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Studying of the temperature influence on stability of fibrinogen macromolecules in aqueous solution: A literature mini-review

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C H R O N I C L E

Article history:
Received March 2, 2022
Received in revised form
April 20, 2022
Accepted August 16, 2022
Available online
August 16, 2022

Keywords:
Dynamic Light Scattering,
Hydrodynamic Radius
Albumin
Fibrinogen
D-dimer

A B S T R A C T

A review of the literature, multiple authors in order to systematize information on the effect of temperature in the range of 25-42 ° C on blood proteins, to conduct further studies of the effect of temperature on the stability of fibrinogen molecules in aqueous solution. Study of works on the determination of conformation and stability of protein molecules in the temperature range of living organisms.

1. Introduction

Due to the important biological functions of polymer molecules, studies of the phenomenon of hydration and the influence of the aquatic environment on the size and structure of molecules are of particular interest.[1] The conformation of proteins and their dynamics (also the stability of macromolecules as one of the aspects of dynamic properties) determine their biological functioning. Intensive studies of the molecular mechanisms of conformational changes carried out in recent years do not provide an answer to the main question: at what stage of the process of protein pre-precipitation the dynamic properties of the aquatic environment play a key role, and at what are the internal properties of the macromolecule itself? It was shown that most conformational changes are caused by changes in the hydrate sphere and the volume of the solvent, while the protein molecule itself provides the so-called "active matrix" necessary to orient the dynamics of water to the corresponding biological conformational changes.[2] It was demonstrated how a change in the dynamic properties of water in the vicinity of 20 Å near the protein molecule affects the conformational properties.[3] A large number of experimental and theoretical works confirm the fact of the relationship between the dynamic properties of water and the unique conformational movements of the protein.[2-5]

2. Literature review

In this part of the article, we will consider works devoted to both the structure and main characteristics of albumin and fibrinogen, and the transformation that these proteins undergo under the influence of temperature.

2.1. Structure and main characteristics of albumin

Albumin accounts for 4–5% of blood plasma (35–40 g/l). It provides 80% of oncotic pressure, which is associated with its relatively low molecular weight (65–70 kdalton) and a large number of molecules in the blood plasma. This effect is

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doi: 10.5267/j.ccl.2022.8.004

achieved by the high ability of albumin molecules to bind water – 18 mL/g, which corresponds to 26–28 mm Hg. The polymer chain albumin consists of basic alanine, aspargic acid, glycine, and cysteine alternating in a certain order. The tertiary structure of albumin contains α-spirals connected by single chains.

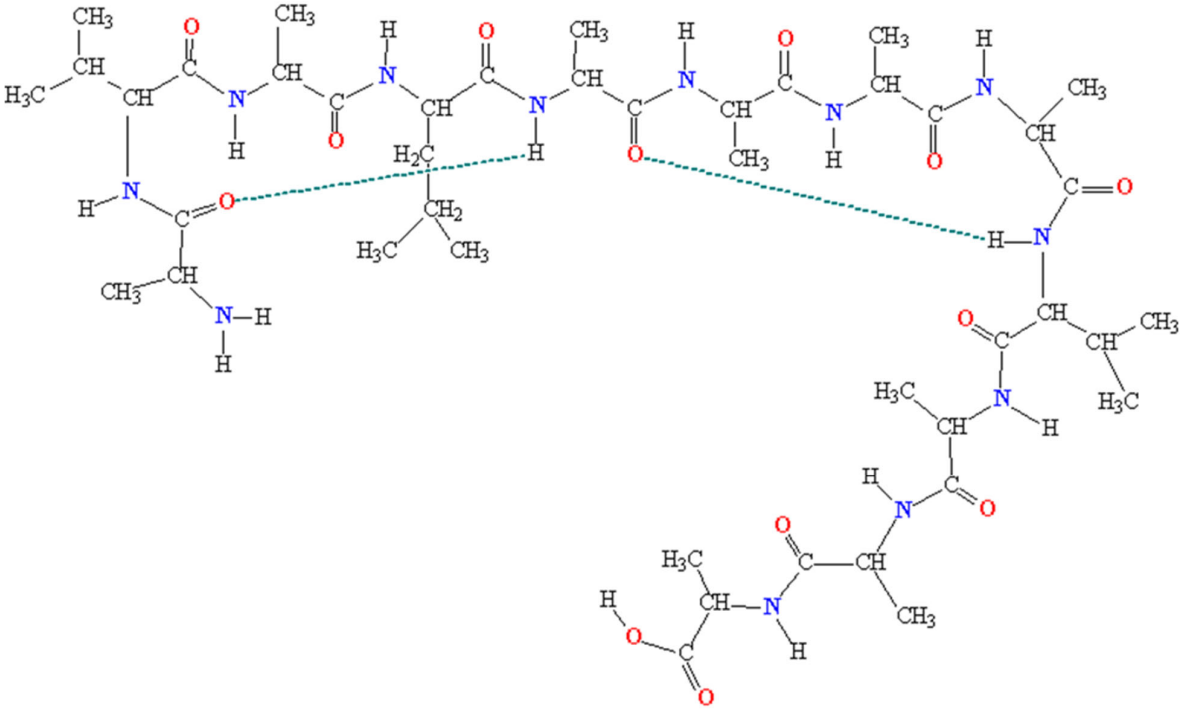

Fig. 1. α-spiral is realized by hydrogen bonds inside a single polymer molecule.

The structure of HSA (human serum albumin) was determined by X-ray crystallography with high resolution.[6] Its structure and dynamics can be influenced by several factors, such as pH, temperature, etc.[7] HSA plays a special role in the transport of metabolites and drug molecules throughout the vascular system, as well as in maintaining the osmotic pressure of plasma acids, metabolites and the binding of various ligands.[8-11] HSA is a single-stranded protein with 585 amino acid residues with a predominant α-helical structure in the shape of a heart.[9,11]

2.2. Structure and dynamics of fibrinogen macromolecule

One of the most important plasma proteins is fibrinogen.[12] As early as 1686, M. Malpighi described the structural basis of a blood clot as a white fibrillar substance that can be seen after washing a red blood clot with water.[13] In 1797, Chaptal proposed the term "fibrin" for this substance. Based on recent studies, a systematic study of physicochemical processes and molecular transformations underlying the transformation of fibrinogen into a three-dimensional fibrin grid has begun. Fibrinogen (Fg) is a multichain glycoprotein weighing 340 kD that can polymerize into fibrin, one of the main components of blood clots. Formation and lysis of fibrin (fibrinolysis) are tightly controlled processes along the path leading to coagulation.[14] After activation by Fg with thrombin, which breaks down fibrinopeptides A and B (FpA, FpB), specific A- and B-B are detected. -pens that bind to the corresponding a- and b-holes of neighboring Fg molecules and initiate the process of polymerization of fibrin. Later, fibrin is stabilized by additional non-covalent and covalent interactions. Interacting with other blood components through integrin binding sites, fibrin plays an important role in the regulation of coagulation and immune response. fibrinolysis, on the other hand, is affected by plasmin, which breaks down fibrin into certain cleavage points in a well-defined time sequence.[15-17] The elongated structure of human Fg, as shown by crystallographic data,[18] is formed by two symmetric units that dimerize through the central globular region E. Each symmetric unit (protomer) consists of 3 peptide chains Aα, Bβ and γ that depart from their N-terminal region (region E), form an elongated section of the helix and end with two globular domains, forming the region D (Fig. 2). C-terminal segment of the chain Aα, that is, the region αC, as well as the N-terminal parts of the chain Aα and Bβ, including FpA and FpB, are mostly disordered (thus not separated in the crystal). Fg, in the polymerized form of fibrin, is a structure that lends itself to mechanical tension. For this reason, early modeling work on Fg was focused on its mechanical properties under the influence of external stress.[16-19] Here instead we report the results of advanced modeling of molecular dynamics (MD) performed on Fg in solution. The simulation allows us to identify large bending movements centered at the hinge point in the area of the collapsed helix Fg. We also present an extensive analysis of the Fg sequence among vertebrate organisms, which suggests that the flexion movements associated with the hinge play one or more functional roles. Simulation we build a simplified representation of the internal flexibility of Fg and use it to match and explain experimental data on the conformational

distribution of a molecule adsorbed on mica. Compliance results indicate the asymmetry of the adsorption properties of different sides of Fg, which can be explained by the presence of large charged spots that are unevenly distributed on the surface of the globular domains of the molecule. allow us to characterize the dynamic properties of the D-region Fg involved in the formation of fibrin and the immune response, emphasizing the presence of related movements between a- and b-holes and the site of binding integrin P1.

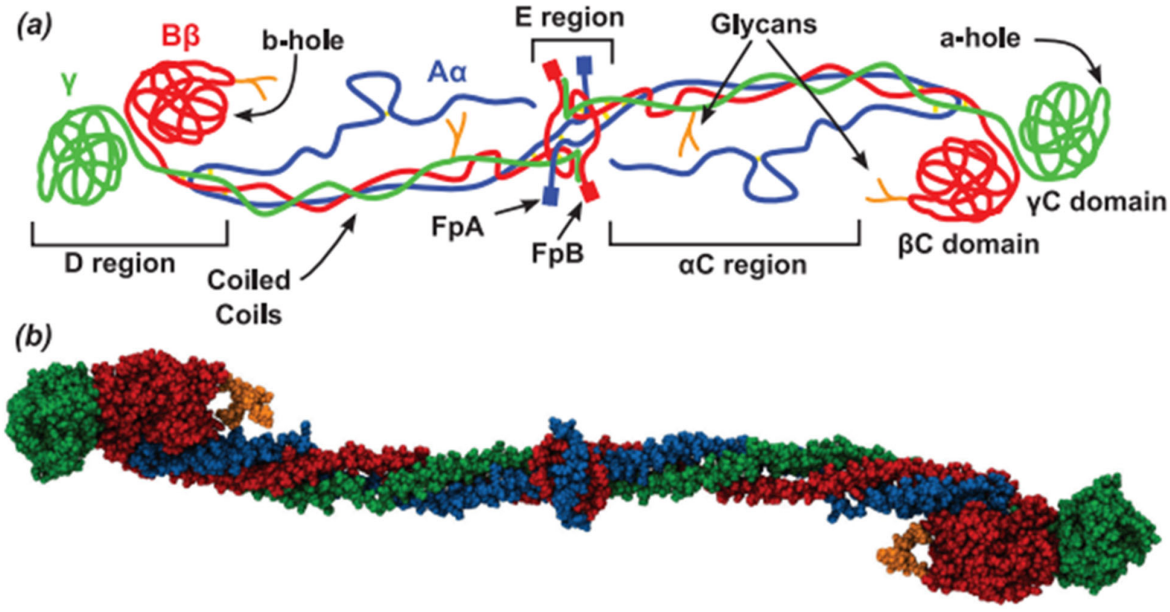

Fig. 2. Fibrinogen molecule. (a) Schematic representation of the fibrinogen molecule. Three chains Fg, Aα, Bβ and γ are shown in blue, red and green, respectively. (b) Mapping of van der Waals of the crystallographic structure (pdb 3GHG) of Fg with color coding, as in (a). Carbohydrates in orange. αC region and peptides FpA and FpB were not separated in the crystal structure.

2.3. The main characteristics of D-dimer

For a comprehensive study and understanding of the influence of the aquatic environment on the molecular mechanisms of confirmation changes in such important proteins as fibrinogen and fibrin, it is necessary to analyze not only the behavior of the macromolecule itself, but also its fragments, one of which is D-dimer.

D-dimer is a fibrin breakdown product, a small protein fragment present in the blood after the destruction of a thrombus (fibrinolysis process). It is called "dimer" because it contains two D-connected fragments of fibrinogen protein.[24-26] D-dimers became an important experiment for patients with suspected thrombotic disorders. While a negative result virtually excludes thrombosis, a positive outcome can be caused by both thrombosis and other factors. Its main benefit, therefore, is to eliminate thromboembolism. In addition, it is used in the diagnosis of a disorder such as intravascular coagulation syndrome.

3. Methodology

This article is based on relevant journals, books, reports, and other secondary materials. Literature analysis is the main method of this research. We reviewed twenty-three articles and books published in internationally well-known academic journals mainly related to supramolecular chemistry, biochemistry, physical chemistry, and other fields to discover the temperature influence on stability of fibrinogen macromolecules.

4. Conclusion

When approaching a point of 42 °C, a local minimum of the hydrodynamic radius of the D-dimer macromolecule is observed. After the temperature point of 42 °C, there is a sharp increase in the size of D-dimer, which is explained by irreversible changes in conformational dynamics. The dimensions of the fibrinogen macromolecule in the investigated temperature range are quite stable. The minimum hydrodynamic radius of the fibrinogen macromolecule is observed in the temperature range of 40-42 °C, at a concentration of 1 mg / mL, and 43-44 ° C, at a concentration of - 2 mg / mL, the minimum depth reaches about 1-1.2 nm. A possible interpretation of the results for fibrinogen is that the external cluster of the aquatic environment is destroyed. The value of the main axis of the albumin macromolecule ellipsoid obtained by micro-viscosimetry is approximately 10 nm. The results of micro-viscosimetry are consistent with the values of the hydrodynamic

radius obtained by FCS methods. The dimensions of the albumin macromolecule are stable in the study temperature range. There is no doubt that organic compounds have different applications and this advantage was shown in a lot of papers published before.

References

1. Bag, M., & Valenzuela, L. (**2017**). Impact of the Hydration States of Polymers on Their Hemocompatibility for Medical Applications: A Review. *International Journal of Molecular Sciences*, 18(8), 1422. (DOI:10.3390/ijms18081422)
2. Frauenfelder, H., Chen, G., Berendzen, J., Fenimore, P. W., Jansson, H., McMahon, B. H., ... & Young, R. D. (**2009**). A unified model of protein dynamics. *Proc Natl Acad Sci*, 106 (13), 5129-34. (DOI: 10.1073/pnas.0900336106)
3. Ebbinghaus, S., Kim, S. J., Heyden, M., Yu, X., Heugen, U., Gruebele, M., ... & Havenith, M. (**2007**). An extended dynamical hydration shell around proteins. *Proc Natl Acad Sci*, 104 (52), 20749-52. (DOI: 10.1073/pnas.0709207104)
4. Born, B., Weingärtner, H., Bründermann, E., & Havenith, M. (**2009**). Solvation dynamics of model peptides probed by terahertz spectroscopy. Observation of the onset of collective network motions. *J. Am. Chem. Soc*, 131 (10), 3752-5. (DOI: 10.1021/ja808997y)
5. Lokotosh, T. V., Malomuzh, N. P., & Pankratov, K. N. (**2010**). Thermal Motion in Water + Electrolyte Solutions According to Quasi-Elastic Incoherent Neutron Scattering Data. *J. Chem. Eng. Data*, 55, 2021-29. (DOI:10.1021/je9009706)
6. Sugio, S., Kashima, A., Mochizuki, S., Noda, M., & Kobayashi, K. (**1999**). Crystal structure of human serum albumin at 2.5 Å resolution, *Protein Eng. 12* 439–446. (DOI: 10.1093/protein/12.6.439)
7. Brown, J.R. (**1977**) *Albumin Structure, Function and Uses*, 1st Ed, Pergamon Press, Oxford, UK,
8. Rothschild, M. A., Oratz, M., & Schreiber, S. S. (**1988**) Serum albumin, *Hepatology 8* 385–401. (DOI:10.1002/hep.1840080234)
9. Carter, D. C., & Ho, J. X. (**1994**) Structure of serum albumin, *Adv. Protein Chem. 45* 153–203.
10. F. Kratz, (**2008**) Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles, *J. Control. Release 132* 171–183.
11. M. Rozga, W. Bal, (**2010**) The Cu(II)/Aβ/human serum albumin model of control mechanism for copper-related amyloid neurotoxicity, *Chem. Res. Toxicol. 23* 298–308
12. Doolittle, R. F. (**2010**). Structural Basis of Signalling Events Involving Fibrinogen and Fibrin. *Handbook of Cell Signalling*, 111–114. (DOI:10.1016/b978-0-12-374145-5.00017-6)
13. Doty, R. L. (**2015**). Handbook of Olfaction and Gustation: Doty/Handbook of Olfaction and Gustation. Hoboken, NJ, USA: John Wiley & Sons, Inc. (DOI:10.1002/9781118971758).
14. Weisel, J.W. (**2007**) Structure of fibrin: impact on clot stability. 5 Suppl 1:116–124. (DOI:10.1111/j.1538-7836.2007.02504.x)
15. Takagi T, & Doolittle R.F. (**1975)** Amino acid sequence studies on the α chain of human fibrinogen. Location of four plasmin attack points and a covalent cross-linking site. *Biochemistry*; 14(23):5149–5156. (DOI: 10.1021/bi00694a020)
16. Takagi, T, & Doolittle, R.F. (**1975**) Amino acid sequence studies on plasmin-derived fragments of human fibrinogen. Amino-terminal sequences of intermediate and terminal fragments. *Biochemistry*; 14(5): 940–946. (DOI: 10.1021/bi00676a010)
17. Mihalyi, E. (**1983**) Kinetics and molecular mechanism of the proteolytic fragmentation of fibrinogen. *Ann NY Acad Sci*.; 408:60–70. (DOI: 10.1111/j.1749-6632.1983.tb23234.x)
18. Kollman, J, Pandi, L, Sawaya, M, Riley, M, & Doolittle R. (**2009**) Crystal Structure of Human Fibrinogen. *Biochemistry*.; 48:3877–3886. (DOI: 10.1021/bi802205g)
19. Lim, B. B., Lee, E. H., Sotomayor, M., & Schulten, K. (**2008**). Molecular basis of fibrin clot elasticity. *Structure*, *16*(3), 449-459. (DOI:10.1016/j.str.2007.12.019)
20. Zhmurov, A., Brown, A. E., Litvinov, R. I., Dima, R. I., Weisel, J. W., & Barsegov, V. (**2011**). Mechanism of fibrin (ogen) forced unfolding. *Structure*, *19*(11), 1615-1624. (DOI: 10.1016/j.str.2011.08.013)
21. Deng, M., & Karniadakis, G. E. (**2014**). Coarse-grained modeling of protein unfolding dynamics. *Multiscale Model Simul*.,12(1) 109–118. (DOI: 10.1137/130921519)
22. Averett, R. D., Menn, B., Lee, E. H., Helms, C. C., Barker, T., & Guthold, M. (**2012**). modular fibrinogen model that captures the stress-strain behavior of fibrin fibers. *Biophys J.*; 103:1537–1544. (DOI: 10.1016/j.bpj. 2012.08.038)
23. Marsh, J. J., Guan, H. S., Li, S., Chiles, P. G., Tran, D., & Morris, T. A. (**2013**). Structural insights into fibrinogen dynamics using amide hydrogen/deuterium exchange mass spectrometry. *Biochemistry*. 52(32), 5491–5502. (DOI: 10.1021/bi4007995)
24. Lugovskoy, E. V., Makogonenko, E. M., & Komisarenko, S. V. (**2013**). Molecular mechanisms of formation and destruction of fibrin. *Kyiv: Naukova Dumka*, – 230 p.
25. Mosesson M.W. (**2005**) Fibrinogen and fibrin structure and functions. *Journal of Thrombosis and Haemostasis*, *3*, 1894-1904. (DOI: 10.1111/j.1538-7836.2005.01365.x)
26. Weisel, J. W., Veklich, Y., & Gorkun, O. (**1993**). The Sequence of Cleavage of Fibrinopeptides from Fibrinogen Is Important for Protofibril Formation and Enhancement of Lateral Aggregation in Fibrin Clots. *J Mol Biol.* 5;232(1):285-97.