Docking method reveals binding patterns of α,ω-dioc acids by albumin

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Introduction:

Serum albumin is a well known transport protein in humans and animals. It is a single-chain α-helix protein consisting of 3 main domains, each of them composed of smaller subdomains [1]. It binds a variety of chemical substances. One of its functions is binding of monocarboxylic fatty acids [1]. But α,ω -dioc acids can also be found in human metabolism. A high concentration of these acids may be an indicator of some pathological processes: for example, Reye`s syndrome. [2]. It is characterized by increased concentration of α,ω - dioc acids which amount can reach 55% of the total fatty acid pool. The ability of an albumin to bind α,ω – dioic acids is known, but its specific sites have not been described [3]. So, our goal was to describe these sites for α,ω – hexadecanedioic acid (HDA) using a molecular docking method.

Materials and methods:

To create a model of HDA, a HyperChem package was used. Then, geometrical optimization of this model was performed using the "Conjugate gradient" method. The protein model used was the 1E7H.pdb file, and the missing atoms were added by the SwissPDB viewer. The partial charges on the protein and on HDA were computed by Gasteiger's mechanism. After these preparations, VinaAutodock was used for the molecular docking procedure [4].

Results:

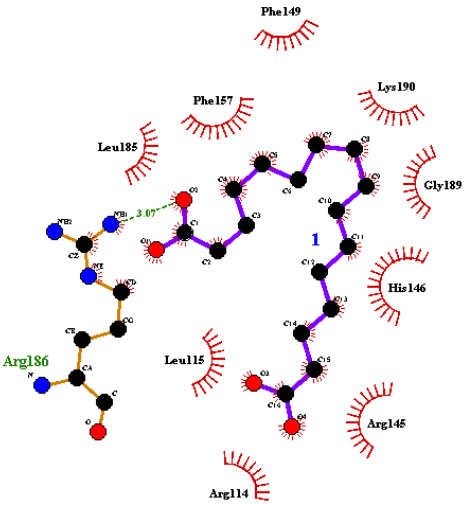
We found 4 potential binding sites for HDA in human serum albumin. The first 3 sites partially match with sites for palmitic acid.

SITE I. The first site is composed of residues belonging to 3 α-helices of the IB subdomain and 3 residues of an unstructured region. One of HDA's carboxylic moieties connects to the N-atom of the Arg186 side-chain by H-bond. Phe157 and Phe149 also play important role in the binding of HDA's methylene chain by hydrophobic interactions. Comparison of these sites for HDA and for palmitate shows similarity but reveals some differences. Palmitic acid produces a greater amount of hydrophobic interactions with the protein.

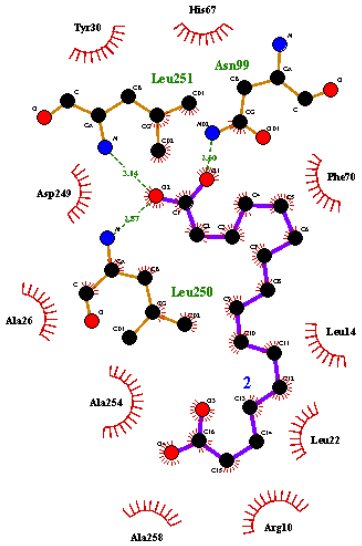
SITE II. The second site is made of residues belonging to 5 α-helices of the IA and IIA subdomains. Nonpolar residues make hydrophobic contacts with HDA. One of HDA's carboxylic group makes 3 hydrogen bonds: the first bond forms a contact with the Asn99 side-chain, and the two others connect with the N-atoms of the protein backbone which belong to Leu250 and Leu251. Dimensionally, SITE II is located near the second binding site of palmitic acid and partially matches with it.

SITE III. The third site is located in the IIIA subdomain and formed by residues which belong to 5 α-helices. Asn391 makes an H-bond with a carboxylic moiety of HDA. The second carboxylic group does not form any contacts. HDA's methylene chain is anchored by hydrophobic interactions with hydrocarbon residues. SITE III is located near the third binding site for palmitate and has some common residues with it (Leu 387, Asn 391). But in the case of palmitic acid, Asn391 does not bind it and its carboxylic moiety is fixed by 3 H-bonds with the Ser342, Arg348, and Arg485 side-chains. SITE III also partially matches with the fourth binding site for palmitic acid.

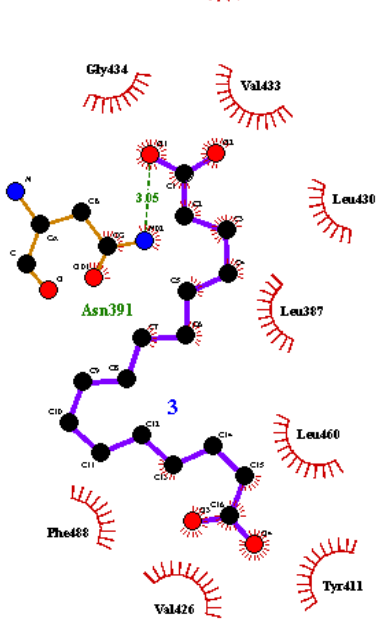
SITE IV. This site is formed by residues of 6 α-helices located in subdomains IB, IIA, IIB, and IIIA. Both carboxylic groups of HDA form H-bonds with the protein. The first one is connected to the Arg218 side-chain and to the amide nitrogen of Val343. The second is connected to the side-chain hydroxyl of Se454. SITE IV is located between the sixth and seventh sites for palmitic acid. There is no significant similarity in the dimensional location of HDA and palmitic acid at this site.



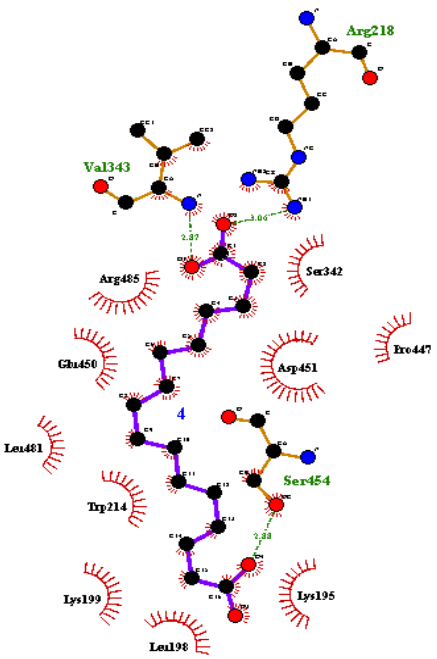
SITE I for HDA



SITE II for HDA



SITE III for HDA



SITE IV for HDA

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