Heme in Cystathionine β-Synthase: A Role in Electron Transfer?

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Human cystathionine β-synthase (CBS) is a unique heme-containing enzyme which catalyzes a pyridoxal-5'-phosphate-dependent β-replacement reaction. Heme is an evolutionarily new requirement for maximal activity in this enzyme, yet has no discernible role in enzyme catalysis. Recent work in our lab uncovered an interesting pH-dependent mechanism for reoxidation of the ferrous iron in CBS. The pH controls the equilibrium amount of ferric and ferrous heme present after reaction of CBS with one-electron reducing agents. A variety of spectroscopic techniques demonstrated that Fe(II) CBS is dominant at pH 9 while Fe(III) CBS is favored at pH 6 when the protein is reduced at room temperature. At low pH, Fe(II) CBS forms transiently but reoxidizes by a proposed proton-gated electron-transfer mechanism. At physiological temperature and pH, however, an apparent ligand switch competes with the aforementioned electron transfer under reducing conditions; the ligand switch dominates at high pH.

Ongoing work is aimed at a detailed qualitative and quantitative chemical and spectroscopic investigation of the electron transfer phenomenon in CBS. Neither addition of S-adenosyl methionine, an allosteric effector, nor the substrate serine affected the rate of intramolecular electron transfer. Chemical alteration and removal of pyridoxal-5'-phosphate, which has been implicated as an electron acceptor in other systems, facilitated the ligand switch process at high pH but did not influence the electron transfer process. The identity of the electron acceptor and the effect of the reoxidation and ligand-switching behavior on the heme reduction potential remain avenues of active research.