ALBUMIN AS FATTY ACID TRANSPORTER

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Long-chain fatty acids (FAs), varying in chain length from 14 to 22 methylene units and zero to 6 unsaturated carbon-carbon bonds, serve as building blocks for membrane phospholipids, precursors for biological active compounds and substrates for cellular energy conversion. The human body is supplied with FAs mainly from lipid-rich food digested in the intestinal tract. Post-prandially, FAs are stored in adipose tissue. On the average a healthy person of 70 kg bodyweight contains 15 kg fat, corresponding to about 60 mol FAs.

FAs are released from the lipid stores when plasma insulin levels drop and adrenalin increase. The human body consumes approx. 0.25 to 1.0 mol FAs/day (from resting conditions to heavy exercise) for oxidative energy conversion. This implies an average FA flux of about 0.15 mmol/min from fat cells in adipose tissue to heart and skeletal muscle cells. Due to the very low solubility of FAs in aqueous environments, plasma carrier proteins are required to accomplish the high flux rate of FAs in the vascular compartment. Plasma albumin fulfills all criteria to act as main FA transporter in blood. The high affinity of albumin for FA was already shown by Kendall in the early forties, while attempting to purify plasma albumin. Detailled studies on the 3-D structure of albumin revealed three homologous domains: domain I, II and III subdivided in A and B with 10 helices each. Moreover, 7 binding sites for FA could be identified: three high affinity sites at site 2, 4 and 5 and four low affinity sites at site 1, 3, 6 and 7 (reviewed by 3). Upon binding to FA the domains I and III appear to swing out from the center. The plasma concentration of albumin is about 0.6 mM; under resting conditions the plasma concentration of FAs is on the order of 0.2 mM, indicating approximately 10% of all high affinity binding sites of albumin are occupied by FAs. Studies of Richieri et al. revealed that the equilibrium (association) constants of the three high-affinity binding sites are in the range of 5-25 nM, which implies that over 99.99% of plasma FAs are bound to albumin. The dissociation rate of the albumin-FA complex is fast, i.e., 3 to 8 sec⁻¹, compared with the mean transient time of blood in the capillary unit (approx. 1 sec). Blood-borne FAs are efficiently taken up by organs such as the heart during one single passage of blood through the microvascular compartment. The endothelium, surrounding the capillary lumen, is supposed to be the first, critical barrier for FAs travelling from the microvascular compartment to the muscle cell interior. The mechanism underlying endothelial permeation by FAs and the nature of the rate-limiting step are, however, incompletely understood. Vesicular transport of the albumin-FA complex through the endothelial cytoplasm can be ruled out because the disappearance rate of albumin from the microvascular compartment is far too low to account for a physiologically relevant FA flux across the endothelium. Diffusion of albumin-bound FA and/or unbound FA through the endothelial clefts is inconsequential because of the high diffusion-resistance of albumin trapped inside the cleft and its limited diffusion area. Therefore, FAs have to dissociate from the albumin-FA complex prior to transversing the endothelial luminal membrane, the cytoplasm and the endothelial abluminal membrane to reach the albumin molecules in the interstitial compartment.

A combination of multiple indicator dilution experiments on isolated rabbit hearts, in which plasma albumin and/or FA concentrations were varied, and mathematical heuristic modeling showed that:

a) albumin-FA complex rather than unbound FA determines transendothelial FA flux rate
b) release of FA from albumin-FA complex is not rate-limiting
c) transfer of unbound FAs through the two endothelial membranes and the endothelial cytoplasm is fast and not rate-limiting
d) diffusion of the albumin-FA complex in the interstitial compartment away from the endothelial abluminal membrane is the main constraint in the overall FA transport in the capillary unit.

References:
1) Kendall, F.E.: J. Biol. Chem. 138: 97-109 (1941)