Protective effect of melatonin on rotenone plus Ca^{2+}-induced mitochondrial oxidative stress and PC12 cell death

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Chronic systemic inhibition of mitochondrial respiratory chain complex I by rotenone causes nigrostriatal dopaminergic degeneration in rats, producing an in vivo experimental model of Parkinson \prime s disease (Betarbet *et al.*, *Nat. Neurosci.* **3**: 1301-1306, 2000). We recently showed that micromolar Ca^{2+} concentrations strongly stimulate the release of reactive oxygen species in rotenone-treated isolated rat brain mitochondria (Sousa *et al.*, *FEBS Lett*. **543**: 179-183, 2003). In the present work, we show that the natural antioxidant melatonin inhibits Ca^{2+} plus rotenone-induced oxidative stress in isolated rat brain mitochondria. In addition, the Ca^{2+} ionophore A23187 strongly potentiates rotenone-induced death of intact cultured pheochromocytoma (PC12) cells, in a mechanism sensitive to melatonin. Moreover, melatonin inhibits the detection of reactive oxygen species release in PC12 cells treated with rotenone plus A23187. Melatonin does not alter free Ca^{2+} concentrations or the inhibitory effect of rotenone on mitochondrial complex I. We conclude that micromolar Ca^{2+} concentrations stimulate neuronal cell death induced by mitochondrial complex I inhibition in a mechanism involving oxidative stress, preventable by the antioxidant melatonin.

Supported by FAPESP, FAEP/UNICAMP and CNPq.