Role of Human Albumin in the Management of Complications of Liver Cirrhosis

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Albumin is a negatively charged, relatively small protein synthesized by liver cells. Is the most abundant protein in extracellular fluid and accounts for about 70% of the plasma colloid osmotic pressure. Therefore it plays a crucial role in regulating fluid distribution in the body. In addition, albumin possesses functional domains with important non-oncotic properties, such as potent anti-oxydant and scavenging activities, binding of highly toxic reactive metal species and a great amount of endogenous and exogenous substances.

We have recently learned that albumin in cirrhosis undergoes a number of post-transcriptional changes that greatly impair its non-oncotic properties. The overall assessment of these changes clearly shows that the relative abundance of the native form of albumin is significantly reduced in hospitalized patients with cirrhosis and that these abnormalities worsen in parallel with the increasing severity of the disease. Thus, it is time to abandon the concept of serum albumin concentration and refer to the *effective albumin concentration*, that is the native intact albumin.

Given the pathophysiological context in which we use human albumin in patients with cirrhosis, who are characterized by peripheral vasodilation and a low-grade but sustained inflammatory state, the use of albumin in patients with cirrhosis should aim at enhancing effective hypovolemia and exploiting its antioxidant and scavenging activities.

The indications for the use of albumin in cirrhosis that clearly emerge from evidence-based medicine are represented by conditions characterized by an acute aggravation of effective hypovolemia and inflammation, such as such post-paracentesis circulatory dysfunction, spontaneous bacterial peritonitis, and hepatorenal syndrome. Other indications to the use of albumin that still require further studies are represented by bacterial infections other than spontaneous bacterial peritonitis, hepatic encephalopathy and long-term treatment of ascites, which has been debated for the last half-century. (J Clin Exp Hepatol 2014;4:302–311)

Keywords: albumin, cirrhosis of the liver, ascites, bacterial infections, non-oncotic properties of albumin

Received: 11.8.2014; *Accepted:* 27.8.2014; *Available online:* 19.09.2014

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Abbreviations: ACB: albumin cobalt binding; ACLF: acute-on-chronic liver failure; EASL: European Association for the Study of the Liver; EPR: electron paramagnetic resonance; HE: hepatic encephalopathy; HPLC: high performance liquid chromatography; HRS: hepatorenal syndrome; IMA: ischemia-modified albumin; MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization with Time of flight technique; MARS: Molecular Adsorbent Recirculating Systems; MELD: model for end stage liver disease; NO: nitric oxide; PPCD: post-paracentesis circulatory dysfunction; RAAS: renin-angiotensin-aldosteron axis; ROS: reactive oxygen species; SBP: spontaneous bacterial peritonitis; SNS: sympathetic nervous system

http://dx.doi.org/10.1016/j.jceh.2014.08.007

STRUCTURE AND FUNCTIONS

Albumin is the most abundant protein in plasma, constituting approximately 50% of the total protein content (3.5–5 g/dl). It is a globular protein, with a primary sequence made up of 585 amino acid residues and weighing 66.5 kDa. In its native form, albumin is moderately elongated, flexible and with a stable structure. Its high solubility and low viscosity are well suited to its role as a vector, scavenger and plasma expander. It consists of a single chain of amino acids that develops through nine loops, which are organized into three domains. In the molecular structure of albumin there are 35 cysteine residues, 34 of which are involved in internal disulfide bonds stabilizing the spatial conformation of the molecule, while the cysteine at position 34 (Cys-34) remains free.[1]

In the human body, albumin assumes the tertiary structure of an ellipsoid, formed by 67% of α-helices, where we can recognize three homologous domains (I-II-III), each containing two sub-domains (A and B). The different

domains are capable of folding into hydrophobic pockets, which can open and close, and accommodate large insoluble anions as fatty acids. On the molecule surface there also are cationic groups capable of forming ionic bonds with many ligands.[2,3]

Liver cells are the only site where albumin is synthesized. They produce about 10–15 g per day, but, if needed, albumin production can increase upto 3–4 fold. The osmolarity and, subsequently, the oncotic pressure of the interstitial fluid in the hepatic parenchyma play a fundamental role in the regulation of albumin synthesis. In health, its production is quite constant, so that only a small intracellular deposit of the protein is required.

Approximately 30%–40% of the albumin pool is retained in the blood stream, while the remaining is distributed in the interstitium, where its concentration is low (1.4 g/dl), as well as in muscles and skin. The exchange of albumin between the plasma and the interstitium is a highly dynamic process: the protein leaves the vascular compartment at a rate of 5% per hour, returning to it via the lymphatic system in an amount equaling the output. The circulatory half-life of albumin, which is approximately 16–18 h, is therefore much lower than its total half-life, which varies from 12.7 to 18.2 days in a young healthy adult.

Albumin synthesis is stimulated by hormonal factors such as insulin, cortisol and growth hormone while, conversely, mediators of inflammation, such as cytokines IL-6 and TNF-α, act as inhibitors. Albumin is mainly degraded by the muscles, liver and kidneys, although its catabolism is a widespread process involving many tissues, which is influenced by the plasma concentrations of atrial natriuretic peptide.[4,5]

Functions

Albumin exerts important physiological roles. A most prominent feature is that albumin is the main modulator of fluid distribution in the various compartments of the body. In fact, about 70–75% of the oncotic pressure of the plasma is determined by albumin due to its direct osmotic property. Moreover, binding of cations, such as sodium, to the negative charges of the protein leads water to move from interstitium to the intravascular compartment (Gibbs–Donnan effect).[6]

Albumin binds and carries a great variety of hydrophobic molecules such as metals, fatty acids, metabolites and drugs, with consequent implications on solubilization, transport and metabolism of many endogenous and exogenous substances (Figure 1). Indeed, through the binding with albumin, many potentially toxic ligands are neutralized and definitively catabolized with the degradation of the protein.

Furthermore, albumin is the major source of extracellular reduced sulfhydryl groups (–SH), which act as potent scavengers of reactive oxygen species (ROS) derived from oxidative stress, thus constituting the main circulating antioxidant system in the body. In healthy adults, approximately 70–80% of albumin contains a free sulfhydryl group in Cys-34 position, the so called human mercaptalbumin. About 25%, instead, presents the Cys-34 involved in a disulfide bond with plasma sulfhydryl compounds, such as cysteine, homocysteine or glutathione. This form of albumin is called non-mercaptalbumin 1. Finally, only a small percentage of albumin circulates in the form of non-mercaptalbumin 2, where the residue Cys-34 is

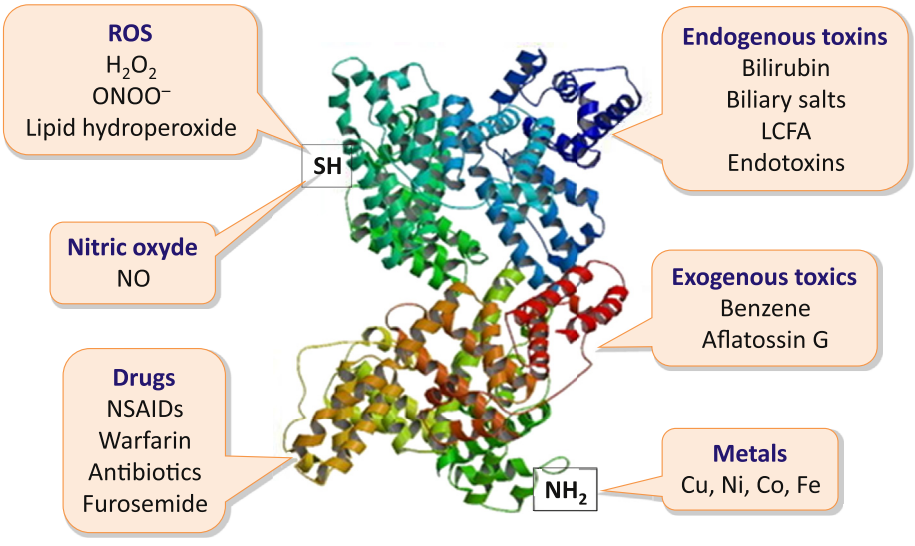

Figure 1 Albumin possesses functional domains with important properties, such as the free cysteine residue (SH) in position 34, which exerts potent anti-oxydant and scavenging activities, the aminoterminal (NH_2) that binds to and removes highly toxic reactive metal species, and other domains that bind a variety of endogenous and exogenous substances including endotoxins and various drugs (ROS: reactive oxygen species; LCFA: long-chain fatty acids; NSAIDs: non-steroideal anti-inflammatory drugs).