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PINEAL HORMONE MELATONIN HELPS IN REDUCING OXIDATIVE STRESS: FINDING THE MECHANISTIC PATHWAY

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Statement of the Problem: Improper control on reactive oxygen species (ROS) elimination process and formation of free radicals causes tissue dysfunction. Pineal hormone melatonin is considered a potent regulator of such oxidative damage in different vertebrates. This study evaluates the levels of oxidative stress and ROS induced damage, and amelioration of oxidative status through melatonin induced activation of signaling pathways.

Methodology & Theoretical Orientation: Hepatocytes were isolated from adult Labeo rohita and exposed to H2O2 at three different doses (12.5, 25 and 50 μM) to observe peroxide induced damage in fish hepatocytes. Melatonin (25, 50 and 100 μg/ml) was administered against the highest dose of H2O2. Enzymatic and non-enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) and glutathione (GSH) was measured spectrophotometrically. Expression level of heat shock proteins (HSP70 and HSP90), HSPs-associated signaling molecules (Akt, ERK, cytosolic and nuclear NFkB), and melatonin receptor was also measured by western blotting analysis.

Findings: H2O2 induced oxidative stress significantly altered ($P<0.05$) MDA and GSH level, SOD and CAT activity, and up regulated HSP70 and HSP90 expression in carp hepatocytes. Signaling proteins exhibited differential modulation of their expression patterns in H2O2-exposed fish hepatocytes, in comparison with control hepatocytes. Melatonin treatment of H2O2-stressed fish hepatocytes restored basal cellular oxidative status in a dose dependent manner. Melatonin induced signaling process by modulation of signaling molecules and melatonin receptor.

Conclusion & Significance: The results suggest that exogenous melatonin at the concentration of 100 μg/ml is required to improve oxidative status of the H2O2-stressed fish hepatocytes. In H2O2 exposed hepatocytes, melatonin modulates expression of HSP70 and HSP90 that enable the hepatocytes to become stress tolerant and survive by altering the actions of ERK, Akt, cytosolic and nuclear NFkB in the signal transduction pathways. Study also confirms that melatonin could act through melatonin receptor coupled to ERK/Akt signaling pathways. This understanding of the mechanism by which melatonin regulates oxidative status in the stressed hepatocytes may initiate the development of novel strategies for hepatic disease therapy in future.