Journal of Molecular Structure xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Clinical relevance of drug binding to plasma proteins ☆

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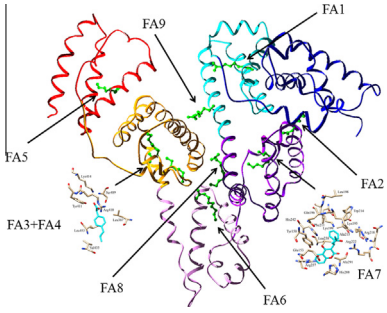
HIGHLIGHTS

- Clinical relevance of drug binding to plasma proteins.
- Binding to plasma proteins highly influences drug efficacy, distribution, and disposition.
- Serum albumin displays an extraordinary ligand binding capacity.
- α-1-Acid glycoprotein is the main carrier for basic and neutral drugs.
- High- and low-density lipoproteins play a limited role in drug binding.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Human serum albumin
Human α-1-acid glycoprotein
Human lipoproteins
Ligand binding properties
Drug binding

ABSTRACT

Binding to plasma proteins highly influences drug efficacy, distribution, and disposition. Serum albumin, the most abundant protein in plasma, is a monomeric multi-domain macromolecule that displays an extraordinary ligand binding capacity, providing a depot and carrier for many endogenous and exogenous compounds, such as fatty acids and most acidic drugs. α-1-Acid glycoprotein, the second main plasma protein, is a glycoprotein physiologically involved in the acute phase reaction and is the main carrier for basic and neutral drugs. High- and low-density lipoproteins play a limited role in drug binding and are natural drug delivery system only for few lipophilic drugs or lipid-based formulations. Several factors influence drug binding to plasma proteins, such as pathological conditions, concurrent administration of drugs, sex, and age. Any of these factors, in turn, influences drug efficacy and toxicity. Here, biochemical, biomedical, and biotechnological aspects of drug binding to plasma proteins are reviewed.

1. Introduction

Drug binding to plasma proteins is often the first step in drug distribution, action and disposition. Human serum albumin (HSA) is the most important drug carrier in adult humans [1] and mainly binds acidic drugs. α-1-Acid glycoprotein (AGP) is the next important one [2–4] and binds basic and neutral drugs; less relevant in drug binding are high- and low-density lipoproteins (HDL and LDL, respectively).

Abbreviations: AGP, human α-1-acid glycoprotein; APO, apoprotein; CETP, cholesterol ester transfer protein; FA, fatty acid; HAART, highly active antiretroviral therapy; HDL, high-density lipoproteins; HPX, hemopexin; HPX-heme-Fe, Fe-heme-hemopexin; HSA, human serum albumin; HSA-heme, human serum heme-albumin; LCAT, lecithin-cholesterol acyl transferase; LDL, low-density lipoproteins; RCT, reverse cholesterol transport; SRB1, scavenger receptor B1; VLDL, very low-density lipoprotein.

☆ This article is part of a special issue titled "Fluorescence studies of biomolecular association processes. Towards a detailed understanding of spectroscopic, thermodynamic and structural aspects".

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0022-2860/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2013.09.053

Drug binding to plasma proteins such as HSA and AGP is usually reversible, occurs at specific sites, and is a major determinant in drug disposition since it highly affects the pharmacokinetics and pharmacodynamics of most commonly prescribed drugs. For instance, it results in increased solubility for lipophilic drugs, thus allowing them to reach their site of action. However, since the protein-bound drugs cannot readily leave the capillaries, only the unbound fractions can be distributed to tissues therefore having pharmacological activity, as well as toxic effects [5–9].

Usually, a drug is considered highly-bound to plasma proteins when the bound fraction exceeds about 90% of the total drug concentration. Besides distribution, binding to plasma proteins also affects drug metabolism and elimination, since both hepatic uptake and glomerular filtration are directly proportional to the free drug fraction present in the plasma. The fraction of total drug that is bound to plasma proteins depends on drug concentration and affinity as well as on the number of available binding sites [9–11].

Several factors influence drug binding to plasma proteins. First of all, the extent of the bound drug is altered in certain diseases. For example, hypoalbuminemia secondary to severe liver disease results in reduced drug binding and therefore in increasing the unbound drug fraction. Also, pathological conditions that induce an acute phase reaction response such as arthritis, myocardial infarction, and cancer lead to elevated levels of AGP, thus enhancing binding of basic drugs [12]. Drug binding to plasma proteins can be altered by the concurrent administration of drugs with similar physicochemical characteristics that compete with each other and with endogenous substances for common or functionally-linked binding sites. Lastly, age and sex are two other factors that can affect drug binding to plasma proteins [7,9,13–15].

Here, biochemical and biomedical aspects of drug binding to plasma proteins are reviewed, highlighting the clinical relevance of this process.

2. Serum albumin

HSA, the most abundant protein in plasma (about 7.5×10^{-4} M), is the main determinant of plasma oncotic pressure and the main modulator of fluid distribution between body compartments. Moreover, HSA displays an extraordinary ligand-binding capacity, providing a depot and carrier for many endogenous and exogenous compounds. In fact, HSA represents the main carrier for fatty acids (FA), affects pharmacokinetics of many drugs, provides the metabolic modification of some ligands, renders potential toxins harmless, accounts for most of the anti-oxidant capacity of human plasma, and displays (pseudo-)enzymatic properties [1,14–25].

HSA may be considered as a biomarker of many diseases, including cancer, rheumatoid arthritis, ischemia, post-menopausal obesity, severe acute graft-versus-host disease, and diseases that need monitoring of the glycemic control [1,26–28]. Moreover, HSA is widely used in the clinical practice to treat several diseases, including hypovolemia, shock, burns, surgical blood loss, trauma, hemorrhage, cardiopulmonary bypass, acute respiratory distress syndrome, hemodialysis, acute liver failure, chronic liver disease, nutrition support, resuscitation, and hypoalbuminemia [1,29–34].

Recently, biotechnological applications of HSA, including implantable biomaterials, surgical adhesives and sealants, biochromatography, ligand trapping, fusion proteins, nanotubes and nanoparticles have been reported [1,35–38].

HSA is a monomeric protein constituted by a single non-glycosylated all-α chain of 66 kDa arranged in a globular heart-shaped conformation containing three homologous domains (labeled I, II, and III). Each domain is made up by two separate helical subdomains (named A and B), connected by random coils [1,18,39,40] (Fig. 1, panel A).

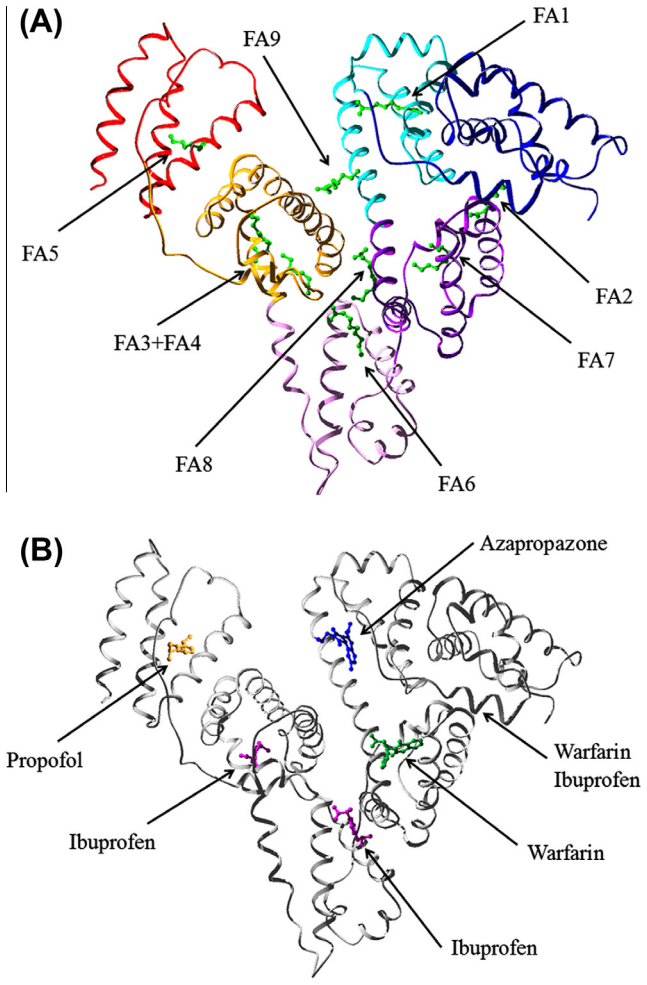

Fig. 1. The HSA structure. Panel A: FA binding to HSA. HSA is rendered with ribbons, colored as follows: subdomain IA: blue; subdomain IB: cyan; subdomain IIA: violet green; subdomain IIB: pink; subdomain IIIA: orange; subdomain IIIB: red. The FA binding sites (FA1 to FA9) are occupied by capric acid (green). FA binding sites are numbered as reported in [42]. Atomic coordinates were taken from PDB entry 1E7E [42]. Panel B: Drug binding to HSA. The FA1 site is occupied by azapropazone (blue) (PDB entry: 2BX8, [23]). The FA2 site has been hypothesized to be the secondary site of warfarin and ibuprofen on the basis of solution studies [57,155]. The FA3-FA4 and FA6 sites are occupied by ibuprofen (magenta) (PDB entry: 2BXG, [23]). The FA7 site is occupied by warfarin (green) (PDB entry: 2BXD, [23]). Both pictures were drawn with Swiss-PDB-Viewer [156]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The multidomain organization of HSA is at the root of its extraordinary ligand binding properties. HSA is able to bind up to nine equivalents of fatty acids (FAs) at multiple sites labeled FA1 to FA9 (Fig. 1, panel A) with different affinity. Crystallographic analysis of different complexes of HSA with a wide variety of exogenous ligands (e.g., drugs) revealed the architecture of the primary drug-binding sites (i.e., the FA3–FA4 cleft and the FA7 site). These cavities, constituted by distinct sub-compartments, are highly adaptable for the binding of several ligands. Moreover, structural data show a variety of secondary binding sites distributed across the protein, overlapping to a variable extent with FA sites [1,23].

The FA1 site (located in subdomain IB) has been evolved to bind the heme with high affinity contributing to the homeostasis and possibly the receptor-mediated endocytosis of the heme by hepatocytes. The FA2 site (located between subdomains IA and IIA) has been reported to be the ibuprofen and warfarin secondary site. Ligand (e.g., FAs) binding to the FA2 site stabilizes the HSA B-conformation. The FA3 and FA4 sites are located in a large cavity in subdomain IIIA that as a whole composes the so-called Sudlow's