Symposium: The Role of Long Chain Fatty Acyl-CoAs as Signaling Molecules in Cellular Metabolism

Role of Acyl-CoA Binding Protein in Acyl-CoA Metabolism and Acyl-CoA–Mediated Cell Signaling[1,2]

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ABSTRACT Long-chain acyl-CoA esters (LCA) act both as substrates and intermediates in metabolism and as regulators of various intracellular functions. Acyl-CoA binding protein (ACBP) binds LCA with high affinity and is believed to play an important role in intracellular acyl-CoA transport and pool formation and therefore also for the function of LCA as metabolites and regulators of cellular functions . The free concentration of cytosolic LCA is efficiently buffered to low nanomole concentration by ACBP and fatty acid binding protein (FABP). An additional important factor is the activity of acyl-CoA hydrolases. The estimated cellular free LCA concentration is two to four orders of magnitude lower than the concentrations reported to be necessary to regulate most LCA-affected cellular functions. Preliminary evidence indicates that the regulatory effect of LCA might be mediated by the LCA/ACBP complex. J. Nutr. 130: 294S–298S, 2000.

KEYWORDS: • *acyl-CoA* • *fatty acids* • *metabolism* • *cell signaling*

Acyl-CoA binding protein

The ACBP protein family. Acyl-CoA binding protein (ACBP)[4] is an 86–103 residue protein with a highly conserved amino acid sequence. It has been isolated from a wide range of species including yeasts, plants, reptiles and humans, but also several proteins translated from gene sequences, especially from *Caenorhabditis elegans*, have been suggested. A total of 30 sequences have been recognized either as proteins or as gene translates (Kragelund et al., 1999). From the alignment, at least four groups of ACBP can be identified (Kragelund et al., 1999).

The first group is the generally expressed ACBP isoform, first isolated from bovine liver (l-ACBP). It contains no cysteine and is 86–92 residues long. This basic isoform, which is expressed in almost every tissue in all eukaryotic species tested including yeast, is most likely the ancestor of all other more specialized ACBP isoforms. The second group is the testis specific isoform (t-ACBP) also called endozepine-like protein (ELP). t-ACBP have now been isolated from three different species and all t-ACBP contain three cysteine (Pusch et al. 1996 and 1998). A putative third group may be a brain specific isoform of ACBP (b-ACBP), which has been deduced from gene sequences from duck and frog brain containing one single cysteine at position 43.

The fourth group of ACBP is a group of longer sequences with up to 533 amino acids. Some of these longer sequences are suggested to be membrane-bound ACBP domain proteins, whereas others remain to be isolated as proteins. Many of these longer forms contain cysteine(s).

A sequence analysis of the entire *C. elegans* genome reveals four sequences homologous to ACBP (Kragelund et al., 1999). One of these sequences codes for the basic l-ACBP isoform. The three other sequences read from longer putative protein sequences containing 125,146 and 385 residues. One of these proteins encodes a potential acyl-CoA dehydratase (Wilson et al. 1994). The presence of only the basic short l-ACBP isoform in *C. elegans* indicates that the more specialized isoforms evolved later.

Tissue distribution and content of l-ACBP. In mammals, the highest concentration of l-ACBP is found in liver, where it is evenly distributed in all hepatocytes (Bovolin et al. 1990). In other tissues, l-ACBP is reported to be high in specialized cells such as steroid-producing cells of the adrenal cortex and testis, in epithelial cells specialized in secretion and in water and electrolyte transport, all of which are characterized by a high energy metabolism. In *Drosophila melanogaster*, l-ACBP has been found expressed primarily in tissues that are associated with high energy production or fat metabolism (Kolmer et al. 1994). Its broad range of distribution throughout the ani-

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[4] Abbreviations used: ACBP, acyl-CoA binding protein; ACC, acetyl-CoA carboxylase; CRBP, cellular retinol binding protein; FABP, fatty acid binding protein; LCA, long-chain acyl-CoA ester.

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mal and plant kingdom and its high degree of sequence similarity among different species suggest that l-ACBP is a housekeeping protein. This was further supported by Mandrup et al. (1992) who demonstrated that the genomic gene of l-ACBP has all of the characteristics of a housekeeping gene.

Structure and binding properties. L-ACBP is folded into a four α-helix–bundle protein. The binding site is located in a hydrophobic groove on the surface of l-ACBP. The acyl chain is buried in the binding pocket and is completely protected from the aqueous solvent by the acyl-CoA head group, which forms a lid on the binding pocket by interacting with specific residues on the rim of the binding cavity. The acyl-CoA head group is able to bind to l-ACBP with low affinity (K_D = 2 μmol/L (Robinson et al. 1996) and plays an important role in determining binding specificity for acyl-CoA esters only (Kragelund et al. 1993). l-ACBP binds medium- and long-chain acyl-CoA esters with very high affinity, with a preference for C:14-C:22 acyl-CoA esters (Færgeman et al. 1996, Rasmussen et al. 1990, Rosendal et al. 1993). l-ACBP does not bind fatty acids, acyl carnitines, cholesterol and a number of nucleotides (Rosendal et al. 1993). The binding affinities decrease with increasing ionic strength of the buffer used (Færgeman et al. 1996).

Function. A number of in vitro and in vivo experimental results strongly indicate that ACBP is able to act as an intracellular acyl-CoA transporter and pool former (Færgeman and Knudsen 1997). Compelling evidence that ACBP participates in acyl-CoA transport in vivo has been obtained from yeast. Disruption of the ACBP-gene in *Saccharomyces cerevisiae* results in a dramatic perturbation of the acyl-CoA level and composition (Schjerling et al. 1996). The level of total acyl-CoA and stearoyl-CoA was increased 2.5- and 7.0-fold, respectively. The primary yeast acb1Δ strain is very slow growing and extremely unstable, and it reverted with a very high frequency to a faster growing strain. The synthesis of very-long-chain (26:0) fatty acids was strongly reduced in the primary acb1Δ yeast strain (Knudsen, unpublished results).

Tissue acyl-CoA concentrations

The total cellular concentration of long-chain acyl-CoA esters has been reported to be in the range of 5–160 μmol/L, depending on the tissue and its metabolic state. The levels of acyl-CoA esters are found to vary significantly in different metabolic conditions such as fasting (Bortz and Lynen 1963, Sterchele et al. 1994, Tubbs and Garland 1964), diabetes (Tubbs and Garland 1964), fat/glucose feeding (Tubbs and Garland 1964) and ingestion of hypolipidemic drugs (Berge and Bakke 1981, Berge et al. 1983, Sterchele et al. 1994). For example, in rats that were food deprived for 48 h, the total level of acyl-CoA esters increased at least two- to fourfold (Bortz and Lynen 1963, Sterchele et al. 1994).

The compartmentation of long-chain acyl-CoA esters is an important unsolved problem, and the actual cytosolic concentration of free long-chain acyl-CoA esters is not known for any tissue. Only a few attempts to estimate the intracellular distribution of long-chain acyl-CoA have been reported (Idell Wenger et al. 1978, Moore et al. 1992, Rasmussen et al. 1993. It has been suggested that 20–40% of the total acyl-CoA pool is cytosolic (Oram et al. 1975). Deeney et al. (1992) estimated that the cytosolic long-chain acyl-CoA level in a clonal β-cell line constituted ~78% of the total long-chain acyl-CoA level, giving a cytosolic concentration of 90 μmol/L.

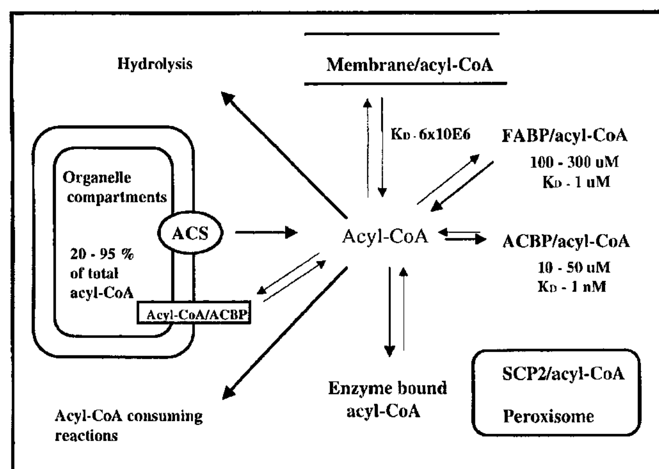

FIGURE 1 Regulation of cytosolic free acyl-CoA concentration. The major players in regulating the cytosolic free long-chain acyl-CoA ester (LCA) concentration are the rate of LCA synthesis and consumption, the concentration of acyl-CoA binding protein (ACBP), fatty acid binding protein (FABP) and the acyl-CoA hydrolase activity. The two binding proteins will buffer large fluctuations in free LCA concentration. The acyl-CoA hydrolases are suggested to function as a "scavenger" system to prevent accumulation of free unprotected LCA and to ensure sufficient free CoA to support β-oxidation and other CoA-dependent enzymes. Sterol carrier protein 2 (SCP2), which binds LCA and very long chain-LCA, is localized in the peroxisomes. SCP2 is suggested to act as a peroxisomal pool former for LCA destined for β-oxidation in this organelle.

Concentration of acyl-CoA in cell cytosol

The most important factors controlling the free concentration of cytosolic LCA are outlined in **Figure 1**. The concentration of ACBP and long-chain acyl-CoA in liver of fed rats has been determined to be 40–50 and 40–60 nmol/g tissue, respectively (Rasmussen et al. 1993, Sterchele et al. 1994), indicating that the acyl-CoA/ACBP ratio might be close to one. At molar ratios of acyl-CoA/ACBP <1, the calculated concentration of free LCA in the cytosol is <10 nmol/L. As the LCA concentration reaches the ACBP concentration (50 μmol/L), the concentration of the unbound acyl-CoA will increase dramatically and approach the total acyl-CoA concentration. However, this situation will not appear because at this point, FABP will take over the LCA buffering function. l-FABP binds long-chain acyl-CoA with a K_D of ~1.0 μmol/L (Rolf et al. 1995). Assuming that the maximal obtainable acyl-CoA concentration in liver cytosol is 150 μmol/L and that the cytosolic FABP concentration is 0.3 mmol/L (0.6 mmol/L binding sites) (Glatz et al. 1988), the calculated free concentration of acyl-CoA will never be expected to exceed 200 nmol/L. Long-chain acyl-CoA ester can also be expected to bind to a number of other proteins in the cell, including the high affinity binding site on acyl-CoA synthetase and acyl-CoA–utilizing enzymes, and the above-mentioned putative membrane-bound ACBP domain proteins. It is tempting to speculate that membrane-associated ACBP domain proteins bind fatty acyl-CoA with high affinity and thus, by competing with the cytosolic ACBP, are able to create a local pool of membrane-bound acyl-CoA esters.

LCA also readily partition into membranes. The partitioning constant for palmitoyl-CoA into phospholipid vesicles can be calculated from the original data of Peitzsch and McLaughlin (1993) as 1.5×10^5 $(mol/L)^{-1}$ and as 5×10^5 $(mol/L)^{-1}$ by Requero et al. (1995). If it is assumed that these values can be

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applied also to in vivo conditions, the calculated free concentration of acyl-CoA in a liver cell in the absence of binding proteins would be ~1 μmol/L if the LCA is allowed to partition freely into membranes.

An additional control factor for ensuring low concentrations of LCA under in vivo conditions is the high activity of acyl-CoA hydrolases, found in most subcellular compartments (Berge and Farstad 1979, Berge et al. 1984, Broustas and Hajra. 1995, Waku 1992, Yamada et al. 1996). The only physiologic role ascribed to these enzymes is termination of fatty acid synthesis by a medium-chain acyl-CoA hydrolase in the mammary gland (Knudsen et al. 1975 and 1976). However, recent results show that a yeast peroxisomal thioesterase homologous to the human peroxisomal thioesterase hTE is required for growth on fatty acids (Jones et al. 1999). A likely explanation for this very unexpected result might be that free CoA is required for the β-oxidation process. The function of the thioesterase would be to "scavenge" excess LCA to ensure sufficient free CoA for β-oxidation and to prevent partitioning of LCA into membranes. This mechanism would require a specific peroxisomal LCA binding protein to form a protected pool of LCA for β-oxidation in the mitochondria. This function might very well be performed by sterol carrier protein 2 (SCP2; Fig. 1), which has been shown to be peroxisomal and to bind LCA with high affinity (Wirtz et al. 1998). We suggest a similar functional relationship between cytosolic acyl-CoA hydrolases and ACBP. Finally, large fluctuations in the cytosolic concentration of free LCA esters will be expected to be prevented by feedback inhibition of the acyl-CoA synthetase (K_i = 4 μmol/L) (Pande 1973).

Long-chain acyl-CoA–regulated cell functions

In vitro experiments suggest that a large number of cellular functions may be regulated by long-chain acyl-CoA esters. These functions include enzymes in carbohydrate and lipid metabolism, translocases, ion channels and pumps, protein kinases, nuclear transcription factors, proteases and protein transport (Færgeman and Knudsen 1997).

A major problem involved in performing these types of experiments and evaluating their physiologic significance is the concentration of LCA used and the physiochemical conditions under which these experiments are performed. LCA is an amphipathic molecule and forms micelles at low concentrations. The critical micellar concentration ranges from 5 to 200 μmol/L depending on chain length, number of double bonds in the acyl chain and salt concentration (Færgeman and Knudsen 1997). The actual free concentration is therefore unknown, if the critical micellar concentration has not been determined under the experimental conditions used. A further critical problem is the fact that LCA readily partitions into membranes (see above). In a large number of the reported experiments with membrane-bound enzymes and ion channels, acyl-CoA esters have been added directly to the membrane suspension without the addition of an acyl-CoA buffering protein. Under these conditions, the added acyl-CoA esters will accumulate to a very high concentration in/on the membrane. The concentration of LCA that the enzyme or ion channel is exposed to might therefore be much higher than the added concentration.

Functions of long-chain acyl-CoA in cellular regulation

Taking all of the above considerations into account, we conclude that the intracellular free acyl-CoA concentration will be in the range of 0.1 to 200 nmol/L under normal physiologic conditions. If the cytosolic acyl-CoA/l-ACBP ratio remains 1, the free concentration will be in the 2–10 nmol/L range. The fact that fatty acid synthesis occurs, although the K_i for inhibition of acetyl-CoA carboxylase is 5.5 nmol/L, strongly indicates that the free concentration of liver cytosolic long-chain acyl-CoA is <5.5 nmol/L during these conditions. If the total free acyl-CoA concentration under normal physiologic conditions is well below 200 nmol/L and most likely <10 nmol/L, the role of acyl-CoA as a physiologic regulator of previously reported cellular processes (Færgeman and Knudsen 1997) will be expected to be limited to the regulation of acetyl-CoA carboxylase and gene expression in *Escherichia coli*, unless the acyl-CoA/ACBP complex can donate acyl-CoA directly to the regulatory protein in question or the complex itself can act as a regulator or enzyme substrate.

The ACBP/acyl-CoA complex as enzyme substrate and regulator

The fact that the acyl-CoA/ACBP complex might indeed act as enzyme substrate is indicated by the observation that the acyl-CoA/ACBP complex at molar ratios <1 can donate acyl-CoA for β-oxidation (Knudsen, unpublished results, Rasmussen et al. 1994). ACBP also stimulated incorporation of arachidonic acid from arachidonoyl-CoA into phospholipids by the acyl-CoA-lysophospholipid acyltransferase in red blood cells at low arachidonoyl-CoA concentrations (Fyrst et al. 1995). This situation is not unique for ACBP bound ligands. It has been demonstrated recently that the retinal/cellular retinol binding protein (CRBP) complex rather than free retinal is the preferred substrate for lecithin-retinol acyltransferase (Ong. 1994) and for the microsomal retinol dehydrogenase (Boerman and Napoli. 1996). The ability of the acyl-CoA/ACBP complex to donate acyl-CoA to utilizing or acyl-CoA–regulated systems is not universal. Acetyl-CoA carboxylase was completely protected against inhibition by acyl-CoA at all concentrations up to 5 μmol/L at acyl-CoA/ACBP ratios <0.8 (Rasmussen et al. 1994). It is tempting, therefore, to speculate that, by binding LCAA, ACBP creates a pool of long-chain acyl-CoA available for specific purposes only.

The regulatory functions of the ACBP/acyl-CoA complex were investigated in experiments with the ryanodine receptor Ca^{2+} release channel from rabbit muscle terminal cisternae. This channel has been shown to be activated by palmitoyl-CoA in the micromolar range (Fulceri et al. 1994). In these experiments, palmitoyl-CoA (6 μmol/L) was added to the rabbit muscle terminal cisternae without the addition of an acyl-CoA buffering protein. However, palmitoyl-CoA appeared to act directly on the channel. Both palmitoyl-CoA and its nonhydrolysable ether analog were able to activate it, and the activation could be blocked by the specific channel blocker Ruthenium red (Fulceri et al. 1994). To elucidate the role of ACBP in the regulation of the channel, we decided to reinvestigate the activation of the ryanodine receptor by LCA in the presence of physiologic concentrations of ACBP. Addition of 6 μmol/L palmitoyl-CoA in the presence of 6.6 μmol/L bovine ACBP to the terminal cisternae did not affect Ca^{2+} release significantly; but it reduced significantly the rate of reuptake of an added Ca^{2+} pulse. However, preincubation of the terminal cisternae membranes with increasing concentrations of palmitoyl-CoA/ACBP complex strongly potentiated caffeine-induced Ca^{2+} release. This effect was proportional to the complex concentration and independent of the calculated free palmitoyl-CoA concentration (Fulceri et al. 1997). These results strongly indicate that the acyl-CoA/

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ACBP complex can either donate acyl-CoA directly to the ryanodine receptor or act as a regulator of the receptor itself.

Regulation of gene expression by long-chain acyl-CoA ester and ACBP

The level of acetyl-CoA carboxylase (ACC) in *Saccharomyces cerevisiae* is repressed by long-chain fatty acids in the growth medium (Kamiryo et al. 1976). However, a mutant strain of *S. cerevisiae* that is defective in acyl-CoA synthetase exhibits little repression of acetyl-CoA carboxylase by fatty acids, indicating that the activation of exogenously supplied fatty acids is required for repression of acetyl-CoA carboxylase (Kamiryo et al. 1976). Similar observations have been made with regard to repression of transcription of the OLE1 gene, coding for the Δ9-desaturase, by Δ9-unsaturated fatty acids in yeast (Choi et al. 1996). These observations, combined with the observation that deletion of the yeast ACB1 gene, coding for yeast ACBP, induced a three- to fivefold increase in the level of Δ9- desaturase mRNA (Choi et al. 1996, Schjerling et al. 1996,) strongly indicate that ACBP is involved in donating LCA for gene regulation.

In *E. coli*, fatty acid biosynthesis and degradation are coordinately regulated at a transcriptional level by the product of the *fadR* gene, FadR (DiRusso et al. 1992). Using DNA-protein gel retardation assays, DiRusso et al. (1992) demonstrated that binding of purified FadR to DNA containing the *fadB*-promoter was prevented by LCA, but not by short-chain acyl-CoA esters and fatty acids. The K_i for palmitoyl-CoA and oleoyl-CoA was ~5 nmol/L, and for myristoyl-CoA and decanoyl-CoA 250 nmol/L and 2 amol/L, respectively. These data provide strong evidence that long-chain acyl-CoA esters bind to FadR and thereby inhibit DNA-binding activity of FadR. A direct interaction between long-chain acyl-CoA and FadR was shown with the use of a fluorescence quenching assay; the K_D for FadR binding of oleoyl-CoA was determined to be 12.1 nmol/L (Raman and DiRusso 1995).

The above-mentioned repression of acetyl-CoA carboxylase and Δ9-desaturase strongly indicates that a transcription factor similar to FadR might also exist in yeast and that ACBP may play a role in regulation of gene expression by delivering LCA to, or interact directly with this transcription factor.

Reduction of ACBP expression in 3T3-L1 cells by expression of an ACBP antisense cDNA has been shown to block differentiation into adipocytes (Baldursson et al. 1995, Mandrup et al. 1998). The cause of this defect at the molecular level is unknown. One difficulty in explaining these results is the fact that there is no correlation between the inhibitory effect of the antisense and the antisense RNA expression level and ACBP level (Knudsen, unpublished results).

SUMMARY

Taking the concentration and the binding affinity of the major LCA binding proteins into consideration, the free concentration of LCA in cell cytosol will be expected to be in the low nanomolar range (1–20 nmol) and not >200 nmol under the most extreme conditions. This means that the role of acyl-CoA as a physiologic regulator of a number of cellular functions must be reevaluated. ACBP has been shown, by both in vivo and in vitro experiments, to fulfil the necessary requirements to act as an intercellular acyl-CoA transporter and pool former. The results also show that ACBP is able to interact with or donate acyl-CoA esters to enzymes (i.e., carnitine-palmitoyl-CoA transferase) and acyl-CoA-regulated proteins (i.e., the ryanodine receptor). Strong indications have been obtained for the role of ACBP in fatty acid mediated regulation of gene expression.

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