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# COPPER ENHANCEMENT OF L-DOPA-INDUCED OXIDATIVE DNA DAMAGE AND CELL DEATH VIA REDOX CYCLING

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Dopamine, a principal neurotransmitter in the central nervous system, accounts for 90% of total catecholamines. It serves as a precursor of certain hormones, melanins, noradrenalin and adrenalin. Parkinsonian disease (PD) is characterized by selective loss of dopaminergic neurons in the substantia nigra pars compacta and a significant diminution in the neostriatal content of dopamine and its metabolites. L-3,4-Dihydroxyphenylalanine (L-DOPA), which is converted to dopamine in the brain, has been widely used for dopamine replenishment in the surviving neurons. Although L-DOPA can alleviate many symptoms of PD, the therapy paradoxically has adverse effects towards dopaminergic neurons. In the present study, we have found that L-DOPA undergoes redox cycling to produce reactive oxygen species (ROS) capable of DNA oxidation (8-OHdG formation), which was accelerated in the presence of Cu(II). PC12 cells treated with L-DOPA and Cu(II) exhibited increased intracellular ROS accumulation and cytotoxicity compared to those cells exposed to DOPA or Cu(II) alone. Pretreatment of PC12 cells with buthionine sulfoximine, an inhibitor of gamma-glutarmyl transpeptidase which functions in the biosynthesis of cellular glutathione (GSH), markedly reduced the cell proliferation. Blockade of the hydroxy functional group of L-DOPA abolished its capability to cause oxidative cell death and intracellular ROS formation. Taken together, the above findings suggest that L-DOPA treatment may cause adverse effects through enhanced gerneration of ROS, particularly in the presence of Cu(II).