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OXIDATIVE DNA DAMAGE AND APOPTOSIS INDUCED BY TETRAHYDROPAPAVEROLINE IN PC12 CELLS

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Tetrahydropapaveroline (THP), a dopamine-derived 6,7-dihydroxy-1-(3',4'-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline, has been suspected as a possible dopaminergic neurotoxin to elicit Parkinsonism. Autooxidation or enzymatic oxidation of THP and subsequent generation of reactive oxygen species (ROS) may contribute to the degeneration of dopaminergic neurons induced by this isoquinoline alkaloid. In the present study, we have found that THP undergoes redox cycling in the presence of Cu(II) to produce ROS capable of causing DNA strand scission. THP plus Cu(II)-induced DNA damage was protected by bathocuproine disulfonic acid (copper chelator), catalase and certain antioxidants. Reaction of THP with calf thymus DNA in the presence of Cu(II) caused formation of 8-hydroxydeoxyguanosine. THP exerted cytotoxicity in cultured rat pheochromocytoma (PC12) cells. Reduced glutathione and *N*-acetyl-L-cysteine attenuated cytotoxicity induced by THP. PC12 cells treated with THP exhibited increased intracellular ROS accumulation, and underwent apoptotic death as determined by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL). THP caused activation of JNK, ERK1/2 and p38 MAP kinases. THP treatment transiently increased the level of phosphorylated Akt and activated the transcription factor NF-κB, followed by induction of inducible nitric oxide synthase (iNOS). Pretreatment of PC12 cells with the iNOS inhibitor N^G-nitro-arginine methylester (NAME) ameliorated the THP-induced cytotoxicity. Taken together, the above findings suggest that THP-induced cell death is associated with reactive oxygen-and/or nitrogen species-mediated apoptosis.