Received: 4 January 2022 | Revised: 25 February 2022 | Accepted: 26 February 2022

DOI: 10.1111/1440-1681.13639

CEPP Clinical and Experimental Pharmacology and Physiology WILEY

LETTER TO THE EDITOR

Melatonin increased hypoxia-inducible factor (HIF) by inhibiting prolyl hydroxylase: A hypothesis for treating anaemia, ischaemia, and covid-19

HYPOXIA-INDUCIBLE FACTOR AND ITS BIOLOGICAL EFFECTS

Hypoxia-Inducible Factor (HIF) is a transcriptional factor that acts as an oxygen sensor in the cell and is secreted in the absence of oxygen, leading to improvement of the cell's ability to resist hypoxia.[1,2] Interestingly, Gregg L. Semenza won the 2019 Nobel prize in physiology for discovering this vital cell factor as the main agent of cell sensing and adapting to oxygen availability.[3] HIF consists of two main parts, HIF-α subunit (functional part) and HIF-β subunit (structural part), which are constantly transcribed by the nucleus, if the conditions in the cytoplasm are suitable, HIF-α and β form HIF. HIF enters the nucleus from the cytoplasm and could trigger a cascade of cellular reactions by activating various genes. Regarding these activities, erythropoietin secretion is improved and subsequently increases the number of erythrocytes. Also, HIF helps to improve the metabolism of iron in the direction of haematopoiesis by increasing the secretion of transferrin, furin and decreasing the secretion of hepcidin. These processes have the potential to be effective in treating anaemia.[4] Furthermore, HIF helps treat ischaemia through multiple pathways, including increasing the secretion of angiogenic growth factors, enhancing resistance to reactive oxygen species (ROS) in hypoxic conditions, reducing the size of infarcts, and improving vascular function. HIF reduces inflammation by activating Th17 cells and anti-inflammatory agents.[1] Recent studies have shown that HIF may ease the management of COVID-19 patients by reducing angiotensin-converting enzyme 2 (ACE2) receptors (reducing the chance of infection), decreasing the rate of tissue inflammation, and increasing the body's resistance against the virus.[5]

THE ROLE OF PROLYL HYDROXYLASE ON HYPOXIA-INDUCIBLE FACTOR SECRETION

Although HIF-α and HIF-β are regularly produced in the cytoplasm, under normal conditions, HIF is not formed in the cell because HIF-α is constantly hydroxylated in the presence of O_2 (substrate), α-ketoglutarate (substrate), Fe^{2+} (cofactor), and Vit C (cofactor) by an enzyme called prolyl hydroxylase (PH) and removed from the cell. The PH is inhibited in the absence of oxygen (oxygen partial pressure less than 5%) by an ROS-dependent pathway, and HIF is formed in the cell. Therefore, if a compound suppresses the PH in normal and non-critical conditions, the HIF cellular level enhances and consequently exerts mentioned positive effects. Roxadustat, vadadustat, and molidustat are synthetic PH inhibitors that have been synthesised for this purpose.[6]

WHY MAY MELATONIN BE A PROLYL HYDROXYLASE INHIBITOR?

Melatonin is a neurohormone that is often secreted in the nervous system by the pineal gland. Melatonin is effective in treating anaemia,[7] ischaemia and heart disease,[8] and covid-19.[9,10] Melatonin may exert these effects by inhibiting PH and increasing HIF. HIF increases angiogenesis in target tissues through mediating various factors such as vascular endothelial growth factor (VEGF). Studies have shown that the presence of melatonin in embryo cells,[11] retinal pigment epithelial cells,[12] and submandibular salivary glands of diabetic rats[13] has been associated with increased secretion of VEGF and VEGF receptor-1 (VEGFR-1) levels in target tissues. Moreover, melatonin inhibits oxidative stress and ROS by affecting melatonin receptor 3 (MT3) and inhibiting electron transfer from quinones in various tissues. All of these mechanisms could be effectively applied in the treatment of cardiovascular diseases, especially ischaemia.[8] Melatonin efficiently heals anaemia by improving erythrocyte levels[7] due to increased erythropoietin.

The use of PH inhibitors seems to be associated with a decrease in the number of ACE2 receptors.[5] Evaluation of 11,672 patients showed that melatonin reduced the likelihood for positive COVID-19 testing. This appears to be associated with ACE2 receptor uptake or receptor depletion due to hormonal regulation.[14] The lower risk of infection and severity of the disease in children[15] and the higher resistance of bats to viral diseases (especially for COVID-19 infection), which had a higher melatonin level in the body, could confirm this hypothesis. Melatonin potentially helps decrease tissue inflammation by reducing TNF-α, IL-6, and IL-10. Indeed, PH inhibitors stabilised the DNA of lymphocytes and ultimately increased the immune system's resistance.[16] Two randomised, double-blind clinical trials showed that daily use of melatonin (3 mg/day) could significantly

reduce cough rate, dyspnoea, fatigue, C-reactive protein levels, pulmonary involvement, time of hospitalisation, time of return to baseline health,[9] and improve blood oxygen saturation.[10] Also, a meta-analysis of three randomised controlled trials confirmed that MLT consumption increases clinical recovery rate, decreases risk of intensive care unit admission, and mortality rate in covid-19 patients.[17] However, further large-scale researches are needed to decisive conclusion.

In contrast, Park et al. reported that melatonin did not affect the degradation of HIF-1α in prostate cancer cells.[18] Also, Li et al. showed that melatonin increases the expression of PH genes in atherosclerotic plaque.[19] But we know that the ROS level is elevated remarkably in cancerous and atherosclerotic cells due to the chronic and severely hypoxic conditions.[20,21] The high level of ROS in cells inhibited PH through a cascade reactions activation.[6] So, PH inhibition activity of melatonin, HIF production, and biological pathway may be affected in these conditions.

WHY MELATONIN PH INHIBITION ACTIVITY IS IMPORTANT?

Most synthetic PH inhibitors (vadadustat, molidustat, roxadustat, etc.) are in various phases of trials and have not yet been definitively approved. Also, they showed important adverse effects with considerable prevalence rate.[22–24] Nowadays, MLT is known as a safe drug for long-term consumption compared to other sedative drugs. Many clinical trials evaluated its various effects and its safety.[25] If further studies confirm the PH inhibitory activity of MLT, it could be used as an available primary safe treatment. In addition, studies may lead to discovering new pharmacophores and compounds with fewer side effects.

CONCLUSION

The available evidence for the effects of melatonin on the VEGF, ROS, ACE2, anti-inflammatory agents level and their effects on the improvement of ischaemia, anaemia, and COVID-19, which are all affected by HIF secretion, showed that melatonin may exert the mentioned effects by inhibiting the PH and increasing the HIF level (a new pharmacological mechanism for melatonin). So, more studies are needed.

ACKNOWLEDGEMENTS

None to declare.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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