Chapter 9
The Perioperative Use of Albumin

Ehab Farag and Zeyd Y. Ebrahim

Abstract Human serum albumin (HSA) is the predominant product of hepatic protein synthesis and one of the more abundant plasma proteins. HSA is a monomeric multidomain macromolecule, representing the main determinant of plasma oncotic pressure and the main modulator of fluid distribution between body compartments. HSA displays an essential role in maintaining the integrity of the vascular barrier. HSA is the most important antioxidant capacity of human plasma, in addition to its ability to protect the body from the harmful effects of heavy metals such as iron and copper and reduce their ability to produce reactive oxygen radicals. HSA is the main depot for nitric oxide (NO) transport in the blood. HSA represents the main carrier for fatty acids, affects pharmacokinetics of many drugs, and provides the metabolic modification of some drugs and displays pseudo-enzymatic properties. HSA has been widely used successfully for more than 50 years in many settings of perioperative medicine including hypovolemia, shock, burns, surgical blood loss, sepsis, and acute respiratory distress syndrome (ARDS). Recently, the use of HSA has shown a promising neuroprotective effect in patients with subarachnoid hemorrhage. The most recent evidence-based functions and uses of HSA in the perioperative period are reviewed in this chapter.

Keywords Human serum albumin • Sepsis • Antioxidant • Nitric oxide • Neuroprotection • Endothelium glycocalyx

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E. Farag, MD, FRCA (✉)
Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine, Director of Clinical Research, Staff Anesthesiologist, General Anesthesia and Outcomes Research, Cleveland Clinic, Cleveland, OH, USA
e-mail: farage@ccf.org

Z.Y. Ebrahim, MD
Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

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Key Points

1. Human serum albumin is the most abundant protein in the body.
2. Human serum albumin represents the most important antioxidant agent in the human plasma.
3. Human serum albumin is the main depot for nitric oxide transport in the blood.
4. Human serum albumin plays a very important role in maintaining the integrity of vascular barrier and endothelial glycocalyx.
5. Human serum albumin is successfully used in many settings of perioperative medicine.

Introduction

Human serum albumin (HSA) is the most abundant protein in the human plasma (40–50 g/L). HSA has many functions; it is the main regulator of the vascular barrier, antioxidant in the plasma, and transporter of nitric oxide (NO) and fatty acids and drugs.

HSA infusions have been used successfully for more than 50 years since World War II in many perioperative settings such as shock, volume expansion, burns, cardiopulmonary bypass, acute liver failure, sepsis, and many more. Recently, its use has been questioned following a widely publicized meta-analysis in 1998 that reported increased mortality in patients who received albumin solutions; the role of albumin administration in critically ill patients became highly controversial. However, the results of this meta-analysis have been challenged by several meta-analyses, randomized controlled trials that not only proved the safety of HSA but its benefit especially in patients with sepsis, liver failure, hypoalbuminemia, and burns [1–4]. The most recent evidence-based functions and uses of HSA in the perioperative settings are reviewed in this chapter.

Albumin Gene and Structure

Human serum albumin (HSA) is a non-glycosylated, negatively charged plasma protein. HSA is a single polypeptide chain of 585 amino acids and has a molecular mass of 66.5 KDa. HSA consists of α(alpha)-helix but no β(beta)-sheet, and it consists of three homologous domains (I–III) that assemble to form a heart-shaped molecule. Each domain is composed of two subdomains (A & B) with distinct helical folding patterns connected by flexible loops. The center of the molecule is made up of hydrophobic radicals, which are binding sites for many ligands, while the outer part of the molecule is composed of hydrophilic ligands (Fig. 9.1) [5].

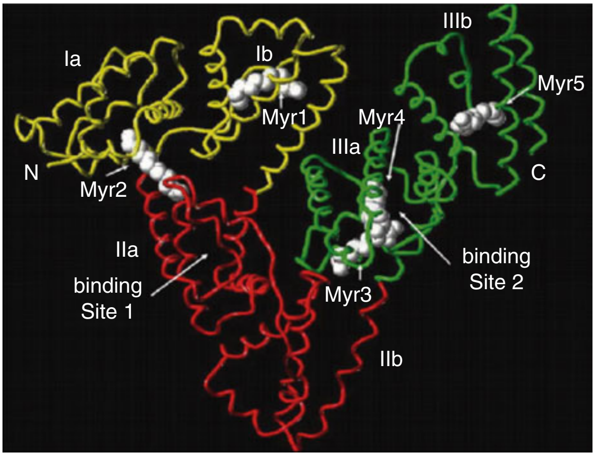

Fig. 9.1 X-ray structure of human serum albumin (Reprinted with permission from Kratz [81]. Proceedings of the Tenth European Symposium on Controlled Drug Delivery)

HSA is a member of the albumin superfamily, which also includes α(alpha)-fetoprotein, vitamin D-binding protein, and afamin (α[alpha]albumin). HSA synthesis is governed by a single copy gene lying on the long arm of chromosome 4, near the centromere for the long arm, at position 4q11-13. The mRNA for HSA encodes a precursor protein (preproalbumin) of 609 amino acid residues. Cleavage of the single peptide of 18 residues and the propeptide (proalbumin) of six residues yields the mature protein of 585 residues [6].

Albumin and Its Role in Endothelial Barrier

HSA plays an integral role in maintaining the integrity of the vascular barrier. HSA enhances the integrity by electrostatic binding to the negatively charged heparin sulfate side chains of core glycoproteins such as syndecan-1 and glypican-1 of the endothelial glycocalyx via its positively charged arginine residues and enhances the availability of sphingosine-1-phosphate (S1P) produced by red blood cells (RBCs). Extracellular sphingosine is taken up and phosphorylated by RBCs sphingosine kinases (SK) into S1P that is stored in the cell membrane of RBC. S1P is extracted from the RBC membrane by Apo lipoprotein M (ApoM) of high-density lipoprotein (HDL) (Apo lipoprotein M is the principal partner of S1P in HDL) and HSA, and this ensures a constant supply of receptor-available S1P for cellular signaling purposes. In contrast to the bond formed between S1P and HDL, HSA facilitates the solubility of S1P in the aqueous solution but not in physical bond to HSA. This unbound S1P is the active form of S1P. It is worth mentioning that one S1P molecule is extracted by 500 serum albumin molecules, indicating that HSA does not physically bind S1P [7–9]. S1P activates the G protein-coupled S1P1 receptor, which rapidly activates the Rho family small GTPase Rac1 in the endothelial cells, leading to peripheral localization of cytoskeletal effectors (cortactin and nonmuscle myosin light chain kinase). This localization promotes adherents' junction (including vascular endothelial-cadherin and associated catenins) and tight junction (occluding, zonula occludens proteins and claudins) formation. Therefore, S1P improves the vascular barrier and stabilizes the endothelial glycocalyx. S1P has been found to reduce matrix metalloproteinase activation, thereby attenuating the loss of endothelial cell surface glycocalyx components. Both actions appear to involve signaling via the S1P receptor [10].

Albumin as a Major Antioxidant

Oxidative stress is defined as a disturbance in pro-oxidant and antioxidant balance leading to damage of lipids, proteins, and nucleic acids. According to Halliwell and Whiteman, an antioxidant is a substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate [11]. Human serum albumin represents a major antioxidant agent in human plasma. The antioxidant activity of HAS results from the redox properties of the Cysteine 34 (Cys 34) and from metal-binding abilities. Among the metal ligands, copper (Cu) and iron (Fe) are very important, as they are able to generate reactive oxygen species (ROS) after a reaction with oxygen. Free Cu (I) and Fe (II) ions can react with H_2O_2 leading to the formation of the deleterious hydroxyl radical via the Fenton reaction. Cu(I) and Fe(II) binding to HSA promotes their oxidation to Cu(II) and Fe (III), thereby limiting their ability to participate in Fenton reaction. Copper ions bind to HSA with high affinity at the N-terminal tripeptide Asp-Ala-His. The first four amino acids of the N-terminus of HSA, Asp-Ala-His-Lys (DAHK), form a tight binding site for Cu(II) ions. DAHK/Cu has a superoxide dismutase activity, which thereby reduces the ROS generation. By trapping Cu(II), HSA prevents low-density lipoprotein (LDL) lipid peroxidation. Moreover, HSA and the tetrapeptide (DAHK) were shown to prevent neuronal death in murine cell cultures exposed to oxidative stress generated by H_2O_2/Cu(I)/ascorbic acid reagent [12]. Therefore, the binding of Cu ions with albumin is considered one of the most important antioxidant functions of albumin as Cu can react with H_2O_2 to hydroxyl radicals 60 times faster than Fe.

HSA is important for heme-Fe scavenging, providing protection against free heme-Fe oxidative damage. During the first seconds after heme-Fe appearance in plasma, more than 80 % of this powerful oxidizer binds to HDL and LDL, and only the remaining 20 % binds to HSA and hemopexin (HPX). Then, HSA and HPX remove most of the heme-Fe from HDL and LDL. Afterward, heme-Fe transits from HSA to HPX, which releases it into hepatic parenchymal cells after internalization of the HPX-heme-Fe complex by CD91 receptor-mediated endocytosis. It should be mentioned that kinetics of heme-Fe transfer from HDL and LDL to HSA and HPX is faster than the heme-Fe-induced lipoprotein oxidation [13, 14].

Albumin-bound bilirubin confers an antioxidant effect by inhibiting lipid peroxidation. Bilirubin bound to albumin was shown to protect α(alpha)-tocopherol from damage mediated by peroxyl radicals and to prolong the survival of human ven-

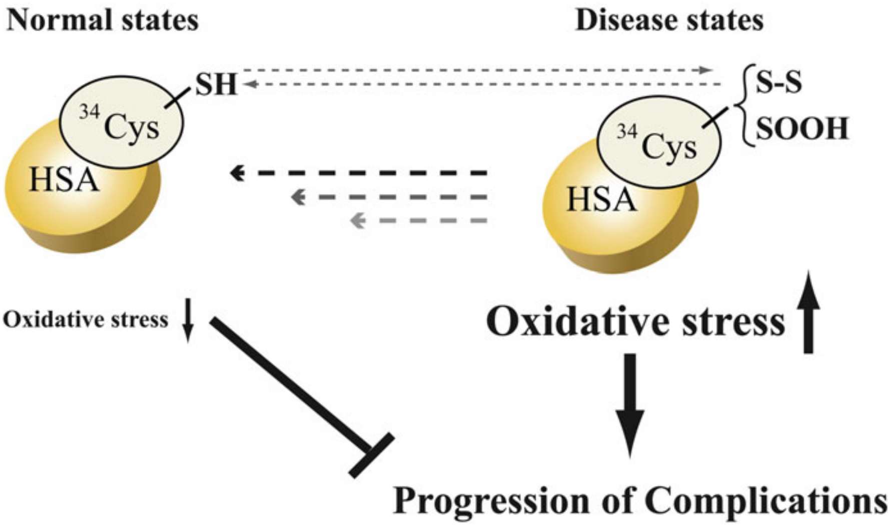

Fig. 9.2 Proposed mechanism for the contribution of Cys34 to the maintenance of homeostasis in blood. The treatments where the levels of Cys34 oxidation are minimized at low levels in several diseases may be beneficial for preventing the onset and progression of serious complications, which affects the prognosis for survival (Reprinted with permission from Anraku et al. [82])

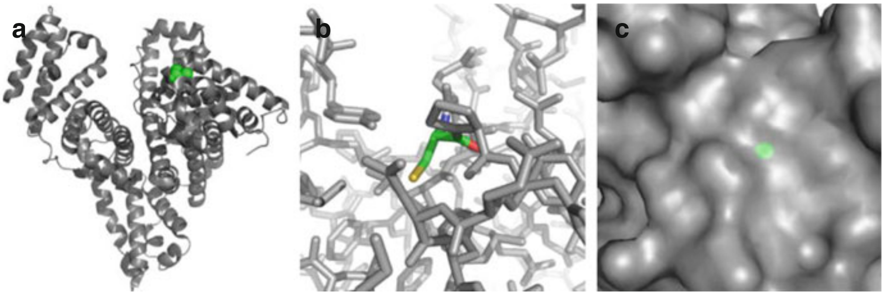

Fig. 9.3 Three-dimensional structure of human serum albumin, local environment, and surface exposure of Cys34. (**a**) Cys34 is shown in *green*. (**b**) Thiol microenvironment: C, *green*; O, *red*; N, *blue*; S, *yellow*. (**c**) Surface exposure of Cys34. Atomic coordinates were downloaded from Protein Data Bank, Accession Code 4EMX. The figures were prepared using PyMOL v0.99 (www.pymol.org) (Reprinted with permission from Turell et al. [83])

tricular myocytes against in situ–generated oxidative stress [15, 16]. Cholesterol undergoes oxidation in vitro and in vivo, forming biologically active derivatives known as oxysterols. Oxysterols bind to albumin with high affinity. Oxysterols carried by albumin are less rapidly released to cells than cholesterol. By this, albumin could limit detrimental effects of oxysterols on cells. Furthermore, binding homocysteine by HSA protects from atherosclerosis as elevated plasma homocysteine is a well-known risk factor for atherosclerosis (Figs. 9.2 and 9.3) [17].

Physiologically, HAS exists predominately in a reduced form (i.e., with free thiol, HSA-SH) and is known as mercapto-albumin. However, a small but significant proportion of albumin pool exists as mixed disulfides (HSA-S-S-R); where R represents low-molecular-weight, thiol-containing substances in plasma – chiefly cysteine and glutathione [18]. Mixed disulfide formation increases as part of the aging process and during disease processes characterized by oxidative stress that enhances endothelial cell damage through oxidative stress and increase in apoptosis levels. Cysteine 34 (Cys 34) represents the largest fraction of free thiol in human plasma, HAS being the most abundant protein in plasma. Cys34 is located at the surface of HAS, close to Aspartate 38 (Asp38), Histidine 39 (His39), and Tyrosine 84 (Tyr 84). These three residues affect the ionization state of Cys34, thus modulating its reactivity [13]. In healthy adults, about 70–80 % of the Cys34 in albumin contains a free sulfhydryl group, whereas about 25–30 % of the HSA molecules have Cys34 forming a mixed disulfide with either cysteine or homocysteine or glutathione, thus affecting the Cys34 redox potential. Oxidation of Cys34 leads to the formation of sulfenic acid (RSOH), which is further oxidized to sulfinic (RSO_2 H) or sulfonic acid form (RSO_3 H). Sulfenic acid constitutes a central intermediate in both the reversible and irreversible redox modulation by reactive species. Reactive nitrogen species (RNS) constitute nitrogen-centered species analogous to ROS. RNS such as nitric acid (NO) contribute to various biological processes. HSA acts as a NO depot and a NO transducer. Moreover, 82 % of NO in blood (~7 μ[mu] M) is transported as an S-nitrosothiol bound at the HSA residue Cys34. S-nitrosylated HSA may represent a circulating endogenous reservoir of NO and may act as an NO donor. S-nitrosylated HSA acts primarily as a vasodilator in vivo and represents a stable reservoir of NO that can be released when the concentrations of low-molecular-weight thiols are elevated [19]. S-nitrosylated HSA has been shown to reduce either ischemia or reperfusion injury in pig and rabbit hearts after unprotected warm ischemia through long-lasting release of NO [13]. Other RNS, such as peroxynitrite ($ONOO^-$), constitute powerful oxidants and nitrating species [20]. The -SH group of albumin represents an important antioxidant against peroxynitrite as the thiol group was oxidized to a sulfenic acid (HSA-SOH). Subsequently, HSA-SOH can be converted to a disulfide and then back to mercapto-albumin (HSA-SH). HSA administration favorably influences plasma thiol-dependent antioxidant status, as well as levels of protein oxidative damage in patients with sepsis and acute respiratory distress syndrome (ARDS) [21, 22]. Moreover, HSA is able to scavenge strongly oxidant compounds such as hypochlorous acid (HOCI) and hypothiocyanous acid. Cys34 is oxidized preferentially by hypochlorous and hypothiocyanous acid with the corresponding sulfenyl derivative. HSA is able to scavenge HOCI, preventing alteration of its preferential biological target α(alpha)$_1$-antiprotease [23]. Interestingly, West Nile virus is neutralized by hypochlorous acid-modified HSA that binds to domain III of the viral envelope protein E [24].

During its long life (~3 weeks), an HSA molecule makes 15,000 passes through the circulation, incurring some damages that affect its ligand-binding and antioxidant properties. Diabetes mellitus is one of the main pathological conditions that impairs the antioxidant functions of albumin. In this disease, albumin undergoes increased glycation. The level of glycated HSA in normal humans is about 10 %, and increased to 20–30 % in hyperglycemic patients. Glycation corresponds to the nonenzymatic attachment of glucose molecule to a free amine residue. HSA glycation is associated with oxidation of His and Trp residues, main chain fragmentation, and loss of both secondary and tertiary structure. Both the use of diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) and aspirin reduces the levels of advanced glycation [25]. The glycation of HSA impairs its antioxidant activity and its copper-binding ability. Glycation of HSA induced a marked loss of its antioxidant activity to copper-mediated oxidation of LDL, probably by the generation of superoxide. Moreover, the Fe(III)-binding antioxidant capacity of HSA is markedly reduced in diabetic patients. Finally, the HSA transport of tryptophan (Trp), which is the largest and essential amino acid, is reduced after its glycation. HSA glycation alters the binding of endogenous and exogenous ligands; in particular, glycation of Lys 199 enhances warfarin binding, but decreases bilirubin affinity [13].

Several receptors for advanced glycation end products initiate intracellular signaling and enhance ROS formation in the cells through recognition and binding of glycated (macro) molecules including HSA. Moreover, hypochlorous acid-mediated carbonylation of Lys residues of glycated HSA represents a major antigenic advanced glycation end product in hyperglycemia and in inflammation [26]. Glycated albumin was shown to impair vascular endothelial NO synthase activity in vivo in aortas of rabbits [27]. Glycated HSA displays a toxic effect on microglial cells associated with impairments in cellular proteolytic systems, possibly reflecting the role of advanced glycation end products in neurodegenation.

HSA may protect other proteins including hemoglobin, insulin, and immunoglobin from glycation in the early stages of diabetes due to its long half-life and its high concentrations compared to other proteins [28]. The irreversible damages associated with diabetes such as retinopathy, nephropathy, neuropathy, and coronary artery disease could be attributed to reduced antioxidant properties of glycated HSA.

Alterations in antioxidant properties of HSA were very recently identified in vivo in patients with obstructive sleep apnea syndrome. This reflects the impaired antioxidant HSA activity, which is associated with the enhanced glycation level of HSA in patients with obstructive sleep apnea syndrome. That might have increased the perioperative risks in those patients [29].

Anticoagulant Effect

HSA has anticoagulant and antithrombotic functions. These functions may in part be mediated by the HSA capacity to bind NO forming S-nitrosothiols, thereby inhibiting the rapid inactivation of NO and allowing prolongation of its antiaggregatory effects on platelets [30]. Therefore, the use of HSA might be very beneficial in cases with hypercoagulable conditions such as during the perioperative period.

Enzymatic Properties of HSA

The interaction between HSA and another molecule results in enzymatic activity. This property of HSA is called an enzyme-like or a pseudo-enzymatic activity. The esterase activity involving lysine (Lys) 199 is able to split acetylsalicylic acid (aspirin) into salicylic acid, which is released and the acetyl group is transferred to especially Lys 199. Therefore, aspirin but not other salicylates induce the aspirin resistance syndrome, as the acetylation of albumin molecule can be allergic. Asthma, rhinitis, and nasal polyps characterize aspirin resistance syndrome. Moreover, Lys 199 and penicillins can covalently bind via an aminolysis, generating a penicilloyl-containing peptide. The covalent labeling of Lys 199 can have clinical consequences. The penicilloyl-HSA complex has no antibacterial activity; however, it represents the major antigenic determinant of penicillin allergy. HSA acts as a phosphotriesterase activity, which thereby inactivates organophosphorus compounds. HSA can catalyze RNA phosphodiester bond cleavage; therefore, it participates in the degradation of endogenous extracellular RNA and of circulating pathogenic nucleic acids. HSA possesses enolase activity toward dihydrotestosterone, converting it from the 3-keto to the 3-enol form. In addition, HSA facilitates the isomerization and the stereoselective hydrolysis of glucuronide conjugates and the removal of glucuronide conjugates, thereby reducing their plasma levels by reversible and/or irreversible binding. Finally, HSA seems to have a significant role in both the biosynthesis and the elimination the prostaglandins. HSA has no enzymatic effects on leukotrienes or thromboxanes. However, it binds and thereby stabilizes thromboxane A_2. Binding could play a major role for the inactivation of these potent compounds, diminishing the biological activities of substances that may be harmful for the body if present in too large amounts [6, 13].

Hypoalbuminemia

Hypoalbuminemia is generally defined as serum albumin concentration $\leq$30 g/L and is usually very common in critically ill patients. The albuminemia could result from increased loss of HSA into the gastrointestinal tract, increased capillary permeability leading to redistribution from the intravascular to the interstitial space, and reduced hepatic synthesis of HSA caused by cytokines and stress of critical illness.

Hypoalbuminemia is considered an independent risk factor for worse outcomes in critically ill patients. HSA levels <20 g/L were associated with higher mortality risk in burn patients with 84 % sensitivity and 83 % specificity [31]. In surgical septic patients, every 1 g/L decrease in albumin below 23 g/L was associated with a 19.4 % increase in hospital mortality and 28.7 % increase in the incidence of multiple organ failure [32]. Moreover, in a meta-analysis of 90 cohort studies that evaluated hypoalbuminemia as a prognostic biomarker in acutely ill patients, each 10 g/L in serum albumin was associated with a 137 % increase in morbidity, and a 71 % increase in length of hospital stay [33]. Preoperative low serum albumin (<4.0 g/dl) was shown to be an independent risk factor for acute kidney injury (AKI) following off-pump coronary artery bypass surgery (OPCAB). AKI was associated with prolonged stay in the intensive care unit (ICU) and hospital and a high mortality rate [34].

Human Serum Albumin Metabolism

HSA circulates from the blood across the capillary wall into the interstitial compartments, including cerebrospinal fluid, and returns to the blood through the lymphatic system with a circulation half-life of approximately 16 h. The movement of HSA across the capillary wall is defined as the transcapillary escape rate (5 % per hour), which indicates the percentage of intravascular HSA leaving the intravascular compartment per hour [13]. In its long half-life of ~2–3 weeks, 1 HSA molecule could make about 15,000 passes through the circulation. HSA is mainly synthesized in the liver. In healthy young adults, about 12–25 g of HSA per day is synthesized in polysomes bound to endoplasmic reticulum of hepatocytes. HSA is not stored hepatically and there is therefore no reserve for release on demand [30]. Under physiological circumstances, only 20–30 % of hepatocytes produce HSA and its synthesis can be increased up to 200–300 % on demand. HSA synthesis is regulated by colloid osmotic pressure and the osmolality of the interstitial liquid around the hepatocytes. Insulin plays an important role in stimulating HSA synthesis; therefore, diabetic patients could suffer hypoalbuminemia. Estrogens do not affect HSA transcription, but act by modifying the stability of the HSA mRNA. HSA synthesis can be enhanced by corticosteroids, insulin, and amino acids administration. HSA synthesis can be rate-limited by amino acid deficiencies, but these are rarely seen clinically, except in states of extreme starvation and malnutrition [30]. In acute-phase reactions, such as in trauma and the perioperative period, the synthesis of HSA is depressed by hepatic cytokines such as interleukin-6 and tumor necrosis factor-α(alpha).

Immunoglobulin G (IgG) and albumin, despite their disparate forms and functions, have long been known to share two unique characteristics, namely, their lengthy life spans and inverse relationship between their serum concentrations and half-lives. The long half-lives are attributed to the efficient receptor-mediated recycling pathway involving the neonatal Fc receptor (FcRn). FcRn is a heterodimer of a nonclassical major histocompatibility class I (MHC I) α(alpha)-chain and β(beta)$_2$ microglobulin (β[beta]$_2$m) that binds the two abundant serum proteins IgG and albumin in the body. FcRn binds both IgG and albumin simultaneously on the opposite sides of the receptor, where the net transport can be basolateral to apical, apical to basolateral, or apical to apical (endothelial cells). FcRn interacts with IgG and albumin in a strictly pH-dependent manner; therefore, it binds them at acidic pH and not at physiological pH. Pinocytosed IgG and albumin bound by the receptor within acidified endosomes are transported back to the cell surface where physiological pH of the blood triggers release of the ligands into the blood circulation. The intracellular nonbound fractions are targeted for lysosomal degradation. FcRn is also largely responsible for transporting the IgG across the placenta whereby the IgG concentration in newborns at term normally exceeds that of the mother. Animals deficient in FcRn catabolize IgG and albumin more rapidly than normal animals and manifest low plasma concentrations of both molecules. Familial hypercatabolic hyoproteinemia, where deficiency of FcRn is due to mutation in β (beta) $_{2m}$ results in hypercatabolism and low plasma concentrations of both albumin and IgG. However, patients with myotonic dystrophy (DM) exhibit plasma deficiency only in IgG but not albumin caused by reduced affinity of FcRn to IgG [35–37].

The catabolism of HSA takes place in several organs at a rate of about 14 g per day in a 70 kg healthy adult, or 4 % of whole body protein turnover. The rate of HAS catabolism is increased by protein and caloric deprivation as HSA is used as a source of energy. The mechanism of HSA breakdown involves protein uptake into endocytotic vesicles, which fuse with lysosomes of endothelial cells.

Circulating HSA is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides that are reabsorbed. There is minimal urinary loss of HSA in healthy subjects. It is worth mentioning that of the 70 kg of HSA that passes through the kidneys each day, only a few milligrams are secreted from kidney tubules [13].

The Use of Albumin in Perioperative Settings

The Use of Albumin in Sepsis

The use of human albumin in critically ill and septic patients has been through much controversy in the last two decades. In 1998, a Cochrane meta-analysis for albumin administration in critically ill patients was published in the *British Medical Journal* [38]. The average sample size of the selected 32 studies in this meta-analysis was just 46 patients. The results of this meta-analysis showed increased mortality of almost 70 % in patients given albumin. The results of this Cochrane report changed the practice rapidly around the world with dramatic reduction in albumin use especially in Europe. The validity of this meta-analysis has been disputed for several methodological reasons, such as omission of relevant trials, small trials bias, and combination of heterogeneous trials, which included adults and high-risk neonates, inadequate assessment of the effect of methodological quality on outcome, and the absence of a plausible mechanism to explain albumin-associated excess mortality [39, 40]. Moreover, the meta-analysis did not include burns trials in which the mortality rate was lower in albumin [41]. Finally, the crossover pattern in which the most seriously ill patients in the control group were switched to albumin as a rescue measure, therefore, would bias the pooled estimates of relative risk in favor of the control group [40]. Only a few years later, this meta-analysis was followed by an updated meta-analysis, in which 55 trials involving 3,504 randomly assigned patients had been included and 525 deaths occurred [40]. Pooled relative risk estimates among trials with blinding and those with 100 or more patients were 0.73 (CI, 0.48–1.12) and 0.94 (CI 0.77–1.14), respectively. The relative risk was also consistently less than 1.0 for trials that had two or more of the four attributes indicating higher methodological quality such as blinding, mortality as an endpoint, no crossover, and 100 or more patients. These observations suggest that albumin therapy reduces mortality. Overall, the results of this meta-analysis supported the safety of albumin use in critically ill patients. In 2004, the results of the Saline versus Albumin Fluid Evaluation (SAFE) randomized control trial (RCT) in 7,000 critically ill patients were published, showing that a 4 % albumin solution was as safe as normal saline as resuscitative fluid in critically ill patients [42]. Furthermore, the subgroup analysis of the SAFE study showed benefit of using albumin in patients with severe sepsis, with an adjusted odds ratio (OR) for death of 0.71 (95 % CI, 0.52–0.97; $P = 0.03$) for albumin compared with saline. Therefore, the authors concluded that administration of albumin compared to saline did not impair renal function or organ function and may have decreased the risk of death in patients with severe sepsis [1].

Moreover, Guidet and colleagues assessed the cost-effectiveness of albumin, as given in the SAFE study on patients with severe sepsis and septic shock, who were admitted to 1 of 35 French ICUs. Based on a presumed 4.6 % reduction in mortality associated with albumin therapy as shown in the SAFE trial, 513 lives were saved among the 11,137 patients included, with an estimated life expectancy for each life saved of 9.8 years. Therefore, the authors suggested that albumin administration was a cost-effective intervention in patients with severe sepsis or septic shock [4].

In a subsequent meta-analysis that included 17 studies with randomized 1,977 participants, there were eight studies that included only patients with sepsis and where patients were a subgroup of the study population. The use of albumin for resuscitation of patients with sepsis was associated with a reduced mortality, with the odds ratio of 0.82 % (CI 95 % 0.67–1.0, $P = .047$) [1]. Caironi and colleagues randomized 1,818 patients with severe sepsis in 100 ICUs to receive either 20 % albumin and crystalloid solution or crystalloid solution alone. During the first 7 days, patients in the albumin group had a higher mean arterial pressure and lower net fluid balance ($P < 0.001$). At 28 days the mortality rate was 31.8 % in the albumin group and 32.0 % in the crystalloid group. At 90 days the mortality rate was 41.1 % in the albumin group and 43.6 % in the crystalloid group. However, there was improved survival associated with albumin in patients with septic shock (1,121 patients; 90-day mortality, 43.6 % in the albumin group vs. 49.9 % in the crystalloid group; relative risk 0.87; 95 % CI, 0.77–0.99; $P = 0.03$) [43]. The results of a recent meta-analysis, which included 14 studies (18,916 patients with sepsis), showed that resuscitation with balanced crystalloids or albumin in patients with sepsis seems to be associated with reduced mortality [44]. Furthermore, the improved survival associated with albumin in patients with septic shock was confirmed in a recent meta-analysis. In this meta-analysis, 3,658 with severe sepsis and 2,180 with septic shock patients were included in the analysis [45]. Compared with crystalloid, a trend toward reduced 90-day mortality was observed in severe sepsis patients resuscitated with albumin (OR 0.88; 95 % CI, 0.76–1.01; $P = 0.08$). However, in septic shock patients the use of albumin for resuscitation significantly decreased 90-day mortality (OR 0.81; 95 % CI, 0.67–0.97; $P = 0.03$) [45].

Albumin resuscitation in sepsis has a unique feature compared to crystalloid as its effectiveness as a plasma-volume expander does not change in pathophysiological conditions associated with increased microvascular permeability as sepsis. In addition, in severe sepsis the ratio of albumin to crystalloid for equal plasma volume expansion is approximately 1–4.5 [46]. The use of intravenous albumin in addition to antibiotics in patients with cirrhosis and spontaneous bacterial peritonitis reduced the incidence of renal impairment, death, and paracentesis-induced circulatory collapse in comparison with treatment with an antibiotic alone [47, 48]. In patients with acute respiratory distress syndrome, the use of albumin improved oxygenation but did not affect mortality [49].

The only exception for the benefit of using albumin in patients with sepsis was shown in the Fluid Expansion as Supportive Therapy (FEAST) trial as evidenced in increasing mortality with the use of albumin and saline boluses compared to no bolus (control group) in pediatric patients infected with malaria in eastern African countries. The bolus-therapy-induced hypervolemia by albumin and saline boluses in those patients could explain the increased mortality in this study compared to control group [50].

Albumin as a Neuroprotective Agent in Animal Experiments and Clinical Settings

Human serum albumin is a unique pleiotropic protein with neuroprotective properties. Rats received 2-h middle cerebral artery occlusion (MCAO) and were treated with human albumin or saline after 30 min of recirculation. The cortical blood vessels were examined afterward by laser-Doppler perfusion imaging (LDPI). Albumin therapy resulted in significant increases in arteriolar diameter, and reversing stagnation, thrombosis, and corpuscular adherence within cortical venules in the reperfusion phase after focal ischemia [51]. In a rat model of acute ischemic stroke induced by MCAO, rats received 1.25 g/kg intravenously at 2, 3, 4, or 5 h after onset of MCAO. Albumin therapy markedly improved neurological function, and reduced infarction volume and brain swelling [51]. The neuroprotective effects of albumin have been confirmed in a study with permanent MCAO in rats, where albumin treatment led to 48 % increases in cortical perfusion ($P<0.002$), but saline in the control group caused no change [51].

Moreover, functional magnetic resonance imaging (fMRI) was used to assess the albumin treatment during stroke recovery in rats. Albumin treatment was associated with restoration of fMRI response magnitudes and temporal profiles [52]. Rats underwent subarachnoid hemorrhage by endovascular perforation. Albumin of either 0.63 or 1.25 g/kg was injected immediately after the surgery. Albumin at low-to-moderate doses markedly improves long-term neurobehavioral sequelae after subarachnoid hemorrhage [53].

There are only two large published trials for the use of albumin after acute ischemic stroke and subarachnoid hemorrhage (SAH). In a randomized, double-blind, parallel-group multicenter trial in patients with acute ischemic stroke with a baseline

National Institutes of Health Stroke Scale (NIHSS), 422 patients were randomly assigned to receive 25 % albumin (2 g [8 ml] per kg; maximum 750 ml) and 419 to receive an equivalent volume of isotonic saline. The primary outcome was favorable, defined as either a modified Rankin scale score of 0 or 1, or an NIHSS score of 0 or 1, or both, at 90 days. The rate of favorable outcome did not differ between the groups. However, the patients in the albumin group had more mild-to-moderate pulmonary edema and symptomatic intracranial hemorrhage [54]. The reason for the negative outcome of this well-designed study was the high dose of albumin given as a single bolus, which might have induced those unfavorable effects and obscured the neuroprotective effect of albumin.

Albumin in the dose of 1.25 g/kg/day/7 days was tolerated by the patients with SAH without major complications and may be neuroprotective. Albumin in the dose of 1.25 g/kg/day/7 days had lower rates of cerebral vasospasm measured by transcranial Doppler (TCD), delayed cerebral ischemia (DCI), and cerebral infarctions. The main physiological effects of albumin treatment were elevation of the serum albumin concentration and mean arterial blood pressure. In addition, serum albumin remained elevated 7 days after treatment, which might be beneficial throughout the critical period of DCI [55, 56].

The mechanisms of the neuroprotective effects of albumin could be explained by its ability to attenuate brain edema and inhibit the endothelia cell apoptosis [57, 58]. Albumin administration may improve microcirculatory blood flow, increase organ perfusion, decrease leukocyte rolling and adherence, and reduce the inflammatory response [59]. Albumin preserves the blood brain barrier (BBB) by abolishing the hyperactivation of metalloproteinases −2 and −9 (MMP-2/9) following subarachnoid hemorrhage, suggesting MMP-2 and MMP-9 are key mediators for the albumin-induced neurovascular protection [53]. Moreover, albumin is considered the major antioxidant agent in the body. Albumin functions as an endogenous nitric oxide (NO) reservoir via binding of its sulfhydryl moiety of cysteine 34 residue with NO to form S-nitrosothiols (RSNO). It is worth mentioning that 82 % of NO in blood is preserved in stable form as RSNO [13]. Therefore, albumin is able to neutralize the excessive circulating NO so as to prevent the nitro-oxidative stress and, on the other hand, to continue to release NO when the concentrations of low-molecular thiols are elevated. Thereby, albumin via RSNO-adducted NO can relax blood vessels, inhibit platelet aggregation, and increase aortic blood flow [53].

Albumin Use in Patients with Traumatic Brain Injury

In the SAFE trial, patients with traumatic brain injury (TBI) treated with albumin had worse outcomes than saline, most probably because the hypo-osmolar (4 %) albumin solution with mean measured osmolarity of 266 (266–267) mOsm/kg H_2O used in the study induced increases in intracranial pressure but not the use of albumin per se [60, 61]. However, the use of 4 and 20 % solutions in 93 patients with severe TBI and Glasgow Coma Score ≤ 8 in addition to a neutral or to a slightly negative fluid balance was associated with low mortality in those patients [62]. Therefore, the correct conclusion should be hypo-osmolar solutions should not be used in patients with TBI [63].

Albumin and Cardiac Surgery

The activation of systemic inflammatory and hemostatic systems that takes place during cardiopulmonary bypass (CPB) results in fibrin formation, platelet activation/consumption, and endothelial damage. However, the use of 5 % albumin in priming the CPB machine has many advantages, such as preservation of oncotic pressure, preventing fibrinogen and platelet adhesion, and endothelial glycocalyx protection. In addition, it maintains the vascular barrier competency, prevents interstitial edema, and keeps the integrity of the microcirculation [64].

Oliver et al. compared 5 % albumin priming with fresh frozen plasma (FFP)-based priming in pediatric patients [65]. Patients in the 5 % albumin group had significantly lower administration of blood products. It was shown that using albumin for the priming volume, a dilution of coagulation factors is accepted during CPB. This will lead to less thrombin generation and consumption of coagulation factors and the FFP will be supplemented after protamine administration. However, the use of FFP as a priming solution will result in enhancing the thrombin formation during CPB, thereby more heparin is needed and more consumption of coagulation factors is triggered.

The use of albumin in priming the adult CPB may compete with fibrinogen in the formation of the protein layer coating the circuit and the oxygenator, and the preadsorption of albumin prevents fibrinogen adsorption and platelet adhesion. Russell et al. have shown in their meta-analysis that albumin compared with crystalloids as a priming solution exerts a number of beneficial effects, including platelet count and colloid osmotic preservation [66].

The use of albumin in the postoperative period after cardiac surgery has resulted in the preservation in clot formation time and maximum clot firmness. However, the use of low molar hydroxyethyl starch solutions (HES) (6 % 200/0.5 or 130/0.4) resulted in prolongation in clot formation time and reduction in maximum clot firmness [67]. Moreover, the use of old high-molar HES and gelatin solutions correlated with the amount of postoperative bleeding after cardiac surgery, but the use of 4 % albumin solution did not [68]. The same results have been confirmed in a meta-analysis comparing the use of HES solutions with albumin. Hemodynamics were similar in both groups, but the use of albumin decreased blood loss, the amount of blood products transfusions, and the need for reoperation postoperatively [69]. The presence of hypoalbuminemia (cutoff 18 g/L) after cardiac surgery was found to be a better predictor for mortality after cardiac surgery – even better than EUROscore [70]. In a recently published prospective, randomized, double-blind, placebo-controlled trial, the preemptive correction of a low preoperative albumin level by administering HSA in patients undergoing off-pump coronary artery bypass (OPCAB) is associated significant reduction in the incidence of AKI, from 26 % in the control group to 13.7 % in the albumin group. The editorial that accompanied the study has suggested that restoring the target level is associated with reduction in AKI in amplitude greater than that of any known intervention in patients undergoing OPCAB [71, 72].

Albumin Solutions

Edwin Cohn's development of stable albumin solution during World War II was based on a fractionation scheme, which was rapidly adopted by a number of pharmaceutical companies. The pasteurization technique used in albumin solutions production is very effective in eliminating the risk for viral and bacterial infections. Moreover, the recent introduction of ion exchange chromatography in the production of albumin is very effective in reducing the risk of prion disease transmission by albumin solutions [73]. The use of albumin is considered safe practice; in a study evaluating adverse event reporting between 1998 and 2000, the incidence of all reported serious nonfatal and fatal adverse events was just five per million doses, and no patient death was classified as probably related to albumin administration [74].

Currently available human albumin solutions may differ in protein content and composition, binding capacity, metal ion content, antioxidants prosperities, and capacity to bind drugs [75]. It is noteworthy to mention that cysteine 34 – the most important antioxidant residue in HSA – is oxidized in 23 % of healthy human volunteers versus 54–60 % in commercial preparations [76], which may influence the properties and hence the clinical impact of albumin solutions [77].

Albumin solutions are available in a variety of concentrations, mainly 20–25 % or 4–5 %. Iso-oncotic preparations of HSA are more effective than crystalloids solutions in maintaining the intravascular volume (>80 % vs. <20 %) [78]. Hypertonic albumin (20–25 %) is used in patients with edema as it avoids excessive sodium and chloride loads [75]. Nevertheless, hypotonic 4 % solutions should not be used in patients with traumatic brain injuries.

The excessive need for the HSA solutions has encouraged its production using recombinant DNA technology in both prokaryotic and eukaryotic hosts. HSA molecule structure is quite complicated; with 35 cysteine residues, 34 of them form disulfide bonds. Such complicated structure in this large recombinant protein could be a burden in both protein synthesis and folding system, which could result in the low expression or incorrect folding of recombinant HSA (rHSA). Recently, transgenic rice *Oryza sativa* has been used successfully as a novel bioreactor to produce sufficient quantities of safe rHSA. However, to establish appropriate impurity removal and detection methods in rHSA manufacturing remains a challenge (Fig. 9.4) [79, 80].

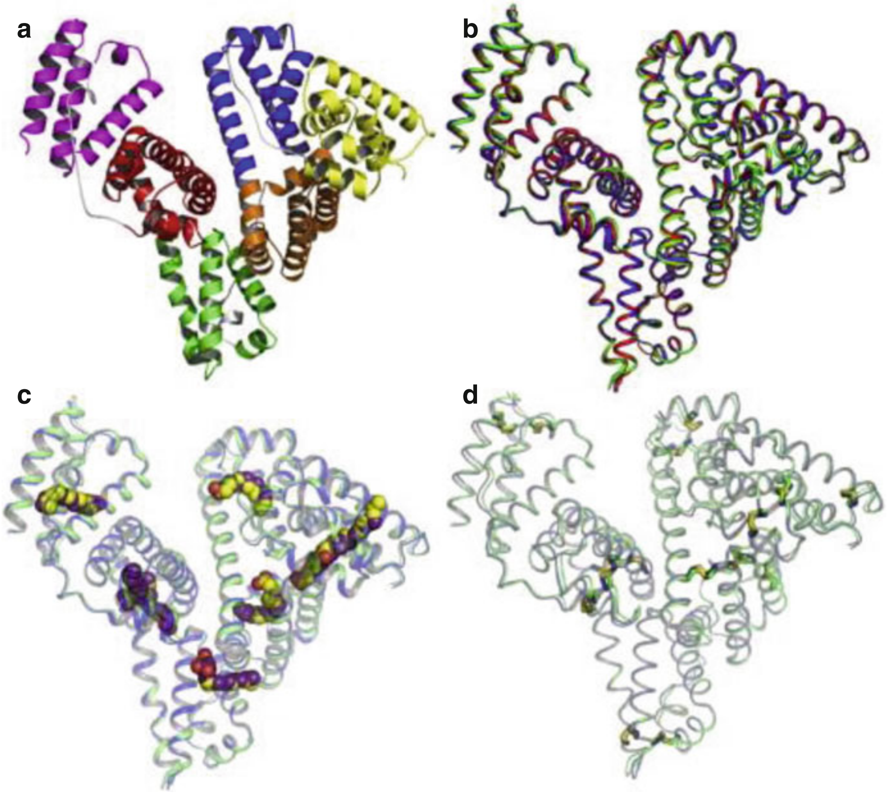

Fig. 9.4 Structures of rHSA from yeast and rice. (**a**) Overall structure of recombinant human serum albumin. (**b**) Comparison of recombinant HSA from rice (*green*, PDB: 3SQJ) or yeast (*blue*, PDB: 1E7G) to HSA from plasma (*red*, PDB: 2I2Z), the RMSDs of two rHSAs to pHSA were 0.605 and 0.374 Å, respectively. (**c**) Fatty acids binding in rHSAs. The fatty acids bound to rHSA from plant (*green*) and yeast (*blue*) were represented by sphere coloring as *yellow* and *brown*. (**d**) Disulfides in rHSA from yeast and rice. Disulfide bonds were shown as yellow sticks (Reprinted with permission from Chen et al. [79])

Conclusion

HSA has many physiological and biochemical properties that render its use relevant to many aspects of the disordered vascular and cellular functions. HSA has not yet showed all its secrets, and its benefits can only be realized by conducting clinical trials appropriately powered to relevant clinical endpoints.

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