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The Keap1-Nrf2-antioxidant response element pathway: a review of its regulation by melatonin and the proteasome.

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Abstract

Both melatonin and proteasome inhibitors upregulate antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GP), hemoxygenase 1 (HO-1), and NADPH:quinone oxidoreductase (NQO1). Recent evidence suggests that the antioxidant action of both melatonin and proteasome inhibitors involves the Keap1-ARE (Keap1 antioxidant response element) pathway via the upregulation of Nrf2. Melatonin and proteasome inhibitors suppress the degradation of Nrf2 and also enhance its nuclear translocation. In the nucleus Nrf2, together with a cofactor, stimulates the transcription of antioxidant enzymes and detoxifying enzymes. The ligase (E3) complex (Keap1-Cul3-Rbx1) responsible for ubiquitinating Nrf2, prior to proteasomal degradation, also ubiquitinates IkB kinase and the antiapoptotic factor Bcl-2, and possibly additional proteins. In various systems, NF-κB, which is inhibited by IkBα, is downregulated by proteasome inhibitors as well as by melatonin. Similarly in leukemic cells, Bcl-2 is down-regulated by the proteasome inhibitor, bortezomib, and also by melatonin. Thus melatonin administration modulates the activity of three separate substrates of the Keap1-Cul3-Rbx1 ubiquitin ligase. These facts could be accounted for by the hypothesis that melatonin interacts with the ubiquitin ligase complex or, more likely, by the hypothesis that melatonin acts as a proteasome inhibitor. A recent study documented that melatonin acts as a proteasome inhibitor in cancer cells as well as inhibiting chymotrypsin-like activity in cell-free systems of these cells. Further studies, however, are needed to clarify the interaction of melatonin and the ubiquitin-proteasome system as they relate to oxidative stress.

KEYWORDS: Bax; Bcl-2; Keap1; Melatonin; NF-κB; Proteasome

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