BioXAS Investigations on Cu and Zn in β-amyloid Aggregates


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Metalloproteins are most often related to important, biological redox processes. Due to strong scattering from metal centers combined with limited data resolution, the metal coordination is often poorly determined. In addition, the metal centers are subject to photo-reduction in the X-ray beam. Nevertheless, an accurate description of the redox center in different oxidation and/or coordination states is the key to understand the mechanisms of such a protein and for rational drug design. In the last ten years XAS has significantly improved the situation. XANES and EXAFS give detailed information of the metal center coordination, often with standard errors in distances better than 0.05 Å.

In the current study, we investigate the binding of copper and zinc ions to different genetic variants of β-amyloid peptides that are associated with Alzheimer’s Disease. Two different variants at the same amino acid position have shown protective and pathogenic behavior, respectively. Metal binding is known to enhance aggregation and change the properties of these peptide aggregates and are increasingly thought to play a central role in the disease. Previous studies of the metal site using XAS has successfully determined the coordination of copper and zinc in the wild-type peptide.

Peptides were monomerized by a published protocol. Samples were prepared by adding equimolar metal ion to the peptide at different pH values, and fibrillation was monitored by a standard assay (ThT fluorescence). Data was collected at SAMBA Beamline at SOLEIL and FAME Beamline at ESRF at 10 K on upconcentrated samples. From initial XANES evaluations, zinc appears to have multiple coordination modes, while copper has not. A full EXAFS and XANES analysis is in progress.

References


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