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Chinese Chemical Letters 18 (2007) 357–360
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Molecular dynamics studies of the inhibitory mechanism of copper(II) on aggregation of amyloid β-peptide

Yong Jiao, Pin Yang *

Institute of Molecular Science, Key Laboratory of Chemical Biology and Molecular Engineering of Ministry of Education, Shanxi University, Taiyuan 030006, China

Received 31 August 2006

Abstract

The inhibitory mechanism of copper(II) on the aggregation of amyloid β-peptide (Aβ) was investigated by molecular dynamics simulations. The binding mode of copper(II) with Aβ is characterized by the imidazole nitrogen atom, Nπ, of the histidine residue H13, acting as the anchoring site, and the backbone's deprotoned amide nitrogen atoms as the main binding sites. Drove by the coordination bonds and their induced hydrogen bond net, the conformations of Aβ converted from β-sheet non-β-sheet conformations, which destabilized the aggregation of Aβ into fibrils.

Keywords: Copper(II); Amyloid β-peptide; Inhibitory mechanism; Alzheimer's disease; Molecular dynamics; Radial distribution function (RDF)

One of the defining hallmarks of Alzheimer's disease (AD) is deposits of amyloid β-peptide (Aβ), which may be due to the Aβ coordinating metal ions [1]. Interestingly, copper(II) (Cu(II)) induces the aggregation of Aβ at mildly acidic condition, and yet strongly inhibits the aggregation at neutral and basic pH values [2,3]. The inhibitory characteristic of Cu(II) suggests that Cu(II) potentially play a significant role in the normal brain preventing Aβ from aggregation [3]. However, the inhibitory mechanism remains to be clarified. Based on molecular dynamics (MD) simulations and RDF analysis of the MD data, a novel *Q*-function was established to explore the binding sites of Cu(II) by evaluating the coordination priority of atoms in Aβ Drove by the synergistic effect of the coordination bonds and hydrogen-bond net, the conformations of Aβ convert from the initial β-sheet into non-β conformations, which destabilize the aggregation of Aβ into fibrils.

1. Models and methods

Based on the solid-state NMR data [4], $A\beta_{10-21}$ ($Y_{10}EVHHQKLVFFA_{21}$) with β-sheet conformation was built as the model of full length $A\beta_{1-40/42}$. $A\beta_{10-21}$ contains the crucial metal binding histidine dyad, H13 and H14, and the core segment $A\beta_{17-21}$ known to be critical for the aggregation of Aβ [5]. MD simulations were carried out by InsightII 2000/Discover 3.0 module with the canonical ensemble (NVT) at 310 K. The ESFF force field was applied and a cutoff

* Corresponding author.
E-mail address: yangpin@sxu.edu.cn (P. Yang).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2006.12.028

distance for nonbonded interactions was 10 Å. Each MD simulation was performed for 2 ns and the time step was 1 fs. The RDF were evaluated by the InsightII 2000/Analysis module.

2. Results and discussion

Based on the experimental data that the imidazole nitrogen atoms of histidine residues have high coordination affinity to metal ions [3], four starting structures of the first substituted Cu(II)–Aβ complex were built by selecting H13(Nπ), H13(Nπ), H14(Nπ) and H14(Nπ) as the anchoring site to substitute one of the coordinated water molecules of Cu(II), respectively. After MD simulations, the trajectory data were analyzed by RDF. The *Q*-function (Eq. (1)) was constructed to evaluate the coordination priority of atoms in Cu(II)–Aβ complexes. The *Q*-function comprehensively evaluates the RDF data, including $[g(r)]_p$ (the peak value of $g(r)$), R_p (the corresponding R value of $[g(r)]_p$), and $\Delta r = r_{max} - r_{min}$ (the range of radial distribution). The bigger the *Q*-value is, the higher the coordination priority is. R_0 is the mean value of the coordination bond of [Cu–N]/[Cu–O] (R_0 assigned as 2.00 Å):

$$Q = \frac{R_0}{R_p \lg(\Delta r)}[10g(r)_p] \quad (1)$$

The potential coordination atoms were arranged in their *Q*-values order and obtained the preferential coordination atom, which was used to substitute the another coordinated water molecule of Cu(II). So the starting structure of the second substituted Cu(II)–Aβ complex was built. Repeating the above MD and RDF analysis procedure, the preferential coordination atoms for higher substitution degrees, the second, third and fourth, were obtained step by step. The calculation results indicated that H13(Nπ), as the anchoring site, forms the steadily and completely substituted complex. Table 1 shows the RDF analysis data for the Cu(II)–Aβ complex. The bold values in Table 1 are data highlighted for the preferential coordination atoms.

Taking the initial β-sheet Aβ as the benchmark, the conformation transition of the dynamic average conformations of Cu(II)–Aβ complexes with different substitution degrees were analyzed by the root-mean-square (RMS) method (Fig. 1). The trend of the conformation transition of the hydrophobic segment $L_{17}VFFA_{21}$ can be divided into two parts: (i) a sharp conformation transition of the first substituted complex; (ii) a mild fluctuating of the conformation transition of complexes with substitution numbers from two to six. For the hydrophilic segment $Y_{10}EVHHQK_{16}$, the trend can be divided into three parts: (i) a marked conformation transition of the first substituted complex; (ii) a gradual conformation transition of complexes with substitution numbers from two to four; (iii) a slight conformation transition of complexes with substitution numbers from four to six. Particularly, the trend of the conformation transition of total $Aβ_{10–21}$ is nearly parallel to that of the hydrophilic segment from the first substitution to sixth.

Table 1
The RDF evaluation of the coordination priority of atoms in Cu(II)–Aβ complexes

Substitution order	Coordination shell		RDF analysis[a]				
	Coordinated atoms	Preferential atoms	$[g(r)]_p$	R_p	Δr (r_{min}, r_{max})	*Q*-value[b]	*Q*-value
First	H13(Nπ)		0.28651	2.0	1.9, 2.1	0.95177	
		13:N	**0.02423**	**2.7**	**2.5**, **4.1**		**0.87930**
Second	H13(Nπ)		0.30028	2.0	1.9, 2.1	0.99751	
		12:N	**0.03309**	**2.8**	**2.6**, **4.4**		**0.92590**
	13:N		0.28017	1.9	1.8, 2.0	0.97969	
Third	H13(Nπ)		0.30013	2.0	1.9, 2.1	0.99701	
		11:N	**0.02174**	**2.8**	**2.6**, **4.5**		**0.55707**
	12:N		0.25389	1.9	1.8, 2.0	0.88779	
	13:N		0.30229	1.9	1.8, 2.0	1.05703	
Fourth	H13(Nπ)		0.29140	2.0	1.9, 2.1	0.96801	
	11:N		0.28610	2.0	1.9, 2.1	0.95040	
	12:N		0.27871	1.8	1.7, 1.9	1.02873	
	13:N		0.27854	1.9	1.8, 2.0	0.97398	

[a] RDF analysis based on the conformation space with 2,000,000 conformations.
[b] The *Q*-values of coordinated atoms.

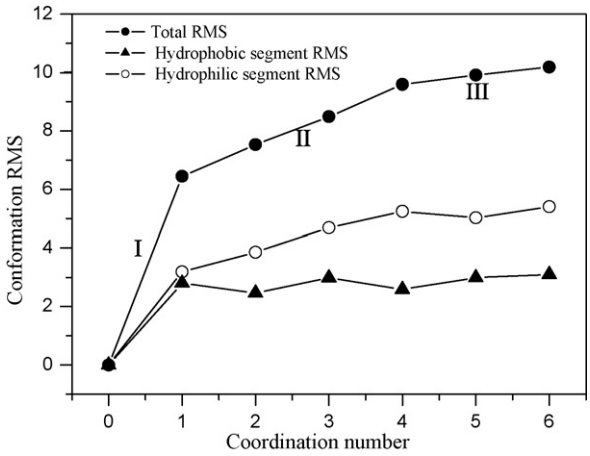

Fig. 1. The RMS analysis of the conformation transition.

The detailed conformation analysis indicated that the coordinated water molecules of Cu(II) directly form several hydrogen bonds with Aβ and induced it formation of more intramolecular hydrogen bonds (Fig. 2). Thus the coordinated waters of Cu(II) bridge the coordination bonds and hydrogen bonds as a net, which drives the sharp conformation transition of the first substituted complex. With the increase of the substitution degrees, more coordination bonds form and continually drive the conformation transition. As the coordination in axis direction is weaker, the fifth and sixth substitutions just bring about slight conformation transition. From the first substitution, the hydrogen bond net has formed and driven the hydrophobic segment almost to finish its conformation transition. So the conformation of the hydrophobic segment just fluctuates with the increase of the substitution degree. The conformation transition of total $A\beta_{10-21}$ is the sum of that of the hydrophilic and the hydrophobic segment. The curve of total $A\beta_{10-21}$ which is nearly parallel to that of the hydrophilic segment indicates that the conformation transition of $A\beta_{10-21}$ is determined mainly by the hydrophilic segment. Driven by the synergistic effect of coordination bonds and hydrogen bond net, the conformations of Aβ convert from β-sheet to non-β ones, such as local *quasi*-β-turn.

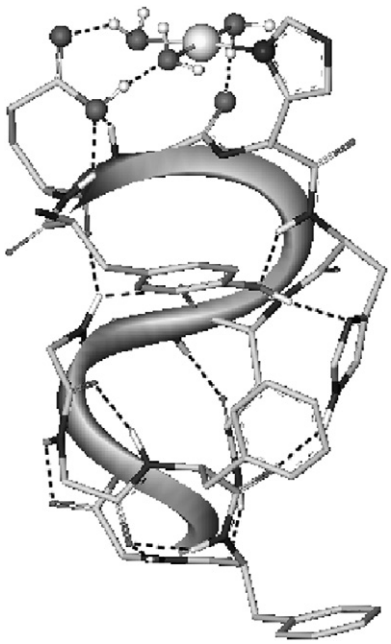

Fig. 2. The conformation transition of the first substituted complex driven by the coordination bonds and hydrogen bond net.

Our previous work has indicated that the aggregation stability of the fibril assembled by non-β monomers is far lower than that of the fibril by β-sheet one [6]. The coordination of Cu(II) on Aβ makes its conformation to convert from β-sheet to non-β random coils, so inhibits the aggregation of Aβ into fibrils.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 30470408 and 20637010).

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