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Melatonin protects against copper-mediated free radical damage

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Abstract: Copper is an essential trace element which forms an integral component of many enzymes. While trace amounts of copper are needed to sustain life, excess copper is extremely toxic. Copper has been implicated in various neurodegenerative disorders, such as Wilson's and Alzheimer's diseases. Previous studies showed that melatonin, the principle secretory product of the pineal gland, binds Cupric chloride (Cu^{2+}) and that this may have implications in copper-induced neurodegenerative diseases. In the present study, in vitro copper-mediated lipid peroxidation was induced. Melatonin (5 mM) protected against copper-mediated lipid peroxidation in liver homogenates. Electron micrographs of in vivo administered Cu^{2+} and melatonin show that melatonin affords some protection to rat hepatocytes in the presence of copper. Electrochemical studies performed show that melatonin, in addition to binding Cu^{2+}, may provide protection against copper-mediated free radical damage by binding Cu^{1+}. The findings of these studies provide further evidence for the neuroprotective role of melatonin.

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Introduction

Copper is involved in the neuropathology of various neurodegenerative disorders including Wilson's, Menke's, Parkinson's, Alzheimer's, amyotrophic lateral sclerosis, and Prion diseases [1, 2]. Copper overload results in many pathological conditions that are consistent with oxidative damage to membranes or molecules. Cu^{1+} is known to generate free radicals by a Fenton type reaction. Copper ions are able to catalyze the formation of hydroxyl radicals via the Haber-Weiss reaction (in vitro):

$$O_2^- \cdot + Cu^{2+} \rightarrow O_2 + Cu^{1+} \quad (1)$$

$$Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + OH^- + \cdot OH \quad (2)$$

Cupric chloride can also react with hydrogen peroxide to yield Cu^{1+} and the superoxide radical ($O_2^-\cdot$). Cu^{1+} formed can then react with hydrogen peroxide (H_2O_2) according to Equation (2), increasing the potential for free radical damage.

Lipid peroxidation in biological membranes causes impairment of membrane functioning, decreased fluidity, inactivation of membrane-bound receptors and enzymes, and an increased non-specific permeability to ions such as Ca^{2+}. Free, ligand-bound and vesicular copper is present throughout the brain. Copper is a rapidly acting neurotoxin at physiological concentrations (10–100 μM) [3]. Upon exposure to iron or copper ions, lipid hydroperoxides decompose, resulting in hydrocarbon gases, for example, ethane and pentane, radicals that can abstract further hydrogen atoms from fatty acid side chains and cytotoxic carbonyl compounds [4].

Lipid peroxidation is often a late event, accompanying rather than causing final cell death [5]. Thus, a failure to protect against tissue damage by chain-breaking antioxidant inhibitors of lipid peroxidation does not rule out free radical damage as an injury mechanism [6].

Transition metals promote lipid peroxidation in two ways (1): by catalyzing the formation of oxygen free radical species capable of initiating lipid peroxidation and (2) by catalyzing the decomposition of preformed lipid peroxides to propagate lipid peroxidation [7]. Elevated copper levels induce a variety of changes in tissues. In the liver, copper overload results in hypertrophy of hepatocytes, hepatitis, hepatocellular necrosis and eventually hepatocellular death [8].

Melatonin, the principle secretory product of the pineal gland is a potent free radical scavenger and general antioxidant [9]. It efficiently scavenges the hydroxyl radical (·OH) [10] and possibly the peroxyl radical (LOO·) [11]. Utilizing adsorptive cathodic stripping voltammetry, an electrochemical method which has been used with success to examine metal–ligand complex formation at an electrode, Limson et al. reported that melatonin binds heavy metals including Fe^{3+}, Cu^{2+}, Pb^{2+}, Cd^{2+} and Zn^{2+} [12]. This implies that melatonin, besides acting as an antioxidant, may bind these metals and prevent them from partaking in free radical generation.

In vivo studies have shown that melatonin offers neuroprotection against mercury [Hg(II)] toxicity in rats [13].