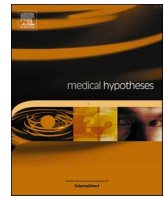




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Daylight is critical to preserve 5-methoxytryptophol levels in suspected and confirmed COVID-19 patients

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ABSTRACT

Declared as a pandemic by the World Health Organization, COVID-19 causes damage to tissues with the cytokine storm. It even causes death in people who are fond of it. In this case, the role of the immune system is vital. In particular, the cycle of melatonin and 5-methoxytryptophol released from the pineal hormone ensures that immunity continues for 24 h. While 5-MTX is active in sunlight, melatonin secretion increases in the dark at night. 5-MTX, like melatonin, has shown antioxidant and immunomodulatory properties in studies. Therefore, people who are sick and those who are not must strictly comply with the 24-h circadian rhythm during this period. We think that it is crucial in terms of being protected from the disease that we should carry out our activities according to the circadian rhythm.

Background

5-Methoxytryptophol (5-MTX), an indolamine, is a hormone synthesized from the pineal gland. 5-MTX is activated by radiative stimuli such as the sun that is active in many species such as amphibians, reptiles, fish, birds and mammals. This indolamine synthesized from serotonin and melatonin has been reported to have a 24-h circulation pattern with melatonin and the same physiological effects as melatonin [1]. However, unlike melatonin, 5-MTX is released during daytime hours, and the blood levels are inversely proportional to melatonin levels [2].

Hypothesis

In studies conducted on circadian and seasonal rhythms from various types, it was found that the levels of 5-MTX are high in the day time and low in the night. Besides, the production of 5-MTX in summer is higher at night than in winter due to the photoperiod in summer [3]. Considering the physiological effects of 5-MTX, we hypothesized that the 5-MTX could be a possible treatment agent against COVID-19 through its antioxidant and immunomodulatory mechanisms [4,5].

5-Methoxytryptophol (5-MTX)

It has antioxidant and immunomodulatory properties such as 5-methoxytryptophol, melatonin. Studies have shown that 5-MTX increases the levels of antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT). Thus, it prevents lipid and protein oxidation [6]. In the study conducted by Savtekin et al., It was revealed that 5-MTX both prevented synovial inflammation and suppressed the development of temporomandibular arthritis, similar to melatonin. In these studies, it has been shown that 5-MTX inhibits the activation of matrix metalloproteinases 2 and 8, TNF- α and IL-1 β and Rapidly Accelerated Fibrosarcoma 1 (RAF-1), Signal Transducer and Activator of Transcription 3 (STAT-3) and Cyclooxygenase-2 (COX-2) [4,5]. Lissoni et al. [7] suggests that 5-MTX and melatonin should be used together to be protected for 24 h since the secretion of 5-MTX in the daytime and the secretion of melatonin at night increase. In particular, it is found that 5-MTX increased anti-inflammatory cytokine IL-2 levels in serum and decreased proinflammatory cytokine IL-6 levels [8]. Besides, 5-MTX has been shown to affect human gingival fibroblasts and accelerate wound healing in periodontal diseases or dental implantology by increasing the levels of collagen III a1 (COL3A1), decorin (DCN) tissue inhibitor of metalloproteinases 1 (TIMP1) and IL-10, decreasing the expression of pro-fibrotic markers. The potential use of this agent,

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especially in the treatment of periodontal diseases, is considered because it increases collagen synthesis, provides scar-free tissue healing, decreases ROS level, stimulate the immune response, has antibacterial activity and slows alveolar bone loss [9].

5-MTX also has hypothermic and hypotensive effects. In a study conducted on rats, it was suggested that it has an anxiolytic effect by modulating the stress response. This effect is likely to be since it increases GABAergic activity like melatonin, decreases metabotropic glutamatergic activity, and modulates the opioidergic system. Together with melatonin, it is involved in the regulation of the sleep cycle [5].

COVID-19

An effective treatment has not yet been found to prevent and cure (COVID-19) caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), which is the current pandemic. Its rapid spread makes it difficult to prevent and control. The virus binds to angiotensin-converting enzyme 2 (ACE2) receptor, a membrane protein, invading the host cell and viral replication starts [10]. ACE2 is expressed in many organs such as the lung, heart and liver [11]. Therefore, many organs are the target of the virus.

In response to the virus invasion, the immune system steps in and initiates a counter attack [12]. However, this counterattack results in failure and ultimately causes a hyperinflammatory response. This situation determines the course of the disease [13]. According to published studies that SARS-CoV infection played a role in the inflammation caused by tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) by affecting proteins on T cells [14]. Besides, COX-2, Janus kinase (JAK)/signal transducer of activators of transcription (STAT), is activated by the STAT-3 protein in which the JAK/STAT pathway is activated [14]. In recent studies, SARS-CoV2 infection increases the expression levels of multiple proinflammatory cytokines, including TNF- α , MCP1, and IL-6, in serum, suggesting that cytokine storm may play a role in the progression of COVID-19 [15]. These cytokines synthesized from proinflammatory cells play a critical role in the physiopathology of the disease and worsen the prognosis [16].

Another effect of COVID-19 infection is that it causes mitochondrial dysfunction and thus triggers the formation of reactive oxygen species (ROS), thus causing oxidative stress [17]. At this point, it is thought that the hyperinflammatory response developed due to viral invasion is the most important factor causing mitochondrial damage [18]. It is thought that this situation may play a role in triggering multiple organ failure [19]. They play a role in the mitochondrial ROS modulation of TNF- α and IL-6. In addition, cytokine expression is also induced depending on ROS [20]. As a result, disruption of mitochondrial energy pathways and damage prevents the survival of cells [21]. Therefore, it is suggested that it will be useful in attempts to reduce oxidative stress with antioxidant support. [22].

Conclusion

Accompanied by all these findings, it is understood that 5-MTX, which is released in light with the dark hormone melatonin, plays a protective role on the body with its antioxidant and immunomodulatory effect for 24 h. Although studies are emphasizing that melatonin can be effective on COVID-19 [23], 5-MTX has no studies on COVID-19. In light of current bibliography, maintaining a balanced light-dark cycle of the patient, thus keep 5-MTX levels normal during COVID-19 is likely to accelerate the recovery of the patient by preventing the cytokine storm. Besides, there is not any drug having 5-MTX as an active matter. We suggest that to carry out studies for the development of a formulation with 5-MTX may be promising for regulating the circadian rhythm and improving the immune system.

Author contribution statement

All authors have equally contributed to the study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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