X.1999.tb00617.x.
122. Zhdanova I V., Wurtman RJ, Balcioglu A, Kartashov AI, Lynch HJ (1998) Endogenous melatonin levels and the fate of exogenous melatonin: Age effects. *J.Gerontol. - Ser A Biol. Sci. Med. Sci.* **53**: 293–298. doi:10.1093/gerona/53A.4.B293.
123. Klante G, Brinschwitz T, Secci K, Wollnik F, Steinlechner S (1997) Creatinine is an appropriate reference for urinary sulphatoxymelatonin of laboratory animals and humans. *J. Pineal Res.* **23**: 191–197. doi:10.1111/j.1600-079X.1997.tb00354.x.
124. Grof E, Grof P, Brown GM, Arato M, Lane J (1985) Investigations of melatonin secretion in man. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **9**: 609–612. doi:10.1016/0278-5846(85)90026-0.
125. Levallois P, Dumont M, Touitou Y, Gingras S, Mâsse B, Gauvin D, Kröger E, Bourdages M, Douville P (2001) Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin. *Am. J. Epidemiol.* **154**: 601–609. doi:10.1093/aje/154.7.601.
126. Talarowska M, Szemraj J, Zajączkowska M, Gałecki P (2014) ASMT gene expression correlates with cognitive impairment in patients with recurrent depressive disorder. *Med. Sci. Monit.* **20**: 905–912. doi:10.12659/msm.890160.
127. Kripke DF, Nievergelt CM, Joo E, Shekhtman T, Kelsoe JR (2009) Circadian polymorphisms associated with affective disorders. *J. Circadian. Rhythms* **7**: 1–10. doi:10.1186/1740-3391-7-2; 10.1186/1740-3391-7-2.
128. Galecki P, Szemraj J, Bartosz G, Bienkiewicz M, Galecka E, Florkowski A, Lewinski A, Karbownik-Lewinska M (2010) Single-nucleotide polymorphisms and mRNA expression for melatonin synthesis rate-limiting enzyme in recurrent depressive disorder. *J. Pineal Res.* **48**: 311–317. doi:10.1111/j.1600-079X.2010.00754.x.
129. Soria V, Martínez-Amorós E, Escaramís G, Valero J, Pérez-Egea R, García C, Gutiérrez-Zotes A, Puigdemont D, Bayés M, Crespo JM, *et al.* (2010) Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacology* **35**: 1279–89. doi:10.1038/npp.2009.230.
130. Ribelayga C, Pevet P, Simonneaux V (2000) HIOMT drives the photoperiodic changes in the amplitude of the melatonin peak of the Siberian hamster. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* **278**: R1339–R1345.
131. Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. *Sleep MedRev* **9**: 11–24. doi:10.1016/j.smrv.2004.08.001.
132. Etain B, Dumaine A, Bellivier F, Pagan C, Francelle L, Goubran-botros H, Moreno S, Deshommes J, Moustafa K, Le dudal K, *et al.* (2012) Genetic and functional abnormalities

of the melatonin biosynthesis pathway in patients with bipolar disorder. *Hum. Mol. Genet.* **21**: 4030–4037. doi:10.1093/hmg/dds227.

133. Braam W, van Geijlswijk I, Keijzer H, Smits MG, Didden R, Curfs LM (2010) Loss of response to melatonin treatment is associated with slow melatonin metabolism. *J. Intellect. Disabil. Res.* **54**: 547–555. doi:10.1111/j.1365-2788.2010.01283.x.
134. Veatch OJ, Pendergast JS, Allen MJ, Leu RM, Johnson CH, Elsea SH, Malow BA (2015) Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. *J. Autism. Dev. Disord* **45**: 100–110. doi:10.1007/s10803-014-2197-4.
135. Tordjman S, Anderson GM, Pichard N, Charbuy H, Touitou Y (2012) Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. *Biol. Psychiatry* **57**: 134–138.
136. Jonsson L, Anckarsater H, Zettergren A, Westberg L, Walum H, Lundstrom S, Larsson H, Lichtenstein P, Melke J (2014) Association between ASMT and autistic-like traits in children from a Swedish nationwide cohort. *Psychiatr. Genet.* **24**: 21–27. doi:10.1097/YPG.0000000000000010.
137. Kulman G, Lissoni P, Rovelli F, Roselli MG, Brivio F, Sequeri P (2000) Evidence of pineal endocrine hypofunction in autistic children. *Neuro. Endocrinol. Lett.* **21**: 31–34.
138. Ormstad H, Bryn V, Saugstad OD, Skjeldal O, Maes M (2018) Role of the immune system in autism spectrum disorders (ASD). *CNS Neurol. Disord. Drug Targets* **17**: 489–495. doi:10.2174/1871527317666180706123229.
139. Batllori M, Molero-Luis M, Arrabal L, De Las Heras J, Fernandez-Ramos JA, Gutiérrez-Solana LG, Ibáñez-Micó S, Domingo R, Campistol J, Ormazabal A, *et al*. Urinary sulphatoxymelatonin as a biomarker of serotonin status in biogenic amine-deficient patients. *Sci. Rep.* (2017) **7**: 1–9. doi:10.1038/s41598-017-15063-8.
140. Brown GM, Young SN, Gauthier S, Tsui H, Grota LJ (1979) Melatonin in human cerebrospinal fluid in daytime; its origin and variation with age. *Life Sci.* **25**: 929–936. doi:10.1016/0024-3205(79)90498-3.
141. Iguchi H, Kato KI-I, Ibayashi H (1982) Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J. Clin. Endocrinol. Metab.* **55**: 27–29. doi:10.1210/jcem-55-1-27.
142. Waldhauser F, Weiszenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper MF (1988) Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J. Clin. Endocrinol. Metab.* **66**: 648–652.
143. Sack RL, Lewy AJ, Erb DL, Vollmer WM, Singer CM (1986) Human melatonin production decreases with age. *J. Pineal Res* **3**: 379–388.
144. Bojkowski CJ, Arendt J (1990) Factors influencing urinary 6-sulphatoxymelatonin, a major melatonin metabolite, in normal human subjects. *Clin. Endocrinol. (Oxf)* **33**: 435–444.
145. Haimov I, Laudon M, Zisapel N, Souroujon M, Nof D, Shlitner A, Herer P, Tzischinsky O, Lavie P (1994) Sleep disorders and melatonin rhythms in elderly people. *Br. Med. J.* **309**: 167.
146. Yie S-M, Liu G-Y, Johansson E, Brown C, Brown GM (1992) Age-associated changes and sex differences in urinary 6 -sulphatoxymelatonin circadian rhythm in the rat. *Life Sci.* **50**: 1235–1242. doi:10.1016/0024-3205(92)90323-H.
147. Reiter RJ, Craft CM, Johnson JEJ, King TS, Richardson BA, Vaughan GM, Vaughan MK (1981) Age-associated reduction in nocturnal pineal melatonin levels in female rats.

Endocrinology **109**: 1295–1297. doi:10.1210/endo-109-4-1295.
148. Stoschitzky K, Sakotnik A, Lercher P, Zweiker R, Maier R, Liebmann P, Lindner W (1999) Influence of beta-blockers on melatonin release. *Eur. J. Clin. Pharmacol.* **55**: 111–115. doi:10.1007/s002280050604.
149. Mayeda A, Mannon S, Hofstetter J, Adkins M, Baker R, Hu K, Nurnberger J (1998) Effects of indirect light and propranolol on melatonin levels in normal human subjects. *Psychiatry Res.* **81**: 9–17. doi:10.1016/S0165-1781(98)00069-9.
150. Deacon S, English J, Tate J, Arendt J (1998) Atenolol facilitates light-induced phase shifts in humans. *Neurosci. Lett.* **242**: 53–56. doi:10.1016/S0304-3940(98)00024-X.
151. Vasanthakumar N (2020) Can beta-adrenergic blockers be used in the treatment of COVID-19? *Med. Hypotheses* **142**: 109809. doi:10.1016/j.mehy.2020.109809.
152. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, *et al*. (2020) Renin–angiotensin–aldosterone system inhibitors and risk of covid-19. *N. Engl. J. Med.* **382**: 2441–2448. doi:10.1056/NEJMoa2008975.
153. Kennedy SH, Brown GM (1992) Effect of chronic antidepressant treatment with adinazolam and desipramine on melatonin output. *Psychiatry Res.* **43**: 177–185. doi:10.1016/0165-1781(92)90132-M.
154. Kennedy SH, Davis BA, Brown GM, Ford CG, D'Souza J (1993) Effects of chronic brofaromine administration on biogenic amines including sulphatoxymelatonin and acid metabolites in patients with bulimia nervosa. *Neurochem. Res.* **18**: 1281–1285. doi:10.1007/BF00975048.
155. von BC, Ursing C, Yasui N, Tybring G, Bertilsson L, Rojdmark S (2000) Fluvoxamine but not citalopram increases serum melatonin in healthy subjects-- an indication that cytochrome P450 CYP1A2 and CYP2C19 hydroxylate melatonin. *Eur. J. Clin. Pharmacol.* **56**: 123–127.
156. Skene D, Bojkowski C, Arendt J (1994) Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans. *Br. J. Clin. Pharmacol.* **37**: 181–186. doi:10.1111/j.1365-2125.1994.tb04258.x.
157. Kinsey EW, Dupuis R, Oberle M, Cannuscio CC, Hillier A (2019) Chronic disease self-management within the monthly benefit cycle of the Supplemental Nutrition Assistance Program. *Public Health Nutr.* **22**: 2248–2259. doi:10.1017/S1368980019001071.
158. Darmon N, Drewnowski A (2015) Contribution of food prices and diet cost to socioeconomic disparities in diet quality and health: A systematic review and analysis. *Nutr. Rev.* **73**: 643–660. doi:10.1093/nutrit/nuv027.
159. Merhout F, Doyle J (2019) Socioeconomic status and diet quality in college students. *J. Nutr. Educ. Behav.* **51**: 1107–1112. doi:10.1016/j.jneb.2019.06.021.
160. Loopstra R, Reeves A, Tarasuk V (2019) The rise of hunger among low-income households: An analysis of the risks of food insecurity between 2004 and 2016 in a population-based study of UK adults. *J. Epidemiol. Community Health* **73**: 668–673. doi:10.1136/jech-2018-211194.
161. Earnesty DS, Hourani M, Kerver JM, Weatherspoon LJ (2019) Dietary guidelines are not met by in-home child care providers in low-income areas. *J. Nutr. Educ. Behav.* **51**: 1150–1158. doi:10.1016/j.jneb.2019.08.001.
162. Beck AL, Iturralde EM, Haya-Fisher J, Kim S, Keeton V, Fernandez A (2019) Barriers and facilitators to healthy eating among low-income Latino adolescents. *Appetite* **138**: 215–

222. doi:10.1016/j.appet.2019.04.004.
163. Ong MM, Ong RM, Reyes GK, Sumpaico-Tanchanco LB (2020) Addressing the COVID-19 nutrition crisis in vulnerable communities: applying a primary care perspective. *J. Prim. Care Community Health* (2020) **11**: 2150132720946951. doi:10.1177/2150132720946951.
164. Young SN (1988) Tryptophan availability in humans: effects on mood and behavior. In *Amino acid availabilty and brain function in health and disease*, ed. G. Huether (Berlin/Heidelberg: Springer-Verlag), 267–274.
165. Huether G, Hajak G, Reimer A, Poeggeler B, Blömer M, Rodenbeck A, Rüther E (1992) The metabolic fate of infused l-tryptophan in men: possible clinical implications of the accumulation of circulating tryptophan and tryptophan metabolites. *Psychopharmacology (Berl)* **109**: 422–432. doi:10.1007/BF02247718.
166. Tan D-X, Hardeland R (2020) Estimated doses of melatonin for treating deadly virus infections: focus on COVID-19. *Melatonin Res.* **3**: 276–296. doi:10.32794/mr11250062.

Please cite this paper as:
Pandi-Perumal, S., Cardinali, D., Reiter, R.J. and Brown, G. 2020. Low melatonin as a contributor to SARS-CoV-2 disease. Melatonin Research. 3, 4 (Oct. 2020), 558-576. DOI:https://doi.org/https://doi.org/10.32794/mr11250079.