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Human Serum Albumin: A Novel Drug Delivery Carrier System

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscripts.

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Review Article

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ABSTRACT

Serum albumin, often referred to simply as albumin, is a globular protein that in humans is encoded by the ALB gene. Albumin is a multifaceted, highly soluble, stable, nontoxic, non-poisonous, biocompatible and biodegradable plasma protein. Albumin has been widely studied as a protein carrier for drug delivery. Because of its versatile nature, it can also be used for the delivery of the hormones, metals and fatty acids by binding to its specific binding sites. Various studies revealed that albumin can be used to increase the circulating half-life and bioavailability of drug molecules which are smaller than the renal filtration threshold and are rapidly lost from the circulation leading to limiting therapeutic potential. This review article presents advantages, disadvantages, functions, importance, different nanoparticles that can be crowned with an albumin and the special features of albumin as a drug carrier, and how the understanding of these features is currently being employed to optimize the circulatory half-life albumin.

Keywords: Albumin; Binding site; drug carrier; drug delivery; nanoparticles, cancer therapy.

ABBREVIATIONS

HAS : Human Serum Albumin
RA : Rheumatoid arthritis
MTX : Methotrexate
ARDS : Adult Respiratory Distress Syndrome

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HDN : Hemolytic Disease of the New born
NPs : Nanoparticles

1. INTRODUCTION

1.1 Human Serum Albumin

Human Serum Albumin (HSA) is the most abundant protein in plasma, accounting for more than half of human plasma protein [1-3]. Albumin is primarily responsible for 75%-80% of plasma's normal colloid oncotic pressure. It has solubilising long chain fatty acids, delivery of nutrients to cells, and balancing plasma pH. Serum albumin is produced by the liver, occurs dissolved in blood plasma. Too much or too little circulating serum albumin may be harmful [3]. It may play an important role as a carrier in improving the pharmacokinetic property of small drug molecules, peptides or protein based drugs. Albumin is emerging as a versatile protein carrier for drug targeting and for improving the pharmacokinetic profile of peptide or protein-based drugs. The molecular weight of Albumin is around 66.5 kDa. Like most of the plasma proteins, albumin is synthesized in the liver where it is produced at a rate of approximately 0.7 mg/h for every gram of liver (i.e. 10–15 g daily); HSA is used for treating shock, burns, hypoalbuminemia, surgery or trauma, cardiopulmonary bypass, acute respiratory distress and hemodialysis. As an substitute to blood derived albumin, recombinant human serum albumin (Recombumin) has been developed and is a genetically engineered protein expressed in yeast cells that has shown comparable safety, tolerability, pharmacokinetics and pharmacodynamics to native HAS [3]. HSA is playing an increasing role as a drug carrier in the clinical setting. Principally, three drug delivery technologies can be distinguished:

a. Coupling of low-molecular weight drugs to exogenous or endogenous albumin
b. Conjugation with bioactive proteins
c. Encapsulation of drugs into albumin nanoparticles

1.2 Advantages of Using HSA as Drug Carrier

a. Human Serum Albumin (HSA) is native to the body. It is biodegradable in nature, nontoxic and non-immunogenic [3].
b. HSA is a robust macromolecule. It is stable over a wide pH range 4-9, could be heated at 60°C for up to 10 h without deleterious effect, is unchanged by denaturing agents and solvents at moderate concentrations. Therefore, albumin could remain stable under typical processing conditions [3].
c. As the most abundant protein in plasma, albumin is readily available. It has been used in clinical setting for more than 30 years[3]
d. The half-life of albumin is 19 days in blood circulation [3]

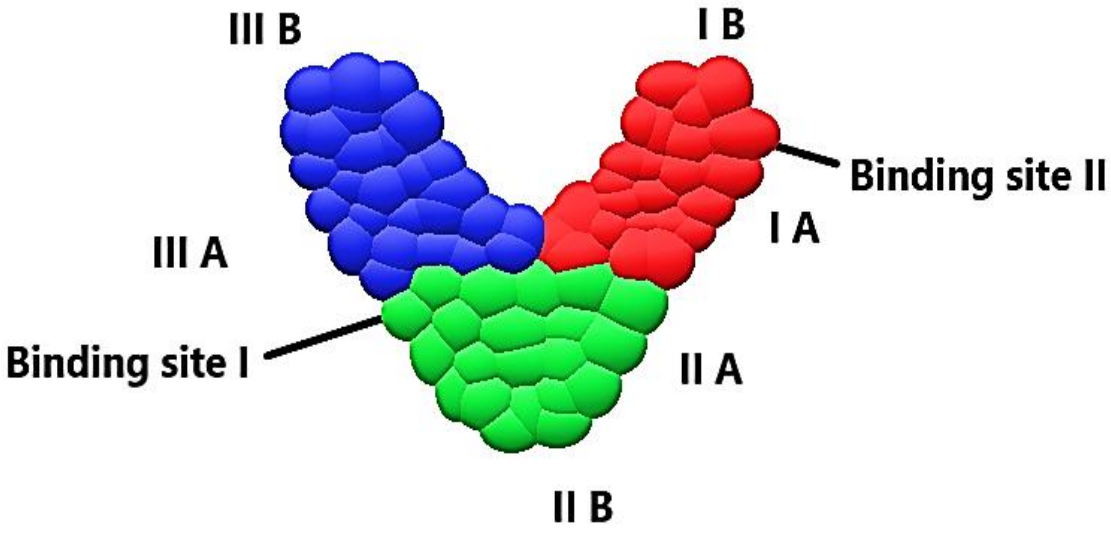

Fig. 1. The structure of Human Serum Albumin (HSA). The three domains of HSA are coloured as follows: domain I: red; domain II: green; domain III: blue

1.3 Disadvantages of HAS

In spite of its wide range of properties and endogenous origin, it shows potential for allergic reactions and transmission of infections. Hyper oncotic albumin may cause kidney damage.

2. SPECIAL FEATURES OF ALBUMIN AS A DRUG CARRIER

Albumin is best known for its remarkable ligand binding capacity. It is a versatile protein with antioxidant, immunomodulatory, detoxifying properties and can act as a potent drug carrier [4]. Albumin can be used as an exogenous or endogenous protein for the treatment of various diseases like cancer, rheumatoid arthritis, diabetes and hepatitis. Albumin-based drug delivery systems include albumin-drug nanoparticles, albumin fusion protein, pro-drugs and peptide derivatives that bind covalently to albumin as well as physically bind to the antibody fragments and therapeutically active peptides. During the last decade, the use of albumin has been a source of the debate focusing on whether albumin can act as a better drug carrier for delivery of macro-molecules or not . Human albumin has the capacity to bind an extraordinarily diverse range of molecules. Following are the main features which explain its specificity as drug carrier Albumin provides a depository for a wide variety of compounds that may be available in quantities well beyond their bioavailability in plasma. This is feasible because the negative charge of HSA (Human Serum Albumin) facilitates electrostatic binding of various ligands with albumin, acting as a depot and carrier for many drug compounds Albumin also performs transport functions through the binding sites which are present in its tertiary structure. The substances transported by albumin includes large number of drugs, bilirubin, bile acids hormones, metals, anions, long-chain fatty acids, L-thyroxine, nitric oxide, endotoxins and other bacterial products such as the protein G-like albumin-binding molecule The methodology, selectivity and capacities of ligand binding to albumin are as assorted as the compounds, which has the capacity to bound. The modes of binding include complex formation with metals, hydrophobic and electrostatic interactions and covalent binding. Several binding sites are present on albumin molecules. For fatty acids, seven binding sites have been describing the most eminent sites for drug binding are the site I and site II located on the sub-domains IIA and IIIA, respectively. Complex formation and high-affinity binding are principally reversible, or irreversible manner [5].

3. THE MECHANISMS FOR THE IMPROVEMENT OF HALF LIFE OF THE THERAPEUTIC COMPOUNDS BY ALBUMIN

Size of albumin is above the renal threshold so it has specific interaction and recycling by the specific receptors, which leads to its long circulatory half-life (19 days). Accordingly, to improve the pharmacokinetic profile, various drug molecules had been joined to albumin covalently and non-covalently.

3.1 Covalent Binding of Therapeutic Molecules to Albumin

Recently, therapeutic compounds have also been generated by the covalent attachment of drug molecules to the albumin, either by conjugation, where proteins or small molecules are exogenously joined to albumin by a chemical bond, or by gene fusion where the gene for a protein is engineered to that of albumin and expressed in a suitable host resulting in the production of a single polypeptide. Conjugation of drug molecules to albumin has been used by researchers in which small molecules (doxorubicin or methotrexate) are coupled to albumin for the development of anticancer and anti-rheumatic drugs. Products of albumin formed by covalent binding with active pharmaceuticals include GLP-1 and Exendin-4 [6].

3.2 Non-Covalent Binding of Therapeutic Molecules to Albumin

Albumin reversibly binds to a broad range of endogenous ligands such as fatty acids, bilirubin, bile acids, thyroxine and exogenous ligands such as penicillins, warfarin and diazepam. Binding affects the pharmacokinetic properties of these molecules; generally, it enhances their distribution and bioavailability. For example, albumin has several fatty acids binding sites and their binding affinity depends upon the fatty acid chain length. In recent technologies, drug molecules are attached to a fatty acid. On injection, the molecules bind to the endogenous albumin in the blood through its fatty acid binding sites from where it slowly dissociates, hence prolonging its half-life and bioavailability. This

technology has been used to enhance the pharmacokinetics of insulin by forming insulin analogue Levemir (insulin detemir).Another examples of application of this technology includes products of GLP-1 (Glucagon-Like Peptides-1) and G-CSF (Granulocyte Colony-Stimulating Factor) scFv (Single Chain Antibody), IFNα-2b, IL-1RA (Interleukin-1 receptor antagonist),Fab and Anti-EGFR (Anti Epidermal growth factor receptor) [7].

3.3 By Modulation of Albumin's Affinity to FCRN Receptors

The main key to this technology is the optimization of the albumin/ FcRn interaction – producing albumin analogue which has longer and shorter half-life than natural albumin. This approach extends the previous work by researchers in the identification of domain III in this interaction and allows specific molecular interactions to be predicted and tested [8].

4. BASIC FUNCTIONS OF ALBUMIN

Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones in the blood and it plays a major role in stabilizing extracellular fluid volume by contributing to oncotic pressure (known also as colloid osmotic pressure) of plasma because smaller animals (for example rats) function at a lower blood pressure, they need less oncotic pressure to balance this, and thus need less albumin to maintain proper fluid distribution. The functions and binding properties of HSA are multifold (i) it acts as the solubilizing agent for long chain fatty acids and is therefore essential for the metabolism of lipids, .(ii) it binds bilirubin (the breakdown product of heme); (iii) it binds a great number of therapeutic drugs such as penicillins, sulfonamides, indole compounds, and benzodiazepines, (iv) it binds copper(II) and nickel(II) in a specific manner and calcium(II) and zinc(II) in a relatively nonspecific manner and (v) acts as the transport vehicle for these metal ions in the blood, (vi) it is the major protein responsible for the colloid osmotic pressure of the blood (vii) If when HSA is broken down, the amino acids provide nutrition to peripheral tissue [9].

5. DIFFERENT TYPES OF NPS CROWNED WITH AN ALBUMIN

Nanomaterials are organized into various groups based on their shape, composition and dimension. Association of proteins with these diverse types of nanomaterials is an area that has been delved into extensively in the recent times. Specifically, highlighted NPs have been crowned with albumin [10].

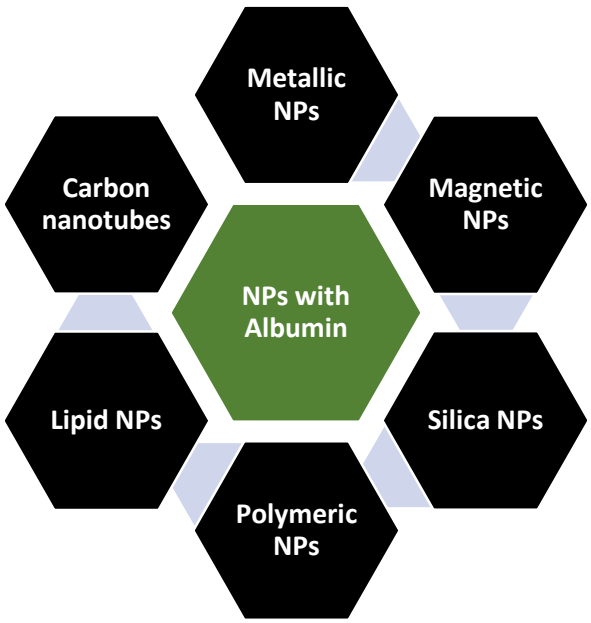

Fig. 2. Different types of NPs crowned with an albumin

6. IMPORTANCE OF HSA AS CARRIER IN TREATMENT OF DIFFERENT DISORDER

6.1 Tumor

Albumin accumulates in malignant and inflamed tissue due to a leaky capillary combined with an absent or defective lymphatic drainage system. Tumour uptake in preclinical models can be easily visualized by injecting the dye evens blue that binds rapidly and tightly to circulating albumin and makes subcutaneously growing tumours turn blue within a few hours post-injection. As an alternative to drug targeting, conjugating therapeutic peptides or cytokines with albumin is an attractive approach of improving their pharmacokinetic profile due to the long-half-life of albumin in the body. Clinically a methotrexate-albumin conjugate, and albumin-binding prodrug of doxorubicin, i.e. the (6-maleimic) a proylhydrazone derivative of doxorubicin (DOXO-EMCH), and an albumin paclitaxel nanoparticle (Abraxane) have been evaluated clinically. Abraxane has been approved for treating metastatic breast cancer. An alternative strategy is to bind a therapeutic peptide or protein covalently or physically to albumin to enhance its stability and half-life [11-12]. Serum proteins are potential drug carriers of antineoplastic agents due to their accumulation in tumor tissue. Uptake of these proteins in solid tumors is mediated by a number of factors including an increased metabolic activity of tumors, an enhanced vascular permeability of tumor blood vessels for circulating macromolecules, and a lack of afunctional lymphatic drainage system in tumor tissue. Recently, a number of acid-sensitive albumin and transferring conjugates with anthracyclines and the alkylating agent chlorambucil have shown promising in vitro activity. In addition, acid-sensitive doxorubicin conjugates with monoclonal antibodies and albumin doxorubicin conjugates prepared by glutaraldehyde cross-linking have shown promising antitumor efficacy in vivo [11].

6.2 Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects a large number of people throughout the world. Uncontrolled active rheumatoid arthritis causes joint damage, disability. Methotrexate (MTX) is a commonly used drug for treating RA and cancer. To overcome the lack of specificity with regard to the inflamed tissue as well as increasing the half-life, methotrexate-albumin conjugate (MTX-HSA) was developed by directly coupling MTX to lysine residues of HSA. Meanwhile; MTX-HSA has shown to significantly reduce synovial fibroblastinvasion and cartilage degradation in a humanized rheumatoid arthritis [11,13].

6.3 Hypovolemia

Hypovolemia is a possible indication for albumin. Its effectiveness in reversing hypovolemia depends largely upon its ability to draw interstitial fluid into the circulation. It is most effective with patients who are well hydrated [11,14].

6.4 Burns

An optimum regimen for the use of albumin, electrolytes and fluid in the early treatment of burns has not been established; however, in conjunction with appropriate crystalloid therapy, albumin may be indicated for treatment of oncotic deficits after the initial 24 hour period following extensive burns and to replace the protein loss which accompanies any severe burn [11,15].

6.5 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in those who are critically ill or who have significant injuries. It is often fatal, the risk increasing with age and severity of illness. People with ARDS have severe shortness of breath and often are unable to breathe on their own without support from a ventilator. A characteristic of ARDS is a hypoproteinemic state, which may be causally related to the interstitial pulmonary edema [11].

6.6 Cardiopulmonary Bypass Surgery

A recent meta-analysis focused on the usage of albumin in priming solution for cardiac surgery showed favorable results of albumin in keeping the colloid oncotic pressure on a physiological level as compared with that of crystalloid hence albumin has been recommended prior to or during cardiopulmonary bypass surgery, although no clear data exist indicating its advantage over crystalloid solutions [11,16].

6.7 Hemolytic Disease of the Newborn (HDN)

Hemolytic Disease of the Newborn (HDN), also known as erythroblastosis fetalis, isoimmunization, or blood group incompatibility,

occurs when fetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the fetal circulation and result in RBC destruction. Albumin may be administered in an attempt to bind and detoxify unconjugated bilirubin in infants with sever HDN [11].

6.8 Diabetes

The treatment of juvenile diabetes or advanced type 2 diabetes is done by counterbalancing the lack of insulin production in the body. Preferably, a long-acting form of insulin is used to decrease and normalize the blood glucose level over 24h. The recent technology includes the attachment of a fatty acid to insulin which subsequently binds to 5–7 fatty acid binding sites present in the HSA molecule and eventually enhances the bioavailability of insulin. The peptide hormone GLP-1-(7-37) is produced from selective cleavage of the proglucagon molecule and increases insulin secretion in pancreatic cells, but has a half-life of 1.5– 2 min only due to degradation by enzymes. Due to which it has limited use. By the same technology of Levemir®, GLP-1-(7-37) is derivatized with a fatty acid, palmitic acid, at the ε-amino position of lysine introduced at the N-terminal position of glutamic acid in the GLP-1 peptide sequence. The resulting new drug liraglutide (Victoza®) is an albumin-binding derivative of GLP-1 and is stable against metabolic degradation by enzymes due to albumin-binding and has a plasma half-life of 11–15 hours after subcutaneous administration [11].

7. CONCLUSION

Albumin is turning out as one of the most important drug carriers for therapeutically active drugs, peptides, and antibodies. It is used especially for the treatment and diagnosis of malignant, inflammatory, metabolic and viral diseases. The elucidation of binding of serum albumin to FcRn receptors that control its half-life is a key point in designing of albumin-based therapeutic or diagnostic agents for optimizing their pharmacokinetics and drug targeting properties. The high abundance, versatility, stability, multiple binding sites, and very long half-life of serum albumin make it an ideal endogenous serum protein for improving the pharmacokinetic properties of therapeutically active drugs, peptides or small-sized antibody moieties. Considering the commercial success of products that use albumin as a drug carrier and the ongoing clinical trials as well as due to the advent of many diverse technologies for improving the pharmacokinetic profile and drug targeting potential of therapeutic and diagnosis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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