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Review Article

Melatonin as an add on therapy for SARS CoV-19 pandemic

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ABSTRACT

COVID-19 has been reported in over 4.1 million people worldwide as of May 11, 2020 and has resulted in more than 2,83,000 deaths. As of June 6, globally 66,63,304 confirmed cases and 3,92,802 deaths. More than 180 countries on all continents except Antarctica have reported laboratory-confirmed cases of COVID-19. Unlike SARS-CoV, however, which infected just 8,000 people worldwide in 8 months, the new SARS-CoV-2, estimated to be up to 1,000 times more infectious than SARS-CoV or other coronaviruses, has already infected more than 1,20,000 people worldwide in under three months. Melatonin (N-acetyl-5-methoxytryptamine) is a serotonin derivative bioactive molecule released from the pineal gland in the brain with an array of health-promoting properties. Melatonin slows and inhibits thymic involution, and promotes thymocyte regeneration and indirectly regulates the expression of ACE2, a key entry receptor involved in human coronavirus virus infection, like 2019-nCoV / SARS-CoV-2. Melatonin can act as a hormone, paracrine, autocrine or tissue factor to coordinate immune system function. Although melatonin has various properties in different cells of the body, it actively involved in reducing viral infections.

KEYWORDS: Melatonin, SARS-CoV, Viral diseases, Melatonin receptors

INTRODUCTION

Viral diseases continue to arise, and pose a significant public health problem, according to the World Health Organization (WHO).[1] Many viral epidemics, such as the Severe Acute Respiratory Coronavirus Syndrome (SARS-CoV) in 2003 affected more than 8,000 people worldwide with a mortality rate of 10%[2] and H1N1 influenza in 2009, have been reported in the last twenty years. Most recently, Saudi Arabia first described Middle East Respiratory Coronavirus Syndrome (MERS-CoV) in 2012which is closely related and caused by acute pneumonia similar to SARS-CoV.[3,4] And in December 2019, a novel corona virus designated SARS-CoV 2 has caused an international outbreak of respiratory illness termed Novel Corona virus.[5] COVID-19 has been reported in over 4.1 million people worldwide as of May 11, 2020 and has resulted in more than 2,83,000 deaths. As of June

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6, globally 66,63,304 confirmed cases and 3,92,802 deaths.[6] More than 180 countries on all continents except Antarctica have reported laboratory-confirmed cases of COVID-19. In the United States, as of May 11, 2020, more than 1.3 million COVID-19 cases have been confirmed resulting in more than 79,000 deaths. As of 26 March 2020, the United States had more infections confirmed than any other country in the world, including China and Italy. India reported the first confirmed case of the coronavirus infection on 30 January 2020 in the state of Kerala. The affected had a travel history from Wuhan, China.[7] To study the extent of spread of COVID-19 cases, ICMR had tested for Severe Acute Respiratory Coronavirus Syndrome (SARS-CoV-2) in samples from patients admitted with severe acute respiratory illness (SARI) in multiple centers spread across India from Feb 15 to Apr 2, 2020.[8] The new SARS-CoV-2, with 79% similarity to SARS-CoV, also induces adult patients with pneumonia of varying severity regardless of age. Unlike SARS-CoV, however, which infected just 8,000 people worldwide in 8 months,[9] the new SARS-CoV-2, estimated to be up to 1,000 times more infectious than SARS-CoV or other coronaviruses, has already infected more than 1,20,000 people worldwide in under three months.[10] Now recently of September 25, 2020, india reports 58,18,571 including 9,70,116 active cases active cases, 92,290 deaths and 47,56,165 recovered.[11]

BRIEF OUTLOOK TO COVID 19 VIRUS

Corona virus 19 (CoVs) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope (coronam is the Latin term for crown). The Coronaviridae subfamily Ortho-coronavirinae (order Nidovirales) classifies into four CoV genera: (alphaCoV) Alpha-coronavirus, (betaCoV) Beta-coronavirus, (deltaCoV) Delta-coronavirus, and (gammaCoV) Gamma-coronavirus. In addition, the genus betaCoV divides into five subgenera or lineages.[12] Genomic analysis has shown that the gene origins of alphaCoVs and betaCoVs are likely bats and rodents. On the contrary, avian species tend to dominate the deltaCoV and gammaCoV gene sources.[13] In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.[14]

Common human CoVs: HCoV-OC43 and HCoV-HKU1 (A-lineage betaCoVs); HCoV 229E, and HCoV-NL63 (alphaCoVs). In immunocompetent individuals, this can cause common colds and self-limiting upper respiratory infections. Lower level respiratory tract infections can occur in immunocompromised subjects and the elderly. Most human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (B and C lineage betaCoVs, respectively). Which cause variable clinical severity epidemics that comprise respiratory and extra-respiratory manifestations. The mortality rates for SARS-CoV, MERS-CoV, are up to 10% and 35% respectively.[15]SARS-CoV-2 is in the group BetaCoVs. It has a round or elliptic, often pleomorphic shape, and a diameter of about 60–140 nm. Like other CoVs it is sensitive to heat and ultraviolet rays. These viruses can also be effectively inactivated by lipid solvents, including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform, except chlorhexide.[16]

A research reported by scientists in Germany on March 8, 2020 found that this coronavirus not only infects lower respiratory tracts as seen in early January when COVID-19 patients in China examined showed no apparent symptoms of rhinorrhea (runny nose), sneezing, or sore throat, but all had pneumonia with irregular chest CTs and 29% of those patients examined developed ARDS. The SARS-CoV-2 virus primarily affects the respiratory system, though other organs are involved as well. The initial series of cases from Wuhan, China documented lower symptoms of respiratory tract infection including fever, dry cough, and dyspnea.[17] They also observed headache, dizziness, generalized weakness, vomiting, and diarrhea.[18]

Gao Y et al., on his recent study describes that respiratory symptoms of COVID-19 are now widely recognized as being extremely heterogeneous, ranging from minimal symptoms to significant hypoxia to ARDS. In the above-mentioned Wuhan case, the period between the onset of symptoms and the development of ARDS was as short as nine days, indicating that the respiratory symptoms may progress rapidly.[19] The risk factors of death in-hospital were analyzed using data from two Wuhan hospitals. In the multi-variable analysis, it was shown that older age, higher sequential organ failure assessment (SOFA) score and d-dimer > 1 μg / mL on admission were risk factors.The prevalence of coronary artery disease, diabetes, and hypertension was also known as risk factors in the univariable study.[20]

Du Y in recent research in Wuhan of 85 fatal COVID-19 patients with a median age of 65 years showed that the majority of patients died from multi-organ failure as a result of respiratory failure, shock, and ARDS in 94%, 81%, and 74%, respectively, of cases.[21] As in line with the high prevalence of multi-organ failure, severe diseases have seen high d-dimer levels, fibrinogen and prolonged thrombin time.[22]

MECHANISM OF SARS-COV-2 INVASION INTO HOST CELLS

The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host (attachment) receptors, they enter host cells via endocytosis or membrane fusion (penetration). When viral contents inside host cells are released, viral RNA occupies the nucleus for replication. The viral mRNA is used for the development of viral proteins (biosynthesis) new (maturing) viral particles are produced and released. Coronaviruses are composed of four structural proteins; spike (S), membrane (M), envelope (E), and nucleocapside(N).[23] Spike is composed of a trans membrane trimetric glycoprotein protruding from the viral surface that determines the coronavirus diversity and host tropism. Spike consists of two functional subunits; the subunit S1 is responsible for binding to the host cell receptor and the subunit S2 is responsible for viral and cellular membrane fusion. Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV.[14] Structural and functional research showed that the SARS-CoV-2 spike also correlated to ACE2.[24,25] In lung, ACE2 was highly expressed on lung epithelial cells. Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. The primary cleavage of S1 and S2, the subunits S1 and S2 remain non-covalently bound, and the distal subunit S1 contributes to the perfusion stabilization of the membrane-anchored subunit S2. The spike of coronavirus is unique among viruses, since it can be cleared and triggered by a number of different proteases.[26]

THE COVID-19 VIROPORIN CONNECTION WITH ARDS/ALI, CYTOKINE STORMS AND NLRP3 INFLAMMASOMES

Critically ill patients suffering from COVID-19 often experience acute respiratory distress syndrome and acute lung injury (ARDS / ALI). As ARDS progresses into the acute stage, alveolar flooding (edema), interstitial inflammation and atelectasis of compression, as well as increase in lung tissue and decrease in volume of lung gas are observed.[27,28]COVID-19 patients with ARDS/ ALI often need intubation and intrusive mechanical ventilation to assist with breathing difficulties because of the elevated hypoxemic respiratory failure.[29] Acute respiratory distress syndrome and acute lung injury (ARDS / ALI) are also characterized by neutrophil aggregation in the lungs, and increased development of inflammatory cytokines, chemokines, proteases, and oxidants. ARDS / ALI initiation and growth depends on the activation of inflammasomes. Inflammasomes are part of our innate immune system. In a postmortem assessment of a COVID-19 patient with severe ARDS, specimens of infected lungs demonstrated bilateral diffuse alveolar damage with edema, pneumocyte desquamation and hyaline membrane formation.[30,31]

CORONAVIRUSES LIKE SARS-COV-2 USE VIROPORINS TO STIMULATE IMMUNE RESPONSES AS PART OF THEIR PATHOGENICITY-POSSIBLE MECHANISMS

Viroporins are virus-encoded proteins in the ion channels. The ORF3a and E protein viroporins play critical roles in the replication and pathogenesis of viruses.[32] A virus that lacks both the proteins E and ORF3a will not be viable. Maximum replication and virulence of SARS-CoV coronavirus has been shown to result directly from viroporin E and ORF3a proteins.[33]For several years, scientists have recognized that viroporin envelope (E) protein is responsible for the SARS-CoV virulence. Studies have correlated the activities of the E protein ion channel (IC) in SARS-CoV with increased pulmonary damage, accumulation of edema, and death.[34] Edema is the main determinant of ARDS which could lead to death. Whenever activities on the channel of E protein ions were detected, pro-inflammatory response mediated by both edema and IL-1β was increased. Deletion of the E protein in SARS-CoV resulted in a substantial reduction in IL-1β expression in the lung airways of infected animal models missing the conductivity of E protein ions.[35]SARS-CoVviroporin E proteins in cell membranes form protein-lipid channels which allow the passage of calcium ions. These ion channel movements involving calcium are unique triggers for the activation of inflammatory NLRP3, resulting in overproduction of IL-1β cytokines. Calcium transport through these channels of E protein ions initiates the cytokine production cascade, which can ultimately lead to uncontrollable cytokine storms, and ARDS/ALI in bilateral interstitial pneumonia.[36]

MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) is a serotonin derivative bioactive molecule released from the pineal gland in the brain with an array of health-promoting properties.[37,38] Melatonin is mainly synthesized by amino acid tryptophan pinealocytes that are hydroxylated (tryptophan-5-hydroxylase) in 5-hydroxytryptophan, then decarboxylated (5-hydroxytryptophan decarboxylase) in serotonin.[39,40] The peak development of melatonin for most people is between the hours of 2 am to 3 am. Highest levels of melatonin measured in healthy adults aged between 65 and 70 years seemed to be around 49.3 picograms / ml (pg / ml). Adults over 75 have a maximum output volume of 27.8 pg / ml only.[41]

Toddlers, by comparison, have relatively high rates of melatonin compared with adults. The average rates reported for young children showed a decrease as age increased. Children aged 1 to 5 years had peak melatonin at 325 pg / ml, although those aged 5 to 11 years had already decreased to 133 pg / ml.[42] A young child can easily have ten times the amount of peak melatonin levels, compared to healthy adult seniors. But even then there is exceptionally low real physiological concentration. One milligram is the equivalent of 1,000,000,000 picogram. This is why the commonly prescribed physiological dose for melatonin supplementation is about 0.3 milligram.[43]

Melatonin is the reason that babies under the age of 9 rarely have serious symptoms. In addition, even though they have been infected with SARS-CoV-2, children can display mild or even no symptoms at all.[44] The probable utilization of melatonin in parasite, bacterial and virus infections have been discussed in various reviews.[45,46] Here, we will focus on the potential effects of melatonin on deadly virus infections such as SARS, MERS and COVID-19.[47] Melatonin cannot be expected to directly kill the parasites, bacteria, pathogenic fungi and viruses but can protect them against many forms of biotic or abiotic stress as a universal antioxidant and regulator.[48]

INNATE IMMUNITY TARGET OF MELATONIN

Virus infections can attack the melatonin synthetic system resulting in reduced melatonin levels in hosts. Mitochondrially transmitted reactive oxygen species (ROS) activate the innate immune signaling cascade and increase inflammation of cytotoxic stimuli beyond microbial infection.[49] Mitochondria evolved from 5-007-proteobacteria and still retrain some features of their ancestors, including circular CpG-unmethylated DNA, N-formyl peptides, cytochrome C, membrane cardiolipin, elevated succinate. Upon release from mitochondria under stressful conditions, they may all serve as DAMPs to activate innate immune responses including autophagy, inflammatory activation of NLRP3 and apoptosis.[50] High levels of mitochondria generated Melatonin may provide security in site.[51] The mitochondrial membrane potential has been shown to be sustained by regulating the mitochondrial transition pore (mPTP) and thus preventing the release of mitochondrial contents.[52] Across the same, melatonin blocks the secondary cytokine inflammatory storm caused by mitochondrial DAMPs. Melatonin's anti-inflammatory actions that can be mainly attributed to the modulation of the innate immune system have been shown to involve numerous additional mechanisms.[53] These effects include reduction of cyclooxygenase-2 and NO-mediated phagocyte and microglia activation; stimulation of Nrf2 signaling, which counteracts NF-πB induced pro-oxidant and pro-inflammatory actions; up-regulation of sirtuin-1 expression, a receptor that also exhibits anti-inflammatory effects, including inhibition of TLR4 activator HMGB1 (high-mobility group box 1), mTORC1 (mTORC1). In addition, melatonin has recently been confirmed as shifting macrophage polarization from pro-inflammatory type M1 to anti-inflammatory type M2. Corresponding effects can be expected for macrophage-like tissue-resident cells like microglia, in which the polarity of M1/M2 is also present.[54]

ADAPTIVE IMMUNITY TARGET OF MELATONIN

Melatonin shows different beneficial effects with respect to the adaptive immunity.[55]

One of the significant targets of melatonin on the adaptive immune system is the thymus that is experiencing atrophy with aging, resulting in reduced thymus-specific cytokine development and reduced maturation potential, positive and negative T lymphocyte selection. Melatonin slows and inhibits thymic involution, and promotes thymocyte regeneration. Melatonin thus facilitates the activation and differentiation of T-cells including Th17, Treg cells and even T-cells in memory.[56]

In the regulatory functions of melatonin in T-cell biology, multiple cell signaling pathways, including ERK1/2-C / EBPα, participate.[57]In addition, melatonin positively regulates the B lymphocyte proliferation in human tonsillar tissue.[58]In mice, the administration of melatonin prevents the apoptosis of precursor B cells in bone marrow and substantially promotes the survival of newly developed B cells that mediate humoral immunity.[59] Injection of melatonin into sheep increases the amount of antibody titer[60] and serum Immunoglobulin. As a result, melatonin is recommended to be used as the adjuvant of the vaccine, which contributed to a significantly higher production of antibodies and also maintained it for a longer time than that without melatonin adjuvant.[61] Interestingly, the immune systems including the thymus, bone marrow, lymphocytes, and other immune cells are capable of biosynthesizing melatonin.[62,63] Melatonin can act as a hormone, paracrine, autocrine or tissue factor to coordinate immune system function.[64]

INFLAMMATION AS A PROTECTIVE RESPONSE

Inflammation is a protective immune response mounted to harmful stimuli, such as pathogens, dead cells or irritants, by the evolutionarily

reconstructed innate immune system, and is tightly regulated by the host.[65] Innate immune function depends on the recognition of pathogen-associated molecular patterns (PAMPs), derived from harmful pathogens, and molecular hazard-associated patterns (DAMPs). PAMPs or DAMPs activation of PRRs triggers downstream signaling cascades and results in the production of Type I interferon (interferon-α and interferon-β) and pro-inflammatory cytokines.[66] Inflammasome activation is a key function that is mediated by the innate immune system, and recent advances have greatly enhanced understanding of inflammatory macromolecular activation. Several PRR families are important components of the inflammasome complex, including the nucleotide-binding domain, leucine-rich protein-containing repeat (NLRs, also known as NOD-like receptors) and absence of melanoma 2-like receptors (ALRs, AIM2-like receptors) in both mice and humans.[67] Inflammasomes play either causative or leading roles in the initiation of inflammatory disease, and often exaggerate the pathology in response to host-derived stimuli.[68]

MECHANISMS OF ACTION OF MELATONIN

Although melatonin has effects on different cells in the human body[69], its sleep-promoting activities are mainly due to its input to the (SCN) suprachiasmatic nucleus (master clock), specifically on the melatonin receptors (MT1 and MT2).[70] By acting on the SCN, melatonin helps synchronize the circadian rhythm through influencing both sleep phase and sleep amplitude.[71,72] Neuronal firing is proposed to be suppressed via MT1 receptors while MT2 receptors are responsible for phase shifts. Melatonin is sometimes recommended for sleep disturbance patients and has been shown to be effective in helping to relieve other sleep disorders, such as jet lag and elderly insomnia.[73] Melatonin is rapidly distributed after intravenous administration (average half-life of 0.5 to 5.6 minutes).[74] After intravenous or oral administration, melatonin is quickly metabolized, mainly in the liver and secondarily in the kidney. However, after intravenous administration, the hepatic bio-degradation is less important due to the absence of hepatic first pass.[75] It undergoes hydroxylation to 6-hydroxymelatonin by the action of the cytochrome P450 enzyme CYP1A2, followed by conjugation with sulfuric acid (90%) or glucuronic acid (10%) and is excreted in the urine. About five percentage of serum melatonin is excreted un-metabolized also in urine.[76]

MELATONIN IN COVID 19

The evidence demonstrates that melatonin in Covid-19 can produce two very different types of effects, each depending on dosage and severity of the disease.[77]

NLRP3 GENE

The NLRP3 gene (also known as CIAS1) provides instructions for making a protein called cryopyrin. Cryopyrin is a member of a family of proteins called nucleotide-binding domain and leucine-rich repeat containing (NLR) proteins, which are found in the fluid inside cells (cytoplasm).[78] The inflammasome NOD-like receptor 3 (NLRP3) is part of the innate immune response occurring during lung infection, including influenza A virus, syncytial virus, and bacteria. Innate defenses rely on identifying molecular patterns known to be associated with bad microbes, unlike the more complex cytotoxic (immune cells that kill) and humoral (antibodies that clump or tag) immunity. These patterns stimulate toll-like receptors (TLRs) that then cause a variety of inflammatory cascades, including the inflammasome of NLRP3.[79]Viral pathogens activation leads NLRP3 to intensify the inflammation. Melatonin's effectiveness in controlling NLRP3 has been demonstrated in radiation-induced lung injury, allergic inflammation of the airway and other types of induced lung injury.[80] In these, melatonin decreased the penetration of macrophages and neutrophils into the injured lung because of its inflammatory inhibition of NLRP3. Inhibition of NLRP3 gene increased mortality in the early phase of infection, while eliminating NLRP3 at the peak of infection allowed a protective effect. This can mean that the best use of high-dose of melatonin is in the acute lung injury, where the most serious is inflammation. Melatonin being beneficial in prevention /early stage treatment in low doses (3-6 mg /day) and helpful for the management of lung injury/ ARDS in higher doses (20-40mg day).[81,82]

ACE2

Melatonin can have direct antiviral activity against COVID-19, besides being a potent antioxidant. Melatonin rates in healthy people drop after 40 years of age. In addition to declining antioxidant levels, this can explain in part the increased risk of death in COVID-19 patients.[83] Melatonin indirectly regulates the expression of ACE2, a key entry receptor involved in human coronavirus virus infection, like 2019-nCoV / SARS-CoV-2. Specifically, melatonin has been reported to inhibit a calcium-binding protein (calmodulin) that interacts with ACE2 by inhibiting the shedding of its ectodomain (the portion of the membrane protein extending into the extracellular space), a key infectious p.[84] Melatonin may also have indirect benefits in treating critical care patients by decreasing vessel permeability, anxiety, sedation use, and enhancing sleep quality, all of which can

also help COVID-19 patients for improved clinical outcomes.[85]

Daily variations in melatonin in young people (age 26±2 years) were in the region of 7 pg/ml, and in people aged 84±2 years, the level of melatonin dropped to 2 pg/ml. A significant difference was also observed in the production of melatonin at night. A night peak of melatonin for young people was observed at the level of 83±20 pg/ml, while for the elderly only 11.2±1.6 pg/ml.[86] A study conducted in people to access the melatonin level from birth to elderly, the results shows that the highest concentration of melatonin (329.5±42 pg/ml) was in 1-3 year old children. After this age, there was a sharp decline in the average melatonin level by almost 80%. Then a negative correlation between age and melatonin concentration remained over the period of 20-90 years. Thus, the application of melatonin may partially alleviate age-related co-morbidities exacerbating SARS-CoV-2 infection and increasing its risk.[87]

MELATONIN REDUCES INFECTION-ASSOCIATED OXIDATIVE STRESS

Viral respiratory infections are associated with oxidative stress characterized by elevated levels of reactive oxygen (ROS) and/or nitrogen species (RNS).[88] Oxidative stress sensitive genes were up-regulated in SARS-CoV-1 human patients in the peripheral blood mononuclear cells. A positive feedback loop can be created by viral infections that cause severe lung damage and oxidative stress in the lungs.[89] SARS-CoV, for example, induces oxidative stress; oxidative stress induces phospholipase expression of PLA2G2D; higher expression of PLA2G2D decreases anti-viral immunity, rendering the virus more lethal. Notably, the expression ofPLA2G2D is naturally increased with age.[90] At the same time, experimental animals may be more resistant to respiratory viruses with deleted components of ROS-generating machinery. Melatonin has good antioxidant effects. It binds up to 10 free radicals per molecule, while only one is binding on such classic antioxidants as vitamins C and E.[91]

MELATONIN & ANTI-INFLAMMATION

Melatonin exerts anti-inflammatory effects over different pathways.Sirtuin-1 (SIRT1) is capable of mediating anti-inflammatory actions melatonin by inhibiting boxechromosomal protein from high mobility group 1 (HMGB1), and also down-regulating macrophage polarisation towards pro inflammatory type. The kappa-B nuclear factor (NF-πB) is closely associated with the pro-inflammatory and Pro-oxidative responses though ALI is an inflammatory mediator. The anti-inflammatory effect of melatonin involves the suppression of NF-κB activation in ARDS.[92,93] Melatonin reportedly down-regulateNF-κB activation in T cells and lung tissue.[94] The stimulation of NF-E2-related factor 2 (Nrf2) is crucial in protecting lung from injury. In related studies, melatonin induces Nrf2 up-regulation with Hepatoprotection, cardio protection, preventive effects etc. It remains unknown whether Nrf2 is involved in the CoV-induced ALI; but the close association between SIRT1, NF-yB and Nrf2 suggests their involvement in ALI / ARDS, induced by CoV.[95] Inflammation iscommonly associated with an elevated production of cytokines andchemokines, while melatonin causes a reduction in the pro-inflammatory cytokines. TNF-α, IL-1β, IL-6, and IL-8, and an elevation in the level of anti-inflammatory cytokine IL-10 however, some concerns about the potential pro-inflammatory actions of melatonin when used in very high doses or under suppressed immune conditions where it may induce an increase production of pro-inflammatory cytokines, IL-1β, IL-2, IL-6, IL-12, TNF-α, and IFN-γ.[96]

MELATONIN & ANTI-OXIDATION

In the early stages of coronaviruses infection, dendritic cells and epithelial cells are activated and express a cluster of pro-inflammatory cytokines and chemokines including IL-1β, IL-2, IL-6, IL 8, both IFN-α/ β, tumor necrosis factor (TNF), CeC motif chemokine 3 (CCL3), CCL5,CCL2, and IP-10, etc. These are under the control of immune system. Thus, the overproduction of these cytokines and chemokines contributes to the development in disease.[97,98] The anti-oxidative effect of melatonin cooperates with its anti-inflammatoryactions by up-regulating anti-oxidative enzymes (e.g. superoxidedismutase), down-regulating pro-oxidative enzymes (e.g. nitric oxide synthase), and it may also interact directly with free radicals, functioning as free radical scavenger.[99,100]In a SARS-induced ALI model, the production of oxidized low density lipoprotein activatesinnate immune response by the overproduction of IL-6 alveolar macrophagesvia Toll-like receptor 4 (TLR4)/NF-kB signaling, there by leading to ALI.[101] TLR4 is a receptor for the innate immune system, and it is also a therapeutic target for melatonin. There are situations in which melatonin suppresses the features of viral infections. In mice whose central nervous system is infected by virus (e.g., encephalitis), the use of melatonin caused less viremia, reduced paralysis and death, and decreased virus load.[102]

MELATONIN REDUCE THE RISK OF MECHANICAL VENTILATION

Imai Yet al., in his review states that elderly people possess a higher mortality rate, a high number of young COVID-19 patients receive mechanical ventilation due to low blood oxygen saturation and

difficulty breathing. Mortality was increased in patients even with moderate hyperoxemia (with Pa (O2)> 100mm Hg), staying for 1 to 7 days on artificial respiration apparatuses, as shown by the multicenter cohort observational study.[103] Ventilation was reported to enhance pulmonary inflammation in acute lung damage[104] and increased oxidative stress in the alveoli.[105] As presented above, melatonin may be quite effective against oxidative stress. Thus, melatonin may resolve a contradiction between the urgent clinical necessity to give patient mechanical ventilation and the threat this ventilation may possess.[106]

MAINTENANCE DOSAGES DURING COVID-19 PANDEMIC

Exogenous intake during COVID-19 is only recommended because normal endogenous development may not be adequate for defense against COVID-19 for adults. Children under 9 are shielded from COVID-19 because they have the usual amount of adults up to ten times. Our high-tech world, light exposure at night has significantly reduced adult melatonin levels that are normally low.[107] Additional protection against infections can be provided by supplementing a minimum physiological dose during COVID-19 pandemic. An adult with no major health challenges should take no more than the recommended physiological dosage below. The following is a selection of dosages. The upper end of the spectrum refers to individuals who are older or whose wellbeing is slightly poorer. And a stable young adult may need no more than the lowest 0.2 mg physiological dose.[108]

CONCLUSION

Melatonin is a circulating neurohormone secreted predominantly at night, thereby called as hormone of darkness. It can cross all physiological barriers to exert widespread regulatory effects on body tissues. Melatonin is a universal antioxidant with multifunctional activities such as anti-inflammatory, anti-apoptotic, and antioxidant effects in addition to its function as a synchronizer of the biological clock and seasonal reproduction. Melatonin and its derivatives have been shown to be powerful direct free radical scavengers. Besides direct scavenging of ROS/RNS, melatonin also stimulates antioxidant enzymes; suppresses pro-oxidant enzymes; improves mitochondrial function, hence reducing radical formation; and reduces metal-induced toxicity. Results from previous studies support these effects on several diseases including cancer, diabetes, neurodegenerative, cardiovascular, liver; and kidney diseases. Melatonin is the best candidate to serve as a complementary and perhaps regular conventional treatment for life-threatening viral diseases and further research is needed.

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