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MOLECULAR DYNAMICS SIMULATION OF CONFORMATIONAL BEHAVIOR OF AMYLOID- β PEPTIDE (25-35)

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The conformational behavior and flexibility of Amyloid beta-peptide (25-35) have been investigated in a vacuum and in the polar medium using molecular dynamics method. Amyloid peptide ($A\beta$) is the major component of senile plaques found in the brain of patients of Alzheimer's disease. β -amyloid peptide (25-35) ($A\beta$ 25-35) is a biologically active fragment of $A\beta$. The calculation showed that the spatial structure of this peptide tends to adopt an α -helical conformation from Lys²⁸ to Met³⁵. The conformational behavior of this peptide can be described by a set of similar low-energy conformations having α -helical structure at the C-terminal sequence. The permissible changes of values dihedral angles of Amyloid beta-peptide (25-35) lowest energy conformations and stability of the secondary structure elements have been investigated by molecular dynamics simulation. The comparative study results have shown that the preferred conformations of this molecule are not fully disordered structure in the solvent, but it has a stable helical segment at the C-terminal part of molecules.

Keywords: Amyloid beta-peptide (25-35), conformation, α -helical structure, molecular dynamics

INTRODUCTION

The knowledge of the conformational behavior of the biologically active peptides allows a more rational investigation of the mechanism of action and structure-function relationships of these molecules. The conformational and dynamic properties of Amyloid beta-peptide (25-35) were studied in this work. Amyloid beta-peptide ($A\beta$) is the major component of senile plaques found in the brain of patients of Alzheimer's disease. β -amyloid peptide (25-35). $A\beta$ (25-35) is a biologically active fragment of $A\beta$. $A\beta$ (25-35), having an amino acid sequence of Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met that contains both hydrophilic domains (Ser²⁶-Gly²⁹) and six hydrophobic residues of the transmembrane region have been reported to have biologically active fragment and contribute to aggregation [1-3]. The three-dimensional structure of $A\beta$ (25-35) in aqueous solution with 50% (vol/vol) TFE determined by NMR spectroscopy previously adopts an α -helical conformation from Ala³⁰ to Met³⁵ [4]. A-beta (25-35) is a biologically active fragment of A-beta and exhibits some sequence homology with the tachykinin family. The most studied tachykinin, substance P (SP), was first isolated from the equine brain and intestine. Its amino acid sequence was identified as Arg¹-Pro²-Lys³-Pro⁴-Gln⁵-Gln⁶-Phe⁷-Phe⁸-Gly⁹-Leu¹⁰-Met¹¹-NH₂. In previous paper, the molecular mechanics method was employed to study the spatial structures of the SP and amyloid beta-peptide (25-35) molecules. Both peptides have alpha-helical structures in their C-terminal regions. A molecular conformation is largely determined by its environment, so the aim of this present work is the study the differences in the conformations of amyloid beta-peptide (25-35) in a vacuum and in an aqueous environment using a molecular dynamics method.

MATERIAL AND METHODS

The conformational energy is considered the sum of independent contributions of nonbonded E_{nb} , electrostatics E_{el} , torsional interactions E_{tor} and hydrogen bonding E_{hb} energies. Conformational energy was calculated with a computer using a program written in FORTRAN [5]. The conventions used for torsion angles are those of IUPAC-IUB Commission [6]. The conformational

dynamics of the molecule have been investigated by molecular dynamics simulations method with molecular modeling package. Molecular dynamics involves the calculation of the solution to Newton's equations of motions. The qualities of the results from a standard molecular dynamics simulation are extremely dependent on the starting conformation of the system [7]. Often molecular dynamics trajectory will become trapped in a local minimum and will not be able to step over high energy conformational barriers. The quality of the results from a standard MD simulation is extremely dependent on the starting conformation of the molecule. So, the low-energy structures, including the best and the worst of the calculated structures were used as starting conformations for molecular dynamics simulations ϕ , ψ and χ angles were analyzed for changes in each conformation. Runs were performed for 300 ps (picosecond) at 300 K (Kelvin). The total length of the simulation depends on the system being studied and the type of information to be extracted. For example, in simulations of the biological system a time step of 1 fem to second is commonly used. To ensure that information about the highest frequency in the system is $\pm 30^\circ$ about a mean position during the molecular dynamics simulations. The length of the simulation (after equilibration) has to be long enough to enable the slowest modes of motion to occur. The forcefield parameters were those of the all atom version of AMBER by Cornell et al [7-9]. A harmonic force towards the center of the sphere was added to atoms when they moved out of the sphere. The nonbonded cutoff distance was 12 Å (angstrom). The time step was 0,5 fs (femtosecond). The program Hyper. Chem. 8.01 was used for the MD simulations.

RESULTS AND DISCUSSION

The lowest energy structures of amyloid beta- peptide (25-35) exhibit the most favorable dispersion contacts and therefore may be expected to become the most preferred in a strongly polar medium when electrostatic interactions do not play a significant role. The lowest energy α -helical structure at the C-terminal fragment is stabilized by a network of hydrogen bonds. Molecular mechanics of amyloid beta-peptide (25-35) has shown that this molecule can form one global, i.e. the lowest-energy structure, which consists of one β - turn on N-terminus and on the C-terminal part α -helical segment. MD simulation, using the 4 starting lowest energy structures of the molecule was shown the significant differences in the conformations of the molecule in a vacuum environment. Structures from the last 15 ps of the run were energy-minimized and two of these are shown in Fig. 1. The mobility of the backbone and side-chain of some residues is more restricted as compared to preceding residues of molecules in a vacuum.

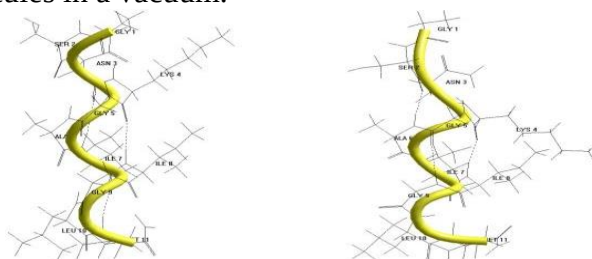


Fig. 1. The source structure (a) and optimized structure of amyloid beta peptide (25-35) molecule in condition of the vacuum (b)

Corresponding changes of the kinetic, potential and total energies for lowest conformation are presented as a dependency from time in Figure 2. MD simulations show that the molecule backbone can adopt only a limited number of conformations while the sidechains of the residues may populate all three major rotamers. Large flexibility of the Gly¹-Lys⁴ amino acid sequence was observed in the vacuum in contrast to polar simulation.

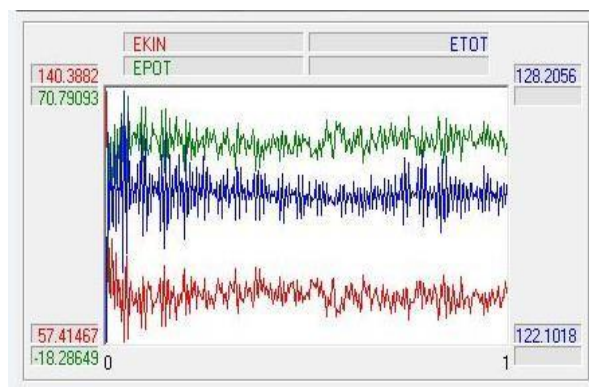


Fig. 2. The time dependency of the kinetic, potential and total energies

CONCLUSION

Our calculation has shown that the spatial structure of this peptide has a tendency to adopt an α -helical conformation from Lys²⁸ to Met³⁵. The conformational behavior of this peptide can be described by a set of similar low-energy conformations having α -helical structure at the C-terminal sequence. The permissible changes of values dihedral angles of Amyloid beta-peptide (25-35) lowest energy conformations and stability of the secondary structure elements have been investigated by molecular dynamics simulation. The comparative study results have shown that the preferred conformations of this molecule are not fully disordered structure in the solvent, but it has a stable helical segment at the C-terminal part of molecules. MD simulation in this study supports the results, obtained by NMR investigation about an α -helical structure at the C-terminal part of amyloid beta-peptide (25-35). These theoretical results may be important to develop a tool to control the amyloid deposition observed in Alzheimer's disease patients, it will be meaningful to study how to manipulate the condition to promote the α -helical conformation of A β (25-35).

REFERENCES

1. Beyreuther, K., and C. L. Masters. Alzheimer's disease: the ins and outs of amyloid_peptide. Nature.1997.389:677–678.
2. Kohno, T., K. Kobayashi, T. Maeda, K. Sato, and A. Takashima. Three-dimensional structures of the amyloid_peptide (25–35) in membrane-mimicking environment. Biochemistry 1996.35:16094–16104.
3. Shanmugam, G., and Jayakumar, R. Structural analysis of amyloid beta peptide fragment (25–35) in different microenvironments. Biopolymers, 2004, 76, -p. 421–434.
4. Sangwon Lee and Yangmee Kim, Molecular Dynamics Simulations on β Amyloid Peptide (25–35) in Aqueous Trifluoroethanol Solution, Bull. Korean Chem. Soc. 2004, 25, No. 6, -p.838–842.
5. Maksumov, I.S., Ismailova, L.I., Godjaev, N.M. The program for semiempirical calculation of conformations of the molecular complexes, J. Struct. Khim., 1983, 24, -p. 147–148.
6. Commission on Biochemical Nomenclature Abbreviations and symbols for description of conformation of polypeptide chains // Pure Appl. Chem., 1974, 40, -p. 291–308.
7. J.A.McCammon., S.C.Harvey. Dynamics of Proteins and Nucleic Acids, Cambridge Univ. Press, New York, 1987.
8. W.D. Cornell., P.Cieplak., C.I.Bayly., I.R.Gould., K.M.Merz., Jr., D.M.Ferguson, D.C.Spellmeyer, T.Fox, J.W.Caldwell., P.A.Kollman. A Second Generation Force Field for the Simulation of Proteins, Nucleic Acids, and Organic Molecules, J. Am. Chem. Soc., 117, 1995, -p. 5179–5197.
9. N.L.Allinger, Y.Yuh, Mm2 program, QCPE 395, Quantum Chemistry Program Exchange, Indiana Univ., Indiana, 1982.



AMİLOİD- β PEPTİDİN (25-35) KONFORMASİONAL DAVRANIŞININ MOLEKULAR DİNAMİKASI SİMULYASIYASI

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Amiloid beta-peptidinin (25-35) konformasiya xüsusiyyətləri və elastikliyi molekulyar dinamika üsulu ilə vakuumda və polyar mühitdə tədqiq edilmişdir. Amiloid peptid ($A\beta$) Alzheimer xəstəliyi olan xəstələrin beyində aşkar edilən qocalıq lövhələrinin əsas komponentidir. β -amiloid peptid (25-35) $A\beta$ (25-35) -nin bioloji aktiv fraqmentidir. Hesablama göstərdi ki, bu peptidin fəza quruluşu Lys²⁸-dən Met³⁵-ə qədər α -spiral konformasiyasını qəbul etməyə meyllidir. Bu peptidin konformasiya xüsusiyyətləri C-terminal ardıcılığında α -spiral quruluşa malik oxşar aşağı enerjili konformasiyalar dəsti ilə təsvir edilə bilər. Amiloid beta-peptidinin (25-35) ən aşağı enerjili konformasiyalarının dihedral bucaqlarının qiymətlərinin icazə verilən dəyişmələri və ikincil struktur elementlərinin dayanıqlığı molekulyar dinamikanın simulyasiyası ilə tədqiq edilmişdir. Müqayisəli tədqiqatın nəticələri göstərdi ki, bu molekulun üstünlük verdiyi konformasiyalar həlledicidə tam nizamsız struktur deyil, lakin molekulların C-terminal hissəsində sabit spiral segmentə malikdir.

Açar sözlər: Amiloid beta-peptid (25-35), konformasiya, α -spiral quruluş, molekulyar dinamika

МОЛЕКУЛЯРНО-ДИНАМИЧЕСКОЕ МОДЕЛИРОВАНИЕ КОНФОРМАЦИОННОГО ПОВЕДЕНИЯ ПЕПТИДА АМИЛОИД- β (25-35)

Г.З. Наджаfoва

Конформационное поведение и гибкость бета-пептида амилоида (25-35) исследовали в вакууме и в полярной среде методом молекулярной динамики. Амилоидный пептид ($A\beta$) является основным компонентом сенильных бляшек, обнаруживаемых в головном мозге пациентов с болезнью Альцгеймера. β -амилоидный пептид (25-35) ($A\beta$ 25-35) представляет собой биологически активный фрагмент $A\beta$. Расчет показал, что пространственная структура этого пептида имеет тенденцию принимать α -спиральную конформацию от Lys²⁸ до Met³⁵. Конформационное поведение этого пептида может быть описано набором подобных низкоэнергетических конформаций, имеющих α -спиральную структуру на С-концевой последовательности. Методом молекулярной динамики исследованы допустимые изменения значений двугранных углов амилоидного бета-пептида (25-35) низших энергетических конформаций и стабильность элементов вторичной структуры. Результаты сравнительных исследований показали, что предпочтительными конформациями этой молекулы являются не полностью разупорядоченная структура в растворителе, а наличие стабильного спирального участка в С-концевой части молекулы.

Ключевые слова: бета-амилоидный пептид (25-35), конформация, α -спиральная структура, молекулярная динамика