Abstract Submitted
for the MAR09 Meeting of
The American Physical Society

ESR Spectroscopy Provides Direct Evidence of Cu^{2+} Coordination by Three Histidine Residues in Aβ_{1-16}[1] BYONG-KYU SHIN, SUNIL SAXENA, University of Pittsburgh — We provide direct evidence that all three histidine residues in amyloid-β_{1-16} (Aβ_{1-16}) coordinate to Cu^{2+}. In our approach, we generate three Aβ_{1-16} analogues, in each of which a selected histidine residue is isotopically enriched with ^{15}N. Pulsed electron spin resonance (ESR) experiments such as electron spin echo envelope modulation (ESEEM) and hyperfine sublevel correlation (HYSCORE) clearly show that each of the three histidine imidazole rings at position 6, 13, and 14 in Aβ_{1-16} binds to Cu^{2+} as each of the three Cu^{2+}–^{15}N-labeled Aβ_{1-16}complexes displays ESEEM and HYSCORE spectra which are distinctively different from those of the Cu^{2+}–nonlabeled Aβ_{1-16} complex. The method employed here does not require either chemical side-chain modification or amino acid residue replacement, each of which is traditionally used to determine whether an amino acid residue in a protein binds to a metal ion. We also find that the histidine coordination in Aβ_{1-16} is independent of the Cu^{2+}-to-peptide ratio, which is in contrast to the case of Aβ_{1-40}. The ESR results suggest tight binding between the histidine residues and the Cu^{2+} ion, which is likely the reason of the high binding affinity of Aβ peptide to Cu^{2+}.

[1]This work was supported by an NSF CAREER grant (MCB 0346898).

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Date submitted: 20 Nov 2008 Electronic form version 1.4