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Local atomic structure and oxidation processes of Cu(I) binding site in amyloid beta peptide: XAS Study

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Abstract. There are two different motifs of X-ray absorption spectra for Cu(I) K-edge in amyloid-β peptide which could be due to two different configurations of local Cu(I) environment. Two or three histidine ligands can coordinate copper ion in varying conformations. On the other hand, oxidation of amyloid-β peptide could play an additional role in local copper environment. In order to explore the peculiarities of local atomic and electronic structure of Cu(I) binding sites in amyloid-β peptide the x-ray absorption spectra were simulated for various Cu(I) environments including oxidized amyloid-β and compared with experimental data.

1. Inroduction

Alzheimer's disease is a complex multifactorial neurodegenerative disease and this creates difficulties in accurate identification of its etiology [1, 2]. The main morphological feature of Alzheimer's disease is the formation of insoluble deposition of amyloid-β peptide into amyloid plaques [4]. It is also known that the brains of patients with Alzheimer's disease exhibit high levels of oxidative stress and high levels of redox active transition metals such as copper and iron [3]. Metal ions play a key role in amyloid beta aggregation processes [5].

The copper and iron ions can be involved in production of reactive oxygen species (ROS) via Fenton and Haber-Weiss reactions [6]. Under aerobic conditions, oxidation of copper/iron ion leads to the formation of hydrogen peroxide H_2O_2, O_2^- superoxide and hydroxyl radical OH. The formation of ROS causes the oxidation of amyloid-β peptide (oxidation of amyloid-β peptide occurs through oxidation of individual amino acids, such as methionine and histidine) as well as other biomolecules in the vicinity [6, 7].

2. Methods and experiment

We have prepared Aβ(1-16)-Cu complexes in phosphate buffer saline (PBS) as described [8, 9] and mixed them with 10-fold molar ratio of ascorbate dissolved in water. Aβ(1-16) was obtained from Auspep Pty Ltd. Immediately after preparation the samples were injected into solution cells and rapidly frozen. The Cu^{2+} concentration in solution cells was up to 2.2mM. A series of Cu *K*-edge (8980.4 eV) XAS scans were obtained from samples in a fluorescence mode at 15-20K using a helium displex cryostat. The experiments were conducted at the PNC-CAT 20BM bending magnet beamline at the Advanced Photon Source (APS), USA. The experimental set up and data processing were identical to those reported [8]. Energy calibration was accomplished using the first inflection point of a Cu foil spectrum measured simultaneously with each scan. Up to 15-40 min scans were measured for each sample. No X-radiation reduction of Cu^{2+} to Cu^{1+} was detected by comparing edge spectra for consecutive scans. Each scan was collected from freshly exposed region of the sample by moving the sample stepwise within the cell window area. The XANES regions were extracted from the experimentally measured absorption coefficient using background subtraction and normalization methods implemented in the program ATHENA [10], an interface to IFEFFIT [11].

Atomic structure of Cu(I) binding site and oxidation processes in amyloid-β peptide were studied by combination of quantum chemical calculations and advanced theoretical XANES analysis (X-ray Absorption Near Edge Structure). Theoretical models of Cu(I) binding site in amyloid-β peptide were calculated using the ADF (Amsterdam Density Functional) package [12]. The calculation of theoretical X-ray absorption spectra was carried out using an accelerated version of the FDMNES code [13]. The acceleration code for FDMNES was developed by International Research Center "Smart materials" [14].

3. Results and discussions

There are two different motifs of X-ray absorption spectra for Cu(I) *K*-edge in amyloid-β peptide which corresponds to different structures of Cu(I) binding site in amyloid beta peptide. On one hand, this can be explained by two different configurations of local Cu(I) environment: two or three histidine ligands coordinate copper ion in varying conformations [15, 16]. On the other hand, oxidation of amyloid-β peptide could play an important role in local copper environment as well. In order to explore this hypothesis the X-ray absorption spectra were simulated for various Cu(I) environments including oxidized amyloid-β and compared with experimental data [17].

Two different motifs of X-ray absorption spectra for Cu(I) *K*-edge in amyloid-β peptide are shown in Fig. 1. For comparison X-ray absorption spectrum of Cu(II) *K*-edges in amyloid-β peptide is also shown in black in Fig.1. The first group of spectra for Cu(I) *K*-edge is characterized by two main spectral features: pre-edge A and edge B. The second group of experimental spectra is characterized by three main spectral features: pre-edge A, edge B and peak C.

A B

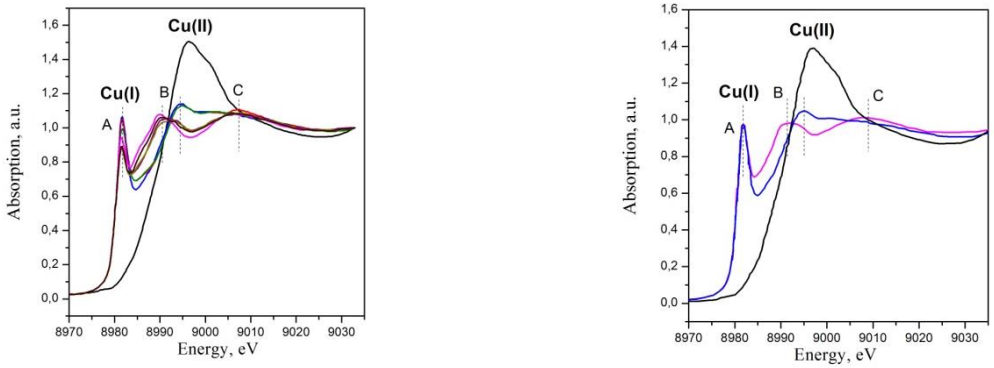


Figure 1. Experimental X-ray absorption spectra for Cu(I) and Cu(II) *K*-edge in amyloid-β peptide (A). Selected experimental motifs for Cu(I) – "Blue" and "Pink", Cu(II) – "Black"

There are two hypotheses that can be proposed to explain the existence of two experimental motifs. The first hypothesis is related to mixture of Cu(I) and Cu(II) species due to incomplete reduction of Cu(II) to Cu(I) with ascorbate and the second is related to the existence of two different structures of Cu(I) binding site in amyloid-β peptide.

To test the first hypothesis a linear combination two groups of experimental spectra for Cu(I) *K*-edge and Cu(II) *K*-edge were constructed (Figure 2). As can be seen from Fig. 2, this hypothesis is somewhat true in one case (Fig. 2A) showing possible 15% contribution from Cu(II) and the hypothesis is false in the seconds case (Fig. 2B).

To test second hypothesis that there exist two different structures of Cu(I) binding site in amyloid-β peptide, we utilized two proposed geometries of copper (I) binding site in amyloid-β peptide [11]:

Linear (two-coordinate structure)

His – Cu – His

Three-coordinated

His – Cu – His
|
His

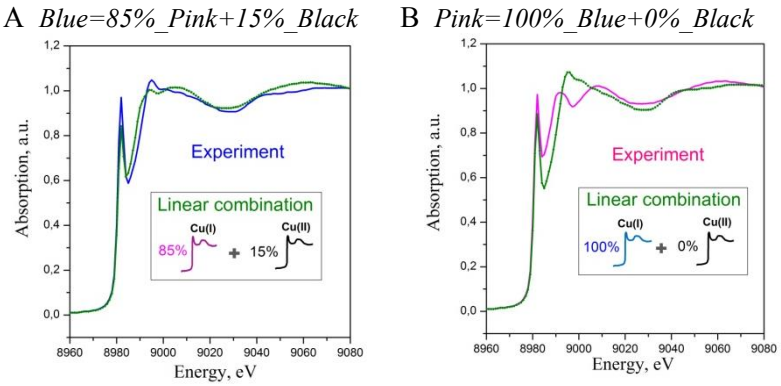
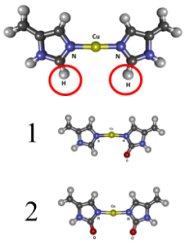
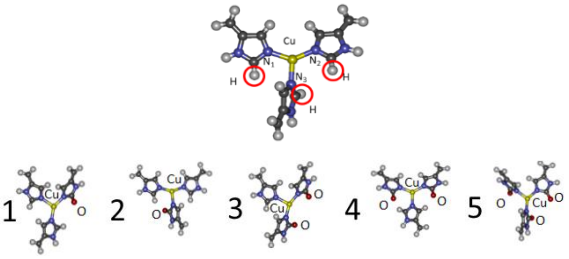


Figure 2. Linear combination spectra for three main motifs of Cu(I) and Cu(II) experimental XANES spectra in amyloid-β peptide. A – Linear combination for experimental motif "Blue", R-factor=0.014, B - Linear combination for experimental motif "Pink", R-factor=0.029

For the basis of linear model (two-coordinate structure) was used a simple structure consisting of a copper ion coordinated by two imidazole rings. The three-coordinated model of Cu(I) binding site in amyloid beta peptide is consists of copper coordinated by three imidazole rings forming a T-shaped structure. Geometric optimization of local structure was carried out by minimizing the total energy of system by using the exchange-correlation potential in generalized gradient approximation Becke-Perdew and basis set DZ (Double Z) and +1 net charge. For linear model and three-coordinated model the structural parameters were obtained (Table 1) and theoretical XANES spectra were calculated for linear model and three-coordinated model, respectively (Figure 3 A and Figure 3 B, red line).

Table 1. Linear and three-coordinated Cu(I) binding sites in amyloid-β-Cu(I) complexes.

	Linear models	Three-coordinated models
		
Bond length (Non-oxidized models)	Cu-N = 1.88 ± 0.01Å	N1 – Cu = 1.96Å ± 0.01Å, N2 – Cu = 1.97 Å ± 0.01Å, N3 – Cu = 2.04Å ± 0.01Å
Angles (Non-oxidized models)	N-Cu-N = 178.4° ± 0.7 °	N1 – Cu – N2 = 136.1° ± 0.2°, N1 – Cu – N3 = 117.49° ± 0.2°, N2 – Cu – N3 = 106.21° ± 0.2°

Modelling oxidation of amyloid-β near the Cu(I) binding site for linear and three-coordinate binding sites was based on histidine oxidation [17]. Theoretical X-ray absorption spectra were calculated for all amyloid-β oxidized models of Cu(I) binding site shown in Figure 3 A, B.

4. Conclusions

The main structural parameters such as interatomic distances and bond angles were obtained by means of *in vacuo* density functional theory for both: histidine two-coordinated linear and histidine three-coordinated copper (I) binding site configurations of amyloid-β. The X-ray absorption spectra are particularly sensitive to the changes in the nearest environment such as replacement of hydrogen atoms on oxygen atoms. It was found that linear two-coordinated model copper (I) binding site with its oxidized histidines version is better suited for the description of one experimental motifs. Possible

oxidation of Cu(I) to Cu(II) (or incomplete reduction of Cu(II) to Cu(I)) may also contribute to the final spectra.

A B

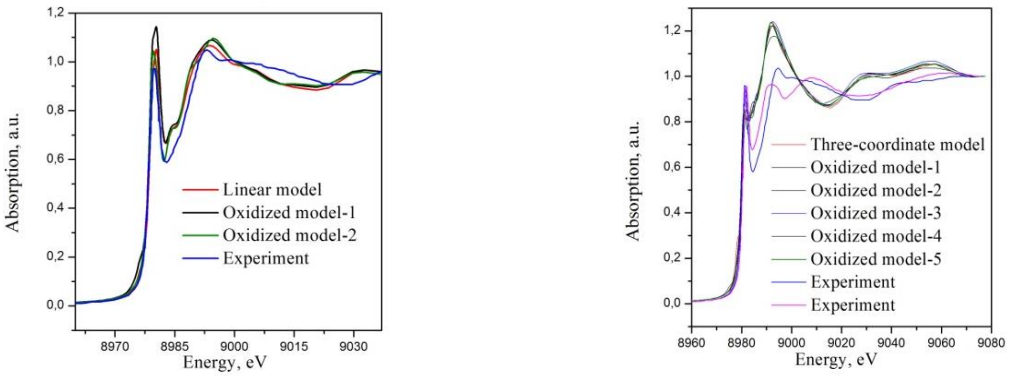


Figure 3. Comparison theoretical and experimental X-ray absorption spectra for Cu(I) linear non-oxidized and oxidized models (1,2) and three-coordinated non-oxidized and oxidized models (1-5)

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