Advances in Clinical and Medical Research

Genesis-ACMR-2(2)-22
Volume 2 | Issue 2
Open Access
ISSN: 2583-2778

Role of Melatonin in Curtailing Oxidative Stress during COVID-19

Felix Polyak[1*], Roman Rozencwaig[2], Anna Veksler[2] and Eugene Paransky[3]

[1]Carrier Therapeutics Inc, Montreal QC, Canada
[2]McGill University, Montreal General Hospital, Montreal QC, Canada
[3]EMP Materials Inc, Montreal QC, Canada

***Corresponding author:** Felix Polyak, Carrier Therapeutics Inc, Montreal QC, Canada

Citation: Polyak F. (2021) Role of Melatonin in Curtailing Oxidative Stress during COVID-19. Adv Clin Med Res. 2(2):1-10.

Received: October 14, 2021 | **Published**: October 30, 2021

Abstract

Several studies carried out during the ongoing COVID-19 pandemic revealed that oxidation stress is a major factor in the disease development, in particular in its severe complications, such as ALI and ARDS. It has been hypothesized that the well-known natural hormone melatonin may play a significant role in countering oxidative stress and consequently easing the progression of COVID-19. The present review summarizes available information on the contribution of oxidation stress during the pathogenesis of COVID-19 and several other diseases, and the rationale of their possible treatment with melatonin. This research direction will further expand our knowledge about melatonin beyond its role as the regulator of the circadian rhythm, and towards its application as an efficient adjuvant treatment for various diseases, including COVID-19 infection.

Keywords

Oxidative stress; COVID-19; Melatonin

Introduction

The ongoing COVID-19 pandemic is rapidly approaching a 2 years mark. Despite intensive vaccination campaigns, the disease is still spreading around the world, at this time with more than 500,000 new daily positive tests, in their major part due to the highly contiguous Delta variant of SARS-CoV-2. Since the early days of the pandemic, researchers applied significant efforts in order to understand the nature of the disease, its clinical character and elaborate the pathways to efficient treatments. Although the COVID-19 disease may typically affect several organs and tissues, the respiratory tract is still the major target of SARS-CoV-2, and in many cases it evolves into the site of the most severe inflammation, resulting in ALI and ARDS cases with poor prognosis. The elucidation of the mechanism, which brings about the severe progression of the disease in the respiratory organs, revealed that oxidative stress process represents one of the major factors behind the inflammation. It is reasonable to assume that the suppression of oxidative stress and application of certain remedies, capable of reducing or even eliminating it, could form the basis of an efficient method to treat COVID-19 and its complications.

Oxidative Stress (OS) is a state of the biological system characterised by an imbalance between accumulation of free radicals (FR) in cells, organs and tissues and its ability to detoxify these reactive agents [1,2]. Free radicals are molecules carrying a highly reactive ion with an unpaired electron in the external orbit, which causes them to react vigorously with cell constituents. The most important and highly reactive group of free radicals is related to oxygen, (reactive oxygen species, ROS); followed by nitrogen (reactive nitrogen species, RNS) and sulphur (RSS). Under physiological conditions the most common ROS is the superoxide anion (O_2•−), abundantly generated by mitochondria. The most reactive one is the hydroxyl radical (OH•). The other common ROS include singlet oxygen ($^1O_2$), oxygen peroxide (H_2O_2) and ozone (O_3). In the case of RNS the common reactive species are nitric oxide (NO), peroxynitrite (ONOO-), the nitrosyl cation (NO+), the nitrosyl anion (NO-) and nitrous acid (NH_2O_2).

The introduction of free radicals into the biological systems may be induced by environmental factors such as UV and ionizing radiation, pollutants, as well as heavy metals and xenobiotics. However the majority of the ROS and RNS are endogenous species, generated in the course of various intra-cellular processes where they contribute to the normal functioning of cellular compartments, especially the mitochondria and the endoplasmic reticulum. Mitochondria in particular represent one of the crucial ROS sources in animal cells. Both ROS and RNS in the cells are involved in a multitude of oxidative processes, such as protein phosphorylation, activation of transcriptional factors, apoptosis, immunity, and cell differentiation. In particular, they play an important role in cell signalling, regulation of cytokines and they are also involved in the natural aging of the human organism. In other words, ROS and RNS generation is a normal part of healthy physiological functioning, as long as their excessive accumulation inside the cells is prevented by the action of various antioxidant pathways. When the balance is broken between oxidizing agents and antioxidant systems due to overproduction of FR or their inadequate trapping by antioxidants, then an excess of free radicals appears, creating oxidative stress conditions. These free radicals will react with, oxidize, and damage all biomolecules – first of all lipids, but also proteins, and nucleic acids, extending their harmful effect to the membranes (by lipid peroxidation) and various organelles of the cells. In particular, the highly reactive hydroxyl FR is able to oxidize rapidly anymacromolecule in its proximity, including DNA, phospholipids, and proteins.

DOI: https://doi.org/10.52793/ACMR.2021.2(2)-22

Many of the ROS and RNS are able to initiate cascades of oxidative reactions causing extensive damage not to a single, but several biomolecules in their vicinity [1-3] are able to initiate cascades of oxidative reactions causing extensive damage not to a single, but several biomolecules in their vicinity [1-3].

On the systemic level, the cell damage and disruption of the cellular functions may lead to inflammatory immune response, apoptosis, mutations and tumorigenesis. As a clinical manifestation, the oxidative stress may either trigger or contribute significantly to the progression of various pathologies such as cancer, autoimmune and neurodegenerative diseases, diabetes mellitus, cardiovascular, chronic kidney disease, metabolic disorders, atherosclerosis, and many others. The complications of various viral infections due to development of oxidative stress occupy an important place on this list. In [4] the role of free radicals during the course of a viral infection is considered in detail. It is an established fact that the biological system under viral attack generates ROS as part of its defence mechanisms, and various endogenous ROS are at play eradicating viruses that were phagocytosed by the immune cells. The ROS also take part in signal transduction between various cells mounting the defences of the immune system to the viral attack. Pulmonary alveolar macrophages usually produce relatively low amounts of ROS as intermediates in intracellular signaling. It should be emphasized that the adequate response to viral infection involves a strictly maintained homeostasis that ensures timely consumption of excessive ROS species. A shift towards ROS production that is either excessive or not counteracted adequately by antioxidant agents leads to the development of oxidative stress, which ultimately results in the damage to the cells and tissues.

In the case of infectious diseases it is important to elucidate both the common and the specific - particular to the viral species - mechanisms that are responsible for the departure from equilibrium ROS level, towards oxidative stress condition. One likely common underlying mechanism is the augmented generation of ROS as a by-product of the immune reaction of a body to the viral attack. Following this approach, the review [4] presents comprehensive analysis of sources of oxidative RS produced by various viral diseases, including COVID-19. The different pathways that may lead to emergence of oxidative stress during viral infections are presented, as proposed initially for the case of Sendai virus, and later for the rhinoviruses, human influenza virus and respiratory syncytial virus. The role of excessive production of ROS by NOX-2 oxidase in the immune cells is a likely key to OS emergence for human influenza virus. The occurrence of oxidative stress in the course of viral infections is manifested on micro level by oxidized macromolecules – lipids, proteins and DNA, and on the system level - by apoptosis, impaired immune function, followed by organ and tissue dysfunction.

Since the beginning of COVID-19 pandemic the major role of oxidative stress in the pathogenesis of the disease became gradually evident. Thus the search for efficient remedies that would tackle OS acquired particular importance. Since OS encompasses a multitude of reactive species, interactions and molecular mechanisms under its umbrella, a substance with an appropriately wide spectrum of action is desirable to counteract them. Among many candidates for this role, melatonin emerges as a substance of special interest due to its unusual combination of properties. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone. In the human body it is synthesized mainly in the pineal gland, but also produced and found in other organs and tissues, including bone marrow cells, heart, muscle, liver, stomach, intestine, and epithelial cells. Since 1965, when melatonin was isolated and identified chemically,

numerous studies have focused on its properties as a circadian rhythm regulator and as an antioxidant [5,6].

Melatonin has several distinct features that make it a unique and versatile player in a multitude of biochemical processes in the human body. The amphiphilic nature of melatonin allows it to penetrate all physiological barriers including phospholipid membranes, placenta and brain blood barrier, so that it may rapidly reach virtually any tissues, organs and cells [7]. It is safe and non-toxic even in high doses, can be synthesized in large quantities via fast and inexpensive route and it may be self-administered by patients.

The direct antioxidant power of melatonin lies in its ability to scavenge multiple free radicals. Melatonin is able to detoxify a wide spectrum of ROS and RNS including the most toxic oxidizing agents, hydroxyl radical and the peroxynitrite anion, as well as singlet oxygen, superoxide anion radical, hydrogen peroxide, nitric oxide, hypochlorous acid HClO and many others [5,8,9]. Furthermore, unlike other antioxidant molecules, melatonin does not exhaust its detoxifying ability after disabling a single free radical, but remains potent and able to handle up to 10 free radicals in the cascading reactions where its metabolites act as efficiently [5]. By acting fast to deplete the cell environment of multiple free radicals, melatonin succeeds in protecting macromolecules from oxidative damage and in some cases even to reverse it. Additionally, melatonin can bind and chelate heavy metal ions, preventing formation of the hydroxyl radicals [6,10].

Importantly, antioxidant reach of melatonin goes far beyond its direct scavenging of free radicals and reactive species in the cascading reaction chains. By the intermediary of other macromolecular actors - inside the cell or in the cell membrane (such as melatonin receptors MT1 and MT2) - melatonin also modulates antioxidative action of other intrinsic antioxidants. Those include various enzymes (glutathione peroxidase, glutathione reductase, superoxide dismutase and others) [8-12]. As well, melatonin upregulates the synthesis of highly effective antioxidant glutathione and contributes to improvement of redox potential of cells and tissues. There is more to the indirect antioxidant action of melatonin. Through its effects on multiple enzymes it modulates the quantity of ROS and RNS generated. In particular, in mitochondria it reduces the amount of superoxide anion radical; enhances ATP production and protects mitochondrial proteins and DNA from oxidative damage [13]. By scavenging free radicals and enhancing the activity of the antioxidant enzymes melatonin protects the morphological and functional aspects of the cell membrane [11-13]. Melatonin also throttles the amount of oxidative reactions by strengthening circadian rhythms [10].

The effects of melatonin in reducing OS cannot be considered completely in separation from its other powers, in particular anti-inflammatory action, as oxidative stress and inflammation processes are closely linked. Since melatonin contributes to inflammation control in tissues and the unfolding of inflammation is accompanied by emission of free radicals, this anti-inflammatory action indirectly suppresses free radical damage and therefore reduces OS [6,10]

The diverse powers that melatonin possesses to fight oxidative stress may shape its future role as antiviral supplement. As follows from the analysis of available sources in the course of a viral infection OS may be brought into play either as a part of viral pathogenesis per se, or it builds up as a by-product of bodily reaction to the viral attack. The activation of the innate immune system implies among its many actions the abundant generation of ROS, which may veer towards oxidative overload. Then the inflammatory processes, especially in the vulnerable patient with existing health pre-conditions, may tilt towards overproduction of pro-inflammatory cytokines, accompanied by emission of many more ROS. It is expected that melatonin would exert its antioxidant, anti-inflammatory and immuno-modulating powers in such cases. Indeed, studies in mice intranasally inoculated with RSV reported beneficial effects of melatonin, represented by considerably decreased levels of malondialdehyde and nitric oxide, and by boosted glutathione and superoxide dismutase activities. It was concluded that melatonin can potentially inhibit RSV-induced injury to airway structures through oxidative stress inhibition and proinflammatory cytokine production. In a similar vein, in the case of VEE viral infection it was reported that melatonin enhanced survival rate through inhibition of oxidative stress measured by decreased nitrite and lipid peroxidation products levels in the brain of affected animals [14,15].

It may be safely concluded that melatonin adjuvant treatment would be beneficial in a wide variety of viral infections due to its proven potency in reducing inflammation-promoted oxidative stress and moderating inflammatory response. There is an additional, no less worthy rationale in adding melatonin supplementation to the anti-viral medicamentation regimen: the viral attack may disrupt and possibly completely suppress endogenous melatonin production by the pineal gland and other organs. It can be argued that normal circulation of melatonin is crucial for healthy functioning of several body systems, in particular immune, respiratory and cardiovascular systems. Taking the argument further, melatonin deprivation at the early stages of viral infection may be a factor in the dysregulation of immune response and of mitochondria functionality, enhancing viral replication, leading to exaggerated inflammatory response of the body and subsequent damage to the lung tissues and other vulnerable systems [16].

Given the severity of inflammatory and other symptoms that often accompany the COVID-19 infection and the accumulated knowledge of oxidative stress role in spreading the damage caused by a viral attack, the emerging interest in the oxidative stress mechanisms specific for COVID-19 is not surprising. Recent research findings and reports indicate that OS has a major role in the pathogenesis of COVID-19, contributing to promotion of the cytokine storm and to the evolution of cellular hypoxia and coagulopathy [1,17,18]. To bring OS level assessment during COVID-19 infection into a practical plane, amenable to clinical usage, a number of promising attempts were reported to develop a measurable quantitative index, based on reliable OS markers - such as levels of glutathione, thiol, IL-6 or lipid peroxidation - and to correlate it with the severity and prognosis of the disease in the ICU/ER environment [19-21].

Interestingly, it was observed that epidemiological profiles of patient subsets with reduced melatonin production and high COVID-19 risk converge. Further, we consider the evolution of COVID-19 disease, and the possible role melatonin may play in fighting oxidative stress as it is related to COVID-19 pathogenesis at all stages of the disease - starting with the possibility to prevent or minimize the infection and finishing with mitigating its most severe symptoms and complications.

In the case of SARS-CoV-2 the viral attachment starts with virions binding their RBD domain of the spike (S) protein to the ACE2 receptors on the surface of the susceptible cells, then proceeding with viral envelope fusion to the cell membrane and viral load entering the cell. In the case of SARS-CoV-2 the affinity of the virus to the ACE2 receptor molecules is a crucial factor in successful binding and subsequent penetration into the cell. Successful binding requires appropriate conformation of the protein domains – which is highly sensitive to the redox balance of the cell, in particular its thiol-disulfide balance [1,22]. Oxidative stress facilitates disulphide formation, thus increasing SARS affinity to ACE2. Moreover, as the authors of [22] point out, concentrations of several other constituents of the chemical environment of the cell, in particular the concentrations of NADPH oxidase, glutathione and thioredoxin, are shown to affect the redox balance and therefore to influence the level of oxidative stress components.

It was demonstrated that the shift to the more reduced potential suppresses the binding of the viral S proteins to the ACE2 receptors [13]. Conversely, if the condition of oxidative stress is present locally at the level of the attacked cells, either through the viral action or due to a pre-existing condition, it will render them more susceptible to successful binding. The ability of melatonin to act as an indirect inhibitor of ACE2 receptor binding to SARS-CoV-*2* through shift in the redox balance away from high oxidation potential will reduce the number of successful penetrations and minimize the load on the immune system in the next stages. We hypothesize that it may be a crucial element to tip the scales towards eradicating the disease at the earliest stages.

Preventing at least partially viral attachment is an important but not the only argument for administration of melatonin very early in the course of disease, or even prophylactically. As documented in [23,24] the decrease in ACE2 due to viral binding leads to increased levels of angiotensin that has pro-inflammatory, oxidant properties. Furthermore, if the person under viral attack is burdened by the pre-condition of oxidative stress due to other ailments, the progression of COVID-19 may veer towards a more severe course.

The effectiveness of viral attack as measured by viral load or amount of cells successfully penetrated by SARS-CoV-2 virions, sets the stage for the evolution of oxidative stress in the next stages of the infection. The negative effect of OS in the attachment stage is two-fold: it increases the binding efficiency of SARS virions to the ACE2 receptors, and it also boosts the severity of the subsequent infection - by depressing ACE2 antioxidant function and creating a cycle of oxidative stress. It follows that the presence of antioxidants may be beneficial very early - at the viral entry stage - as it may counter both the pre-existing and evolving oxidative stress.

There is another important reason to consider prophylactic melatonin supplementation for non-infected persons, especially the vulnerable cohort of elderly and ailing. This group will likely have their endogenous melatonin production weakened, while the SARS-CoV-2 attack will suppress it even further [16]. The suppression of melatonin production by pineal gland and by macrophage mitochondria at the onset of COVID-19 deprives the immune system from its inherent immunoregulator that would normally reduce the cytokine storm and neutralize the generated free radicals, preserve cellular integrity and prevent lung damage [14,16]. Having a steady supply of melatonin before the SARS-CoV-2 attack unfolds will assist with curbing the acute forms of the disease.

While the body mounts the defence against the virus already internalized by the cells, the immune system's multi-pronged but measured reaction is crucial for limiting the damage and eradicating the threat. A healthy immune system will enact a large number of protective measures starting with the innate immune system. It includes activation of macrophages and dendritic cells and production of cytokines, and also generation of ROS to fight the pathogens undetected by immune factors. Oxidative stress dynamics at this stage are particularly volatile as the production of a large amount of ROS is an inherent part of the immune system reaction to pathogens. The danger lies in tilting the balance towards the cycle of self-sustaining OS, provoked by high viral load and a vulnerable state of the immune system. Successful suppression of oxidative stress at this stage will affect the further course of the disease. If oxidative stress was not contained on the viral attachment stage then the excessive pro-inflammatory and oxidative responses to SARS-CoV-2 attack will likely aggravate the pathology of COVID-19. In particular, a massive generation of pro-inflammatory cytokines (IL-1beta, Il-6, IL-7, TNF-alpha and others) otherwise known as cytokine storm initiates a self-sustaining cycle of oxidative stress and inflammatory reaction. A number of biochemical reaction chains contributes to this plot. The augmented ROS production - initially a healthy defence against pathogen attack - leads to activation of inflammosomes [7], which initiates the release of pro-inflammatory interleukins IL1b and IL18. Hydrogen peroxide, generated along with other ROS, triggers the expression of genes upregulating pro-inflammatory cytokines; then at the later steps it promotes the formation of toxic to mitochondria NOS of peroxynitrite and NO [25]. The phospholipid bilayers of the cell membranes are oxidized by ROS, adding to cytokine overproduction and contributing to lung injury [6,18]. In their turn, diminished oxygen saturation associated with alveolar edema, high neutrophil content [21] and inhibition of antioxidant enzymes by ROS-tilted NF-kB signal pathway [17,18,26] all contribute to further OS boost [24]. This self-sustaining interplay between cytokine storm and oxidative stress production eventually leads to multi-organ failure in the patients affected by COVID-19.

Hemolysis and coagulopathy is another common companion of the severe COVID-19 disease closely linked to OS effects. Several ROS easily oxidize phospholipids, damaging the membrane of erythrocytes [21,27]. In the process even more ROS are produced, including the superoxide radicals, H_2O_2 and ultimately, the highly destructive to DNA and proteins hydroxyl radicals. This cascade leads to cell death by apoptosis and to blood coagulation.

In our opinion, applying adjuvant melatonin treatment at the beginning of the inflammatory cycle will assist significantly in curbing the cytokine storm development and support the immune system action towards milder disease. The protective powers of melatonin against oxidative stress are particularly useful due to the variety of pathways, both direct and indirect, that it employs. Acting directly, melatonin counters oxidative stress by trapping toxic ROS [6,14,10,28]. Thus oxidation of proteins, lipid peroxidation, and DNA damage are all minimized by the removal of ROS and binding of the free metal ions, as well as by DNA repair mechanisms, particular for melatonin [13,28]. Consequently, oxidative driving force for cytokine production is diminished. Adding to multi-stage, cascading direct antioxidant power of melatonin is its indirect contribution, especially its role in upregulating anti-oxidative enzymes and downregulating pro-oxidative enzymes, and its involvement in multiple signaling paths that lead to reduced oxidative damage [6]. In summary, melatonin administration will promote a timely and controlled action of the immune system, limit the lipid peroxidation of the cell membranes and damage to the proteins and DNA, as well as maintain the balance of pro-inflammatory and anti-inflammatory

cytokines on the early stages of COVID-19 evolution. As a result, a more positive clinical path may be followed and the more severe cases and complications may be avoided.

Even if not enacted early, adjuvant melatonin treatment at the later stage, when the galloping inflammation and severe oxidative damage are already present will still be helpful due to unique combination of melatonin antioxidant powers with its anti-inflammatory and immunoregulatory functions. A number of studies report that melatonin supplementation regulates the activation of the immune system and suppresses exaggerated inflammatory response [10,7]. Melatonin modulates various aspects of the immune response, such as the production of IL-1β, IL-2, and TNF-α [6]. Acting synergistically, the anti-inflammatory, anti-oxidative, and immune-boosting properties of melatonin may help to quell the cytokine storm and limit negative effects on cardiovascular and other systems.

COVID-19 progression may lead to significant complications and collateral damage to various organs, especially in the elderly patients, or those with compromised immune systems and pre-existing health conditions. The complications most often involve the pulmonary issues, while in the particularly severe cases extensive damage to lung tissue may lead to the acute lung injury (ALI). It is noted that virus-induced diminution of pulmonary ACE2 exacerbates airway inflammation and promotes tissue fibrosis resulting in the diagnosis of acute respiratory damage syndrome (ARDS) [14].

The restorative effect of melatonin on damaged lung tissues was reviewed in [15]. The administration of melatonin led to a notable reduction in lung lesions. The lipid peroxidation of the lung surfactant is the result of production of oxygen free radicals from the activated phagocytes. Melatonin acting as direct scavenger of reactive species reduced lipid peroxidation of the pulmonary surfactant, improved the histopathological changes in the lungs and decreased cellular infiltration [6,15].

The exposure to melatonin in intubated COVID-19 patients was associated with a more positive disease outcome [28]. The authors of [7] refer to two studies in which newborns treated with melatonin as adjuvant antioxidant therapies of RDS had improved outcomes, attributed to suppression of pro-inflammatory cytokines and anti-oxidative action of melatonin.

Excessive and sustained increase in ROS generation plays a pivotal role in the initiation, progression, and clinical consequences of cardiovascular diseases [18,29]. The active pathway is likely to involve the NADPH oxidase-2 (NOX-2) which both contributes to myocardial damage and constitutes an important source of superoxide ROS. Melatonin plays an important role in the regulation of several parameters of the cardiovascular system. It is thought to have cardio-protective properties due to its direct andindirect antioxidant activity together with its significant anti-inflammatory properties. The authors [14] note that melatonin treatment significantly reduced the myocardial damage by acting to suppress inflammation. Therefore, melatonin has the potential to be used as a therapeutic agent for viral myocarditis.

Oxidative stress and inflammation developed in the course of severe COVID-19 promote renal injury by inflicting oxidative damage to macromolecular components of the kidney cells. The action of ROS results in the loss of significant functional properties, lipid peroxidation of cell membrane and decreased membrane viability. Multiple ROS interactions in the nephron increase further production of free

DOI: https://doi.org/10.52793/ACMR.2021.2(2)-22

radicals [14]. Melatonin was recently found to reduce kidney injury by counteracting oxidative stress and lower the risk of kidney failure by restoring renal mitochondrial function [30].

Conclusion

The studies reported here demonstrate that elevated level of oxidative stress is a major factor increasing the severity of COVID-19 via multiple mechanisms, on all stages of the disease. Adjunctive treatment with melatonin will reduce oxidative stress as well as related over-inflammation, limit damage to cells and minimize the risk of complications spreading to other organs and tissues. This way more satisfactory outcome, in particular a milder and shorter disease course may be attained.

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