Review

Albumin as Fatty Acid Transporter

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Summary: Fatty acids play critical roles in mammalian energy metabolism. Moreover, they are important substrates for the synthesis of membrane phospholipids and biologically active compounds like eicosanoids and leukotrienes. Because of their low solubility in aqueous solutions such as blood plasma and interstitial fluid, fatty acids are in need of binding proteins to increase their concentration in vascular and interstitial compartments. Albumin acts as main fatty acid binding protein in extracellular fluids. Plasma albumin possesses about 7 binding sites for fatty acids with moderate to high affinity, enhancing the concentration of fatty acids by a several orders of magnitude. Despite the high affinity of albumin for fatty acids, uptake of fatty acids by parenchymal cells such as skeletal and cardiac myocytes seems not to be hampered by albumin. In contrast, experimental findings suggest that albumin may facilitate the uptake of fatty acids by organs in need of these substrates. In the present overview the following issues will be briefly discussed: (i) transport and storage of fatty acids in the mammalian body, (ii) biosynthesis of albumin in the liver, (iii) localization and concentration of albumin in body fluids, (iv) interactions between albumin and fatty acids, (v) albumin structure and fatty acid binding sites, (vi) uptake of fatty acids by organs and roles for plasma albumin and (vii) lessons from patients and experimental animals lacking plasma albumin.

Keywords: albumin; fatty acids; transport; binding kinetics; plasma

Introduction

The mammalian body heavily relies on fatty acids as suppliers of chemically stored energy, building blocks of cellular membranes and signal transducers.1) The main source of fatty acids is dietary lipid, digested in the gastro-intestinal tract by the catalytic action of pancreatic hydrolytic enzymes. Part of fatty acids is produced by the liver with carbohydrates as substrate. The bulk of fatty acids are stored in fat cells composing adipose tissue, although most organs contain a substantial number of fat cells either as short distance storage sites of fatty acids or as insulation or protection material. Fatty acids are transported in the body via the lymphatic and vascular system. Basically, two transport forms are at hand: fatty acids are transported as triacylglycerols, the main lipid component of circulating lipoproteins such as chylomicrons and very-low density lipoproteins (VLDL), or as non-esterified fatty acids (FA). Due to their low solubility in aqueous solutions, FA require a transporter both in plasma and in the interstitial compartment to allow for bulk transport of FA from fat cells in adipose tissue to FA-consuming cells like cardiac and skeletal myocytes.

In the present review attention is paid to i) qualitative and quantitative aspects of transport and storage of fatty acids either as triacylglycerol or FA, ii) the need for a FA transporter in aqueous solutions, iii) features of albumin as FA-binding protein and iv) roles of albumin in the supply of FA to fatty acid-consuming cells such as skeletal and cardiac muscle cells.

Transport and Storage of Fatty Acids in the Mammalian Body

The average western diet of a healthy adult person contains approximately 75 g fat per day. This number corresponds to an average supply of 0.3 mol exogenous fatty acids per 24 hours. A person of 70 kg body weight contains about 15 kg fat, corresponding to about 60 mol fatty acids. These values underline the notion that the body is capable of storing sufficient amounts of chemical energy in the form of neutral lipids to survive a couple of week's food deprivation. Exogenous fatty acyl moieties, supplied to the body as dietary triacylglycerols, are digested to FA and monoacylglycerols in the small intesti-
Fig. 1. Simplified schema of flow of fatty acids from diet triacylglycerols to parenchymal cells such as skeletal and cardiac muscle cells, and hepatocytes

FA, TG, MG and PL refer to fatty acid, triacylglycerol, monoacylglycerol, and phospholipid, respectively. VLDL refers to very-low density lipoprotein.

tine by pancreatic lipases (Fig. 1).

After transport through the luminal membrane of the intestinal epithelial cells, the digestion products are resynthesized to triacylglycerols, incorporated in chylomicrons and transported through the basal membrane of the epithelium to the lymphatic system. Via the thoracic duct, venous system, cardiac chambers and arterial system chylomicrons are supplied to organs in need of fatty acids (Fig. 1). The majority of fatty acids is used eventually for energy conversion; a relatively minor part is incorporated in membrane phospholipids or utilized for the production of biologically active eicosanoids.

Under resting conditions, the bulk of chylomicrons reach adipose tissue. Catalytic action of lipoprotein lipase, attached to the luminal endothelial membrane, releases FA from the neutral lipid core of the chylomicron particle and allows for FA uptake in the adipose cells. Thereafter, FA are stored temporarily in the adipocytes in the form of cellular triacylglycerols until signals reach the fat cell to hydrolyze part of their intracellular neutral lipids (Fig. 1). FA diffuse back to the capillary lumen and are transported via the blood stream to organs such as heart and skeletal muscle to fulfill their energy requirements. Excess of circulating FA is taken up by the liver, incorporated as triacylglycerol in very-low density lipoproteins (VLDL) and released to the blood compartment. VLDL subsequently transfers their esterified fatty acid load to adipose tissue and muscle. The concentration of fasting plasma triacylglycerol is in the order of 2.7 mmol fatty acid moieties per liter. The explanation for the relatively high plasma concentration of esterified fatty acids, compared with FA, is the slow turnover rate of plasma VLDL.

When the body is chemically in equilibrium, about 0.3 mol FA should be transported via blood plasma from fat tissue to FA-consuming organs each 24 hours. Assuming an average cardiac output of 5 liter per minute (about 3 liter of blood plasma per minute) and utilization rate of 25% during one single capillary passage, FA concentration in blood plasma should be in the order 0.3 mM. This value is very close to the experimentally determined FA concentration in blood of healthy human beings and experimental animals. Since the solubility of FA in aqueous solutions such as blood plasma is far below 0.3 mM, the mammalian body is in need of FA-binding and transporting moieties to guarantee a sufficient transport capacity of FA from adipose tissue to the FA-consuming organs. The most likely candidate to fulfill this critical role in fatty acid homeostasis is plasma albumin.

**Biosynthesis of Albumin in Liver**

Circulating human albumin is composed of about 585 amino acid residues and contains 17 disulfide bridges. The disulfide bridges add substantially to the stability of the protein, explaining its relatively long biological half-life of about 20 days. The daily production of albumin in a normal healthy person amounts to approximately 15 gram per day. The liver as site of albumin synthesis is identified by studies of Peters and coworkers in the early fifties. Albumin is encoded by a single autosomal gene on chromosome 4q13.3. Inside the hepatocyte, the biosynthesis of albumin starts with the production of
preproalbumin. The preprotein is converted into proalbumin in the lumen of the endoplasmic reticulum. Subsequently, an N-terminal 6 amino acid long oligopeptide is cleaved in the trans-Golgi network by furin yielding the mature plasma protein albumin with 585 amino acid residues.\(^{11}\) Secretion of albumin from the hepatocyte does not require further chemical processing such as glycosylation, neither are substantial amounts of albumin stored in the liver cell.\(^{9}\) The rate of synthesis closely depends on amino acid supply, in particular tryptophan, which may be the cause of enhanced production of albumin after each meal.\(^{9}\) Suggestions have been made that proalbumin plays a role in regulating the biosynthesis rate of albumin.\(^{11}\)

**Localization and Concentration of Albumin in Body Fluids**

The concentration of albumin in blood plasma is in the order of 42 gram/liter, corresponding to 640 \(\mu\)M. The concentration in the interstitial compartment varies between 150–450 \(\mu\)M, depending on the tissue and measuring technique.\(^{12}\) Due to the big difference between fluid volume in plasma and interstitium approximately 60% of total body albumin is located outside the vascular compartment. Recent studies of Wiig and colleagues\(^{13}\) show that in skeletal muscle the interstitial albumin concentration amounts to about 70% of blood plasma. Earlier findings of Ullal and co-workers\(^{14}\) suggest that in the myocardium, the relative concentration in the interstitial fluid is in the same order of magnitude. The transfer rate of albumin from plasma to the interstitial compartment is low in skeletal and cardiac tissue, and relatively high in visceral organs.\(^{15}\) The transfer rates are roughly proportional to the vascularity of the tissues investigated.

**Interaction between Albumin and Fatty Acids**

The first scientific report on FA-binding properties of albumin is most likely the 1941 Forrest E. Kendall’s paper “Studies on human serum proteins”.\(^{16}\) In attempts to purify albumin from human blood samples, the author noted that “albumin which has crystallized four times was still yellow by the presence of serum pigments. It was suspected that this pigment might be lipoidal in nature”. Analysis by the author revealed that crystalline serum albumin is associated with a free fatty acid.\(^{16}\) Interest in albumin exponentially increased in the years that followed due to the need of stable albumin preparations for the armed forces on the battlefield. Contamination of crystalline albumin by organic anions such as fatty acids could be a threat to the quality of the albumin preparation.\(^{17}\) After the Second World War the physiological significance of interaction between albumin and FA was increasingly appreciated in a more positive way. The binding of medium- and long-chain FA to albumin became the subject of numerous studies.\(^{18,19}\) Pioneering studies of D.S. Goodman using Scatchard-plot analysis definitely showed the propensity of plasma albumin to bind to FA with high affinity and, hence, its ability to transport bulk amounts of FA in the vascular compartment.

The 1958 study of Goodman indicated the presence of 2 high affinity binding sites, 5 sites with intermediate affinity and more than 20 low affinity binding sites of FA per human serum albumin molecule.\(^{20}\) The corresponding affinity (= association) constants for oleate were about 1.1 \(\times\) 10^9, 4.0 \(\times\) 10^8 and 1 \(\times\) 10^7 \(\text{M}^{-1}\) for the high, intermediate and low affinity sites, respectively, measured at 23°C (Table 1). Affinity was found to be chain length dependent as affinity increased from laurate (10 carbon atoms) to oleate (18 carbon atoms). However, the association constant of bovine serum albumin for oleate, measured at 37°C, was 1.65 \(\times\) 10^7 \(\text{M}^{-1}\) for the highest binding affinity site, about one order of magnitude lower than human serum albumin (Table 1). The association constants of oleate for sites with intermediate binding affinity varied from 1.9 \(\times\) 10^6 to 1.8 \(\times\) 10^5 \(\text{M}^{-1}\). Later studies by Ashbrook and colleagues\(^{22}\) on human serum albumin, also applying the step-wise equilibrium method at 37°C, confirmed the earlier findings of Goodman. Association constants for oleate were in the order of 10^6 \(\text{M}^{-1}\) for the two highest binding affinity sites. Ashbrook and colleagues pointed out that the distinction between high affinity and intermediate affinity binding of FA is arbitrary since the experimental data indicate a continuum of binding affinities from high to low without clear demarcation lines.\(^{22}\) Wosilait and Solar-Argilaga\(^{23}\) computed that 80% to 85% of all FA bound are attached to the two bindings sites with highest affinity when the FA/albumin concentration ratio is in the physiological range of 0.5 to 1.0. The collected findings were reviewed extensively in 1981 by Kragh-Hansen.\(^{24}\) In the years that followed the issue of how strong albumin binds FA was scrutinized again by a number of research groups often with highly sophisticated techniques. The data are summarized in Table 1. In general, the conclusion can be drawn that no major differences exist between human and bovine serum albumin and that the value of the highest affinity binding of palmitate is on the order of 10 \(\times\) 10^9 to 25 \(\times\) 10^8 \(\text{M}^{-1}\). Binding of FA to albumin is closely related to the three-dimensional structure of albumin. In recent years, a wealth of detailed information has become available on both features, i.e., FA-binding and...
three-dimensional structure of plasma albumin.

**Albumin Structure and Fatty Acid binding Sites**

Crystallographic studies of He and Carter,\(^2^{5}\) at a resolution of 2.8 Å revealed that the secondary structure of human serum albumin is purely \(\alpha\)-helical. Later studies indicated that the protein comprises three homologous domains (I-III), each containing ten helices that assemble to form a heart-shaped molecule. Each domain is the resultant of two distinct subdomains (A and B) possessing common structural motifs.\(^1\)\(^2\) The protein shows a substantial degree of conformational alteration associated with variations in pH, ambient calcium concentration and fatty acid-binding.\(^1\)\(^3\) Defatted albumin is present in the so-called N ("neutral") form. Transition to the B ("basic") form occurs within the pH range of 6 to 9. There is a striking parallel between the N to B conformational shift and structural change of albumin associated with binding of FA to the protein.\(^1\)\(^2\) Pioneering studies of Carter and coworkers\(^2\)\(^6\) reported crystals of human serum albumin and FA. Later studies of Curry and colleagues showed the presence of seven FA-binding sites on the protein.\(^2\)\(^7\) The seven common, high affinity FA-binding sites are distributed throughout the albumin protein in an asymmetric manner with regard to the internal homology of the domains.\(^1\)\(^2\) The first binding site is located in subdomain IB, the second lies at the interface between IA and IIA, sites 3 and 4 are both identified within subdomain IIIA, site 5 is located in subdomain IIIB, site 6 at the interface between IIA and IIB, and site 7 is associated with subdomain IIA.\(^1\)\(^2\)

As pointed out by Curry in his excellent 2004 review,\(^1\)\(^2\) precise identification of the sites with the highest affinity for FA has been the subject of many studies encountering a great number of methodological difficulties. At present, general agreement exists about at least 2 to 3 sites with high affinity (see also Table 1) and 4 to 5 sites with intermediate affinity for FA, although sharp demarcation lines seem not to be present. The secondary FA-binding sites show affinities that are only 5 to 10 times lower than the primary sites.\(^1\)\(^2\) Recent NMR studies on human serum albumin have revealed that the primary sites are represented by sites numbered 2, 4 and 5. The secondary sites correspond to sites 1, 3, 6 and 7.\(^2\)\(^8\),\(^2\)\(^9\) Sites 2, 4 and 5 appear to offer the most favorable conditions for high-affinity binding of FA, since they provide the most enclosed environment on albumin that allows the aliphatic chain of the FA molecule to bind in an almost linear conformation. Moreover, the presence of one or more basic amino acid side-chains offers the possibility for specific salt bridge interactions with the fatty acyl carboxylic head group.\(^2\)\(^8\) Since the amino acid sequence of bovine serum albumin is 75% identical to the human protein, its FA-binding properties are very similar to those of human serum albumin.\(^3\)\(^0\) It is of interest to note that experimental data indicate that the structure of the albumin molecule is stabilized due to binding to their natural ligands, i.e., FA.\(^2\)\(^4\)

**Uptake of Fatty Acids by Organs: Possibles Roles of Plasma Albumin**

The finding that albumin binds fatty acids with high affinity, resulting in a physiological plasma concentration of FA on the order of 5 to 10 nM, begs the question how

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**Table 1. Binding affinities of bovine and human serum albumin for palmitate and oleate**

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>Palmitate</th>
<th>T</th>
<th>Oleate</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Goodman(^9)(^6)</td>
<td>Heptane partitioning</td>
<td>6</td>
<td>23°C</td>
<td>11</td>
<td>23°C</td>
<td>HSA; (K_i (n = 2))</td>
</tr>
<tr>
<td>Spector et al.(^1)(^9)</td>
<td>Heptane partitioning</td>
<td>2.9</td>
<td>23°C</td>
<td>—</td>
<td>—</td>
<td>BSA; (K_i (n = 3))</td>
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<tr>
<td></td>
<td></td>
<td>0.7</td>
<td>37°C</td>
<td>0.4</td>
<td>37°C</td>
<td>BSA; (K_i (n = 3))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1</td>
<td>23°C</td>
<td>—</td>
<td>—</td>
<td>HSA; (K_i (n = 3))</td>
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<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>37°C</td>
<td>—</td>
<td>—</td>
<td>HSA; (K_i (n = 3))</td>
</tr>
<tr>
<td>Spector et al.(^2)(^7)</td>
<td>Heptane partitioning</td>
<td>3.3</td>
<td>37°C</td>
<td>1.7</td>
<td>37°C</td>
<td>BSA; (K_i (n = 1))</td>
</tr>
<tr>
<td>Ashbrook et al.(^2)(^8)</td>
<td>Heptane partitioning</td>
<td>25.5</td>
<td>37°C</td>
<td>25.6</td>
<td>37°C</td>
<td>HSA; (K_i (n = 1))</td>
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<tr>
<td>Bojesen and Bojesen(^6)(^1)</td>
<td>RBC ghost receptor</td>
<td>10.1</td>
<td>38°C</td>
<td>—</td>
<td>—</td>
<td>BSA; (K_i (n = 3–4))</td>
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<tr>
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<td>RBC ghost receptor</td>
<td>—</td>
<td>—</td>
<td>34.5</td>
<td>23°C</td>
<td>BSA; (K_i (n = 1))</td>
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<tr>
<td>Richieri et al.(^4)(^6)</td>
<td>ADIFAB acceptor</td>
<td>12.2</td>
<td>37°C</td>
<td>12.7</td>
<td>37°C</td>
<td>BSA; (K_i (n = 1))</td>
</tr>
<tr>
<td>Rose et al.(^5)(^9)</td>
<td>albumin-sepharose</td>
<td>14.8</td>
<td>37°C</td>
<td>10.4</td>
<td>37°C</td>
<td>BSA; (K_i (n = 1))</td>
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<tr>
<td>Elmehdouh et al.(^6)(^5)</td>
<td>Heptane partitioning</td>
<td>22</td>
<td>37°C</td>
<td>11.8</td>
<td>37°C</td>
<td>HSA; (K_i (n = 1))</td>
</tr>
<tr>
<td>Demant(^6)(^1)</td>
<td>BSA-HSA acceptor</td>
<td>1</td>
<td>20°C</td>
<td>4.5</td>
<td>20°C</td>
<td>BSA; (K_i (n = 4–5))</td>
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<tr>
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<td>12.5</td>
<td>22°C</td>
<td>13.5</td>
<td>22°C</td>
<td>BSA; (K_i (n = 7–8))</td>
</tr>
</tbody>
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HSA, BSA and RBC refer to human serum albumin, bovine serum albumin and red blood cells, respectively. \(K_i\) refers to equilibrium constant of the binding site(s) with the highest affinity; \(n\) refers to the (combined) number of binding sites with the highest affinity measured in the study. \(T\) refers to temperature.
tissues such as heart and skeletal muscle, and liver are able to extract plasma FA in a highly efficient manner. Original studies of Weisiger and colleagues on liver FA-uptake suggest the existence of a receptor for albumin on the liver cell surface mediating the uptake of FA in hepatocytes by accelerating the release of FA from the albumin molecule. In later studies, the notion of albumin-receptor to facilitate hepatocyte FA uptake was abandoned. Instead, the importance of a diffusion limitation caused by an unstirred water layer was put forward.

High albumin concentrations could effectively reduce this diffusion barrier imposed on FA transversing the unstirred water layer adjacent to the hepatocyte plasma membrane. Extrapolation of data obtained in the hepatic context to the heart and skeletal muscle should be done with great caution, because of the fundamental difference between hepatic and cardiac endothelium, i.e., fenestrated vs. non-fenestrated capillary wall, affecting the availability of plasma albumin for parenchymal cells and differences in organ blood supply and perfusion, although the existence of an effective unstirred water layer close to the endothelial luminal plasma membrane cannot be neglected.

Due to the non-fenestrated character of the endothelium in heart and skeletal muscle, endothelial cells lining the capillary plasma compartment may be the first, potential barrier for blood-borne FA on their way to cardiac and skeletal muscle cells. Pioneering studies of Rose and Goresky, applying the multiple indicator dilution technique in the intact heart, strongly suggest the endothelium to serve as a barrier for plasma FA to reach muscle parenchymal cells. In contrast to transport of FA through the muscle cell membrane, the mechanism of FA transport across muscle endothelium has attracted relatively little attention. Besides uncertainties about the precise mechanism of endothelial permeation by FA, the identity of the main rate-governing step in overall muscle FA uptake is incompletely understood.

Various theoretical pathways for FA to be transported through the muscular endothelium to the interstitial compartment are depicted in Figure 2.

Route number 1 reflects diffusion of the plasma albumin/FA complex through endothelial clefts to the interstitium. Route number 2 represents transport of the plasma albumin/FA complex through endothelial cells by endocytosis and intracellular vesicle transport. Route number 3 indicates dissociation of FA from plasma albumin in the capillary lumen followed by diffusion of free, non-protein bound FA through endothelial clefts. Route number 4 predicts dissociation of the plasma albumin/FA complex in the capillary lumen prior to transport of non-albumin bound FA through endothelial cells and their subsequent release into the interstitial compartment. Route #1 requires unimpeded diffusion of albumin from plasma to interstitium through the clefts to carry their FA to the final destination, i.e., sarcolemma of the parenchymal cells. To avoid accumulation of interstitial albumin, a comparable number of albumin molecules, devoid of FA, must diffuse back from the interstitium to capillary lumen within the same time frame. As discussed before by Bassingthwaighte and colleagues, this transport route is inconsequential for the supply of plasma FA to muscle cells because of the very small diffusional cross-sectional area of the clefts and tethering of albumin inside the cleft fluid compartment. This notion is supported by experimental findings of Dewey showing that only a small amount of albumin escapes from muscle capillary lumen. Later multiple indicator dilution experi-

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**Fig. 2.** Schematic representation of 4 different, hypothetical pathways of fatty acid transfer through skeletal or cardiac endothelium

FA and FABP refer to fatty acid and fatty acid-binding protein, respectively.
ments performed on intact hearts are in line with Dewey’s observation. Trans-endothelial transport of the non-dissociated plasma albumin/FA complex by vesicle transport through the endothelial cell interior (route #2) has been suggested by, among others, Simionescu and coworkers. They showed by electron-microscopic techniques that gold-labeled albumin transverses the cytoplasm of cardiac endothelium by vesicular transport. Specific albumin-binding proteins located at the luminal side of the endothelial cell were considered to facilitate endocytosis of the albumin/FA complex. However, the estimated transfer time is on the order of 5 minutes, far too slow to account for bulk transport of plasma FA. Route #3, diffusion of non-protein bound plasma FA through the endothelial clefts, can also be discarded as quantitatively of importance. The diffusional cross-sectional area of the clefts is too small to contribute significantly to trans-endothelial permeation of FA and the diffusion rate of FA through the clefts will be substantially depressed by binding to albumin trapped inside the cleft fluid compartment.

By exclusion, transport route #4 is a likely mechanism for trans-endothelial transfer of plasma FA in cardiac and skeletal muscle. Tschubar and associates investigated the transfer of palmitate across the endothelium in the intact, isolated rat heart. And found that the endothelium acts as barrier for plasma FA. To explain the nature of the barrier, the authors suggest that the rate of dissociation of FA from the albumin-FA complex in the capillary lumen is the major rate-governing step in FA transport across cardiac endothelium. This is in line with measurements of the release rate of FA from plasma albumin. Scheider and associates investigated the transfer of palmitate across the endothelium in the intact, isolated rat heart. And found that the endothelium acts as barrier for plasma FA. To explain the nature of the barrier, the authors suggest that the rate of dissociation of FA from the albumin-FA complex in the capillary lumen is the major rate-governing step in FA transport across cardiac endothelium. This is in line with measurements of the release rate of FA from plasma albumin. Scheider and associates reported release rates varying from 0.003 to 0.14 sec⁻¹, much too low to maintain an extraction ratio on the order of 30% to 60% of plasma FA during one passage of blood through the cardiac capillary lumen, commonly lasting 0.8 to 1 sec. In addition, albumin-binding proteins such as albonidin, present on the endothelial luminal membrane, have been proposed to accelerate the release of FA to the endothelium by facilitating the release of FA from plasma albumin. Since later studies using highly sophisticated techniques revealed that the release rate of FA from albumin is substantially faster than reported in the past, i.e., on the order of 3 to 8 sec⁻¹, it is highly unlikely that inadequate buffering by plasma albumin of FA transported through the endothelium represents the first bottleneck in overall cardiac FA uptake. Goretsky and colleagues reported that a specific membrane-associated fatty acid-binding protein (plasmalemmal FABP) is pivotal in cardiac trans-endothelial permeation of FA. This protein may facilitate the absorption of FA into and subsequent transfer through the luminal endothelial membrane. Although the existence of this protein at the endothelial membrane has been confirmed by studies of Cechetto and coworkers, it remains uncertain whether absorption and transfer of FA is a slow process in need of facilitating accessory proteins. In this respect, experiments described by Hamilton and coworkers are noteworthy, showing that FA are rapidly absorbed into and permeate through biological membranes in vitro. Suggestions have been made that endothelial cytoplasmic fatty acid-binding proteins (cFAPB) are important in trans-endothelial FA transport. Since the affinity of endothelial cFAPB is relatively low as is the cytoplasmic concentration, it is uncertain whether this protein is required for FA permeation through the endothelium. Moreover, the very short diffusion distance between the luminal and abluminal endothelial membrane does not plea for a pivotal role of cytoplasmic binding proteins in trans-endothelial FA transport. This notion is supported by mathematical studies performed by Vork and coworkers. Recent unpublished pilot studies from our laboratory suggest that interplay between plasma and interstitial albumin is critical in the transfer of FA from plasma to interstitium and vice versa. These experiments may point to a rapid equilibration of FA between the high affinity binding sites of plasma albumin on the one side and interstitial albumin on the other, followed by relatively slow diffusion of the interstitial albumin/FA complex in the direction of the cardiomyocyte. Further experimentation is warranted to definitively prove the potential critical role of interstitial albumin in overall cardiac FA uptake and utilization.

**Lessons from Patients and Experimental Animals Lacking Plasma Albumin**

An increasing number of patients has been found to show mutations in albumin synthesis, often resulting in analbuminemia. This defect can be caused by nonsense mutations, mutations affecting splicing and frameshift/deletion. The plasma concentration commonly drops to values significantly lower than the concentration in healthy subjects, which is on the order of 45 gram per liter plasma. Despite the low circulating albumin concentration, the patients do not generally show a severe phenotype, the only consistent finding being a slight tendency to develop ankle edema. These findings may challenge the notion that albumin plays a critical role in the lipid economy of the body. The same conclusion may be drawn from observations in Sprague-Dawley rats, an analbuminemic colony of which was first described by Nagase and colleagues. It is of note that the residual plasma albumin concentration showed considerable inter-patient variation. Due to the high capacity of plasma albumin to bind to FA, even substantially reduced albumin levels may still fulfill the role of a plasma FA-carrier. Moreover, it cannot be excluded that the decline in albumin-FA binding capacity is compensated by increased expression of other plasma proteins with FA binding
properties. It is noteworthy that in analbuminemic rats and patients, the plasma concentrations of circulating lipoproteins, and in particular low-density lipoproteins (LDL), were significantly enhanced with normal or slightly decreased plasma FA levels.11 The observation that non-esterified fatty acids are accumulated in the LDL particles, points to a compensatory role of LDL in FA transport in the vascular compartment when albumin is low or absent.11

References

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