Iron Binding and Oxidation Studies of Iron Neuromelanin Model Complexes

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Neuromelanin (NM) is a dark brown pigment that accumulates in dopaminergic neurons during normal aging, and in Parkinson's disease (PD), neurons with this pigment selectively degenerate. Although the structure, biosynthesis and physiological function of NM have yet to be clarified, the augmented iron load in NM of PD brains suggests that iron-NM interactions may be involved in the pathogenesis of PD. In this study, we present the iron binding and oxidation properties of NM precursor molecules 5,6-dihydroxy-*N*-methyl-indole (Me-DHI), 5,6-dihydroxyindole-1-carboxylic acid (DHICA) and dopamine. Deprotonation constants for model NM units were determined by anaerobic potentiometric and spectrophotometric titrations. Anaerobic pH dependent spectrophotometric titrations indicated that the speciation of Fe(III)-Me-DHI, Fe(III)-DHICA and Fe(III)-dopamine complexes can be controlled by pH. Equilibrium constants for the proton dependent Fe(III)-Me-DHI, Fe(III)-DHICA and Fe(III)-dopamine systems were determined. Me-DHI and DHICA were found to be stronger iron chelators than dopamine at physiologically relevant pH. Oxidation studies suggest that these Fe(III)-NM model complexes undergo oxidation via a substrate activation mechanism.