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Drug Interactions with Human serum albumin

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Abstract:

Albumin is the most abundant plasma protein present in humans and accounts for about 55-60% of the measured serum protein. The most crucial role of Human serum albumin (HSA) is to transport drugs, metabolites, and endogenous ligands in the bloodstream. Binding of a drug to HSA controls its free and active concentration which provides a platform for a prolong duration of action and ultimately affects the absorption, metabolism, distribution and excretion of drugs. HSA attracts great interest in the pharmaceutical industry as it can bind to a significant types of drugs which impacts their delivery and efficacy. This review focuses on the binding properties of HSA and impact of drug binding on the pharmacokinetic and pharmacodynamic properties.

Introduction:

Plasma proteins play an important role in the transportation and deposition of substances such as fatty acids, hormones and medicinal drugs in the circulatory system [1]. Human serum albumin is the most abundant protein of blood plasma. HSA is produced in the liver and exported to blood stream in the single non-glycosylated form. HSA has extraordinary ligand binding quality due to which different types of compounds are transported in large quantities even beyond their solubility in blood plasma. Under normal physiological conditions, HSA accommodates up to two moles of unesterified fatty acids but during certain diseased states, it may carry up to six moles of the substance[2]. It has very important role in various types of physiological functions like regulation of colloidal osmotic pressure, exporting of number of different biomolecules such as fatty acids, amino acids, bile acids, hormones, toxic metabolites etc. [3,4,5]. A wide variety of drugs also binds with HSA and delivered to their target organs/tissues. [3,4,6] Binding of drugs with HSA represent its role in protecting the bound drugs from oxidation and induces the drug distribution in the whole body. HSA binding administer the overall pharmacodynamics and pharmacokinetics of

the drug[7]. Serum albumin is the primary criterion of nutrition so it is used to detect the nutrient deficiency in persons having chronic kidney disease[8]. HSA contains number of binding sites for the primary ligands which bind to it. Crystallographic studies showed the existence of seven binding sites which are occupied by saturated fatty acids from medium to long chain[9].

Human Serum Albumin and its binding sites

HSA is a non-glycosylated polypeptide with single chain. It is negatively charged and water soluble protein[8]. Its molecular weight is 66,500 Da with 585 amino acids in the chain and has 67% of its secondary structure is alpha helix [3]. HSA is composed of three homologous domains that congregate together to form a heart-shaped structure and each domain is made up of two subdomains, A and B. These subdomains share common structural motifs and stabilized by 17 disulphide bonds. The primary sites of ligand binding are situated in the hydrophobic cavities present within subdomains IIA and IIIA and shows similar chemistry[10,11]**.** There are seven binding sites of HSA localised within subdomains IB, IIIA and IIIB and on the interfaces of subdomains. Ligands with aromatic and heterocyclic structures are found to be bind primarily within subdomains IIA and IIIA which is also known as site I and site II, respectively [11,12]. Various studies showed that endogenous substances like bilirubin, hemin etc. and some drugs such as azapropazone, indomethacin etc. are found to bind within IB subdomain. Other drugs such as diflunisal, halothane and ibuprofen have been found to bind within IIA-IIIB domains [12]. Site 1 is located in subdomain IB, site 2 is present at the interface between subdomains IA and IIA, both site 3 and site 4 are localised within subdomain IIIA which is also a drug binding site II), site 5 is present within subdomain IIIB, site 6 is a shallow excavation at the interface between subdomains IIA and IIB and the last binding site 7 is the entire drug-binding pocket of domain IIA which is also known as drug site I[9].

Binding of substances to human serum albumin

Human Serum Albumin has a crucial role in the transportation and deposition of substances due to which it has become important to reveal the interaction between drugs and proteins in the bloodstream. Studies revealed that the HSA contains multiple binding sites for its primary ligand i.e. fatty acids[13,14] Recent studies of X-Ray crystallography demonstrated that HSA possess seven binding sites that may or may not be filled by both medium and long-chain saturated fatty acids of varying chain length which ranges from C10 to C18[15,16,17] . Some in vivo studies showed that two-third of fatty acids bound to albumin under normal conditions are unsaturated in nature. The most common types of unsaturated fatty acid bound are oleic acid, linoleic acid and arachidonic acid which are 33%, 20% and 5% respectively, of the fatty acids bound with albumin in normal serum conditions but these proportions may be influenced by changing in dietary habits of individual[9]. Interaction of human serum albumin with a wide variety of artificially synthesized drugs used in certain diseased states may affect the bioavailability and effectiveness of drugs. Therefore several recent studies have focused on disclosing the molecular details behind these interactions [18,19]. Binding to HSA may affect the bioavailability, distribution and elimination of pharmaceutical or nutraceutical active compounds inside the body [20]. Binding of drugs to HSA may

prolong the their in vivo half life which is one of the most important factors in characterizing the pharmacokinetics of drugs[21]. In many cases more than half of the clinically administered anesthetics bound to the HSA and in some cases 80% of intravenous agent like propofol also bound to it[17]. Propofol, Aspirin and Halothane are some anti-inflammatory drugs whose docking studies with HSA proved the binding at the specific sites of human serum albumin[22]. Molecular docking studies revealed the binding properties of various steroidal and non-steroidal anti-inflammatory drugs by investigating the interactions between Human serum albumin and anti-inflammatory drugs[23].

Conclusion & Future prospects

As, HSA is a major drug carrier of the blood stream therefore it may help in the selective drug delivery to the tumor area and may facilitate drug access for lipoproteins into the cell via different receptor processes. On the other hand, HSA may also cause a decrease in the drug amount available for the binding on receptor by the fast removal from the blood circulation. There is a balance between these two contrary activities which might be different for different carrier proteins and also different among different drugs [24]. Therefore, it is crucial to understand the molecular details of the particular interactions of drugs with HSA for the safe formulations drugs and their effective dosages [20,25].

Since the world is expected to see about 20 million cases of various cancers in the next two decades, it is essential to study the specific interaction of anticancer drugs with Human Serum Albumin (HSA) [20]. The ideal drug carrier should improve efficiency of drugs and control the release of drugs at the right place with right rate. The structural analysis of HSA complexes may help us in guiding rational design of HSA protein by altering its drug binding capacity using various strategies such as modification of structure of compounds or editing certain HSA amino acids which leads to make the HSA as a more effective carrier for drug delivery to the target site.

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