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Folding Simulation of α -S2 Casein Phosphopeptide

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Abstract

Different types of casein phosphopeptides are isolated from casein hydrolysis. The most abundant fragment of casein is KNTMEHV(pS)(pS)(pS)EESII(pS)QET, α -S2 casein phosphopeptide, which contains four phosphoserines. This phosphopeptide plays an important role in immune response and in stimulation of bone and teeth mineralization. Casein phosphopeptides are confirmed to enhance the absorption of calcium, zinc and iron, and formulated in milk for infants and functional foods. We examined structural folding and stability of α -S2 casein phosphopeptide in aqueous solution using molecular dynamics simulation.

Key words: casein phosphopeptide, phosphoserine, molecular dynamics simulation, AMBER.

Фолдинг моделирование α -S2 казеина фосфопептидов

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Аннотация

Различные типы фосфопептидов казеина изолированы от гидролиза казеинов. Самый популярный фрагмент казеина это KNTMEHV(pS)(pS)(pS)EESII(pS)QET, который содержит четыре фосфосерина. Эти пептиды играют важную роль в иммунном ответе и стимуляции костей и минерализации зубов. Казеин фосфопептид применяется для повышения абсорбции кальция, цинка и железа, а также вводится в молоко для младенцев и функциональные продукты питания. Мы исследовали стабильность пептида в водном растворе с использованием моделирования молекулярной динамики. Мы исследовали структурную фолдинг и стабильность α -S2 казеина фосфопептида в водном растворе с использованием моделирования методом молекулярной динамики.

Ключевые слова: казеина фосфопептид, метод молекулярной динамики, AMBER.

Introduction

Casein is one of the most abundant proteins in milk and composes around 80% of milk protein. It is main source of amino acids for young mammals. A -S1-, α -S2-, β - and κ - casein phosphopeptides are isolated from casein by tryptic digestion [1]. There are α S1-casein, β -casein, α -S2-casein and κ - casein at 10-12 mg/ml, 10 mg/ml, 3.7mg/ml, and 3.4 mg/ml, respectively [2].

These phosphopeptides stimulate the proliferation of human peripheral blood lymphocytes [3] and mineralization of bone and teeth [4], enhance of both phagocytosis and immune response [5]. They are involved in calcium, copper, iron and zinc binding [6-8] and dental remineralization [9].

The CPPs contain acidic motif which has a sequence -S(p)-S(p)-S(p)-E-E-, where S(p)s are phosphoserine residues. This negatively charged segment of these peptides provides them resistant to further proteolytic attack, prevents insoluble calcium phosphate, and allows them to form calcium and phosphate ions in aqueous solution and make these essential nutrients bioavailable [10].

Casein phosphopeptides are extensively studied experimentally. Experimental methods give limited information for structural transition and interactions occurring during protein folding. Therefore theoretical studies can become complement and extension of experiments; atomic level information of folding and unfolding processes requires Molecular Dynamics (MD) simulation [11]. Some example of computational works are the simulation of chymotrypsin inhibitor 2 [12], molecular dynamics simulation of β -casein phosphopeptide [13].

In this work, we report a 100 ns molecular dynamics simulation of the folding process and stabilization of α -S2-casein phosphopeptide with AMBER force field and a Generalized Born continuum solvent model. The simulation run from fully extended initial structure to more stable and folded structure. We find a structure that is the lowest energy during the simulation.

Materials and Methods

We initiated the simulation using only α -S2-casein phosphopeptide amino acid sequence (KNTMEHV(pS)(pS)(pS)EESII(pS)QET) [14], with an extended initial structure built by *xleap* module of AMBER14 [15]. MD simulation was fully unrestrained and carried out SANDER module; the FF14SB force fields was employed. Solvation effects were incorporated using Generalized Born model [16], which is implicit solvent method, as implemented in AMBER [17]. We gradually increased temperature from 0 to 325 K and performed 100 ns MD simulation at 325 K.

Results and Discussions

The potential energy of the casein phosphopeptide is monitored during the simulation and shown in Figure 1a as a function of simulation time. Before the MD simulation we increased the temperature from 0 to 325 K, slowly. During the heating phase, systems potential energy was -1551.4606 kcal/mol. Then simulation started and the lowest potential energy value is -1621.8512 kcal/mol at 35.087 ns. We assigned this structure as our folded state and selected the snapshot with the lowest potential energy during the simulation as our reference structure. In Figure 1b, we show the backbone RMSD relative to this structure during the simulation. There is a clear correlation between potential energy and RMSD. Five different folded states are shown from the graphic of RMSD in the 15 - 25 ns, 25 - 49 ns, 49 - 65, 65-80, and 80 - 95 ns regions.

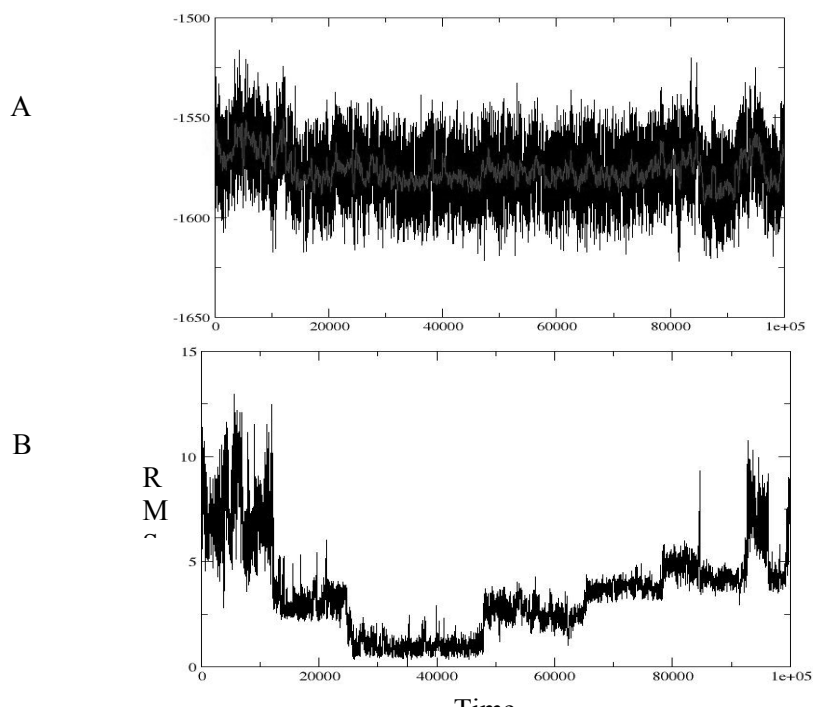


Figure 1. (A) Potential energy of α -S2-casein phosphopeptide as function of time during MD. Gray line is a running average over 100 ps. (B) Backbone RMSD during the simulation, compared to the lowest energy structure

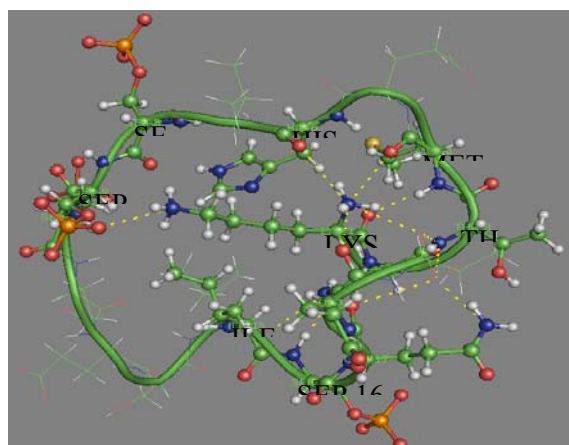


Figure 2. The structure with the lowest potential energy. Dash lines represent hydrogen bonds between amino acids

Sequence: KNTMEHVSSSEESIISQET
SS : TTSS S TTT

Figure 3. Secondary structure assignment using DSSP program. Turn (T) and Bend (S) secondary structures are folded in the structure. SS- secondary structure

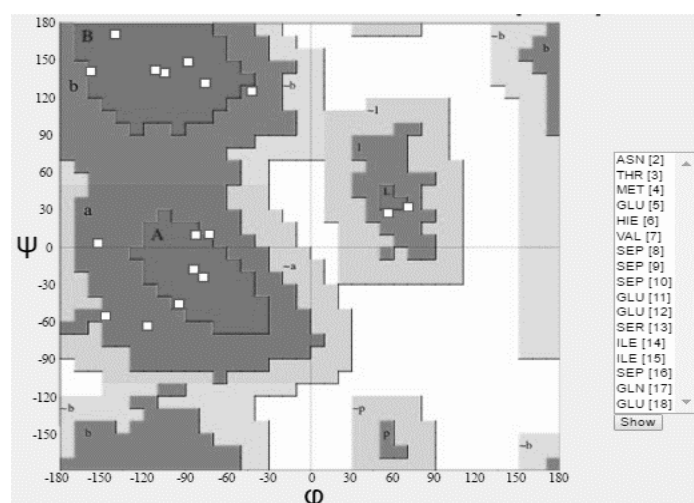


Figure 4. Ramachandran plot analysis of the structure. Here, dark region indicates favored, gray region for allowed and white for disallowed region

The structure with the lowest potential energy is shown in Figure 2. From this figure, N-terminal and LYS 1 amino acid is main contributor for the folding of α -S2-casein phosphopeptide that connects HIS 6, MET 4, THR 3, GLN 17, SER(P) 9 with hydrogen bonds. It also reflects that LYS1 is also packed in hydrophobic core with ILE 15 and HIS 6 residues and four phosphoserines are ready to connect metal ions.

We performed secondary structure assignment using DSSP program (Figure 3). Turn and Bend secondary structures are folded in the structure. Ramachandran plot was done by PROCHECK to measure the accuracy of protein model (Figure 4). All the amino acids are located on the allowed regions.

Conclusions

This folding simulation explores the structural stability of 19-residue long α -S2-casein phosphopeptide. These 100 ns simulation suggests that possible structure of the phosphopeptide but did not include other experimental data. We also noticed that LYS 1 amino acid in the N-terminal plays an important role for the stability. Finally, all amino acids located on allowed regions of Ramachandran plot. Therefore the structure may occur naturally.

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AB-initio Study of Electronic Structure and Magnetic Properties of Ferrites

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Abstract

The paper presents the results of studying the electronic structure and magnetic properties of ferrite compounds (CuFe₂O₄, MgFe₂O₄) using the density functional theory based first-principles method as implemented by the package program WIEN2k for electronic structure simulations.

Key words: ab-initio, ferrite, magnetic property.

I. Introduction

Spinel ferrites with the general formula AB₂O₄ (A=Mn, Mg, Co, Cu and Ni) are very important magnetic materials because of their interesting magnetic properties combined with chemical and thermal stability [1]. Spinel oxides have long played an important role in various applications. In normal spinels AB₂O₄, A is generally a divalent cation occupying tetrahedral sites, while B is a trivalent cation occupying octahedral sites. In inverse spinels, half of B cations occupy the tetrahedral sites, and the formula is rewritten as B [AB] O₄.

We present here, structure and magnetic properties of Cu-Mg ferrites in relation to their crystal structure. The normal and inverse spinel compounds of CuFe₂O₄ and MgFe₂O₄ have been extensively studied. Magnesium ferrite, MgFe₂O₄ is regarded as an important candidate of the spinel family. It has a cubic structure of the normal spinel type and is a soft magnetic n-type semiconducting material, which finds a wide number of applications in heterogeneous catalysis [2-5], gas sensors [6,7], transformers, ferrofluids and magnet core of coils [3,8-11]. It has been demonstrated that this material can be used for thermal coagulation