Letter to Editor

Melatonin, cardiovascular disease and COVID-19: A potential therapeutic strategy?

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ABSTRACT

The mechanism for SARS-CoV-2 infection is the requisite binding of the virus to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) and internalization of the complex by the host cell. SARS-CoV-2 induced endothelial dysfunction and cardiovascular injury are probably initiated by increases in the phosphorylation levels of JAK2 and STAT3 and resultant reactive oxygen species (ROS) formation. These pathological alterations are speculated to be strikingly reversed by melatonin.

Key words: melatonin, cardiovascular disease, angiotensin-converting enzyme 2, COVID-19.

The majority of patients with COVID-19 exhibit severe cardiovascular damage and those with underlying cardiovascular disease appear to have an increased risk of death (1). Angiotensin-converting enzyme 2 (ACE2) has been identified as a potential receptor for SARS-CoV-2. This virus binds to ACE2 through its glycosylated outer membrane spike proteins. ACE2 is expressed in the heart and plays a major role in the cardiovascular system (2).

Recently Paniz-Mondolfi and colleagues (3) demonstrated the presence of viral particles of SARS-CoV-2 in neural endothelial cells, which may be the route of entry of SARS-CoV-2 into the central nervous system. Cardiomyocytes and coronary endothelial cells express ACE2 (2). Normally, angiotensin I is converted to angiotensin II via angiotensin converting enzyme (ACE) which is inhibited by ACE inhibitors. Angiotensin II can also be converted to angiotensin 1-7 via ACE2 which stimulates the Mas receptor promoting anti-inflammatory benefits (4). Angiotensin II activates several other signalling cascades such as the Janus Kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathways, which results in myocardial hypertrophy and increased fibrosis (4). Endothelial cells are crucial

for maintaining the physiological functions of the cardiovascular system. Increasing evidence suggests that oxidative stress in endothelial cells, as characterized by an imbalanced cellular capability to produce and eliminate reactive oxygen species (ROS), is involved in the pathophysiology of several vascular diseases, such as atherosclerosis, diabetes and hypertension (5).

Melatonin is an endogenously-produced molecule involved in the regulation of circadian rhythms, immunity, and cardiovascular function among others. Scientific evidence has identified new actions of melatonin in different cardiovascular settings: coronary artery disease, hypertension, pulmonary hypertension, vascular diseases, diabetes mellitus and lipid metabolism (6). Melatonin protects the cardiac microvasculature through the following actions: 1) maintaining the endothelial barrier function, 2) preserving endothelial permeability, 3) reducing cellular excessive oxidative stress, and 4) alleviating endothelial-dependent NO overproduction (6).

In the viral pathophysiology of COVID-19 the ACE2 mediates S protein binding which stimulates viral entry into host cells resulting in infection and viral replication (4). SARS-CoV-2 induced endothelial dysfunction is initiated by increases in the phosphorylation levels of JAK2 and STAT3, producing increased amounts of ROS promoted by the induction of enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-ox) and uncoupling of mitochondrial oxidative phosphorylation and endothelial nitric oxide synthase (7). These changes can be strikingly reversed by administration of melatonin through of two mechanisms: 1) abating the production of superoxide anion, hydrogen peroxide and peroxynitrite by inhibiting the JAK2/STAT3 signalling pathway, these leads to subunit p47phox expression of NADPH-ox and thus decrease the oxidative stress in endothelial cell. 2) in the cardiomyocyte, melatonin inhibits myocardial apoptosis by preventing Bax activation, which decreases the ability of Bcl2 to inhibit cytochrome-C release from the mitochondria into the cytoplasm and subsequent caspase-3 activation, which initiates apoptosis of cardiac cells (Figure1).

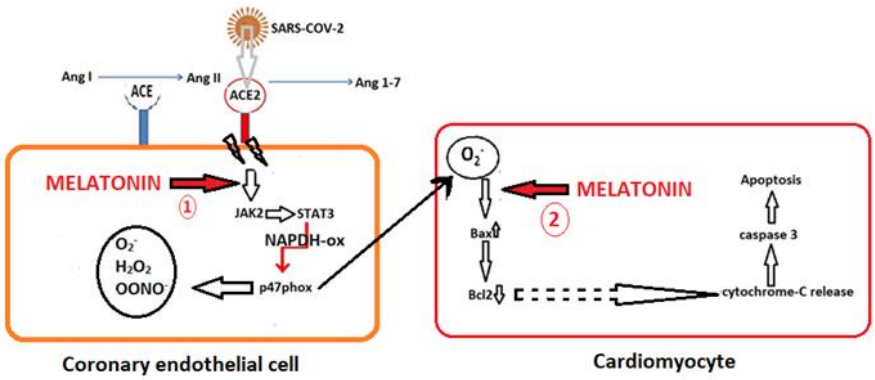

Fig 1. The potential mechanisms of melatonin on the endothelial dysfunction caused by SARS-CoV-2.

1. Melatonin reduces the production of $O_2^{\cdot-}$, H_2O_2, and OONO$^-$ by inhibiting the JAK2/STAT3 signaling pathway, which leads to subunit p47phox expression of NADPH-ox and thus to $O_2^{\cdot-}$, H_2O_2, and OONO$^-$ formation. 2. Melatonin inhibits cardiomyocyte apoptosis by preventing Bax activation, which decreases the ability of Bcl2 to inhibit cytochrome-C release from the mitochondria into the cytoplasm and subsequent caspase-3 activation, which initiates apoptosis. ACE = angiotensin-converting enzyme; ACE2 = angiotensin-converting enzyme 2; Ang I = angiotensin I; Ang II = angiotensin II; Ang 1-7 = angiotensin 1-7; Bax = BCL-2-associated X protein; Bcl2 = B-cell lymphoma-2; H_2O_2 = hydrogen peroxide; JAK = janus kinase; NADPH-ox = nicotinamide adenine dinucleotide phosphate-oxidase; O2- = superoxide; OONO- = peroxynitrite; p47phox = cytosolic protein of 47-KDa phagocyte

oxidase; SARS-COV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; STAT = signal transducer and activator of transcription.

Pineal melatonin synthesis proceeds for 24 h/day; however, majority of the pineal gland derived melatonin is produced and released into the blood at night. In an adult human, approximately 30 μg of melatonin is estimated to be synthesized per day, and the maximum concentration in the blood is reached at the mid-dark period. There is no storage of melatonin in the pineal gland after its production; it is released into the cerebrospinal fluid and into the blood and rapidly degraded in the liver. The liver hydroxylates melatonin in the C6 position under cytochrome P450 monooxygenases A2 and A1 action, which is then converted to the sulphated derivative, 6-sulfatoxymelatonin, which is removed from the body through urine. The amphiphilic nature of melatonin allows it to easily cross cellular and morphophysiological barriers (8).

During aging, the endogenous synthesis of melatonin is remarkably attenuated, producing a state characterized by an increase of inflammation, oxidative stress, and mitochondrial dysfunction (9). The older population is particularly susceptible to SARS-CoV-2 infection and to developing severe disease. The higher morbidity and mortality rates in older subjects have been associated with comorbidity, especially cardiovascular disease (1), and frailty, which weakens the immune response. Due to both the number of affected individuals and the number of countries, the current situation constitutes an ongoing pandemic and a major health emergency. In the situation of the COVID-19 pandemic we find ourselves constitutes one of the most relevant geriatric emergencies of 2020. According to the available data, it probably causes the death or disability of a significant percentage of older adults, especially those with concurrent cardiovascular disease (1). Furthermore, the fact that the drugs used to fight infection have cardiovascular side effects (for example: chloroquine) adds complexity to the treatment of these patients.

Diseases such as hypertension, diabetes, respiratory system disease, cardiovascular disease, and their susceptibility conditions may be linked to the pathogenesis of COVID-19. Chronic diseases share several standard features with infectious disorders, such as the proinflammatory state, and the attenuation of the innate immune response (10) (Figure 2). Overall, the prophylaxis with melatonin could have significant benefits as it would strengthen the appropriate immune response to any subsequent infection (11). As a prophylactic, 10 mg or somewhat more of melatonin daily may be required. Melatonin has a large safety margin without serious adverse effects. The availability and low cost of melatonin allows for its wide use. Melatonin has been used for many decades by millions of persons with no serious side effects having been reported; its high safety profile is well known, and it appears to be a good candidate to mitigate COVID-19 in this world-wide pandemic (11).

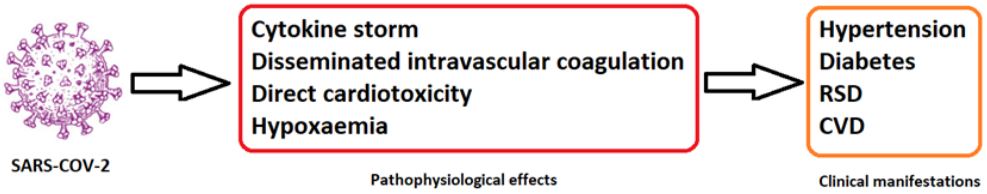

Fig. 2. Illustration of possible mechanisms of cardiovascular injury due to COVID-19.
RSD = Respiratory system disease, CVD = Cardiovascular disease.

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AUTHORSHIP

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. Alberto Dominguez-Rodriguez: Resources, writing original draft, review and editing. Pedro Abreu-Gonzalez: Writing-review and editing, Paul E. Marik: Writing-review and editing. Russel J Reiter: Conceptualization, writing-review and editing,

CONFLICT OF INTEREST

The authors have no potential conflicts of interest that might be relevant to this manuscript.

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