The amyloid precursor protein (APP) does not have a ferroxidase site in its E2 domain.

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Abstract

The ubiquitous 24-meric iron-storage protein ferritin and multicopper oxidases such as ceruloplasmin or hephaestin catalyze oxidation of Fe(II) to Fe(III), using molecular oxygen as oxidant. The ferroxidase activity of these proteins is essential for cellular iron homeostasis. It has been reported that the amyloid precursor protein (APP) also has ferroxidase activity. The activity is assigned to a ferroxidase site in the E2 domain of APP. A synthetic 22-residue peptide that carries the putative ferroxidase site of E2 domain (FD1 peptide) has been claimed to encompass the same activity. We previously tested the ferroxidase activity of the synthetic FD1 peptide but we did not observe any activity above the background oxidation of Fe(II) by molecular oxygen. Here we used isothermal titration calorimetry to study Zn(II) and Fe(II) binding to the natural E2 domain of APP, and we employed the transferrin assay and oxygen consumption measurements to test the ferroxidase activity of the E2 domain. We found that this domain neither in the presence nor in the absence of the E1 domain binds Fe(II) and it is not able to catalyze the oxidation of Fe(II). Binding of Cu(II) to the E2 domain did not induce ferroxidase activity contrary to the presence of redox

active Cu(II) centers in ceruloplasmin or hephaestin. Thus, we conclude that E2 or E1 domains of APP do not have ferroxidase activity and that the potential involvement of APP as a ferroxidase in the pathology of Alzheimer's disease must be re-evaluated.

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Details

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