A Novel Mitochondrial Carnitine-acylcarnitine Translocase Induced by Partial Hepatectomy and Fasting*

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The carnitine-dependent transport of long-chain fatty acids is essential for fatty acid catabolism. In this system, the fatty acid moiety of acyl-CoA is transferred enzymatically to carnitine, and the resultant product, acylcarnitine, is imported into the mitochondrial matrix through a transporter named carnitine-acylcarnitine translocase (CACT). Here we report a novel mammalian protein homologous to CACT. The protein, designated as CACL (CACT-like), is localized to the mitochondria and has palmitoylcarnitine transporting activity. The tissue distribution of CACL is similar to that of CACT; both are expressed at a higher level in tissues using fatty acids as fuels, except in the brain, where only CACL is expressed. In addition, CACL is induced by partial hepatectomy or fasting. Thus, CACL may play an important role cooperatively with its homologue CACT in a stress-induced change of lipid metabolism, and may be specialized for the metabolism of a distinct class of fatty acids involved in brain function.

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Long-chain polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acid, are important nutritional components, serving as structural elements in mammalian cells. They confer fluidity, flexibility, and selective permeability to cellular membranes, and affect cellular and physiological processes (1). In addition, long-chain fatty acids are used as an energy source through the mitochondrial β-oxidation pathway, especially in tissues such as muscle, during periods of fasting and other metabolic stress (2).

The carnitine shuttle system in eukaryotic cells provides for the entry of long-chain fatty acids into the mitochondrial matrix, where β-oxidation takes place (3, 4). Acyl-CoA pools supply activated substrates for many key metabolic pathways, such as the tricarboxylic acid cycle and lipid synthesis. A wide range of activated acyl groups is transferred reversibly from acyl-CoA to carnitine through the actions of carnitine acyltransferases. The transfer from the limited pools of membrane-impermeable CoA to the abundant and mobile carnitine allows transport between compartments.

Acylcarnitines are imported into mitochondria through carnitine-acylcarnitine translocase (CACT) (5, 6). This protein catalyzes a mole to mole exchange of carnitines and acylcarnitines, thereby permitting the fatty acid moieties to be translocated into the mitochondrial matrix. Several cases of CACT deficiency have been reported (7–9). Patients with these defects generally present in early infancy with acute, potentially life-threatening episodes of hypoketotic hypoglycemic coma, induced by fasting during intercurrent disease. The clinical features of these patients include hypoketotic hypoglycemia, mild hyperammonemia, variable dicarboxylic aciduria, hepatomegaly with abnormal liver functions, various cardiac symptoms, and skeletal muscle weakness.

In a search for genes that are up-regulated during liver regeneration after partial hepatectomy in rodents, we found a novel gene that encodes a protein homologous to CACT. Here we report the characterization of the gene product, CACL (for carnitine-acylcarnitine translocase-like). The protein exhibits a mitochondrial carnitine-acylcarnitine translocase activity, and its expression is induced by stresses such as hepatectomy and fasting.

EXPERIMENTAL PROCEDURES

Animals—Eight-week-old C57BL/6J male mice were purchased from CLEA Japan Inc. (Tokyo, Japan). Animals were kept in a temperature-controlled animal room with a 12-h dark/light cycle and were maintained on a commercially available diet (CE-2, CLEA Japan Inc.) consisting (by energy) of 29.2% protein, 58.8% carbohydrates, and 12.0% fat. Mice were either fed ad libitum or fasted for 48 h, and had free access to water. A 70% partial hepatectomy was performed according to the method of Higgins and Anderson (10). The surgery was performed between 8 and 11 a.m. under ether anesthesia. Animals were sacrificed before partial hepatectomy and at 6, 12, 24, and 48 h after the operation. Hearts, livers, brains, and kidneys were excised, immediately frozen in liquid nitrogen, and stored at –80 °C. All experiments were conducted in accordance with the animal care guidelines of the National Institute for Longevity Sciences (Obu, Japan).

Cell Lines and Culture Conditions—NIH3T3 murine fibroblasts were maintained as monolayer cultures in Dulbecco’s modified minimal essential medium (Sigma) supplemented with 10% (v/v) fetal bovine serum (ICN Biomedicals Inc., Aurora, OH), penicillin (100 units/ml), and streptomycin (100 μg/ml; Invitrogen Corp.) at 37 °C in a humidified atmosphere containing 95% air and 5% CO2. The GP-293 retroviral packaging cell line was obtained from Clontech (Palo Alto, CA) and was maintained as monolayer cultures in Dulbecco’s modified essential medium supplemented with 10% heat-inactivated fetal bovine serum. Puromycin (Sigma) was added at a final concentration of 3 μg/ml for the selection of pMXpuro-infected cells.

Construction of Plasmids—A retroviral vector derived from a murine leukemia virus, pMXpuro (11), was kindly provided by Prof. T. Kitamura (University of Tokyo, Tokyo, Japan). Open reading frame regions

case: CACL, carnitine-acylcarnitine translocase-like; PBS, phosphate-buffered saline; PH, partial hepatectomy; MOPS, 3-morpholinosopanesulfonic acid.

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Identification of a Novel Protein Homologous to Carnitine-
acylcarnitine Translocase—During a microarray analysis for genes induced after 70% partial hepatectomy (PH) in rats, we found a novel gene whose expression peaked at 6 h after the surgery (data not shown). A mouse clone homologous to the rat gene was obtained from the I.M.A.G.E. consortium, and the sequence analysis of the full-length cDNA identified an open reading frame of 918 nucleotides (Fig. 1A). The deduced protein, possessing six membrane-spanning regions (Fig. 1B), displayed homology with mitochondrial carrier family proteins. The protein showed the highest similarity (37% identity) with CACT, an inner mitochondrial membrane protein that is essential for the import of long-chain fatty acid moieties into the mitochondrial matrix. Thus, we designated the protein as CACL. A data base search using the BLAST program revealed that it is a conserved protein whose homologues are present in human, fly, and worm (Fig. 1). Amino acid sequences induced after 70% partial hepatectomy (PH) in rats, we found a novel gene whose expression peaked at 6 h after the surgery (data not shown). A mouse clone homologous to the rat gene was obtained from the I.M.A.G.E. consortium, and the sequence analysis of the full-length cDNA identified an open reading frame of 918 nucleotides (Fig. 1A). The deduced protein, possessing six membrane-spanning regions (Fig. 1B), displayed homology with mitochondrial carrier family proteins. The protein showed the highest similarity (37% identity) with CACT, an inner mitochondrial membrane protein that is essential for the import of long-chain fatty acid moieties into the mitochondrial matrix. Thus, we designated the protein as CACL. A data base search using the BLAST program revealed that it is a conserved protein whose homologues are present in human, fly, and worm (Fig. 1A). The human orthologue
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(hCACL) has 97% identity with mCACL at the amino acid level and is mapped on chromosome 14q32. A motif within the sixth hydrophobic domain, R(AS)(VF)PANAA(TC)F, has been shown to be conserved within the carnitine carrier subfamily (17). CACL and its homologous proteins all possess the motif, suggesting that they are involved in the transport of acylcarnitine across membranes.

Expression of CACL in Mouse Tissues—The expression pattern in tissues was surveyed using a mouse multiple tissue Northern blot filter. Mouse CACL mRNA, ~1.9 kb in length, was expressed in several tissues including heart, brain, liver, and kidney (Fig. 2). This pattern of expression was similar to that of its parologue mCACT, except CACT mRNA was rare in brain tissue (Fig. 2A). The expression pattern was further confirmed by Western blot analysis using specific antibodies against CACL and CACT. The CACL protein was present at a comparable level in brain, liver, and kidney, whereas CACT expression was barely detectable in brain (Fig. 2B). These data suggest that CACL is involved in a biological process similar to that of CACT, but may play a specific role in certain tissues such as brain.

CACL Is Localized to Mitochondria—To determine the subcellular localization of the CACL protein, we constructed NIH3T3 mouse fibroblast cells that stably expressed a CACL fusion protein with a myc-His6 tag in the carboxyl terminus. Using the anti-myc polyclonal antibody, CACL-myc-His6 proteins in the fibroblasts were immunostained in a reticulated pattern, which coincided with the mitochondrial staining (Fig. 3, A–C). To exclude the possibility that the tag affected the subcellular localization of the protein, we further addressed the localization of CACL using an affinity purified antibody against mCACL. Although we could not detect specific signals of the endogenous protein (data not shown), overexpressed CACL protein without the tag was co-stained with the mitochondrial marker (Fig. 3, D–F). Based on these observations, we conclude that CACL, like its homologue CACT, is localized to mitochondria.

CACL Has Palmitoylcarnitine Transporting Activity—In yeast, the transport of acyl units to mitochondria is performed via two pathways, namely the glyoxylate cycle-mediated conversion of acetyl-CoA to succinate that occurs in peroxisomes and the carnitine-dependent acyl-CoA transport. The two pathways have been thought to act in parallel, because disruption of either the CIT2 gene, which encodes the peroxisomal glyoxylate cycle enzyme citrate synthase, or one of the genes for the carnitine metabolism in mitochondria, did not affect the growth of yeast on oleate, whereas a mutant with both pathways disrupted failed to grow on the plate because of an inability to oxidize the fatty acid (18).

We constructed a double mutant defective in CIT2 and CRC1, the mitochondrial CACT gene in yeast. As reported previously (15), the Δerc1 Δcit2 mutant could not form colonies on minimal medium containing oleate (Fig. 4A), and the defect was rescued by the introduction of the wild-type CRC1 gene (Fig. 4B). Similarly, the heterologous expression of mCACL could relieve the growth impairment of the double mutant on...
the oleate plate (Fig. 4C), suggesting that the CACL protein possesses an enzymatic activity similar to Crclp.

To examine more directly whether CACL possesses activity similar to that of CACT, we performed a biochemical assay for the acylcarnitine transporting activity of mitochondrial fractions using palmitoyl-[14C]carnitine (16). To this end, we constructed NIH3T3 cells in which CACL or CACT was overexpressed under the control of the retroviral LTR promoter (Fig. 4D). As shown in Fig. 4E, liberation of [14C]carnitine, which was produced enzymatically from palmitoyl-[14C]carnitine in the mitochondrial matrix, was observed in the mitochondrial fractions harvested from cells infected with a control vector, and the activity was significantly elevated in cells overexpressing either CACL or CACT.

Moreover, we constructed a plasmid for the functional expression of the mCACL-His6 fusion protein in E. coli. Cells harboring the plasmid expressed the recombinant protein in an arabinose-dependent manner (Fig. 4F), and the expression of mCACL conferred palmitoylcarnitine uptake activity to E. coli cells (Fig. 4G). Collectively, these data demonstrate that CACL indeed encodes a protein with acylcarnitine transporting activity in mitochondria.

Induction of CACL after Partial Hepatectomy and Fasting—As described above, CACL was found as a gene whose expression was up-regulated after PH in rats. We addressed whether CACL expression was altered in mouse livers after PH.

As shown in Fig. 5A, the expression level of the CACL transcript in the liver before the operation was low, and was increased at 6–12 h after PH (Fig. 5A, left). The CACL transcript level was slightly increased in sham-operated mice at 6 h (Fig. 5A, right). Consistently, the amount of the CACL protein was increased at 12 h after PH, whereas the increase was slight after the sham operation (Fig. 5, B and C). In contrast, a modest increase in CACT expression was observed, but its protein level was not increased significantly (Fig. 5, A–C). The hepatic surgeries did not affect the protein levels of CACL and CACT in other tissues such as heart (Fig. 5D).

Fasting is a stress that is known to cause a metabolic shift to preferentially use free fatty acids. We found that the transcript corresponding to CACL was induced markedly in liver after 12 h of fasting (Fig. 6A). CACT mRNA was also increased under the same condition (Fig. 6A). We further examined the amount of CACL protein in several tissues by Western blot analysis using the anti-CACL antibody. As shown in Fig. 6, B–D, the protein levels of CACL after fasting were markedly elevated in liver, and increased modestly in heart. In contrast, up-regulation was slight in kidney. We also observed an increase in the amount of CACT in livers and hearts after fasting. These data indicate that the expression of CACL and CACT is regulated by fasting in a tissue-specific manner and suggest that the induction of these carnitine carriers may contribute to a metabolic change in specific tissues such as the liver.
DISCUSSION

In the present study we identified CACL, a novel mammalian protein that is localized to mitochondria and exhibits acylcarnitine transporting activity. The CACL transcript was found in tissues such as heart and liver, where its homologue CACT was expressed at a high level. In humans, patients with a CACT deficiency exhibited various cardiac symptoms and abnormal liver functions (7–9). Thus, CACL may not be able to compensate for CACT function in fatty acid metabolism of these tissues.

Fig. 4. CACL possesses acylcarnitine importing activity. A–C, rescue of the growth impairment of the yeast Δcit2 Δcrc1 mutant on oleate by the expression of Crc1p or mCACL. The Δcit2 Δcrc1 cells were transformed with control vector pRS316 (A), p316CRC1 (B), or pKT10-mCACL (C), and the transformants were grown in minimal medium containing 0.3% glucose for 24 h. The cultures were diluted with H2O and spread onto agar plates of minimal oleate medium. Photographs were taken after incubation for 5 days at 30 °C. D, establishment of cells overexpressing CACL or CACT. NIH3T3 cells were infected with pMXpuro/mCACL (lane 2), pMXpuro/mCACT (lane 3), or a control vector pMXpuro (lane 1), and stable infectants were selected. Cell lysates (100 μg/lane) were analyzed by Western blot analysis using antibodies against mCACL, CACT, and β-actin. E, acylcarnitine transport activity in the mitochondrial fraction. Mitochondrial fractions were prepared and used for the acylcarnitine transport assay with palmitoyl-[14C]carnitine (NEC-667, PerkinElmer Life Sciences) as described under “Experimental Procedures.” The data presented are average ± S.D. of three independent experiments. F–G, functional expression of mCACL in E. coli. E. coli cells possessing pBAD/CACL-His6P (lanes 2 and 4) or a control vector pBADgIIIa (lanes 1 and 3) were grown in the presence (lanes 3 and 4) or absence (lanes 1 and 2) of 0.2% arabinose for 18 h at 30 °C. Lysates were subjected to Western blot analysis using anti-CACL or anti-His6 antibodies (F). In G, E. coli cells grown in LB + 0.2% arabinose were incubated with palmitoyl-[14C]carnitine, and the incorporation of 14C into cells at 30 °C was measured as described under “Experimental Procedures.” The data presented are average ± S.D. of three independent experiments.

Fig. 5. Induction of CACL after partial hepatectomy. A, Northern blot analysis. A 70% hepatectomy was performed at time 0, and the remnant regenerating livers were collected at the indicated times after surgery. Livers were also collected from sham-operated C57BL/6 mice. Poly(A)+ RNAs (5 μg/lane) were subjected to Northern blot analysis with mCACL, mCACT, and β2-microglobulin cDNA probes. B and C, Western blot analysis of liver lysates. Livers were collected from three mice without operations and from mice 12 h after the hepatectomy or a sham operation. Postnuclear lysates were subjected to Western blot analysis using antibodies against p53, mCACL, CACT, and β-actin. In C, protein levels were quantitatively measured, and normalized -fold induction after the operations was calculated. Values shown are average ± S.D. for three different mice. Note that the protein levels of p53 increased after the partial hepatectomy, as reported previously (35). D, Western blot analysis of heart lysates. Hearts were collected at the same time points as in B, and postnuclear lysates were subjected to Western blot analysis.
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In contrast, the brain is a unique organ in which CACL is expressed at higher levels than is CACT. Although peroxisomal \( \beta \)-oxidation enzymes are expressed in brain (19), there have been no reports to show that the mitochondrial \( \beta \)-oxidation pathway is operating in the brain. The presence of the CACL transcript suggests that acylcarnitine might be used in this organ. The brain contains relatively high amounts of long-chain polysaturated fatty acids, which are critical for its functions (20). It was recently reported that a novel carnitine palmitoyltransferase was expressed specifically in brain and testis (21) and that carnitine transporters on the plasma membrane, which are involved in carnitine uptake, were expressed in brain (22). Together with the carnitine-handling enzymes expressed in brain, CACL might have specialized roles in the metabolism of a distinct class of fatty acids that are involved in brain function.

The liver is a unique organ with a regenerative capacity. After 70% of the mass is surgically removed, the residual hepatic lobes enlarge to restore the original mass within 7 days, and vascularization is completed within the subsequent 7 days (23). A variety of genes are involved in the whole process of liver regeneration, although the molecular mechanisms underlying the process remain unknown. Recently, Su et al. (24) reported a microarray-based study of the gene expression profile during the priming phase of liver regeneration in mice. They reported up-regulation of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase, which are involved in maintaining glucose levels after an acute loss of liver mass. Thus, a subtle regulation that switches energy metabolism appears to occur in the regenerating liver.

Carnitine has been thought to be one of the key factors in the regulation of liver regeneration, because the carnitine content in the liver increases after PH (25) and liver regeneration is accelerated by the administration of carnitine to hepa- toctomized rats (26). In addition, increases in the mRNA levels of carnitine palmitoyltransferase I and II have been observed in regenerating livers (27). Taken together, these results suggest that the carnitine-dependent pathway is important for energy supply when the liver, a major organ critical to maintaining metabolic and biosynthetic homeostasis, is partially removed. In agreement with this notion, we found that the level of CACL protein was elevated after PH. This acylcarnitine carrier may be involved in one of the key steps that regulate cellular metabolism during liver regeneration.

A change in the energy source from glucose to free fatty acids has been widely observed as an adaptive response to fasting (28). In the fasting heart, intracellular droplet accumulation was observed (29), and the content of glycerides and glycogen was increased through the inhibition of the glycolytic pathway and the enhancement of the \( \beta \)-oxidation pathway (30). A recent study using oligonucleotide microarrays revealed that the expression of a wide range of cardiac genes was affected by fasting, including the up-regulation of genes for fatty acid oxidation and gluconeogenesis and the down-regulation of genes for glycolysis (31). We found that CACL and CACT were up-regulated at the mRNA level in liver, and furthermore, fasting increased the amount of the CACL and CACT proteins in heart and liver. These two organs are prominent in the use of fatty acids upon starvation; fasted cardiac muscles directly use fatty acids as an energy source, whereas hepatic metabolism of fatty acids is mostly directed toward the synthesis of ketone bodies for use as energy sources in tissues such as brain (32). Thus, the up-regulation of CACL and CACT may contribute to the adaptation of the whole body to fasting.

Systemic energy metabolism has been shown to be tightly regulated by the action of hormones, and a disruption of this coordinated regulation causes disorders such as obesity and diabetes (33). Further studies of the coordinating mechanisms of glucose and lipid metabolism in the responsible organs will provide insights for the development of novel approaches to therapy or prevention of these disorders.

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Fig. 6. Induction of CACL after fasting. A, Northern blot analysis. Mice that fasted for the indicated times were sacrificed, and poly(A)\(^+\) RNAs were collected from the livers. Northern blot analysis was performed with probes for mCACL mRNA, mACT mRNA, and \( \beta \)-actin mRNA. Each lane contained 10 \( \mu \)g of poly(A)\(^+\) RNA. B–D, Western blot analysis. Protein lysates were prepared from the tissues of three mice before or after a 48-h fast. Western blot analysis was performed using antibodies against CACL and CACT. Each lane contained 100 \( \mu \)g of protein. Protein levels were quantitatively measured, and normalized -fold induction after fasting was calculated. Values shown are average for three different mice. Tissues examined were as follows: B, liver; C, heart; and D, kidney.
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