

Aging and vascular dysfunction: beneficial melatonin effects

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The study of biological aging has seen spectacular progress in the last decade. Aging is characterized by a progressive deterioration of physiological functions and metabolic processes. Moreover, aging is accompanied with the development of agerelated diseases, such as cardiovascular diseases, which are the major causes of morbidity and mortality in the developed nations.

Sirtuin1 (SIRT1) is a well investigated member of the sirtuin family of protein deacetylases which has attracted attention as a potent mediator of life span extension.

Recently, melatonin, a pleiotropic molecule which functions as a highly effective antioxidant and free radical scavenger, was shown to activate SIRT1 in primary neurons of young animals, as well as in aged neurons of a murine model of senescence. Melatonin is known to modulate oxidative stress-induced senescence and pro-survival pathways.

We treated ApoE-deficient mice with two melatonin formulations (kindly provided by Nathura s.r.l, Reggio Emilia, Italy), showing different pharmacokinetic: melatonin Fast, rapid-release formulation, and Retard, extended-release formulation.

Morphological changes in vessels were evaluated using histological procedures and immunohistochemical analyses of SIRT1, p53, eNOS and ET-1 markers. We demonstrate that SIRT1 and eNOS dropped dramatically in ApoE mice and that atherogenesis induced an elevated expression of p53 and ET-1. Melatonin not only improved the impairment of endothelial damage, but also reduced the loss of SIRT1 and eNOS decreasing p53 and ET-1 expression. Also, the extended-release melatonin preparation (Retard) caused a greater improvement of aorta cytoarchitecture.

In summary, our findings implicated the SIRT1-p53-eNOS axis as one of the important process involved in endothelial senescence. Moreover, the role of SIRT1 as a driver of cellular stress resistance and longevity is noteworthy in the context of its expression profile. Finally, we suggest that extended-release melatonin provides a more appropriate option for cellular longevity compared with rapid-release melatonin administration.

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