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Protective Effects of Melatonin Against Aristolochic Acid-Induced Nephropathy in Mice

Jung-Yeon Kim¹, Kiryeong Kim², A Young Yang¹, **Jaechan Leem¹**

¹Department of Immunology, Catholic University of Daegu School of Medicine, Korea, Republic of

²Department of Physiology, Keimyung University School of Medicine, Korea, Republic of

Objectives: Melatonin, a pineal hormone, is well known to regulate the sleep-wake cycle. Besides, the hormone has been shown to display pleiotropic effects arising from its powerful anti-oxidant and anti-inflammatory activities. Recent studies have reported that melatonin exerts protective effects in animal models of kidney disease. However, the potential effects of melatonin on aristolochic acid (AA)-induced nephropathy (AAN) have not yet been investigated. In the present study, we aimed to examine the potential effects of melatonin on AAN and to explore its underlying mechanisms.

Methods: C57BL/6N mice were intraperitoneally injected with AA (5 mg/kg) for 4 days for inducing AAN. To investigate the effects of melatonin on AAN, the mice were intraperitoneally injected with melatonin (20 mg/kg) from 2 days before the first injection of AA for 16 consecutive days. The mice were sacrificed 14 days after the first injection of AA.

Results: We found that the administration of melatonin ameliorated AA-induced renal dysfunction, as evidenced by decreased plasma levels of blood urea nitrogen and creatinine and histopathological abnormalities such as tubular dilatation and cast formation. The upregulation of tubular injury markers after AA injection was reversed by melatonin. Melatonin also suppressed AA-induced oxidative stress, as evidenced by the downregulation of 4-hydroxynonenal and reduced level of malondialdehyde, and modulated expression of pro-oxidant and antioxidant enzymes. In addition, p53-dependent apoptosis of tubular epithelial cells, infiltration of macrophages and CD4⁺ T cells into damaged kidneys, and renal expression of cytokines and chemokines were inhibited by melatonin. Moreover, melatonin attenuated AA-induced tubulointerstitial fibrosis through suppression of the tumor growth factor- β /Smad signaling pathway.

Conclusions: Our data demonstrate that melatonin protects from AAN through inhibition of oxidative stress, apoptosis of tubular epithelial cells, inflammation, and fibrosis. Melatonin might be a potential therapeutic agent for AAN.