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Research article

Heat conduction by thyroid hormone receptors

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Abstract: Thyroid hormone receptors (THRs) together with hormone binding and dissociation are important in gene expressions. The heat conduction properties such as heat capacity, thermal diffusivity and thermal conductivity of THR isoforms are determined by means of molecular dynamics simulations. Mean energy fluctuations in canonical ensemble at 310 K and theory of mole fraction are used to find the heat capacity of THRs in solution. The larger heat capacity of liganded THR-β than that of unliganded THR-β signifies the effect of receptor-ligand interactions, and hydrophobic, vibrational and conformational changes. The specific heats of THR isoforms in solution range from 2000 to 2200 $Jkg^{-1}K^{-1}$ at 310 K which lie within the experimental range for the native globular proteins. Providing temperature relaxation from 310 K to 200 K across protein-water interface in nano-droplets, the thermal diffusivity of THRs ranges from 1.28×10^{-7} to 1.57×10^{-7} m^2/s which is around 1.46×10^{-7} m^2/s for water. The thermal conductivity of THRs lies in the range 0.26–0.30 $Wm^{-1}K^{-1}$ which is about half the value, 0.64 $Wm^{-1}K^{-1}$ for water at 310 K.

Keywords: thyroid hormone receptors; heat capacity; thermal diffusivity; thermal conductivity

1. Introduction

Thyroid signaling defects broadly depend on the action of thyroid hormone receptors (THRs), local ligands, thyroid hormone (TH) carrier proteins, coactivators, corepressors, neural development and metabolism [1]. There are two THR subtypes (THR-α and THR-β) consisting of ligand binding domain (LBD) and homogeneous DNA-binding domain (DBD). The LBDs of these subtypes differ only by a single amino acid residue: Ser277 in THR-α and Asn331 in THR-β [2]. THR isoforms differ in chain length by amino as well as carbxy termini. THR-α1 (triiodothyronine: T3-binding splice product of THR-α) is expressed in skeletal muscle, heart and brain. THR-β has three

T3-binding splice products: THR-β1 is expressed in wide regions of body tissues; THR-β2 is in retina, brain and inner ear; and THR-β3 is predominant in liver, kidney and lung [1]. THs interact with different signalling pathways and their fuction is based on iodine and nutritional status. The TH-liganded isoforms: THR-β, THR-β1 and THR-α in cartoon view of globular forms are shown in Figure 1. The mutational evidances found in THR isoforms indicate thyroid disorders with resistance to THs (RTH) [1,3]. THR isoform selective agonists interfere with the carboxyterminal helix 12. Helix 12 dynamics is responsible for the interaction of THR with corepressors and coactivators. T3 has higher binding affinity than thyroxine (T4) in THR and the T3 bounded isoforms regulate gene expressions under DNA transcription. The unliganded THR represses basal transcription which is known as transcriptional silencing. The abnormal changes in serum TH concentrations are the indicators of hypothyroidism or hyperthyroidism with subacute thyroiditis which are directly or indirectly associated with T3 regulated gene expressions [4].

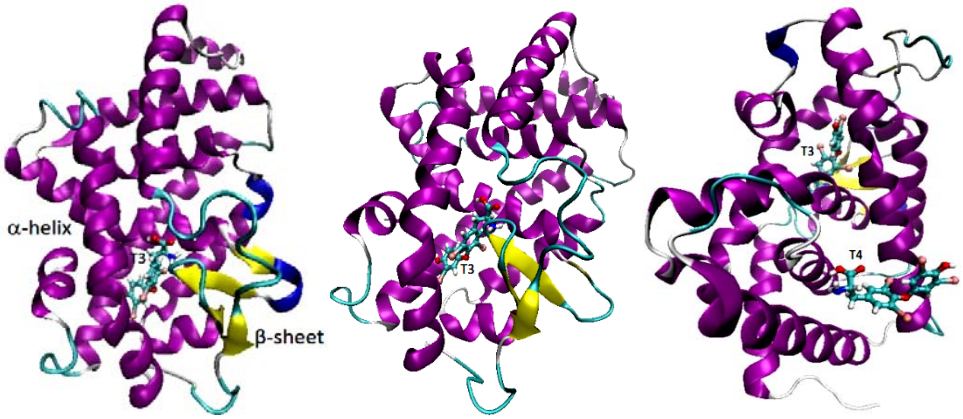


Figure 1. T3- or T4-liganded THR isoforms in the cartoon view of globular proteins: (a) THR-β, (b) THR-β1, and (c) THR-α.

Biologically active molecules are responsible for the heat conduction after the sudden increase in temperature by means of chemical or photochemical reactions. Heat energy transfers through the vibrational states and the residues of globular proteins giving rise to anisotropic flow of energy. It is central to understantand the protein function including ligand binding and dissociation [5]. Heat capacity of a protein-hormone system at a particular temperature depends on folding and unfolding states, polar and non-polar groups in solution, hydration states, and protein-ligand interactions [6]. The heat capacity of a native globular protein is close to the value found from the heat capacities of individual amino acid residues in an extended polypeptide chain [7]. Moreover, T3-liganded and unliganded THRs have the different heat capacities. Anharmonicity enhances thermal conductivity of proteins by the energy flow through localized normal modes of vibration [8]. Heat capacity and thermal conductivity being the temperature dependent quantities, thermal diffusivity also depends on temperature. The temperature gradient differs from chemically active cites to LBDs providing microscopic basis for the signal transduction. The energy fluctuation and dissipation or the temperature dependent changes in internal energy during molecular dynamics simulations (MDS) support to calculate heat capacity of the biomolecular system. The mean energy contributing heat capacity of such complex system is calculated from the ensemble averages of individual terms in

potential function describing the system [6]. The temperature relaxation across protein-water interface is the basis of finding thermal diffusivity and then thermal conductivity [9,10]. This process relies on the principles of transient non-equilibrium thermodynamics.

2. Methodology

2.1. Theory

Enthalpy or mean energy (E) is expressed in terms of ensemble averages of energy terms (U_i) describing a complex molecular system [6], i.e.

$$E = \langle U \rangle = \sum_{i=1}^{N} \langle U_i \rangle = \sum_{i=1}^{N} E_i \tag{1}$$

where i refers to the energy related to bond angle, bond length, dihedral, van der Waal, electrostatic, improper and cross-terms giving rise to Hamiltonian or net potential function (U). Each of these terms contributes heat capacity of the system. The terms $\langle U_i \rangle$ differ in case of any perturbation, or mutation, or liganded and unliganded THR so that the total energy obtained is used to compute Boltzmann weight. The heat capacity, using the method of energy fluctuation in canonical ensemble [6,11], is defined by:

$$C_V = \frac{dE}{dT} = \frac{d\langle U \rangle}{dT} = \frac{\langle \delta U^2 \rangle}{K_B T^2} = \frac{\langle U^2 \rangle - \langle U \rangle^2}{K_B T^2} = mc_V \tag{2}$$

where m is mass and c_V is specific heat capacity of the system, K_B = 0.00198657 kcal $mol^{-1}K^{-1}$ is Boltzmann constant, and T is absolute temperature.

The possible sources of change in heat capacity are protein folding and unfolding including polar and apolar hydration contributions, equilibrium effect, electrostatics, vibrational terms, van der Waal interactions, H-bonding and protein conformational entropy. For the protein in solution, the heat capacity changes due to protein-protein interactions as well as hydration effect. After solvating the globular form of protein in a neutral water-ion solution providing the cellular environment, one can determine the heat capacity of the solvated protein by method of mixture or mole fraction [12,13]. Under thermal equilibrium, $Mc_V = M_P c_V^p + M_W c_V^w$ where the suffix "p" refers to protein-ligands and "w" refers to water-ions. Then, the heat capacity of the protein-hormone system in solution is given by:

$$c_V^p = \frac{Mc_V - M_W c_V^w}{M_P} \tag{3}$$

Knowing the relative masses and the specific heat capacities of mixture and solution, we can determine the specific heat capacity of the protein-hormone system under ideal condition. For this purpose, we perform MDS approach separately for the solvated system or mixture and for the water-ion solution at constant temperature.

The properties of the biological macromolecules explain their functional impact on the living organisms in response to an external perturbation such as thermal gradient. The linear response theory describes the small perturbation relating non-equilibrium transport to equilibrium thermodynamic properties of the system. The complex biomolecular system is solvated under

non-periodic boundary conditions forming a spherical droplet. The local temperature $T(r,t)$ of the system depends on position (r) and time (t) which is governed by the heat diffusion equation:

$$\frac{\partial T(r,t)}{\partial t} = D\nabla^2 T(r,t) \tag{4}$$

where D is thermal diffusivity. For the radius R of the solvated protein-ligand in a globular form, the boundary conditions are: $T(r,0) = T_i$ for $r < R$, and $T(r,t) = T_f$ for $r > R$ where T_i is initial temperature of the system and T_f is final temperature of the surrounding fluid-shell of thickness Δr. Using these boundary conditions, solution of the Eq 4 [14] in the form of mean temperature of the protein-ligand system is written as:

$$\langle T(t)\rangle = T_f + 6\frac{T_i - T_f}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[-\left(\frac{n\pi}{R}\right)^2 Dt\right] \tag{5}$$

Knowing the thermal diffusivity (D) by fitting the simulated data with Eq 5, and using density (ρ) and specific heat (c_V), we can determine thermal conductivity (k) of the protein-hormone system in solution from the relation:

$$k = \rho c_V D \tag{6}$$

2.2. Molecular dynamics simulation

Crystal structures of three THR isoforms consisting of TH-ligands (T3 and/or T4): THRT3-β, THRT3-β1 and THRT3T4-α were obtained from the protein data bank (pdb) codes 3GWS [15], 1XZX [16] and 4LNX [17], respectively. CHARMM-force field topologies and parameters [18–20] were implemented to prepare the simulation packages for solvation, energy minimization, equilibration and production runs by using visual molecular dynamics (VMD) [21] and nanoscale molecular dynamics (NAMD) [22] interfaces. The ligands T3 and T4 were parameterized suitably [20] for the NAMD runs.

The separate THR isoforms: THR-β, THRT3-β, THRT3-β1 and THRT3T4-α were solvated fully in an explicit solvent of neutral water-ions providing the cellular environment. Here, THRT3T4-α was truncated in size by omitting initial residue IDs from 145 to 156 of almost free strand. At first, THR-β as well as THRT3-β was solvated under periodic boundary conditions in TIP3P-water box of cell basis vectors 50.36, 60.92 and 74.78 Å, neutrallized by adding Na^+ and Cl^- ions in the concentration of 0.15 mol/L, performed energy minimization up to 3000 conjugate gradient (CG) steps and then separate equilibration runs were performed up to 2 ns at five different constant temperatures 300, 305, 310, 315 and 320 K. The Langevin constant temperature and pressure (1 atm) controls were used with damping coefficient of 1 ps^{-1} and integrator papameter of 2 fs/step by keeping rigid bonds of H-atoms. The force field related switching, cut-off and pair list distances were 10, 12 and 14 Å, repectively with 1–4 scaling 1.0. The mean energy, $\langle U\rangle$ of THR-β and that of THRT3-β at the five different temperatures were noted down from the last 0.5 ns runs. The slope of straight line fit in $\langle U\rangle$ vs. T plot provides the heat capacity (C_V) of a mixture of solvating T3-liganded or unliganded THR at the body scale temperature 310 K. The same procedure with identical terms and conditions was implemented to a neutral water-ion box of cell basis vectors 30, 45 and 60 Å to find the heat capacity (C_V^w) of the solvent only. It is to be noted that C_V^w

found for the solvent (water) by keeping rigid bonds of H-atoms with 2 fs/step is contributed by the non-bond (electrostatic and van der Waal) energies only. Then, from Eq 3, specific heat capacities (c_V^p) of THR-β and THRT3-β were obtained and compared.

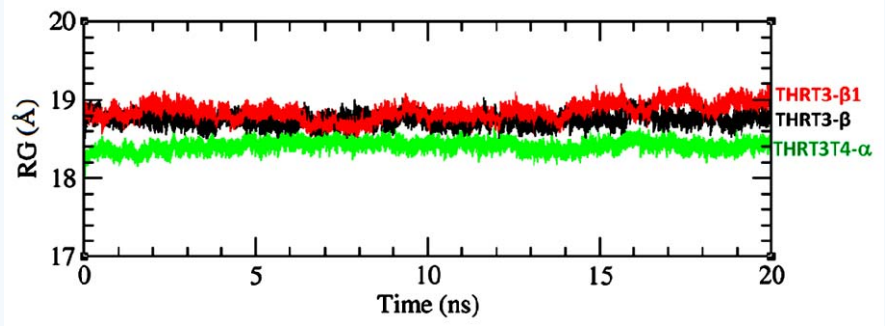
Each of the THR isoforms was solvated in a water-sphere (TIP3P water model) neutralized with Na^+ and Cl^- ions in the concentration of 0.15 mol/L to study their heat conduction properties such as heat capacity (C_V^p), thermal diffusivity (D) and thermal conductivity (k). During the solvation under non-periodic boundary conditions, the radii of THRT3-β, THRT3-β1 and THRT3T4-α related water-droplets were 37.48, 36.99 and 31.29 Å, respectively. The force-filed and integrator parameters, and Langevin dynamics for constant temperature control were fixed as mentioned in the periodic boundary conditions. Each of the systems was geometrically optimized up to the sufficient (2000–5000) CG steps and equilibrated up to 20 ns. Conformational stability of the system was monitored by plotting graphs for root mean square deviation (RMSD) and/or radius of gyration (RG) during equilibration as well as production runs. The systems were also subjected to the additional production runs of 2 ns each in NVT ensemble at 310 K to find the heat capacity (C_V) by using energy fluctuations (Eq 2). Putting C_V of protein-ligand solvated sphere, c_V^w of water-ion solvent, and the related masses in Eq 3, the specific heat c_V^p of a THR isoform was obtained. The specific heat found from $d\langle U\rangle/dT$ by fitting straight line in the periodic boundary conditions as stated above and the specific heat found from energy fluctuation method in non-periodic boundary conditions were compared taking the cases of THR-β and THRT3-β.

The final coordinates of each equilibrated droplet consisting of a THR isoform were taken after its 20 ns run at 310 K. The inner sphere ($r < R$) was kept at initial temperature, T_i = 310 K and the outer shell ($r > R$) was fixed at the final temperature, T_f = 200 K where R = 33 Å and Δr = 4.48 Å for THRT3-β; R = 33 Å and Δr = 3.99 Å for THRT3-β; and R = 27 Å and Δr = 4.29 Å for THRT3T4-α. Then, NAMD simulations of temperature relaxation were performed without any constraint imposed into the atomic vibrations to monitor the change in system's temperature. The cooling process was done up to 20 ps each. By fitting the temperature data with the theoretical expression in Eq 5, the thermal diffusivity of each isoform was obatined and compared. Finally, the system's thermal conductivity was obtained using Eq 6.

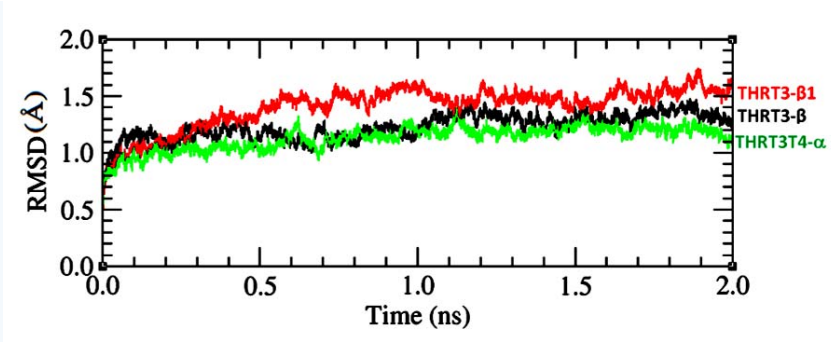
3. Results and discussion

The separately performed 20 ns equilibration runs at 310 K of THR-isoforms solvated in water-droplets result mean ± SD of protein's RMSD: 2.13 ± 0.38 Å for THRT3-β, 1.98 ± 0.21 Å for THRT3-β1, and 2.24 ± 0.31 Å for THRT3T4-α; and the related RGs are 18.74 ± 0.07, 18.84 ± 0.11, and 18.41 ± 0.06 Å, respectively. In case of unliganded THR-β, RG is 18.70 ± 0.09 Å and RMSD is 2.61 ± 0.50 Å during its 20 ns long equilibration. Almost constant values of RG with small SD indicate that the protein-hormone systems are conformationally stable during their equilibration runs as plotted as shown in Figure 2a. The small fluctuations seen in RMSD plots (Figure 2b) are due to formation and breaking of H-bonds among the more stable residues, α-helix and β-sheets of the protein systems while searching for their conformational stability during the course of simulations. The additional production runs up to 2 ns in canonical (NVT) ensemble yield more small values of

RMSD: 1.23 ± 0.11, 1.41 ± 0.18 and 1.13 ± 0.11 Å for THRT3-β, THRT3-β1 and THRT3T4-α proteins, respectively.



(a)



(b)

Figure 2. RG and RMSD plots for the protein backbone in case of (a) equilibration run, and (b) NVT production run of different water-droplets solvating the THR-isoform.

Five NVT simulations up to 2 ns each at temperature difference of 5 K about the body scale temperature 310 K result the values of <U> for liganded and unliganded THR-β under the periodic boundary conditions. The slope of linear fit in <U> vs. T plot (Figure 3a) obtains the heat capacity, C_V of the entire THRT3-β solvated water-box which is 84.59 ± 0.74 kcal $mol^{-1}K^{-1}$ at about 310 K. Since the total mass of THRT3-β solvated water-box is 131765 amu, the related specific heat, c_V is 2688.52 ± 23.52 $Jkg^{-1}K^{-1}$. Similarly, C_V of THR-β solvated water-box (mass = 131186 amu) is 85.59 ± 1.12 kcal $mol^{-1}K^{-1}$ and the related c_V is 2732.31 ± 35.75 $Jkg^{-1}K^{-1}$. Upon implementing the same procedure with identical terms and conditions for the simulations of a neutral water-ion box with 2 fs/step and rigid bonds of H-atoms, its heat capacity, C_V^w contributed by electrostatic and van der Waal energy terms is 31.72 ± 0.43 kcal $mol^{-1}K^{-1}$. Since mass of the modelled water-ion box is 45357 amu, the related specific heat, c_V^w = 2928.75 ± 39.70 $Jkg^{-1}K^{-1}$. Figure 3b shows the best linear fit of <U> vs. T for the water-box where the slope of straight line gives C_V^w. The mass of THR-β is 27640 amu and that of THRT3-β is 28291 amu. By using Eq 3, the specific heat capacities, c_V^p of THR-β and THRT3-β in water-ion solution are 1996.25 ± 20.95 $Jkg^{-1}K^{-1}$ and 1809.88 ± 35.66 $Jkg^{-1}K^{-1}$, respectively. This difference in heat capacity is due to the presence of ligand (T3) in LBD of THR and the T3-receptor interactions as explained in [23,24]. Hydrophobic, vibrational and conformational contributions to the heat capacity changes are involved in the protein-ligand interactions.

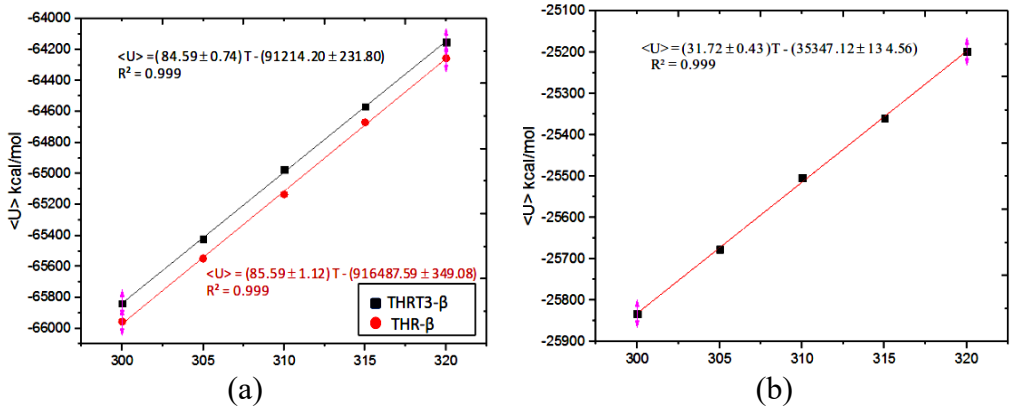


Figure 3. Linear best fits for the change in mean energy or net potential function with temperature of (a) THRT3-β and THR-β solvated water-boxes, and (b) neutral water-ion box where the slope of straight line represents heat capacity of the related system.

The heat capacities of the systems are also determined from the mean energy fluctuations in their canonical ensembles (Eq 2). The specific heat capacities of the globular protein-hormone systems found from this technique (see c_V^p of THR-β and THRT3-β in Table 2) are in close agreement with their values found from the method of linear fit for ⟨U⟩ vs. T (Figure 3a). The flutuations in mean energy of THR-β and THRT3-β solvated droplets are shown in Figure 4a where the values of ⟨U⟩ at 310 K are −66286.35 ± 128.43 and −66218.22 ± 128.76 kcal/mol, respectively. Figure 4b demonstrates the fluctutating energy levels of THR-isoform solvated droplets. The obtained values of mean square fluctuations of energy, masses of THR-isoform slovated droplets and the related heat capacities are depicted in Table 1. We use c_V^w = 2928.75 ± 39.70 $Jkg^{-1}K^{-1}$ and c_V from Table 1 to find the specific heats c_V^p of THRs (Table 2) in solution with the help of Eq 3. c_V^p of the protein-hormone system, determined in this study (e.g. 2030.62 ± 105.32 $Jkg^{-1}K^{-1}$ for THRT3-β) at 310 K, lies within the experimental range: 1200 to 2300 $Jkg^{-1}K^{-1}$ for the native state globular proteins at 25 ºC as given by Privalov et al. 1986 [25]. The heat capacity changes of proteins at different temperatures representing folding and unfolding states are explained by Privalov et al. 2007 [26]. The values of c_V^p for THRs, in this technique, are a bit higher than the heat capacities: 6.5 ± 2.1 $kJmol^{-1}K^{-1}$ for myoglobin and 180 ± 35 $kJmol^{-1}K^{-1}$ for Ca^{2+} ATP-ase (ISU4) in water calculated by Lervik et al. 2010 using MDS method [9]. In the previous studies [8,13,27,28], the average heat capaacity of a native globular protein in solution is about 1500 $Jkg^{-1}K^{-1}$ at 300 K. In a computational work of antifreeze protein performed by Pandey et al. 2017 [29], the hydration states of the protein depending on protein-water H-bonds make influence on its partial heat capacity so that c_V^p ranges from 0.494 cal $g^{-1}K^{-1}$ for the dry state protein to 0.606 cal $g^{-1}K^{-1}$ for the fully hydrated protein at about 300 K. Our results of c_V^p for THRs lie in the range of specific heat for the proteins in the hydration limit given by Pandey's study.

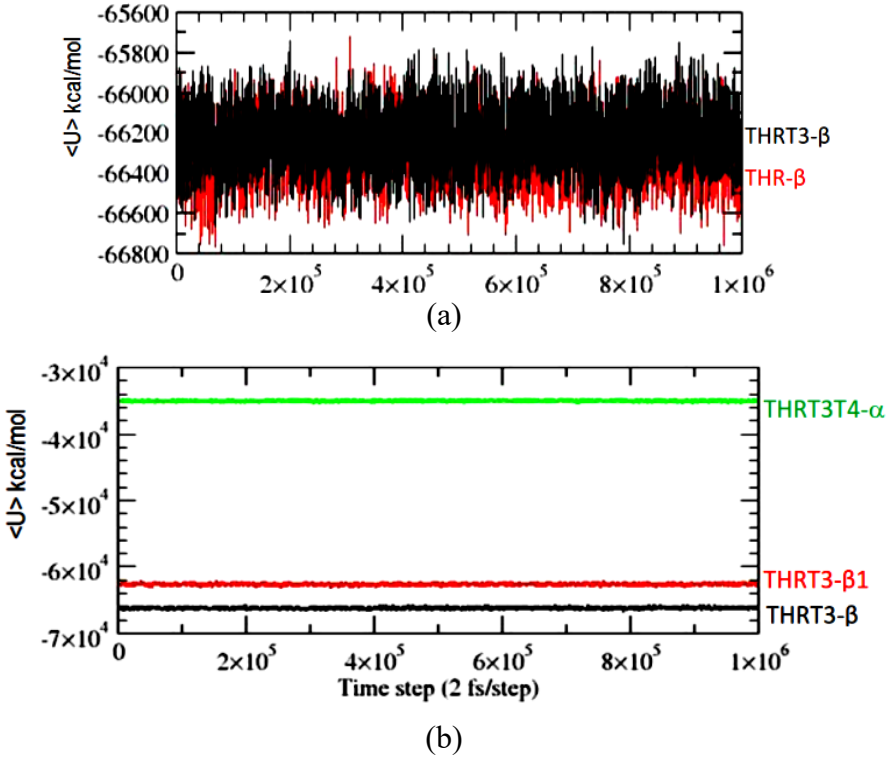


Figure 4. Mean energy fluctuations for (a) liganded and unliganded THR-β, and (b) three THR-isoforms during 2 ns long NVT simulations after 20 ns equilibration run for each system.

Table 1. Heat capacity of THRs solvated droplets (THR-protein + T3/T4 ligand + water + ions) at T = (310 ± 1) K in the NVT ensemble having average poteintial energy ⟨U⟩ where K_B = 0.00198657 kcal $mol^{-1}K^{-1}$.

Molecule in water sphere	No. of atoms in mixture	Total mass, M (amu)	$\langle U^2 \rangle$ (k cal $mol^{-1})^2$	$\langle U \rangle^2$ (k cal $mol^{-1})^2$	$C_V = \frac{\langle U^2 \rangle - \langle U \rangle^2}{K_B T^2}$ (k cal $mol^{-1}K^{-1}$)	c_V (J $kg^{-1}K^{-1}$)
THR-β	21157	132213	4393896241.65	4393879748.25	86.39 ± 0.28[@]	2736.42 ± 8.87
THRT3-β	21192	132864	4384867565.23	4384850985.47	86.85 ± 0.28	2737.51 ± 8.82
THRT3-β1	20266	127468	3925226341.90	3925210205.54	84.52 ± 0.27	2776.85 ± 8.87
THRT3T4-a	12249	79395.7	1225218557.93	1225208975.47	50.19 ± 0.16	2647.36 ± 8.44

[@] The error has been calculated from $C_V = C_V(U, T)$, i. e. $\Delta C_V = C_V \sqrt{\left(\frac{\Delta U}{U}\right)^2 + \left(\frac{\Delta T}{T}\right)^2}$ where ΔU and ΔT are standard errors in potential energy and temperature, respectively.

Table 2. Specific heat capacity (c_V^P), thermal diffusivity (D) corresponding to temperature relaxation between 310 to 200 K and thermal conductivity (k) of THRs in solution where the specific heat contributed by solvent (water + ions) in the droplet is 2928.75 ± 39.70 $Jkg^{-1}K^{-1}$ and density of the protein-hormone system in solution is (950 ± 50) kgm^{-3} at 310 K.

Molecule	No. of atoms	Mass, m_p(amu)	c_V^P ($Jkg^{-1}K^{-1}$)[a]	D (m^2/s)[b]	k ($Wm^{-1}K^{-1}$)[c]
THR-β	3895	27640	2008.75 ± 107.77	(1.56 ± 0.02) × 10^{-7}	0.30 ± 0.023[@@]
THRT3-β	3930	28291	2030.62 ± 105.32	(1.57 ± 0.03) × 10^{-7}	0.30 ± 0.023
THRT3-β1	4014	29069	2244.53 ± 95.73	(1.35 ± 0.05) × 10^{-7}	0.29 ± 0.022
THRT3T4-α	3986	28853	2154.44 ± 46.32	(1.28 ± 0.04) × 10^{-7}	0.26 ± 0.017

[@@] The error has been calculated from $k = k(C_V, D, \rho)$, i. e. $\Delta k = k\sqrt{\left(\frac{\Delta C_V}{C_V}\right)^2 + \left(\frac{\Delta D}{D}\right)^2 + \left(\frac{\Delta \rho}{\rho}\right)^2}$ where ΔC_V, ΔD and $\Delta \rho$ are standard errors in specific heat, thermal diffusivity and density, respectively.

[a] From the calorimetric measurements by Privalov et al. 1986 [25], c_V^P of native globular proteins ranges from 1200 to 2300 $Jkg^{-1}K^{-1}$ at 300 K.

[b] D (water) = 14.6 $Å^2/ps$, D (protein) = 21.1 $Å^2/ps$ for green fluoroscent protein (GFP), 18.7 $Å^2/ps$ for myoglobin [8]; and D (protein) = 4–18 $Å^2/ps$ at the temperature relaxation from 350 to 250 K [9].

[c] k (water) = 0.64 $Wm^{-1}K^{-1}$ & k (protein) = 0.13–0.28 $Wm^{-1}K^{-1}$ at 300 K [8,9].

Thermal diffusivity of THRs ranges from 1.28 × 10^{-7} to 1.57 × 10^{-7} m^2/s at the temperature relaxation from 310 to 200 K that is calculated from the best fitting of theoretical expression (Eq 5) with the simulated data (Figure 5). This result is near to the thermal diffusivity of water (D_w = 1.46 × 10^{-7} m^2/s) and proteins (D_p = 2.11 × 10^{-7} m^2/s for GFP and 1.87 × 10^{-7} m^2/s for myoglobin) reported by Yu et al. 2005 [8]. According to Lervik et al. 2010 [9], D_p ranges from 0.4 × 10^{-7} m^2/s to 1.8 × 10^{-7} m^2/s for the different proteins at the temperature relaxation from 350 to 250 K. We observed a little bit higher thermal diffusivity for THRT3-β than that for THRT3-β1 and THRT3T4-α while cooling them by using the principle of thermal relaxation through the protein-water boundary. The slightly different heat transfer properties observed in THR isoforms (Figure 5) are associated with their structural evidences for the inter-residue H-bonding, energy transport channels and thermal boundary conductance between protein and water [30]. The H-bonding between protein and water facilitate vibrational energy and thermal transport across the interface.

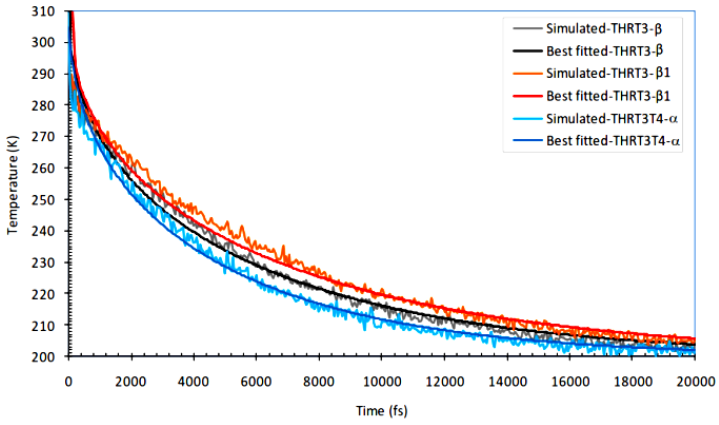


Figure 5. Cooling curves for thyroid hormone receptors.

Thermal conductivity of THR proteins, as depicted in Table 2, ranges from 0.26–0.30 $Wm^{-1}K^{-1}$ provided with the standard error of about 0.02 $Wm^{-1}K^{-1}$. This result shows that the protein-hormone systems are bad conductors of heat in comparision to water (k_w = 0.64 $Wm^{-1}K^{-1}$). As reported by Yu et al. 2005 [8], thermal conductivity of both GFP and myoglobin is k_p = 0.27 $Wm^{-1}K^{-1}$. The value of k_p ranges from 0.13–0.23 $Wm^{-1}K^{-1}$ for the different proteins according to Lervik et al. 2010 [9]. The slightly higher value of k_p has been observed for THRT3-β than that for THRT3-β1 and THRT3T4-α. Such change in heat conduction property is related to the effect of protein surface curvature, hydrophilic and hydrophobic patches and H-bonding between protein residues and protein-water interface [9,30]. According to the theory of non-equilibrium thermodynamics, the development of temperature gradient across THRs-water interface and the related thermal conduction are important biophysical phenomena linked with the functions of the protein-hormone systems towards the regulation of body temperature. The result of lower values of thermal conductivity of proteins than that of water is supporting the principle of body temperature regulation.

4. Conclusion

We have performed molecular dynamics simulations to find heat transfer coefficients of THRs. Heat capcity has been determined by using formula of mole fraction to the constituents of THR solvated periodic-box as well as nano-droplet of water. Numerical differentiation or slope of the best fitted straight line in mean potential function vs. temperature of the periodic box yields the same heat capacity as obtained from the method of mean energy fluctuations of the nano-droplet in canonical ensemble. The heat capacity of THR isoforms in solution ranges from 2000 to 2200 $Jkg^{-1}K^{-1}$ with the standard error limit of about 100 $Jkg^{-1}K^{-1}$ at 310 K. This result lies within the range of 1200 to 2300 $Jkg^{-1}K^{-1}$ as reported by Privalov et al. 1986 and a bit higher than 1500 $Jkg^{-1}K^{-1}$ as given by Yu et al. 2005 for the native globular proteins at 300 K. Our results for the specific heats of the protein-hormone systems are also in the close agreement with that of antifreeze protein in the hydration limit ranging from 2065 $Jkg^{-1}K^{-1}$ for dry state to 2533 $Jkg^{-1}K^{-1}$ for fully hydrated protein at about 300 K as studied by Pandey et al. 2017. In overt hypothyroid disorder, THRs become free of T3. The heat capaity values of T3-liganded and unliganded THR-β are different in some extent due to the change in degrees of freedom, protein-ligand interactions, H-bonding, and hydrophobic, vibrational and conformational changes in presence and absence of T3-hormone in LBD of the receptor. Thermal properties of THRs are directly associated with gene expressions and regulation of body temperature. Thermal diffusivity of THRs has been found to be ranging from 1.28×10^{-7} to 1.57×10^{-7} m^2/s near to 1.46×10^{-7} m^2/s of water at body scale temperature 310 K. A little bit higher value of thermal diffusion coefficient for THRT3-β than that of THRT3-β1 and THRT3T4-α is associated with the effect of inter-residue and protein-water H-bonding, thermal transport channels and boundary conductance in the protein-water interface. Thermal conductivity of THRs ranges from 0.26–0.30 $Wm^{-1}K^{-1}$ with the higher value for THRT3-β in the standard error limit of about 0.02 $Wm^{-1}K^{-1}$ which is about half the value, 0.64 $Wm^{-1}K^{-1}$ for water at 310 K. Our result for the thermal conductivity is also consistent with 0.27 $Wm^{-1}K^{-1}$ as reported by Yu et al. 2005 for GFP and myoglobin. The slightly different values of the heat transfer coefficients for THR-isoforms are related to H-bonding in protein-water interface, surface curvature, and hydrophobic and hydrophillic patches. In conclusion, specific heat, thermal diffusivity and thermal conductivity of THRs are

consistent with that of other proteins as published in the previous literatures supporting the theory and the methodology implemented for their calculations.

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Conflict of interest

The authors declare that they have no conflict of interest.

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