Biochemistry and Biophysics Reports 6 (2016) 63–67

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

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

Molecular docking, a tool to determine interaction of CuO and TiO_2 nanoparticles with human serum albumin

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ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form
3 March 2016
Accepted 10 March 2016
Available online 11 March 2016

Keywords:
CuO NP
TiO_2 NP
HSA
Subdomain III A
Suldow site I
Suldow site II

ABSTRACT

Background: We study the human serum albumin (HSA) protein-CuO nanoparticle interaction to identify the specific binding site of protein with CuO nanoparticles by molecular docking and compared it with HSA-TiO_2 nanoparticle interaction.
Methods: The protein structural data that was obtained using Autodock 4.2.
Results: In case of CuO np-HSA interaction, the distances from the centre of Subdomain IIIA to Arg-472 is 2.113 Å and Lys 475, Glu 492, Ala 490, Cys 487, Ala 490 are the bound neighbouring residues with Lys 475, Glu 492 at aliphatic region. The binding energy generated was -1.64 kcal mol^{-1}. However, for TiO_2 nanoparticle, the binding region is surrounded by Arg 257, Ala 258, Ser 287, His 288, Leu 283, Ala 254, Tyr 150 (subdomain II A) as neighbouring residue. Moreover, Glu 285, Lys 286 forms aliphatic grove for TiO_2-HSA, Ser-287 at the centre region form hydrogen bond with nanoparticle and Leu 283, Leu 284 forming hydrophopobic grove for TiO_2 nanoparticle-HSA interaction. The binding energy generated was -2.47 kcal mol^{-1}.
Conclusions: Analysis suggests that CuO bind to suldow site II i.e subdomain III A of HSA protein where as TiO_2 nanoparticle bind to suldow site I i.e subdomain IIA of HSA protein.
General significance: The structural information that derives from this study for CuO and TiO_2 nanoparticles may be useful in terms of both high and low-affinity binding sites when designing these nanoparticles based drugs delivery system.

1. Introduction

Human serum albumin (HSA) is one of the important transport proteins in the human blood and can bind to any ligand that injected into blood stream thus play important role in drug delivery system. Structurally, a single polypeptide chain of HSA consists of 585 amino acids. HSA consists of three homologous domains (I, II, and III) and each comprised of subdomain A and B. The subdomains IIA and IIIA of HSA consists of high affinity ligand binding sites and is referred as Sudlow's site I and II, respectively [1,2].

The high surface areas and unusual crystal morphologies endue CuO NPs with antimicrobial activity. CuO NPs are most frequently used as antimicrobial (antiviral, antibacterial, antifouling, antifungal), antibiotic treatment alternatives, nanocomposite coating, catalyst, lubricants. Also, used in applications like gas sensors, solar energy conversion, electrode material in lithium ion batteries, as field emitter, and as a heterogeneous catalyst [3]. TiO_2 NPs drive a strong interest, subsequently intensive experimental and theoretical studies, owing to its unique photocatalytic properties, excellent biocompatibility, and high chemical stability. TiO_2 NPs are used widely in biomedical applications that include the photodynamic therapy for cancer treatment, drug delivery systems, cell imaging, biosensors for biological assay, and genetic engineering. High physical and chemical stability of CuO and TiO_2 nanoparticles renders their extreme use in catalytic applications [4]. However, Nanotoxicology is come forth in the field of toxicology to address the gaps in knowledge and adverse health effects associated with CuO and TiO_2 nanomaterials. CuO NPs exposure results in significantly elevated level of antioxidant enzymes. CuO NPs has also been found to induce hepatotoxicity and nephrotoxicity. CuO NPs can equally exhibit neurotoxicity and genotoxicity [5–8]. TiO_2 NPs has also been found to induced similar toxicity but to lesser extent as compared to CuO NPs [9–12]. Thus, it is very important to understood interaction mechanism of CuO NPs and TiO_2 NPs with serum albumin and accordingly reduces CuO NPs and TiO_2 NPs vulnerability in the system thereby minimizing its toxic effects.

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http://dx.doi.org/10.1016/j.bbrep.2016.03.004

The binding affinity of a ligand with serum albumin helps us to understand its bioavailability, distribution, and elimination from the body. HSA can bind a notable variety of drugs affecting their delivery and efficacy and ultimately altering the drug's pharmacokinetic and pharmacodynamic properties. Additionally, HSA is widely used in clinical assumptions as a drug delivery system due to its potential for improving targeting while decreasing the side effects of drugs. Nanoparticles such as CuO and TiO_2 are widely used in medical application such as drug delivery system [13,14]. Subsequently, the affinity between HSA and nanoparticles as legend becomes crucial interest to study in order to determine nanoparticles binding potential with circulating protein. The binding study conducted through molecular docking can help to infer the duration of its half-life that consequently reveals the efficacy of nanomedication [1]. Drug delivery mechanism is propagated through serum albumin. In order to introduce CuO NPs and TiO_2 NPs in nanodelivery it is most worthy for the researchers to be aware about interaction sites and the region involve in binding with serum albumin so that nanoparticles itself may not become inhibitor for the drug binding sites. Therefore, present study conducted on the comparison of binding affinity of serum albumin with CuO and TiO_2 nps. Thus, it may provide valuable information concerning their therapeutic efficacies.

2. Methods

Molecular docking studies were carried out using AutoDock 4.2 tool to predict the preferred binding mode and binding sites of TiO_2 and CuO with HSA. The structure of TiO_2 and CuO was drawn using ACD/ChemSketch and its geometry was optimized by combine use of Gaussian 03 program and Autodock 4.2. The crystal structure of HSA (PDB ID: 1E7I) was obtained from Protein Data Bank [15]. Before docking analysis Hetatm were removed from the protein and the energy was minimized by SPDBV-Swiss-pdbviewer. For docking calculations, Lamarckian genetic algorithms (LGA) were used and grid parameters were set as $126 \times 126 \times 126$, with a spacing of 1 Å, in AutoDock 4.2. To determine the preferred binding sites on HSA, TiO_2 and CuO molecules were allowed to move within the whole region of HSA via 50 runs to obtain the possible binding gesture. The output from AutoDock was further analyzed with PyMOL and UCSF Chimera software package [16,17].

3. Results

3.1. Different residues in HSA protein and their distances from tryptophan in case of CuO np-HSA interaction

The preferable binding of CuO nanoparticles to HSA protein obtained was through polar residue Arg 472 residue and through Lys 475, Glu 492, Ala 490, Cys 487, Ala 490 bond formation. The measured distances between the surfaces of the CuO np and Arg residue (subdomain IIIA) site II obtained were 2.113 Å, 2.410 Å, with Glu having 1.713 Å as shown in Fig. 1. Therefore, these sites would be the probable binding sites of HSA with CuO nanoparticles.

3.2. Geometrical accommodation and the chemical environment of domain in HSA in case of CuO np-HSA binding

4 hydrogen bonds were predicted involving hydrogen atoms from three different amino acid residues of HSA (Arg-472, Gln-492 and Ala 490) as showed in Fig. 2. Lys 475, Glu 492 residue are charged grove of HSA bind with CuO nanoparticle as depicted in Fig. 3.

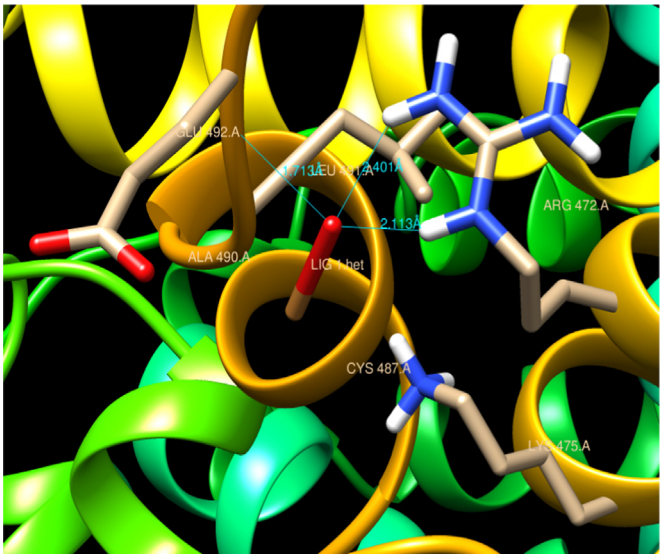

Fig. 1. Residual interactions at the HSA-CuO nanoparticle interface in HSA. Schematic representations of different residues that are involve in binding with CuO NPs and their distances obtained from central subdomain III A.

3.3. Different residues in HSA protein and their distances from surface of TiO_2 np-HSA interaction

The preferable binding of TiO_2 nanoparticles to HSA protein obtained was through polar hydrophilic amino acids Arg 257 residue and thorugh Ala 258, Ser 287, His 288, Leu 283, Ala 254, Tyr 150 form bond formation with TiO_2 np. The measured distances between the surfaces of the TiO_2 np and Arg residue (subdomain II A) obtained were 2.536 Å. However, 2.916 Å, 2.631 Å, 1.779 Å, 2.563 Å, 2.920 Å and 1.972 Å is the bond length with respective amino acids of bound region as shown in Fig. 4. Therefore, these sites would be the probable binding sites of HSA with TiO_2 nanoparticle.

3.4. Geometrical accommodation and the chemical environment of domain in HSA in case of TiO_2 np-HSA binding

4 hydrogen bonds were predicted involving hydrogen atoms from three different amino acid residues of HSA (Tyr 150, Ser-287 and Arg 257) as shown in Fig. 5. Leu 283, Leu 284, Glu 285, Lys 286 residue form hydrophobic pocket of HSA that bind with TiO_2 nanoparticle as depicted in Fig. 6.

3.5. Binding energy predicted for CuO np-HSA interaction and TiO_2 np-HSA interaction

The predicted binding models of CuO with the lowest docking energy (-1.64 kcal mol^{-1}) at site II of HSA were used for binding orientation analysis. Whereas, in case of TiO_2 nanoparticle the lowest docking energy obtained was -2.47 kcal mol^{-1} (Table 1) at the binding region.

4. Discussion

Amino acid sequence of human serum albumin (HSA) consists of 18 tyrosines, 6 methionines, 1 tryptophan (Trp 214), 17 disulfide bridges, and only one free thiol (Cys 34) residue. HSA comprises of three homologous domains (I, II, and III) that assemble to form a cordate molecule. The hydrophobic pockets at subdomains IIA and IIIA is the main regions of ligand interaction with IIIA having the highest affinity for the interaction [2,18]. In our study the whole region of HSA