Eur Biophys J (2008) 37:257–263
DOI 10.1007/s00249-007-0232-5

REVIEW

X-ray absorption and diffraction studies of the metal binding sites in amyloid β-peptide

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Received: 17 August 2007 / Revised: 20 October 2007 / Accepted: 26 October 2007 / Published online: 15 November 2007

Abstract A major source of neurodegeneration observed in Alzheimer's disease is believed to be caused by the toxicity from reactive oxygen species produced in the brain mediated by the Aβ protein and mainly copper species. An atomic model of an amyloid β-peptide (Aβ) Cu^{2+} complex or at least the structure of the metal binding site is of great interest. Accurate information about the Cu-binding site of Aβ protein can facilitate simulation of redox chemistry using high level quantum mechanics. Complementary X-ray diffraction and X-ray absorption techniques can be employed to obtain such accurate information. This review provides a blend of X-ray diffraction results on amyloid structures and selected works on Aβ Cu^{2+} binding based on spectroscopic measurements with emphasis on the X-ray absorption technique.

Keywords Alzheimer's disease · Amyloid β-peptide · Amyloid-β metal complexes · X-ray absorption fine structure · X-ray diffraction

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid β-peptide
XAFS	X-ray absorption fine structure
EXAFS	Extended X-ray absorption fine structure
XANES	X-ray absorption near edge structure
EPR	Electron paramagnetic resonance
NMR	Nuclear magnetic resonance
ROS	Reactive oxygen species

Australian Society for Biophysics Special Issue: Metals and Membranes in Neuroscience.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is mainly characterized by the presence of misfolded protein depositions, described as amyloid plaques. The major constituent of AD plaques is the amyloid β-peptide (Aβ, up to 42 amino acids: DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA) that is cleaved from the membrane-bound amyloid precursor protein via the β/γ-secretase pathway. Aβ is normally soluble and found in all biological fluids. Its structural transition from the native state to a β-sheet aggregated form is accompanied by a gain of neurotoxic function. In vitro, Aβ binds with high affinity transitional metals, mainly Cu, Zn, and Fe. Since elevated levels of these metals are found in amyloid deposits in AD-affected brains, the Aβ neurotoxicity may be related to the metallated forms of Aβ, in particular, to complexes with redox-susceptible ions: Aβ-Cu^{2+} or/and Aβ-Fe^{3+}. These metal binding can result in extensive redox chemical reactions and production of reactive oxygen species causing cellular damage which may be central to the pathological mechanism of AD (Bush 2000).

Because of the growing evidence of metals, in particular copper, involvement in neurological disorders (Strozyk and Bush 2006), accurate details of copper binding site in Aβ may be critical to the etiology of AD. There are relatively few accurate structural studies of the metal binding site of Aβ-Cu^{2+} complexes. The fundamental property of native Aβ peptide to form aggregates with metastable and polydisperse structures significantly limits the use of solution nuclear magnetic resonance (NMR) and X-ray crystallographic techniques. To minimize problems arising from population heterogeneity a number of approaches for producing Aβ samples with maximal primary, secondary,

tertiary, and quaternary structural homogeneity were recommended (Teplow 2006).

The paramagnetic Cu^{2+} center precludes accurate determination of an NMR solution structure (Hou and Zagorski 2006). Therefore, the coordination environment of Cu^{2+} bound to Aβ was extensively studied by Raman (Atwood et al. 2000; Miura et al. 2000), electron paramagnetic resonance (EPR) (Curtain et al. 2001, 2003; Karr et al. 2004, 2005; Karr and Szalai 2007; Kowalik-Jankowska et al. 2003), and recently by X-ray absorption fine structure (XAFS) spectroscopies (Dong et al. 2007; Stellato et al. 2006). These studies indicated that the coordination sphere around the Cu^{2+} ions is nitrogen rich and different types of coordination have been proposed for Cu^{2+} ligand in Aβ-Cu^{2+}.

The Aβ peptide is capable of aggregating into a variety of structures under slightly different conditions (Petkova et al. 2005) and metals, including copper, are certainly contributing to this structural variability. Different metal coordination structures result in a range of distinct self-assembled morphologies (Dong et al. 2007). The discrepancy in metal binding geometry in Aβ peptides has been attributed to the differences in preparation of peptide, buffer conditions, pH, and in the mode of presentation of Cu^{2+} to the Aβ peptide (Ma et al. 2006; Smith et al. 2006; Syme et al. 2004). For instance, some studies showed that NaCl presence in buffer greatly encourages metal-mediated oligomerization of Aβ (Huang et al. 1997; Narayanan and Reif 2005). Atomic force microscopy studies (Klug et al. 2003) demonstrated that Aβ aggregation induced by metals (Zn^{2+}, Cu^{2+}, or Fe^{2+}) or low pH (5.0) occurs via a different pathway from that which involves the slow aggregation of stable Aβ species. The binding of metal ions or protonation of histidines may induce rapid Aβ aggregation by altering the positive charge at the N-terminal region of Aβ and increasing the proportion of β-structure. On the other hand, the NMR structural analysis of Aβ fibrils showed that the residues 1–17 are unstructured and do not participate in the β-sheet packing (Luhrs et al. 2005; Sato et al. 2006). It has also been shown that the full-length Aβ(1–40) or Aβ(1–42) peptides and truncated Aβ(1–28) and Aβ(1–16) peptides bind a high affinity Cu^{2+} ion in the same coordination environment (Karr et al. 2005; Kowalik-Jankowska et al. 2003). Aβ(1–16) does not fibrillize and is much more soluble compared to longer peptides. This makes it an attractive model for accurate X-ray absorption spectroscopic or X-ray diffraction studies on the Cu^{2+} coordination environment. The use of multiple scattering (MS) analysis of the extended XAFS (EXAFS) data from frozen solutions of Aβ-Cu allows some three-dimensional structural information of the metal site to be obtained. The XAFS alone can not provide an absolute determination of the metal site structure, but utilizing the other available information the analysis can often show the preference of one structural model over another as well as provide accurate and precise metal–ligand bond lengths (Levina et al. 2005). EXAFS is a relatively short-range phenomena, the information derived from it is limited to a local environment of the protein centered on the metal atom. In contrast the X-ray diffraction provides comprehensive information about three-dimensional structure beyond the metal environment in protein. The combination of X-ray diffraction information and high-resolution EXAFS may provide a powerful approach for studying the metal-binding protein/peptides, particularly when subtle structural changes are associated with a chemical reaction (Cheung et al. 2000). In the following sections, we will review in greater details recent spectroscopic, in particular X-ray absorption studies focusing specifically on the coordination of Cu^{2+} and in some extend Zn^{2+} in Aβ-metal complexes. Selected works on single-crystal and fiber X-ray diffraction studies of Aβ solid species will be discussed as well. This subject seems relevant here in regard to identification of Aβ peptide structural regions predominantly involved in fibril formation and those regions responsible for metal binding.

Aβ–Cu^{2+} coordination and X-ray absorption studies

Summarizing the proposed models of in the Aβ-Cu^{2+} (or Zn^{2+}) metal binding site in the literature, it appears the nitrogen rich coordination sphere around the metal may include three histidine residues: His6, His13, and His14, and fourth ligand is most likely an oxygen donor atom (Curtain et al. 2001). Figure 1 shows the structure of metal-binding domain of Aβ, Aβ(1–16), complexed with Zn^{2+} from NMR data (PDB 1ZE9) (Zirah et al. 2006). This is the only experimental structural information currently available for Aβ–metal complex. The Glu11 residue has been identified by NMR as providing the carboxylate side chain when Zn^{2+} is bound to Aβ(1–16) (Fig. 1). The other options for fourth ligand include tyrosine (Tyr10) (Curtain et al. 2001, 2003; Tickler et al. 2005), the N-terminal (Asp1) nitrogen or oxygen, or other carboxylate side chains (Glu3) (Karr et al. 2004, 2005; Karr and Szalai 2007) (Fig. 1). Recent EPR study (Karr and Szalai 2007) strongly supported involvement of Asp1 carboxylate side chain via hydrogen-bonding to axial water from first coordination shell of Cu^{2+}. Their previous EPR study (Karr et al. 2005) showed that water molecules can be axial ligands and not equatorial oxygen donors to Cu^{2+} ions.

More complex coordination environments for Cu^{2+} may be expected in the longer Aβ(1–40) peptide in soluble monomeric form as well as in the plaques. It was suggested (Opazo et al. 2002) that Met35 could provide an electron for reduction of Cu^{2+} to Cu^{1+} in catalytic H_2O_2 production.

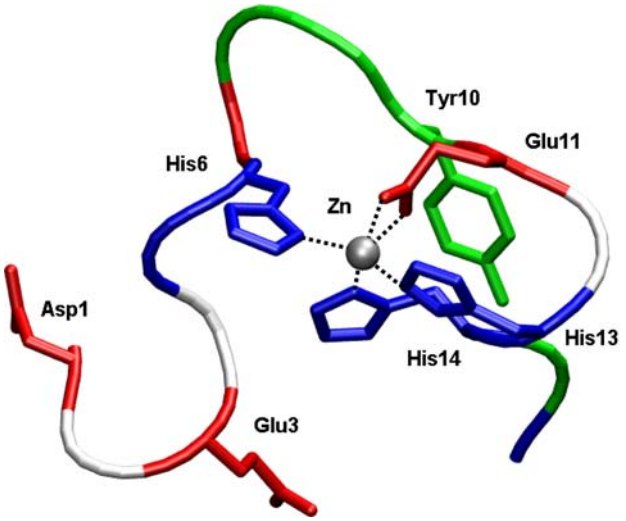

Fig. 1 Structure of metal-binding domain of Alzheimer's disease amyloid β-peptide Aβ(1–16), complexed with a Zinc (II) cation from NMR data (adapted from Zirah et al. 2006), PDB 1ZE9. Peptide backbone is in tube representation. Side chains are shown and labeled for selected residues *colors* correspond to amino acid types (*red*: acidic, *blue*: basic, *green*: polar, and *white*: nonpolar). The Zn^{2+} cation is shown in *silver color*. Image was generated with VMD program (adapted from Humphrey et al. 1996)

However, it seems that in soluble monomeric Aβ form the hydrophobic C-terminal residues 29–42 do not directly coordinate to copper. The role of these C-terminal residues in fibril formation was extensively studied by X-ray diffraction and solid state NMR (ssNMR) and will be discussed below. The Cu^{2+} coordination in monomeric Aβ by Met35 was ruled out by Raman spectroscopy (Miura et al. 2000) and recently by cyclic voltammetry, high resolution mass spectrometry and EPR studies (Guilloreau et al. 2007; Jiang et al. 2007). The remarkable similarity among the voltammetric behaviors of three Cu^{2+} complexes (Aβ(1–16), Aβ(1–28), and Aβ(1–42) excludes the possibility that C-terminal (29–42) can be involved in the Cu^{2+} coordination. The oxidation state of Cu was deduced to be 2+ for all of the complexes, and residues Tyr10 and Met35 are not oxidized in the Aβ (1–42)-Cu^{2+} complex. The C-terminal residues may promote aggregation that facilitates cross-linked dimeric copper complexes of Aβ such as reported by Atwood et al. (2000) in plaques. The mode of copper binding in soluble Aβ forms seems different from that found in oligomeric forms and plaques. An intermolecular His residue bridging binding site of Cu^{2+} in the amyloid fibril (Miura et al. 2000) was indicated and also the formation of the His-bridged dimers (oligomers) in solution was proposed by EPR data (Curtain et al. 2001; Smith et al. 2006). Whereas other results supported an intramolecular Aβ-Cu^{2+} complex existing in both soluble and fibrillar Aβ(1–40) (Karr et al. 2004). EPR based study (Syme et al. 2004) showed no evidence of Aβ(1–28) using bridged histidine coordination to form a dimeric species in solution as previously suggested (Curtain et al. 2001). Dimerization can be a concentration-dependent phenomenon. Also the different conditions used in the EPR studies reported such as addition of glycerol as cryoprotectant may result in different modes of binding and aggregation. The strong tendency for Aβ(1–42) to form aggregates may facilitate cross-linking and formation of a Cu(Aβ)$_2$ species. It is likely that soluble Aβ(1–42) initially forms a one-to-one complex as was seen for Aβ(1–28) (Syme et al. 2004) and was directly observed in monomeric soluble Aβ peptides (1–16, 28, and 42) (Jiang et al. 2007). In amyloid plaques copper was found substoichiometricaly. It was reported that Aβ binds two equivalents of Cu^{2+} (Caine et al. 2007; Guilloreau et al. 2006; Karr et al. 2004; Syme et al. 2004). The first equivalent is probably biologically relevant to soluble monomeric Aβ forms.

Using a range of techniques including visible, infrared, X-ray absorption (EXAFS), and EPR spectroscopies (Dong et al. 2007) revealed a molecular basis for the metal (Cu^{2+} and Zn^{2+}) binding modes and the self-assembly characteristics of Aβ(13–21) peptide. This peptide contains the His13 and His14 previously implicated in metal binding (Miura et al. 2000; Morgan et al. 2002) and part of hydrophobic sequence that is crucial for Aβ assembly (Luhrs et al. 2005; Sato et al. 2006). These results suggest that the N-terminal region of Aβ, starting from His13, can access different metal-ion-coordination (intra- and inter-molecular) environments. The Cu^{2+} *K*-edge EXAFS MS analysis of the Ac-Aβ(13–21)H14A mutant fibrils (hydrated fibril pallets) conducted in (Dong et al. 2007) indicated 3N + 1O or 2N + 2O or 1N + 3O atoms in the first shell at 1.99 Å from the central Cu^{2+} atom. The best fit was obtained with His imidazoles and two additional first-shell N or O atoms suggesting that Cu^{2+} bridging two His13 residues in fibril structure. Recent XAFS data analysis (Stellato et al. 2006) of full-length Aβ(1–40)-Cu^{2+} complex in solution with 1:1 metal/peptide ratio suggested that Cu^{2+} is penta-coordinated to three nitrogens at 1.85–1.94 Å, belonging to three histidines (His6, His13, and His14) (e.g., as in Fig. 1) and two oxygens, one at 2.00 Å belonging to tyrosine (Tyr10) and the other one at 1.91 Å belonging either to water molecule or to some amino acidic residue different from the bound histidine and tyrosine. However, the statistical significance of the fit (high *R* factor of 32%) and overall determinacy of the refinement (ratio of independent data points to the number of refined parameters of 17/9) indicate somewhat limited accuracy of the model proposed. Contrary to some other observation above, (Stellato et al. 2006) reported that the EXAFS spectra of all the five different Aβ(1–40)-Cu^{2+} samples, i.e., two solutions at metal/peptide concentration ratios 0.5 and 1 (subjected to a detailed analysis) and three re-suspended pellets of aggregated

Aβ(1–40)-Cu^{2+} peptides, showed X-ray absorption spectra that are indistinguishable within experimental errors.

Synchrotron X-rays can also be used to map brain tissue sections for metals of interest, and X-ray absorption near edge structure and EXAFS analyses can characterize the oxidation state of Aβ copper complex in the AD brain tissue. For example, fluorescence mapping and microfocus X-ray absorption spectroscopy were already applied to detect and locate iron biominerals in neurodegenerative brain tissue at sub-cellular resolution (<5 μm) (Collingwood et al. 2005; Mikhaylova et al. 2005).

It has been mentioned above that metal–peptide complex preparation conditions such as use of buffers may alter the metal environment. In addition, it is also relevant to mention in the context of X-ray absorption studies the effect of the X-ray beams on aqueous solutions containing copper complexes. The systematic study (Mesu et al. 2005, 2006) showed that Cu^{2+} in aqueous solutions (buffers), especially with the halogen containing salts (e.g., NaCl) can be reduced to Cu^{1+}/Cu^{0} by the intense X-ray beams. The observed phenomena occur not only under a highly focused high-flux X-ray beam, but also (although at different time scales) under low X-ray fluxes. It was shown that the presence of halides could accelerate the reducing effect of the X-ray beams but the extent of Cu^{2+} reduction depended on the ligand type and its coordination environment. These can potentially creates experimental problems in studies by X-ray absorption spectroscopy of the redox processes that occur in biological systems such Aβ-Cu^{2+} complexes.

X-ray diffraction and other structural studies

The structural studies of amyloid fibrils should help to identify regions of the Aβ peptide structure which are not involved in formation of fibrils and therefore may be available for metal binding. Recent advances in structural studies of amyloid fibrils were extensively reviewed by Nelson and Eisenberg (2006a, b) and Kajava et al. (2006). Several structural β-fibrous folds were established by X-ray fiber diffraction measurements. Despite the fact that atomic level structures of amyloid-like fibrils have yet to be determined, many models of fibrils have been proposed. Authors (Nelson and Eisenberg 2006a, b) provided a detailed review of the current structural models of amyloid and amyloid-like fibrils and related features of those models to the common fibril properties. It was shown that the cores of several models contain a packing of the β-strands similar to that in the so-called cross-β spine structure. It is a pair of β-sheets, with the facing side chains of the two sheets inter-digitated in a dry 'steric zipper'. It was determined at 1.8 Å resolution using X-ray diffraction of microcrystals formed from a seven residue peptide from the yeast prion Sup35 (Nelson et al. 2005). Based on this structural study (Eisenberg et al. 2006) provided tentative answers to some fundamental questions related to the tendency of proteins to convert into amyloid-like fibrils. Amyloid fibrils formed from different proteins, each associated with a particular disease, seems contain a common cross-β spine. Recently Sawaya et al. (2007) presented 30 other segments from fibril-forming proteins including segments from the Aβ, that form amyloid-like fibrils and some of them microcrystals. Structures of those (13) microcrystals revealed steric zippers, but with variations that expand the range of atomic architectures for amyloid-like fibrils. Eight classes of steric zippers were proposed and five of which were experimentally confirmed. It is relevant to mention here that metal binding to amyloids such as Aβ is a contributing factor to the variability of self-assembled morphologies. The spectroscopic data discussed above showed that Aβ peptide is capable of aggregating into a variety of structures depending on metals ions and conditions. In addition, the small angle neutron scattering measurement (Morgan et al. 2002) of a rate of Aβ(10–21) fibril formation showed that the presence of metals (Zn^{2+}) increases nucleation rate due to inter-sheet interactions and different fibril morphologies were observed.

Now we focus on studies of atomic level structure of Aβ peptide using recent NMR and other X-ray single crystal diffraction data. Based on a set of experimental constraints from ssNMR spectroscopy (Petkova et al. 2002) proposed a parallel-stacked hairpin-like structure of Aβ(1–40) fibrils. The ssMNR data suggested that the first ten residues were structurally disordered in the fibrils. Residues 12–24 and 30–40 adopted β-strand conformations and formed two parallel β-sheets through intermolecular hydrogen bonding. Residues 25–29 formed a bend in the backbone, bringing the side-chains of two β-sheets in contact. Later combining electron microscopy and ssNMR measurements on Aβ(1–40) fibrils (Petkova et al. 2005) showed that different fibril morphologies have different underlying structures. The predominant structure is determined by subtle variations in fibril growth conditions. Different Aβ(1–40) fibril morphologies also have significantly different toxicities in neuronal cell cultures. A related structure of the fibrils comprising Aβ(1–42), which was obtained by using hydrogen-bonding constraints from quenched hydrogen/deuterium-exchange NMR, side-chain packing constraints from pairwise mutagenesis studies, and parallel, in-register β-sheet arrangement from previous ssNMR studies, was presented by (Luhrs et al. 2005). This model proposes that residues 1–17 are unstructured; residues 18–42 form a β-strand–turn–β-strand motif that contains two intermolecular, parallel, in-register β-sheets that are formed by residues 18–26 and 31–42.

Some single-crystal X-ray diffraction studies of Aβ complexed or fused with other proteins were also recently

attempted. Although, those studies were not involved complexes with metals, the techniques used can be applicable for Aβ–metal binding studies by X-ray diffraction. Crystal structures of insulin-degrading enzyme (IDE) in complex with four substrates including Aβ peptide at the 2.1 Å resolution were reported by (Shen et al. 2006). IDE, a Zn^{2+}-metalloprotease, is involved in the clearance of insulin and Aβ. By repositioning domains, IDE is capable of entraping structurally diverse peptides. However, the residues 1–3 and 16–23 were the only residues of Aβ(1–40) observed in the crystal structure of Aβ-IDE. Recent report (Gardberg et al. 2007) provided up to 1.65 Å resolution crystal structure of the Aβ(1–8) peptide (DAEFRHDS) complexed with two murine IgG2a mAbs, anti-protofibril antibodies (PFAs) PFA1 and PFA2. Crystal structure of the Aβ(28–42) fragment fused with the C-terminal region of ribonuclease HII from a hyperthermophile, *Thermococcus kodakaraensis* (*Tk*-RNase HII) was determined by Takano et al. (2006) at 2.8 Å resolution. Crystal structure analysis of *Tk*-RNase HII(1–197)–Aβ(28–42) showed that Aβ(28–42) forms a β-conformation. This result supports that the C-terminal region of full-length Aβ adopts a β-conformation in an aqueous environment and induces aggregation. This study also indicates that the fusion technique is capable of providing structural information for amyloidogenic peptides at atomic resolution.

Conclusion

The Aβ peptide has been observed to adopt many different confirmations. Causes of this promiscuity in structure, often difficult to reproduce, include the initial aggregation state of the peptide, both in the solid state and immediately after salvation. The variation of metal binding geometry in Aβ peptides can be introduced by the differences in preparation of peptide–metal complexes such as buffer conditions and pH. Furthermore the measurement techniques applied to study the Cu^{2+} environment may influence the state of the Aβ–Cu complex. The reducing effect of the X-ray beam can be significant and misleading in X-ray absorption studies of copper coordination and redox processes mediated by the Aβ–Cu^{2+} complexes. The intrinsic propensity of Aβ peptide to self-association creates experimental obstacles and may lead to different Cu^{2+} binding geometries being observed. The mode of copper binding in solution may be different from that in plaques resulting in intra- or intermolecular metal binding. Cu(II) coordinated with Aβ in a 1:1 stoichiometric ratio is probably biologically relevant to soluble monomeric Aβ forms. The influence of the second coordination sphere around the central atoms was emphasized including participation of the N-terminus region (e.g., Asp1) in stabilizing the Cu^{2+} binding site via a hydrogen-bonding to axial water molecule. The flexibility of N-terminal region may generate different modes of metal coordination. Multiple coordination environments for Cu^{2+} in the Aβ peptides cannot be ruled out. Although X-ray diffraction data has not provided three-dimensional structural information on binding site to date, it is imperative that this approach be pursued in order to elucidate the importance of Aβ N-terminus in metal binding. The N-terminal fragment (1–16) of Aβ is involved in metal binding, does not fibrillize and is much more soluble compared to longer peptides. This makes it an attractive model for accurate X-ray absorption spectroscopic or X-ray diffraction studies on the Cu^{2+} coordination environment. It appears that the fusion technique, where Aβ peptide is fused with a larger protein that will keep the peptide in a soluble and folded state, is promising for obtaining structural information for amyloidogenic peptides at atomic resolution.

Acknowledgment We would like to thank Dr J. Varghese for discussions.

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