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Melatonin is a potent inhibitor for myeloperoxidase.

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Abstract

Myeloperoxidase (MPO) catalyzes the formation of potent oxidants that have been implicated in the pathogenesis of various diseases including atherosclerosis, asthma, arthritis, and cancer. Melatonin plays an important part in the regulation of various body functions including circadian sleep rhythms, blood pressure, oncogenesis, retinal function, seasonal reproduction, and immunity. Here, we demonstrate that melatonin serves as a potent inhibitor of MPO under physiological-like conditions. In the presence of chloride (Cl-), melatonin inactivated MPO at two points in the classic peroxidase cycle through binding to MPO to form an inactive complex, melatonin-MPO-Cl, and accelerating MPO compound II formation, an inactive form of MPO. Inactivation of MPO was mirrored by the direct conversion of MPO-Fe(III) to MPO compound II without any sign of compound I accumulation. This behavior indicates that melatonin binding modulates the formation of MPO intermediates and their decay rates. The Cl- presence enhanced the affinity of MPO toward melatonin, which switches the enzyme activity from peroxidation to catalase-like activity. In the absence of Cl-, melatonin served as a 1e- substrate for MPO compound I, but at higher concentration it limited the reaction by its dissociation from the corresponding complex. Importantly, melatonin-dependent inhibition of MPO occurred with a wide range of concentrations that span various physiological and supplemental ranges. Thus, the interplay between MPO and melatonin may have a broader implication in the function of several biological systems. This dual regulation by melatonin is unique and represents a new means through which melatonin can control MPO and its downstream inflammatory pathways.

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