Journal of Molecular Graphics and Modelling 44 (2013) 70–80

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Conserved water mediated H-bonding dynamics of Ser117 and Thr119 residues in human transthyretin–thyroxin complexation: Inhibitor modeling study through docking and molecular dynamics simulation

Avik Banerjee, Hridoy R. Bairagya, Bishnu P. Mukhopadhyay*, Tapas K. Nandi, Deepak K. Mishra

Department of Chemistry, National Institute of Technology-Durgapur, Durgapur, West Bengal 713209, India

ARTICLE INFO

Article history:
Accepted 29 April 2013
Available online 14 May 2013

Keywords:
Human transthyretin
Amyloid
Molecular dynamics simulation
Ligand modeling
Docking

ABSTRACT

Transthyretin (TTR) is a protein whose aggregation and deposition causes amyloid diseases in human beings. Amyloid fibril formation is prevented by binding of thyroxin (T4) or its analogs to TTR. The MD simulation study of several solvated X-ray structures of apo and holo TTR has indicated the role of a conserved water molecule and its interaction with T4 binding residues Ser117 and Thr119. Geometrical and electronic consequences of those interactions have been exploited to design a series of thyroxin analogs (Mod1–4) by modifying 5′ or 3′ or both the iodine atoms of thyroxin. Binding energy of the designed ligands has been calculated by docking the molecules in tetrameric structure of the protein. Theoretically investigated pharmacological parameters along with the binding energy data indicate the potentiality of 3′,5′-diacetyl-3,5-dichloro-L-thyronine (Mod4) to act as a better inhibitor for TTR-related amyloid diseases.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Human transthyretin (hTTR) acts as a primary transporter of thyroxin (T4) hormone in cerebrospinal fluid (CSF). Under physiological condition 10–25% T4 binds to TTR in blood plasma [1]. It also plays an important role in retinol (vitamin A) transportation on binding with retinol-binding protein (RBP) [2–5]. Several types of small molecules like natural products (e.g., resveratrol), drugs (e.g., diflunisal, flufenamic acid) and toxins bind to TTR [3,6]. The protein may play some role in sweeping up the toxic and foreign compounds from bloodstream [7] and in the pathogenesis of Alzheimer's disease by scavenging A-β peptide [8].

Normally, hTTR circulates in blood as a soluble homotetramer (55 kDa), but in some cases it polymerizes to form insoluble toxic amyloid fibrils and deposit in the extracellular spaces causing several diseases like familial amyloid cardiomyopathy (FAC), senile systemic amyloidosis (SSA), and familial amyloid polyneuropathy (FAP) [9]. In SSA and FAC, wild type TTR amyloids deposit on the cardiac and other tissues [10–12], whereas the mutant TTRs are involved in FAP and affect the nervous system, heart and choroid plexus [13–15]. Amyloid fibril aggregation causes cardio-myopathies, systemic and central neuropathies, etc. [16,17].

Till now no effective therapy is available for TTR related amyloidoses. The existing treatment is only the liver transplantation. However, recently some drugs, e.g., diflunisal, diclofenac and tafamidis [18,19] are used for TTR related amyloid diseases. Several biochemical evidences reveal that the amyloid fibril formation is prevented by binding of TTR with T4 [20]. But excess use of T4 can cause hyperthyroidism and enhance both osteoblastic and osteoclastic activities in cortical and trabecular bone [21]. Further, the detail interaction of T4 with TTR has also been illustrated in the different crystallographic structures of their complexes (PDB code: 2ROX, etc.). So the associative mode of interaction in the complexing mechanism may be used as a strategy for inhibitor design. In the tetrameric structure of TTR, the central channel has two funnel shaped binding sites for the natural ligands (Fig. 1A) and other small molecules [2,3,6,7]. Each binding site consists of three small depressions, which are termed as halogen binding pockets (HBPs). The outermost pocket (HBP-1) is surrounded by the side chains of Met13, Lys15, Thr106 and Ala108 [22]. Central pocket (HBP-2) is formed by Lys15, Leu17, Ala108, Ala109 and Leu110. The hydroxyl groups of Ser117, Thr119, carbonyl groups of Ser117,

Abbreviations: hTTR, human transthyretin; T4, thyroxin; CSF, cerebrospinal fluid; RBP, retinol-binding protein; FAC, familial amyloid cardiomyopathy; SSA, senile systemic amyloidosis; FAP, familial amyloidotic polyneuropathy; HBP, halogen binding pocket; Mod, modified; MD, molecular dynamics; ns, nano-second; ps, pico-second; fs, femto-second; K, Kelvin; TPSA, total polar surface area.

* Corresponding author. Tel.: +91 0343 2547074; fax: +91 0343 2547375/2546753.
E-mail address: bpmk2@yahoo.com (B.P. Mukhopadhyay).

1093-3263/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jmgm.2013.04.010

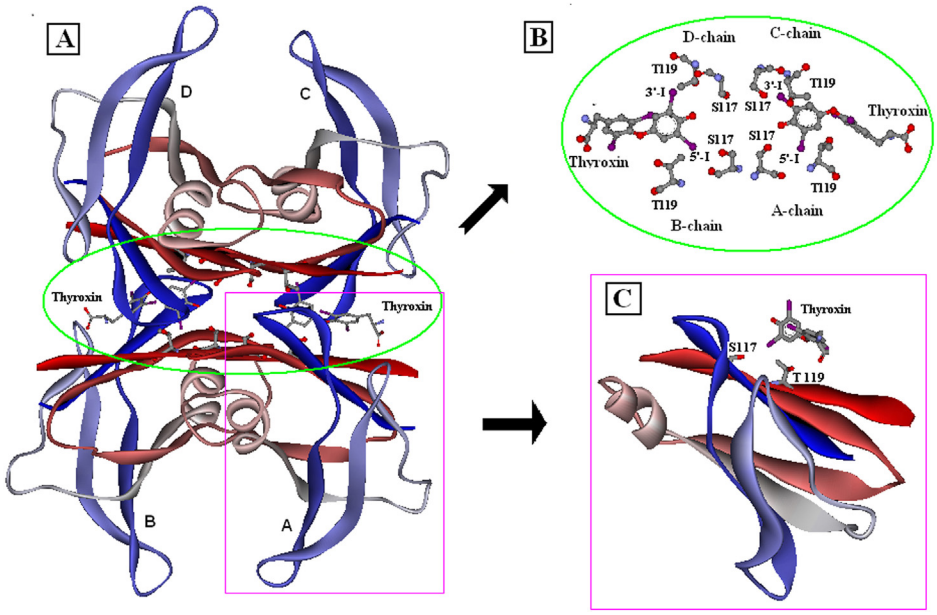

Fig. 1A. Three-dimensional structure of thyroxin bound human tarnsthyretin (tetramer) (PDB code: 1ICT) is shown in (A). Thyroxin bound monomeric transthyretin is shown in (B). Closer look at the inner core of the thyroxin binding cavity is shown in (C).

Thr118, Ala108 and main chain NH groups of Thr119, Ala109 and Leu110 residues form HBP-3 pocket (Fig. 1B). Thyroxin seems to interact with Glu54 [22]. In the X-ray structures, presence of one conserved water molecule at the ligand binding site near Ser117 and Thr119 residues seem to be interesting [23].

So, the presence of water molecules and their interaction at thyroxin binding sites of the unliganded simulated TTR structures may put forward some rational clues on the structural topology of thyroxin (T4) like inhibitors. The hydration susceptibility of T4 binding residues (Ser117 and Thr119) and their dynamics have encouraged us to design some thyroxin analogs. Drug-likeness of those molecules (T4-analogs) can also be judged by computing their molecular properties.

2. Materials and methods

The X-ray crystal structures of human transthyretin [3,23–27] were taken from RCSB Protein Data Bank [28]. The crystallographic and structural information (resolution, *R*-value, number of protein and water molecules in the asymmetric unit, ligands, etc.) of TTR have been included in Table 1. All these structures were found to crystallize as dimer (A and B molecule in the asymmetric unit) and the average temperature factor of B-molecule seem to be higher (~2–7 Å^2) than A-molecule. Swiss PDB Viewer Program [29] was used to separate the A-molecule and construct different structural models for solvation, energy minimization and MD simulation studies.

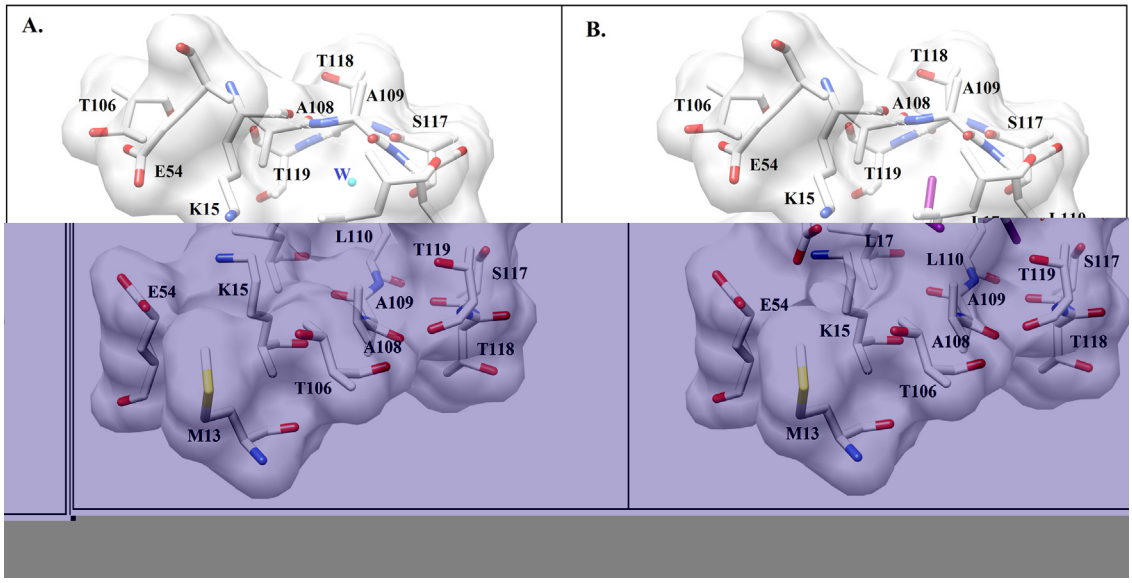

Fig. 1B. The thyroxin (T4) binding pocket of human tarnsthyretin: (A) The occupation of water molecule (W) in the T4 binding pocket (B) occupation of thyroxin in its pocket.

Download English Version:

https://daneshyari.com/en/article/6877756

Download Persian Version:

https://daneshyari.com/article/6877756

Daneshyari.com