

# Melatonin protects the cytochrome P450 system through a novel antioxidant mechanism

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Melatonin, an endogenous hormone, is used as an antioxidant drug in doses quite higher than the endogenous circulating levels of this hormone. Hepatic endoplasmic reticulum contains the cytochrome P450 (CYP450) system, which catalyzes one biotransformation pathway of melatonin; this organelle is also one of the main sources of reactive oxygen species in cells. Therefore, we proposed that the antioxidant activity of this hormone may have a biological relevance in the organelle where it is biotransformed. To evaluate this postulate, we used Fe<sup>3+</sup>/ascorbate, an oxygen free radical generating system that leads to lipid peroxidation, loss of protein-thiol content, and activation of UDP-glucuronyltransferase in rat liver microsomes. We found that mM concentrations of melatonin prevented all these oxidative phenomena. We also found that Fe<sup>3+</sup>/ascorbate leads to structural alterations in the CYP450 monooxygenase, the enzyme that binds the substrate in the CYP450 system catalytic cycle, probably