SIMULATION SPATIAL STRUCTURE OF AMYLOID BETA-PEPTIDE (28-35) DETERMINED BY MOLECULAR MECHANICS METHOD

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Conformational properties of Alzheimer's β-amyloid (28-35) peptide have been studied by molecular mechanics method. Using a fragmentary approach, energy-efficient spatial structures of the molecule were identified. It has been shown that this peptide molecule forms a stable conformation with two different structures: one is a complete α-helical structure, and the other is a beta-freezing structure at the N-terminal complemented by a small alpha helix. Calculations The hypocritical angles of all residues in the low-energy conformations of the amyloid beta (28-35) peptide molecule and their orientations relative to each other were determined. Based on the obtained results, three-dimensional spatial structures of the amyloid-β (28-35) peptide molecule were modelled

Keywords: Amyloid beta peptide (28-35), conformation, α-helical structure, molecular mechanics.
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INTRODUCTION

Alzheimer disease (AD) is an age-related progressive neurodegenerative disorder. Alzheimer's disease is a condition accompanied by degenerative processes in nerve cells leading to increasing impairments to cognitive functions such as language, behavioural activities and memory. AD is associated with accumulation of excess amounts of amyloid-β (Aβ) protein in the form of extracellular senile plaques, with disruption of neuronal interactions and nerve cell death [1].

It is known that β-amyloid peptide molecules play an important role in the pathogenesis of Alzheimer's disease [2]. It is well established that AβP possesses neurotoxic activity. AβP neurotoxicity has been associated to peptide self-aggregation, which leads to the formation of amyloid-like fibrils and eventually to neuronal cell death through apoptosis. The complete β-amyloid peptide molecule consists of 42 amino acid residues. Its biological activity properties are attributed to the peptide Aβ (25-35), which consists of 11 residues. It has been established that the peptide Aβ (25-35) is the shortest Aβ fragment of the whole molecule that retains some amyloidogenic and cytotoxic properties [3] At the same time, the Aβ (28-35), consisting of eight amino acid residues Lys1 – Gly2 – Ala3 – Ile4 – Ile5 – Gly6 – Leu7 – Met8 – NH2, is the main part of the C-terminal of the peptide Aβ (25-35). The role of this region in determining the second peptide structure and neurotoxicity is important. Therefore, the study of the conformational properties of the peptide Aβ (28-35) is of particular interest.

CALCULATION METHODS

In the presented work, the spatial structure of the octapeptide molecule $Lys^1 – Gly^2 – Ala^3 – Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2$ was studied and modeled by molecular mechanics.

Molecular mechanics (MM) study of Aβ (28-35) conformation involves multistage extensive computations of even-increasing fragments, with a set stable forms of each preceding step used as a starting set in the next step. Only those conformations are retained whose energies are smaller than some cut-off values. The sequential method was used, combining all low-energy conformations of constitutive residues For this purpose, the conformational properties of $Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2$ pentapeptide, consisting of five amino acid residues, and $Lys^1 – Gly^2 – Ala^3 – Ile^4$ tetrapeptide, consisting of four amino acid residues, were first studied by molecular mechanics. In the method of molecular mechanics, the total internal potential energy of a molecule is equal to the sum of the energy values of the interactions of each pair of atoms that are not in its valence bond. The conformational energy of peptide molecules is defined on the basis of a mechanical model as the sum of the energies of non-valent, electrostatic, torsional interactions and hydrogen bonds, provided that the valence angles and bonds are constant: $E_{conf} = E_{nb} + E_{el} + E_{tor} + E_{hb}$.

The first term was described by the Lennard-Jones 6-12 potential with the parameters proposed by Scott and Scheraga. The electrostatic energy was calculated in a monopole approximation corresponding to Coulomb's law with partial charges of atoms as suggested by Scott and Scheraga. An effective dielectric constant value ε=1 for vacuum, ε=4 for membrane environment and ε=80 for water surrounding is typically used for calculations with peptides and proteins, which create the effects of various solutions on the conformations of peptides by MM method [4].

Conformational analysis of molecules was carried out on the basis of optimal conformation conditions of the amino acid residues that make up them [5]. Energy is minimized by the gradient method for the first order derivatives. The conformational analysis took into account the Van der Vaals, electrostatic, torsional interactions energy fractions and hydrogen bond energy of the peptides to be studied. Conformational analysis

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of tetrapeptide from a universal program and algorithm developed by N.M Gojayev and I.S Maksumov was used in solving structural problems [6]. The different forms of the main chain of the peptide molecule are divided into several classes: through the folded (f) and open (e) shapes. Thus, the number of chains that can form a peptide molecule consisting of an N amino acid residue can only be 2N-1. Each chain creates its own main and side chain interactions. The conformation of the fossils is indicated by the letters corresponding to the following areas of the Ramachandran map of the hypocritical angles φ, ψ: R ($\varphi=-180^0\div0^0$, $\psi=-180^0\div0^0$), B ($\varphi=-180^0\div0^0$, $\psi=0^0\div 180^0$),L ($\varphi=0^0\div180^0$, $\psi=0^0\div 180^0$); P ($\varphi=0^0\div180^0$, $\psi=-180^0\div0^0$). The calculation of hypocritical angles was carried out according to the IUPAC-IUB nomenclature. [7] Based on these symbols, the conformational state of each residue is described by H_{ij}, using a certain system of identifiers. The indices of the letters (R, B, L, P) characterize the state of the side chain: the number 1 corresponds to the fields ~ 00÷ 1200, the number 2 to the fields ~ 1200÷ -1200, the number 3 to the fields ~ -1200÷ 00. As a result of the calculations, the energy fractions that play a role in stabilizing the optimal conformations of peptide molecules were determined.

RESULTS AND DISCUSSION

The conformational properties of the amyloid-β (28-35) peptide were investigated on the basis of the selected fragmentary [8] calculation scheme shown in Figure 1:

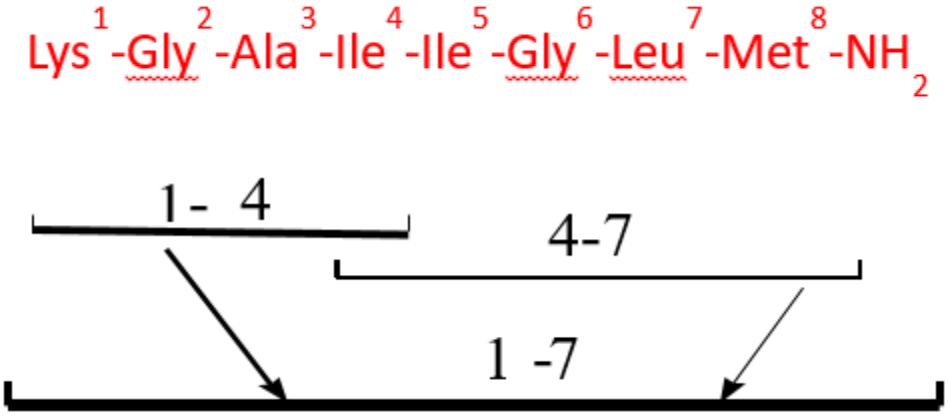

Fig. 1. Scheme for calculating the optimal compatibility of the peptide Aβ (28-35).

Table 1.

The relative energy values of stable structures in separate fragments of Aβ (28-35) peptide

Ile-Ile-Gly-Leu-Met-NH_2 pentapeptide		Lys-Gly-Ala-Ile tetrapeptide	
RRRRR	Relative energy (kcal/mol)	Backbone form	Relative energy (kcal/mol)
RRBRR	0,0	RRRR	0,0
BRBBB	3,0	BRRR	1,0
RBBRR	3,1	BBRR	1,9
BRBRR	3,1	RBRR	2,0
RBBBB	3,6	RBBB	2,4
RBBBR	3,7	BRBB	2,8
BBBBB	3,8	RRRR	3,0
RRRRR	4,6	RRBB	3,7

Theoretical computational studies were performed on the polar medium (dielectric) of the pentapeptide $Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2$, consisting of five amino acid residues [9], and the tetrapeptide $Lys^1 – Gly^2 – Ala^3 – Ile^4$, consisting of four amino acid residues [10]. Table 1 shows the backbone form and the relative energy for each backbone form, for pentapeptide and tetrapeptide molecules.

After determining the most stable conformations, $Lys^1 – Gly^2 – Ala^3 – Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2$ octapeptide was calculated by overlapping this pentapeptide and tetrapeptide. Analysis of the initial structures of the C-terminal Aβ (28-35) octapeptide shows that the α-helical conformation has minimal energy. All other stable conformations have a spiral rotation at the end of the C-terminal. That is, the longer the α-helix at the end of the peptide's C-terminal, the more stable the octapeptide. This conformation is mainly distinguished by the energy of the dispersion interaction. Table 2 shows that only RRRRRRRR form of the octapeptide has minimum energy.

Table 2.

Distribution of calculated conformations of Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-NH2 octapeptide in the relative energy range.

Form of main chain	Relative energy (kcal/mol)					
	0-1	1-2	2-3	3-4	4-5	>5
RRRRRRRR	2	1	7	5	3	Remain
BBBRRRRR	-	-	-	-	-	All
BRRRRRRR	-	-	-	-	-	All
BBRRRRRR	-	-	-	-	-	All
BRBRRRRR	-	-	-	-	-	All
BRRRBBBB	-	-	-	-	-	All
RBBRRRRR	-	-	-	-	-	All
RBBBRRRR	-	-	-	-	-	All
RBRRRRRR	-	-	-	-	-	All
RLRRRRRR	-	-	-	-	-	All
RRRBBRRR	-	-	-	-	-	All
RRRBBBBB	-	-	-	-	-	All
RRRBRBRR	-	-	-	-	-	All
RRRRRBRR	-	-	-	-	-	All
RRRRBRRR	-	-	-	-	-	All
RRRRBRBB	-	-	-	-	-	All
RRRBBRBB	-	-	-	-	-	All
RRRRRBBB	-	-	-	-	-	All

Low-energy octapeptide conformations differ from each other in the stability of the N-terminal therapeutic fragment. The lowest energy octapeptide conformation $R_{22}RR_{12}$ $R_{32}R_{32}RR_{21}R_{32}$ belongs to the α-spiral ffffff shape. Its durability is 1.6 kcal / mol higher than the $B_{22}RR_{12}$ $R_{32}R_{32}RR_{21}R_{32}$ conformation in the ffffff shape. Table 3. shows the low-energy conformations that characterize the C-terminal octapeptide spatial structure.

Table 3.

Energy fractions of interaction forces of optimal conformations of Lys–Gly–Ala–Ile–Ile–Gly–Leu–Met–NH_2 octapeptide.

Form	Conformation	Energy distribution (kcal/mol)				
		E_{nb}	E_{el}	E_{tor}	E_{total}	E_{rel}
RRRRRRRR	$R_{22}RR_{12}$ $R_{32}R_{32}RR_{21}R_{32}$	-38.5	15.0	5.4	-18.0	0
BRRRRRRR	$B_{22}RR_{12}$ $R_{32}R_{32}RR_{21}R_{32}$	-31.4	13.3	3.8	-14.3	3.6
BBRRRRRR	$B_{22}BR_{12}R_{32}$ $R_{32}RR_{21}R_{32}$	-31.5	14.7	4.2	-12.6	5.4
RLRRRRRR	$R_{22}LR_{12}R_{32}R_{32}RR_{21}R_{32}$	-31.6	15.5	4.7	-11.4	6.6
RBRRRRRR	$R_{22}BR_{12}R_{32}R_{32}RR_{21}R_{32}$	-29.7	14.8	4.0	-10.9	7.1
RRRRBRRR	$R_{12}RR_{12}R_{12}B_{22}RR_{32}R_{32}$	-30.4	14.7	5.0	-10.7	7.3
BRBRRRRR	$B_{22}RB_{12}R_{32}R_{32}RR_{21}R_{32}$	-28.7	14.9	3.8	-10.0	8.0
RRRBBBBB	$R_{12}RR_{12}B_{22}B_{22}BB_{32}B_{32}$	-28.3	14.2	4.3	-9.7	8.2
RRRBBRRR	$R_{12}RR_{12}B_{22}B_{22}RR_{32}R_{32}$	-28.3	14.4	4.3	-9.6	8.4
RBBBRRRR	$R_{22}BB_{12}B_{12}R_{32}RR_{21}R_{32}$	-29.3	14.7	5.1	-9.5	8.5
BBBRRRRR	$B_{12}BB_{12}R_{22}R_{32}RR_{21}R_{32}$	-28.8	14.7	4.6	-9.4	8.5
RBBRRRRR	$R_{22}BB_{12}R_{32}R_{32}RR_{21}R_{32}$	-28.2	14.3	4.4	-9.5	8.5
RRRRRBBB	$R_{12}RR_{12}R_{12}R_{32}BB_{32}B_{22}$	-30.0	15.2	5.5	-9.2	8.8
BRRRBBBB	$B_{22}RR_{12}R_{32}B_{22}BB_{32}B_{32}$	-25.7	13.2	3.5	-9.0	9.0
RRRRBRBB	$R_{12}RR_{12}R_{12}B_{22}RB_{32}B_{32}$	-28.6	14.9	4.9	-8.8	9.2
RRRBBRBB	$R_{12}RR_{12}B_{22}B_{22}RB_{32}B_{32}$	-28.2	14.8	4.7	-8.8	9.2
RRRRRBRR	$R_{12}RR_{12}R_{12}R_{32}BR_{32}R_{32}$	-29.3	15.1	5.5	-8.7	9.3
RRRBRBRR	$R_{12}RR_{12}B_{22}R_{32}BR_{32}R_{32}$	-28.1	14.8	5.1	-8.3	9.3

In α-helical conformations, the overall effect of interactions between residues separated by two or three positions is greater than in other octapeptide conformations. However, in the latter conformation, the β-turn at the end of the N-terminal brings the distant residues closer together and causes an interaction between Gly^2 and Met^8 (−1.2 kcal / mol), Ala^3 and Met^8 (−2.7 kcal / mol). In the global α-spiral conformation, hydrogen bonds are regularly formed between oxygen atoms of carbonyl groups and hydrogen atoms of amide groups: NH (Gly^6)… OC (Gly^2), NH (Leu^7)… OC (Ala^3), and NH (Met^8)… OC (Ile^4). Other conformations also have hydrogen bonds, but these are irregular. Subsequent analysis of the C-terminal octapeptide was performed according to the stable conformations of all 8 sheets of the Lys^1 – Ile^4 tetrapeptide. Conformational properties of C-terminal octapeptide were analyzed based on the overlap of low-energy conformations of C-terminal Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2 pentapeptide and Lys^1 – Ile^4 tetrapeptide. Different conformations and orientations of Ile^3 and Ile^5, which are common side chains of Ile^4 – Ile^5 – Gly^6 – Leu^7 – Met^8 – NH_2 pentapeptide and Lys^1 – Ile^3 tetrapeptide, were taken into account when formulating the initial structural variants of the octapeptide molecule.

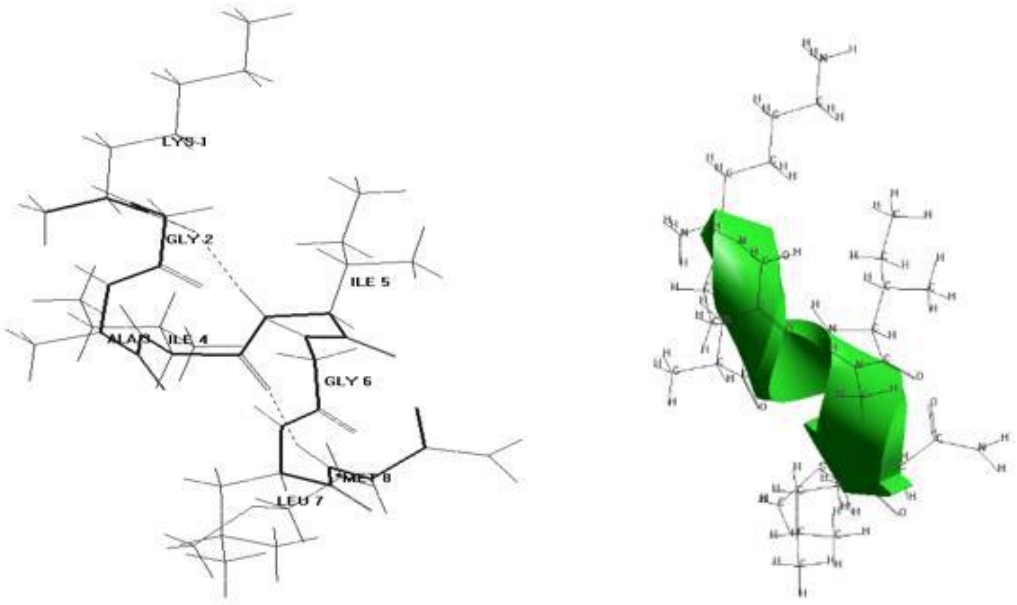

Fig. 2. The most energy-efficient conformation of the peptide Aβ (28-35) ($R_{22}RR_{12}R_{32}R_{32}RR_{21}R_{32}$).

Figure 2 shows a visual projection of the most energy-efficient conformation of the peptide Aβ (28-35) $R_{22}RR_{12}R_{32}R_{32}RR_{21}R_{32}$. As a result of calculations, it was determined that the spatial structure of the octapeptide Aβ (28-35) tends to the alpha-helical structure.

CONCLUSION

The Aβ (28-35) peptide molecule is able to adopt different optimal conformations depending on their environment. Thus, on the basis of conformational studies of Amyloid β-peptide (28-35) molecule it has been suggested that the biologically active conformation of this peptide at its receptor is alpha helix structure in solution. It should be noted that few lowest energy Aβ (28-35) conformations share the same form of the peptide backbone. Some of these conformations are favourable for the polar environment, while the other favours an apolar solution.

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