Life Sciences 253 (2020) 117739

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Commentary

Comment on Melatonin as a potential adjuvant treatment for COVID-19

Emilio A. Herrera*, Alejandro González-Candia

Laboratorio de Función y Reactividad Vascular, Programa de Fisiopatología, ICBM, Facultad de Medicina, Universidad de Chile, Chile

We read the interesting proposal of Zhang et al. in the paper entitled COVID-19: Melatonin as a potential adjuvant treatment, recently published in *Life Sciences* [1] that summarizes clearly the essential pleiotropic effects of melatonin in several pathologies, regarding its antioxidant, anti-inflammatory and immunomodulatory properties.

Considering the urgency of finding an efficient treatment to the current COVID-19 pandemic, we would like to highlight the relevance of this manuscript and add more data to support the use of melatonin in respiratory diseases, particularly due to its vasoactive properties. On the last years we have studied the effects of melatonin as a treatment for the pulmonary arterial hypertension of the newborn (PAHN). Our results show the antioxidant properties of melatonin and support its pulmonary vasodilator effects. The effects of melatonin appear to be very fast since our findings describe that at the first day of oral administration (1 mg/kg), melatonin reduced in 5 mmHg the pulmonary arterial pressure in neonatal lambs born under hypoxia, without side effects such as systemic hypotension or sleepiness [2,3]. Additionally, with either 7 or 21 days of treatment, small pulmonary arteries showed improved endothelial function *ex vivo* with a greater vasodilator capacity [2,3]. The latter was associated with increased nitric oxide -dependent and -independent vasodilator functions. Interestingly, one of the nitric oxide independent affected mechanisms, was the enhanced expression of the prostacyclin vasodilator pathway [3,4]. The aforementioned findings were also associated with increased expression and/or activity of the endogenous antioxidant enzymes, superoxide dismutase and catalase, an enhanced plasma antioxidant capacity and a marked decreased in pulmonary oxidative stress markers [2,3]. Furthermore, these effects were associated with a diminished vascular remodeling of the pulmonary circulation after 1 week of treatment [5].

The vasodilatory effects of melatonin are in part a consequence of the antioxidant and anti-inflammatory effects that reverberates on an improved vascular structure and function, but as well they can be due to its direct effects as a vasodilator (Fig. 1, unpublished data). Although it gives a mild *ex vivo* vasodilation, the global *in vivo* effects of melatonin offer a better pulmonary function.

Melatonin pulmonary effects have also been tested in adult animals. For instance, Maarman et al. [6] demonstrated that melatonin improved right ventricular function and reduced cardiac remodeling in pulmonary hypertensive (PAH) rats, suggesting a pressure decrease in the pulmonary artery. In addition, melatonin has been tested in rats with chronic obstructive pulmonary disease [7], where it attenuated pulmonary hypertension by antagonizing the oxidative injury and restore nitric oxide production. Moreover, the anti-inflammatory effects of melatonin restore vascular homeostasis in PAH mice and improve endothelial integrity [8]. Finally, the direct vasodilator effects of melatonin in pulmonary arteries and vein on adult animals (sheep) have also been reported [9].

Although there are no studies that evaluate the vasoactive properties of melatonin in humans, the evidence of its beneficial effects in animals is convincing.

Based on the similarities of COVID-19 with hypoxic pulmonary hypertension and edema [10], melatonin may be a possible alternative as it may aid to promote pulmonary vascular protection. In conclusion, the proposal by Zhang et al. [1] is supported by several scientific data, and given the global medical urgency, melatonin sounds as a sensible adjuvant treatment.

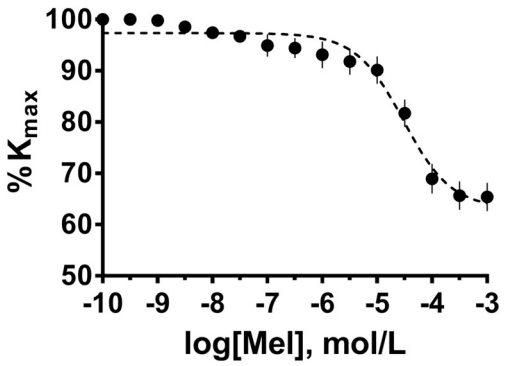

Fig. 1. Vasodilator effect of melatonin on neonatal pulmonary arteries. Cumulative concentration response to melatonin (Mel) of small pulmonary arteries from PAHN lambs (n = 29).
Values are shown as mean ± SEM.

* Corresponding author.
E-mail address: eaherrera@uchile.cl (E.A. Herrera).

https://doi.org/10.1016/j.lfs.2020.117739

Available online 30 April 2020

Acknowledgement

We would like to thank all health and research teams that are currently fighting without rest against the COVID-19 pandemic.

Funding

FONDECYT grants 1151119 & 1201283.

Declaration of competing interest

None to declare.

References

[1] R. Zhang, X. Wang, L. Ni, X. Di, B. Ma, S. Niu, C. Liu, R.J. Reiter, COVID-19: melatonin as a potential adjuvant treatment, Life Sci. 250 (2020) 117583, https://doi.org/10.1016/j.lfs.2020.117583 [Epub ahead of print]. (Review).

[2] F. Torres, A. González-Candia, C. Montt, G. Ebensperger, M. Chubretovic, M. Serón-Ferré, R.V. Reyes, A.J. Llanos, E.A. Herrera, Melatonin reduces oxidative stress and improves vascular function in pulmonary hypertensive newborn sheep, J. Pineal Res. 58 (2015) 362–373, https://doi.org/10.1111/jpi.12222.

[3] A. Gonzaléz-Candia, A.A. Candia, E.G. Figueroa, E. Feixes, C. Gonzalez-Candia, S.A. Aguilar, G. Ebensperger, R.V. Reyes, A.J. Llanos, E.A. Herrera, Melatonin long-lasting beneficial effects on pulmonary vascular reactivity and redox balance in chronic hypoxic ovine neonates, J. Pineal Res. 68 (2020) e12613, https://doi.org/10.1111/jpi.12613.

[4] S.A. Aguilar, P.V. Arias, I. Canquil, G. Ebensperger, A.J. Llanos, R.V. Reyes, A. González-Candia, E.A. Herrera, Melatonin modulates the expression of pulmonary prostanoids, Rev. Med. Chil. 147 (2019) 281–288, https://doi.org/10.4067/S0034-98872019000300281.

[5] C.R. Astorga, A. González-Candia, A.A. Candia, E.G. Figueroa, D. Cañas, G. Ebensperger, R.V. Reyes, A.J. Llanos, E.A. Herrera, Melatonin decreases pulmonary vascular remodeling and oxygen sensitivity in pulmonary hypertensive newborn lambs, Front. Physiol. 9 (2018) 185, https://doi.org/10.3389/fphys.2018.00185.

[6] G. Maarman, D. Blackhurst, F. Thienemann, L. Blauwet, G. Butrous, N. Davies, K. Sliwa, S. Lecour, Melatonin as a preventive and curative therapy against pulmonary hypertension, J. Pineal Res. 59 (2015) 343–353, https://doi.org/10.1111/jpi.12263.

[7] M.W. Hung, H.M. Yeung, C.F. Lau, A.M.S. Poon, G.L. Tipoe, M.L. Fung, Melatonin attenuates pulmonary hypertension in chronically hypoxic rats, Int. J. Mol. Sci. 18 (2017), https://doi.org/10.3390/ijms18061125 (pii: E1125).

[8] J. Zhang, X. Lu, M. Liu, H. Fan, H. Zheng, S. Zhang, N. Rahman, S. Wołczyński, A. Kretowski, X. Li, Melatonin inhibits inflammasome-associated activation of endothelium and macrophages attenuating pulmonary arterial hypertension, Cardiovasc. Res. (2019), https://doi.org/10.1093/cvr/cvz312 (Epub ahead of print, pii: cvz312).

[9] L.B. Weekley, Effects of melatonin on isolated pulmonary artery and vein: role of the vascular endothelium, Pulm. Pharmacol. 6 (1993) 149–154, https://doi.org/10.1006/pulp.1993.1019.

[10] I. Solaimanzadeh, Acetazolamide, nifedipine and phosphodiesterase inhibitors: rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19), Cureus 12 (2020) e7343, https://doi.org/10.7759/cureus.7343(Review).