

Can be Protective Effect Melatonin against covid-19 Induced Gastrointestinal and Liver Damage?

Ahmet Özer Şehirli^{1*}, Tuğrul Çakır², Cebirail Akyüz³ and Serkan Sayiner⁴

¹Faculty of Dentistry, Department of Pharmacology, Near East University, Northern Cyprus

²Department of General Surgery, Antalya Training and Research Hospital, Antalya, Turkey

³Department of General Surgery, Haydarpaşa Training and Research Hospital, Istanbul, Turkey

⁴Department of Biochemistry, Faculty of Veterinary Medicine, Near East University, Northern Cyprus

*Corresponding Author: Ahmet Özer Şehirli, Associate Professor, Faculty of Dentistry, Department of Pharmacology, Near East University, Northern Cyprus.

Received: March 04, 2021

Published: March 29, 2021

© All rights are reserved by Ahmet Özer Şehirli., et al.

Abstract

Since enzymes such as transmembrane serine protease 2 (TMPRSS2) and angiotensin converting enzyme-2 (ACE2) responsible for the invasion of the SARS-CoV-2 virus, known as COVID-19, are also expressed in the gastrointestinal system and liver. The virus also infects these tissues.

Inflammatory pathways are activated by the impairment of T cell activity, especially with increasing free radicals. As a result of the activation of these pathways, cytokine expression increases and this situation causes inflammation-mediated tissue injury. Besides, it is known that the agents used during treatment cause damage to the liver and gastrointestinal system. Therefore, it is thought that melatonin, which is an antioxidant and anti-inflammatory feature released from the pineal gland, may prevent gastrointestinal system and liver damage that will occur during COVID-19 and its treatment. Also, considering that COVID-19 has a more destructive effect on people with immunodeficiency (although this rate is between 1 in 8,500 and 1 in 100,000 among symptomatic individuals), it is a strong possibility that melatonin, which has a pleiotropic immunomodulator feature, may also be beneficial on the liver and gastrointestinal tissue.

Keywords: Covid-19; Gastrointestinal Disorder; Liver Injury; Melatonin

Introduction

It is known that COVID-19, which is a serious health problem with increasing case and death rates, is widely affected the respiratory system as well as the gastrointestinal system and liver [1]. Detecting the presence of SARS-CoV-2, especially in stool samples, and the occurrence of gastrointestinal symptoms such as nausea,

vomiting, diarrhea, increase in liver enzyme levels indicate that this virus causes damage to both the gastrointestinal system and the liver [2,3]. The fact that the enzymes responsible for the invasion of SARS-CoV-2 are also synthesized in tissues such as the stomach, intestine, liver, makes us think that the virus will also invade these tissues and cause a cytokine storm in these tissues [2,3]. As a mat-

ter of fact, studies have shown that free radical levels increase with COVID-19, oxidant/antioxidant balance is disrupted and inflammatory pathways such as nuclear factor- κ B (NF- κ B), Mitogen activated protein kinase (MAP kinase), both in liver tissue and digestive system [4,5]. It has been shown that inflammatory cell death occurs with increased levels of cytokines such as tumor necrosis factor-alpha (TNF- α), interleukins (IL-6, IL-17), interferon- gamma (INF- γ) [6,7]. The fact that the virus causes more widespread damage, especially in the elderly and those with chronic diseases, emphasizes the importance of the immune system as it is in every viral infection [8,9]. Therefore, we aim to examine that melatonin, a hormone that regulates the circadian system with its known antioxidant, anti-inflammatory, and immunomodulatory properties, can suppress gastrointestinal and liver damage that will occur during COVID-19.

COVID-19 gastrointestinal and liver disorder

Gastrointestinal Symptoms such as nausea, vomiting and diarrhea are seen at a very high rate during COVID-19 [2]. It has also been shown that the ACE2 enzyme, which is responsible for the invasion of the virus, is expressed in the esophagus, epithelial cells, enterocytes in the ileum and colon, and the enzymes TMPRSS2 and TMPRSS4 in small intestinal enterocytes [10]. Especially, the demonstration of the presence of SARS-CoV-2 nucleic acids in the stools of COVID-19 patients is considered an indicator of fecal-oral transmission [2]. In addition, elevated liver enzymes have been found in COVID-19 patients with gastrointestinal damage. Increasing cytokine expression together with free oxygen radicals play an important role in affecting both tissues [11]. It has been shown that especially with the impairment of T cell activation, CD4 + and CD8 + levels decrease, and cytokine levels increase with the activation of inflammatory pathways [12]. It has also been proven in pathological findings that the excessive increase in cytokine expression in the body during viral infections causes structural damage in tissues [11]. Examinations of the tissues of COVID-19 patients showed the presence of pyroptotic cells with intense neutrophil infiltration [13]. It is known that damage to the liver and stomach is caused not only by the disease but also by the medications used during treatment [14]. It is obvious that antiviral drugs such as lopinavir/ritonavir and oseltamivir affect the liver tissue and the gastrointestinal system [14,15]. Therefore, it is thought that the administration of an immunomodulator medications, with known antioxidant/anti-inflammatory properties in addition to the treatment performed during the treatment of COVID-19, may prevent as the further damage on the liver and gastrointestinal tissues.

COVID-19 and melatonin

Melatonin does not have a direct effect on viruses. However it has an indirect effect because it is a pleiotropic immunomodulator [16]. Until now, studies on COVID-19 and melatonin have claimed that melatonin can prevent virus invasion by reducing CD147 levels, regulating T cell activation, correcting the decrease in CD4+ and CD8+ levels, inhibiting NLRP3 inflammation, Toll-like receptor4 activations and inhibiting cytokine expression and preventing pyroptosis [16,17]. It has been claimed that especially the elderly and those with chronic illnesses are affected by COVID-19 because of the low melatonin secretion in both pineal and all tissues [18,19].

Gastrointestinal and liver disorder melatonin

It has been shown that melatonin, which is the most important regulator of circadian rhythm, is also released from extrapineal organs such as the gastrointestinal system and liver, as well as the pineal gland [20]. In the examinations, melatonin secreted from the gastrointestinal system was found in a higher concentration compared to the pineal gland and plasma [21]. The low level of melatonin in the urine of pinealectomized rats confirms that melatonin is also secreted in other tissues. The protective effect of melatonin secreted from regions such as the liver and gastrointestinal system against reactive oxygen and nitrogen species is important in terms of protecting the tissues where it is released from inflammation [20,21].

Melatonin is secreted in the gastrointestinal system, especially in tissues such as the stomach, ileum, jejunum, and colon. This secretion occurs independently of the light-dark cycle. It has been shown that exogenously administered melatonin increases the level of gastrointestinal melatonin. It is known that melatonin is also secreted in the liver and it is found in high levels in hepatocytes. Therefore, it is very important in terms of providing oxidant/antioxidant balance with the local effect secreted both from the gastrointestinal system and liver tissue and preventing inflammatory pathways [21].

Conclusion

In conclusion, the expression of ACE and TMPRSS enzymes responsible for COVID-19 invasion in gastrointestinal and liver tissues suggests that these tissues may also be affected by the virus. As a matter of fact, epidemiological findings show that these tissues are affected by SARS-Cov-2. Especially, impairment of T cell activation and increased cytokine expression plays an important

role in the pathogenesis of tissue damage. Additionally, the harmful effects of drugs used during treatment on the liver and gastrointestinal system are known. Therefore, these tissues are more affected both during the disease and during the treatment. Therefore, it is thought that the use of melatonin, which is an antioxidant, pleiotropic immunomodulator with known anti-inflammatory properties, will play an active role in preventing the cytokine storm that occurs during the disease and suppressing the negative effects, thus preventing the gastrointestinal and liver damage that may be caused by COVID-19.

Bibliography

- Mao R., et al. "Implications of COVID-19 for patients with pre-existing digestive diseases". *The Lancet Gastroenterology and Hepatology* 5 (2020): 425-427.
- Zhong P., et al. "COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms". *Signal Transduction and Targeted Therapy* 5 (2020): 256.
- Smyk W., et al. "COVID-19: Focus on the lungs but do not forget the gastrointestinal tract". *European Journal of Clinical Investigation* 50 (2020): e13276.
- Gilroy DW., et al. "Treating exuberant, non-resolving inflammation in the lung; Implications for acute respiratory distress syndrome and COVID-19". *Pharmacology and Therapeutics* (2020): 107745.
- Hadjadj J., et al. "Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients". *Science* 369.6504 (2020): 718-724.
- Jamilloux Y., et al. "Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions". *Autoimmunity Reviews* 19.7 (2020): 102567.
- Pedersen SF and Ho YC. "SARS-CoV-2: a storm is raging". *Journal of Clinical Investigation* 130.5 (2020): 2202-2205.
- Butler MJ and Barrientos RM. "The impact of nutrition on COVID-19 susceptibility and long-term consequences". *Brain, Behavior, and Immunity* 87 (2020): 53-54.
- Meftahi GH., et al. "The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflamm-aging". *Inflammation Research* 69 (2020): 825-839.
- Zang R., et al. "TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes". *Science Immunology* 5 (2020): eabc3582.
- Fan T., et al. "Application of Chinese Medicine in the Management of Critical Conditions: A Review on Sepsis". *The American Journal of Chinese Medicine* 48 (2020): 1315-1330.
- Klenerman P and Oxenius A. "T cell responses to cytomegalovirus". *Nature Reviews Immunology* 16 (2016): 367-377.
- Yap JKY., et al. "Inflammasomes and Pyroptosis as Therapeutic Targets for COVID-19". *The Journal of Immunology* 205 (2020): 307-312.
- Jothimani D., et al. "COVID-19 and the liver". *Journal of Hepatology* 73 (2020): 1231-1240.
- Pilkington V., et al. "A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic?" *Journal of Virus Eradication* 6 (2020): 45-51.
- Zhang R., et al. "COVID-19: melatonin as a potential adjuvant treatment". *Life Sciences* 250 (2020): 117583.
- Liu Z., et al. "Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-kappaB/GSDMD signal in mice adipose tissue". *Journal of Pineal Research* 63.1 (2017).
- Shneider A., et al. "Can melatonin reduce the severity of COVID-19 pandemic? *International Reviews of Immunology* 39.4 (2020): 153-162.
- Sehirli AO., et al. "Role of melatonin in the treatment of COVID-19; as an adjuvant through cluster differentiation 147 (CD147)". *Molecular Biology Reports* 47 (2020): 8229-8233.
- Acuña-Castroviejo D., et al. "Extrapineal melatonin: sources, regulation, and potential functions". *Cellular and Molecular Life Sciences* 71 (2014): 2997-3025.
- Popović B., et al. "The influence of ageing on the extrapineal melatonin synthetic pathway". *Experimental Gerontology* 110 (2018): 151-157.

Assets from publication with us

- Prompt Acknowledgement after receiving the article
- Thorough Double blinded peer review
- Rapid Publication
- Issue of Publication Certificate
- High visibility of your Published work

Website: www.actascientific.com/

Submit Article: www.actascientific.com/submission.php

Email us: editor@actascientific.com

Contact us: +91 9182824667