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Review

Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects

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Abstract

Carnitine palmitoyltransferase (CPT) deficiencies are common disorders of mitochondrial fatty acid oxidation. The CPT system is made up of two separate proteins located in the outer (CPT1) and inner (CPT2) mitochondrial membranes. While CPT2 is an ubiquitous protein, three tissue-specific CPT1 isoforms—the so-called "liver" (CPT1-A), "muscle" (CPT1B) and «brain» (CPT1-C) CPT1s—have been shown to exist. Amino acid and cDNA nucleotide sequences have been identified for all of these proteins. CPT1-A deficiency presents as recurrent attacks of fasting hypoketotic hypoglycemia. Twenty four *CPT1A* mutations have been reported to date. CPT1-B and -C deficiencies have not been hitherto identified. CPT2 deficiency has several clinical presentations. The "benign" adult form (more than 200 families reported) is characterized by episodes of rhabdomyolysis triggered by prolonged exercise. The prevalent S113L mutation is found in about 50% of mutant alleles. The infantile-type CPT2 presents as severe attacks of hypoketotic hypoglycemia, occasionally associated with cardiac damage commonly responsible for sudden death before 1 year of age. In addition to these symptoms, features of brain and kidney dysorganogenesis are frequently seen in the neonatal-onset CPT2 deficiency, almost always lethal during the first month of life. Around 40 CPT2 mutations (private missense or truncating mutations) have hitherto been detected. Treatment is based upon avoidance of fasting and/or exercise, a low fat diet enriched with medium chain triglycerides and carnitine. Prenatal diagnosis may be offered for pregnancies at a 1/4 risk of infantile/severe-type CPT2 deficiency.

Keywords: Carnitine palmitoyltransferase 1; Carnitine palmitoyltransferase 2; Carnitine palmitoyltransferase deficiency; Fatty acids; Fatty acid oxidation; Mitochondria; Hypoglycemia; Hypoketotic

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Contents

Mitochondrial fatty acid oxidation (FAO) is essential for energy homeostasis in situations that require simultaneous glucose sparing and major energy supply, such as prolonged fasting or exercise. Fatty acids are catabolized mostly in the mitochondria through the beta-oxidation pathway. Long-chain fatty acids (LCFA), the major fraction of fatty acids delivered to target tissues, cannot enter the mitochondria by simple diffusion, contrary to medium- or short-chain fatty acids. After

their activation by a long-chain fatty acyl-CoA synthetase on the outer mitochondrial membrane, long-chain fatty acyl-CoAs are imported into the mitochondrial matrix by the carnitine palmitoyltransferase (CPT) system (EC 2. 3.1.21). This enzymatic complex is made up of two distinct proteins named carnitine palmitoyltransferase 1 (CPT1) and 2 (CPT2) (McGarry and Brown, 1997). While CPT2 is the same protein bodywide (Demaugre et al., 1990), three tissue-specific isoforms of CPT1—the so-called "liver", "muscle", and «brain» CPT1s—have been identified (Britton et al., 1995; Yamazaki et al., 1996; Price et al., 2002). Two additional proteins are required for the mitochondrial transport of LCFA: a plasma membrane carnitine transporter dedicated to the maintenance of the intracellular level of carnitine, and a carnitine acylcarnitine translocase that shuttles long-chain acylcarnitines across the inner mitochondrial membrane in exchange for free carnitine (Ramsay et al., 2001). Recessively inherited defects have been described at these distinct levels (Brivet et al., 1999), of which CPT deficiencies are the most common (Bonnefont et al., 1999).

1. Biochemical and molecular aspects

1.1. CPT-system

Transport of LCFA from cytosol into the mitochondrial matrix of mammalian cells via β-oxidation requires a special protein association, the carnitine palmitoyltransferase system that reversibly catalyzes the following reaction:

$$\text{palmitoyl-CoA} + \text{carnitine} \Longleftrightarrow \text{palmitoylcarnitine} + \text{CoA-SH}$$

Since 1963 (Fritz et al., 1963), it has generally been accepted that at least two functionally separate forms of CPT existed: an "outer" CPT1 which catalyzes the formation of acylcarnitine from carnitine and acyl-CoA, and an "inner" CPT2 which catalyzes the formation of acyl-CoA from acylcarnitine and CoA. It was postulated that CPT1 and CPT2 were located at the outer and inner sides of the inner mitochondrial membrane, respectively. By 1987, the currently accepted model included two new data: 1/cooperation with a carnitine/acylcarnitine translocase located within the inner membrane (Pande, 1975) and 2/ reassignment of CPT1 from the outer face of the inner membrane to the outer membrane itself (Murthy and Pande, 1987).

It has been well established that regulation of mitochondrial FAO mainly involves CPT1. In the liver, CPT1 controls the fatty acid flux through the esterification and oxidative pathways due to its sensitivity to malonyl-CoA, a potent CPT1 inhibitor that is the first committed intermediate in the pathway of fatty acid biosynthesis. During fasting, the malonyl-CoA level decreases, CPT1 becomes disinhibited, so that LCFA oxidation and subsequently ketogenesis become enhanced. In the postabsoptive state, the concentration of malonyl-CoA rises, CPT1 is thereafter inhibited and newly formed LCFA are directed towards esterification. The situation is less clear in extra-hepatic tissues. It is however established that CPT1 constitutes an

important element for maintenance of energy homeostasis in heart and skeletal muscle as well (Eaton et al., 2001). Moreover, CPT1 might play a pivotal role in the regulation of insulin secretion in pancreatic β cells (Chen et al., 1994), and some CPT1 inhibitors might be used as potential antidiabetic agents (Giannessi et al., 2001; Anderson, 1989). CPT1 is likely to be involved in other metabolic functions, such as synthesis of complex lipids in pulmonary cells (Arduini et al., 2001). Otherwise, the possible role of CPT2 in the control of FAO remains to be defined.

Apart from mitochondria, other subcellular organelles, such as peroxisomes and microsomes, also contain CPT-like enzyme activities in rat (Nic A'Bhird et al., 1993, Murthy and Pande, 1994). Despite their functional similarity to mitochondrial CPTs, the components involved in these systems are all different. Physiological roles of CPTs from extra-mitochondrial systems have yet to be elucidated.

1.2. Proteins

1.2.1. Primary structure of CPT2

Identification of the rat CPT2 cDNA by 1990 (Woeltje et al., 1990a,b) was soon followed by isolation of the cDNA from its human counterpart (Finocchiaro et al., 1991). The cDNA sequence predicts a nascent product of 658 aminoacids in both species. Both proteins show a strong similarity (85% and 82% identity at nucleotide and aminoacid levels, respectively). However, the human mRNA (~3 kb) is approximately 0.5 kb larger than the rat equivalent.

1.2.2. Primary structure of CPT1s

Liver. Characterization of the CPT1-A protein was made difficult because of its tight membrane association and its loss of activity when removed from the mitochondrial membrane. The full-length cDNA clone isolated from rat liver predicted a protein of 773 aminoacids (88kD) (Esser et al., 1993). It could thereafter be established that the CPT1 protein consists of a single polypeptide containing both the inhibitor binding and catalytic domains, and that CPT1 and CPT2 are distinct entities. Availability of the rat L-cDNA enabled isolation of its human counterpart from a human liver cDNA library (Britton et al., 1995). As previously established for CPT2, both the nucleotide sequence and the predicted primary structure of the human CPT1-A (773 amino acids) proved to be very similar to those of the rat enzyme (82% and 88% identity, respectively). Several structural models of this protein have recently been proposed (Morillas et al., 2001; Gobin et al., 2003; Morillas et al., 2004).

Skeletal muscle. The rat CPT1-B cDNA was first identified in 1995 (Yamazaki et al., 1995). Its human counterpart was subsequently isolated using the rat cDNA as a probe for screening human heart cDNA libraries (Yamazaki et al., 1996). Both the nucleotide sequences and predicted primary structures of the rat and human proteins are highly similar (~85% and 86% identity, respectively). In both species, the transcript size (~3 kb) is smaller than that of CPT1-A (~4.7 kb).

Brain. The mouse and human CPT1-C proteins have recently been identified (Price et al., 2002). The protein primary sequence, deduced from the cDNA sequence

is made up of 798 amino acids. The aligned cDNA sequences of mouse and human proteins show 83.5% identity. The apparent molecular weight is similar to that of CPT1-A. CPT1-A and C are likely to adopt the same membrane topology with two transmembrane segments, and C- and N-terminal segments exposed on the cytosolic side of the outer mitochondrial membrane.

Finally, a structural model of carnitine palmitoyltransferase I based on the carnitine acetyltransferase crystal has recently been proposed (Morillas et al., 2004).

1.2.3. Comparative data regarding CPT1s and CPT2

Human CPT1-B exhibits 63% amino acid identity with its "liver" counterpart (Zammit et al., 2001). CPT1-A and CPT2 share approximately 50% of homology in the major part of their sequences with the exception of their N-termini (Kolodziej and Zammit, 1993). The CPT1-C sequence shows 54.5% and 52.7% identity with CPT1-A and CPT1-B, respectively. The greater sizes of CPT1s compared to CPT2 mainly result from an NH_2-terminal region extended by approximately 170 amino acids, which contains two largely hydrophobic domains (Cohen et al., 1998) reported to be transmembranous segments. CPT1 and CPT2 differ with respect to the tightness of their membrane association and their sensitivity to detergents. While CPT2 is loosely associated with the innner side of the inner mitochondrial membrane, CPT1 is embedded within the outer membrane (Woeltje et al., 1990a,b, Cohen et al., 1998). CPT2 is easily separated from its membrane environment in an active form by mild detergent treatment, while CPT1 is solubilized only as an inactive enzyme by more aggressive treatment (Woeltje et al., 1987).

CPT1 and CPT2 also differ with respect to their subcellular targeting and their sensitivity to malonyl-CoA and structurally related compounds, which specifically inhibit CPT1 activity (McGarry et al., 1978). Unlike CPT2 which contains a cleavable matrix-targeting signal, but likewise other outer-membrane proteins, no NH_2-terminal signal peptide is removed from the nascent CPT1-A during its mitochondrial import (Kolodziej and Zammit, 1993). The NH_2-terminal domain of the rat CPT1-A has been recently suggested to be essential for enzyme activity, malonyl-CoA sensitivity and import into the outer mitochondrial membrane (Cohen et al., 1998).

1.2.4. Tissue expression of CPTs

CPT1-A is the primary isoform in liver, kidney, lung, spleen, intestine, pancreas, ovary, and brain (McGarry and Brown, 1997; Brown et al., 1997), while CPT1-B predominates in skeletal muscle, heart, adipose tissue, and testis (Esser et al., 1996). Mitochondrial CPT1 isoform switching has been established in the developing rat heart: while CPT1-A represents a very minor constituent of the CPT complex in the adult heart, its contribution is much greater in the newborn animal (Brown et al., 1995). Tissue analysis from CPT1 deficient patients showed that human *CPT1* A is expressed in liver, lymphocytes and fibroblasts (Demaugre et al., 1988), but not in skeletal muscle (Tein et al., 1989). CPT1-C is predominantly expressed in brain, with lower levels of protein in testes, ovary, small intestine, and colon (Price et al., 2002).

Conversely, CPT2 is an ubiquitous enzyme both in rat and human (Demaugre et al., 1990; Woeltje et al., 1990a,b).

1.3. CPT genes

1.3.1. Chromosomal mapping

CPT1A, *CPT1B*, *CPT1C*, and *CPT2* genes have been recently localized to human chromosomes 11q13.1-q13.5, 22q13.31-q13.32, 19q13.33, and 1p32, respectively (Britton et al., 1997; Gellera et al., 1994; Price et al., 2002).

These data conclusively established that: 1/CPT1 and CPT2 are distinct entities, 2/ CPT2 is almost certainly the product of a single gene, 3/CPT1 exists as at least three genetically distinct isoforms, the liver, muscle, and brain variants.

1.3.2. Organization of the CPT genes

The human *CPT2* cDNA has a 1974 bp open reading frame (Finocchiaro et al., 1991). The *CPT2* gene structure has been analyzed in several organisms. It is approximately 20 kb in size and is composed of five exons, ranging from 81 bp (exon 1) to 1305 bp (exon 4), separated by four introns varying from 1.5 to 8 kb in length (Verderio et al., 1995). The human *CPT1A* gene contains an open reading frame of 2319 bp (Britton et al., 1995) and it is constituted of at least 19 exons ranging from 62 to 195 bp in size with 18 introns varying from 0.5 to 8.9 kb in size (Gobin et al., 2002). The human *CPT1B* cDNA has an open reading frame of 2316 bp (Yamazaki et al., 1996). The gene encoding human CPT1-B was found to consist of two 5′ non-coding exons (exons 1A and 1B), 18 coding exons and one 3′ non-coding exon spanning approximately 10 kbp (Yamazaki et al., 1997). In the 5′-flanking region, a putative "choline kinase" homologue was found about 300 bp upstream from exon 1A.

1.3.3. Regulation

Most available data have been achieved through animal studies. CPT genes are subject to dietary and hormonal regulation in tissues with high fatty acid utilization rates such as heart, muscle and liver. In the adult liver, the capacity for mitochondrial FAO is mainly regulated at the level of CPT1 gene expression in response to diverse physiologic or pathologic stimuli such as fasting, fat feeding, induction of diabetes or treatment with peroxisomal/mitochondrial proliferating agents, that all increase CPT1 mRNA and activity while CPT2 is not markedly affected (McGarry and Brown, 1997; Louet et al., 2001). In the developing rat heart, both CPT2 and CPT1-B activities increase during the first weeks of life, while CPT1-A activity that contributes approximately 25% to total CPT1 activity in the neonatal period falls to its adult value of 2–3% (Brown et al., 1995; Cook et al., 2001). In the developing rat liver, the activity, protein abundance, and mRNA level of CPT1 increases during the first day of extra-uterine life, and therefore vary according to diet and nutritional state while CPT2 gene expression remains stable (Thumelin et al., 1994).

Recent studies revealed the expression of novel *CPT1B* isoforms generated by alternative splicing of the *CPT1B* transcript, omissions in the 5′ region of the gene

and differential processing of introns 13 and 19 (Yu et al., 1998a). Two promoters in the *CPT1* B gene could be regulated by LCFA levels: an ubiquitous CPT1 promoter and a muscle specific-promotor active in muscle and heart only (Yu et al., 1998b; Rasmussen et al., 2002; van der Leij et al., 2002). Finally, among the numerous factors potentially implicated in the regulation of the CPT genes, a particular attention has been payed on peroxisome proliferator-activated receptors (PPARs), since some of them have been shown to upregulate the expression of genes encoding FAO enzymes (Minnich et al., 2001; Barrero et al., 2003; Djouadi et al., 2003; Gilde et al., 2003).

2. Medical aspects: the CPT deficiencies

2.1. Clinical presentations

2.1.1. CPT1 deficiencies

2.1.1.1. Liver-type CPT1 (CPT1-A) deficiency. In the small number of cases reported to date, the affected enzyme is clearly the "liver" isoform. Since the first report in 1981 (Bougneres et al., 1981), over 20 families have been reported (Demaugre et al., 1988; Tein et al., 1989; Bonnefont et al., 1989; Vianey-Saban et al., 1993; Gray et al., 1991; Stanley et al., 1992; Haworth et al., 1992; Falik-Borenstein et al., 1992; Yamamoto et al., 1994; Bergman et al., 1994; Schaefer et al., 1997; Innes et al., 1997; Ijlst et al., 1998; Olpin et al., 2001; Sim et al., 2001; Invernizzi et al., 2001; Al-Aqeel et al., 2001). The sex ratio is about one. Parents are related in about half cases. Four siblings were reported to have suddenly died between 3 days and 2 years of age. Age of onset is between D0 and 18 mo. It is noteworthy that at least six patients suffered from paroxysmal neonatal manifestations during the first days of life. The first presenting symptom is either a Reye-like attack with hypoketotic hypoglycemia usually but not constantly associated with fasting or a viral illness, or hepatomegaly with or without acute liver failure, with subsequent hypoglycemic attacks. Hepatomegaly is constantly found during the acute attacks, along with an elevation of liver enzymes and ammonia (50–250 μM) in plasma. Heart involvement is classically absent in CPT1-A deficiency but in fact, several cases with slight cardiomegaly or heart beat disorders (Tein et al., 1989; Vianey-Saban et al., 1993; Bergman et al., 1994; Schaefer et al., 1997; Olpin et al., 2001) have been reported, while a slight myocardial steatosis has been documented in one case. These cardiac manifestations most often seem to recover spontaneously. Elevated serum creatine kinase (CK), attributable to the MM isozyme, has been seen in acute episodes in three families (Haworth et al., 1992; Yamamoto et al., 1994; Olpin et al., 2001). Distal renal tubular acidosis has been well documented in three cases while it could be suspected in most other cases from the common finding of marked metabolic acidosis during acute metabolic attacks (Falik-Borenstein et al., 1992; Bergman et al., 1994). In contrast with other defects of mitochondrial FAO (including CPT2 deficiencies), CPT1-A deficiency is almost constantly associated with an elevated level of plasma carnitine (total, 55–250 μM; free, 45–160 μM) that may thus be a highly specific clue

to CPT1-A deficiency (Stanley et al., 1992). In the absence of urinary ketones, a mild dicarboxylic aciduria is occasionally noted. The outcome of the disease is variable. Most index cases survived the first attack and were alive over 4 years of age. Persistent neurologic deficit, probably resulting from the initial insult, is common but not constant. Recurrent episodes are frequent prior to 5 years of age and generally have been successfully treated by symptomatic therapy.

Finally, another clinical picture, consisting of acute liver failure in pregnant women carrying a CPT1-A-deficient fetus, has been reported (Innes et al., 2000; Tein, 2000).

2.1.1.2. Muscle-type CPT1 (CPT1-B) deficiency. Now that muscle and liver CPT1s are known to be different proteins encoded by separate genes the question is raised as to whether a syndrome of muscle CPT1 deficiency exists. To date, no such cases have been reported. A first possibility is that loss of CPT1-B might be incompatible with life, given the importance of this enzyme for heart function. If the condition does however exist, it might be expected to show a clinical phenotype associating cardiomyopathy and lipidic peripheral myopathy in neonates, infants, or possibly in adults.

2.1.1.3. Brain-type CPT1 (CPT1-C) deficiency. As for CPT1-B deficiency, CPT1-C deficiency remains to be described. Since malonyl-CoA, the major physiological inhibitor of CPT1s, has been implicated in appetite control in mouse, (Loftus et al., 2000; Obici et al., 2003), it can be hypothesized that such a deficiency, if compatible with life, could present as an appetite dysregulation syndrom.

2.1.2. CPT2 deficiencies

There are several presentations of CPT2 deficiencies which can be individualized according to the age of onset and the tissue distribution of the symptoms.

2.1.2.1. Adult form. Typical aspects. The more common condition is characterized by a muscular symptomatology. Since the first description in 1973 (Di Mauro and Di Mauro, 1973), more than 200 patients have been reported (Bonnefont et al., 1999; Sigauke et al., 2003). Most of them are males (~80%) though the disease is inherited in an autosomal recessive manner. First symptoms most often occur between 6 and 20 years of age, but age at onset may be over 50 years or as early as 8 months in some patients (Gempel et al., 2001; Hurvitz et al., 2000). The symptomatology usually consists of recurrent attacks of myalgias and muscle stiffness or weakness, occasionally associated with myoglobinuria. Duration of the attacks varies from a couple of hours to several weeks. Clinical condition is normal between the attacks. Frequency of these attacks is highly variable. The rhabdomyolysis may occasionally be complicated by three kinds of life-threatening events: acute renal failure as a result of myoglobinuria, respiratory insufficiency secondary to respiratory muscle involvement (Smolle et al., 2001), and paroxismal heart beat disorders (Thuillier et al., 2000). Symptoms are usually prompted by prolonged exercise, and less commonly by fasting, high fat intake, exposure to cold, mild infection (especially in children),

fever, emotional stress, general anesthesia, or drugs such as diazepam, ibuprofen, valproïc acid. In some cases, no precipitating factor can be found. The phenotypic expression may be highly variable within a family, with a clinical picture ranging from asymptomatic to lethal (Kelly et al., 1989; Schroder et al., 1990; Handig et al., 1996; Vladutiu et al., 2002a,b). In all cases, the clinical symptomatology is restricted to skeletal muscle without liver or heart involvement.

There exist very few biological markers suggestive of CPT2 deficiency in patients with recurrent rhabdomyolysis. Serum CK and transaminase levels are markedly increased (20- to 400-fold compared to control values) during the attacks or after a fasting or a prolonged exercise, while they usually turn into normal during inter-critical periods. Carnitine levels may be decreased or more commonly normal in serum and skeletal muscle as well. Serum triglycerides and cholesterol levels are elevated in about 20% and 10% of patients, respectively. Fasting ketogenesis is commonly delayed and/or decreased while other features of acute liver dysfunction such as hypoglycemia (usually observed in other defects of β-oxidation) are not reported in these patients. Ischemic exercise constantly results in a normal response of glucose and lactate in blood. Skeletal muscle structure appears to be normal in about 50% of cases while muscle lipid storage is found in 20% of patients. Other structural anomalies include atrophy or necrosis of type 1 muscle fibers. In fact, structural features may vary depending on the delay between the attack and the muscle sampling. Ultrastructural abnormalities of mitochondria (''ragged red fibers'') are quite unusual.

Atypical aspects. Permanent muscle weakness is rare (Gieron and Korthals, 1987; Kieval et al., 1983). A clinical picture suggestive of Kearns-Sayre-like syndrome has been reported in a patient (Carey et al., 1987). A partial CPT2 deficiency has occasionally been considered as a cause of exertional dyspnea (Galdi and Clark, 1989), malignant hyperthermia (Vladutiu et al., 1993), recurrent acute pancreatitis (Tein et al., 1994), central nervous system disorders (seizures, quadriplegia, psychomotor retardation) (Suzuki et al., 1991; Ohtani et al., 1994; Shintani et al., 1995), migraine headache (Kabbouche et al., 2003), or cardiomyopathy (Normand et al., 1979; Sacrez et al., 1982). In most of these patients, the relationship between the clinical symptomatology and the CPT defect remains under debate.

2.1.2.2. Infantile form. Typical aspects. Around 15 patients have been reported to date (Bonnefont et al., 1999). Sex ratio is about 1. Parents are related in about half cases. Several siblings were reported to have suddenly died, mostly prior to 1 year of age. Age of onset is between 6 months and 2 years, most often prior to 1 year. The clinical picture involves recurrent attacks of acute liver failure with hypoketotic hypoglycemia resulting in coma and seizures, and transient hepatomegaly. Heart involvement is present in about half of the cases, occurring either as dilated and hypertrophic cardiomyopathy that may spontaneously recover, or as arrythmias and conduction disorders. Metabolic attacks are usually triggered by fasting or febrile illness, while no precipitating factors are found in some cases. Routine laboratory tests of plasma commonly show metabolic acidosis and increased levels of ammonia. Low levels of total and free carnitine associated with an increase in the long chain

acylcarnitine fraction are almost constantly found in plasma. Hepatic steatosis is a constant feature. Sudden death, usually occurring during the first year of life, is supposed to be secondary to paroxysmal heart beat disorders (Demaugre et al., 1991; Elpeleg et al., 1993; Vianey-Saban et al., 1995; Fontaine et al., 1998; Martinez et al., 1997), while other patients die from Reye syndrome. Three patients were still alive and healthy at 5, 9, and 20 years of age, respectively (Taroni et al., 1992; Wataya et al., 1998; Martinez et al., 1997).

Atypical aspects. A "brain-type" CPT2 deficiency has been suggested to exist in two unrelated males with spasms in one and athetotic quadriplegia in the other one, along with recurrent attacks of myolysis (Ohtani et al., 1994).

2.1.2.3. Neonatal form. The neonatal onset form of CPT2 deficiency appears to be markedly more severe than the infantile onset form of the disease. Sixteen unrelated patients have been reported to date (Bonnefont et al., 1999; Elpeleg et al., 2001; Vladutiu et al., 2002a,b; Sharma et al., 2003; Smeets et al., 2003). 11 siblings were reported to have suddenly died most often during the first month of life. Onset of the disease is suggested to occur prenatally in some cases due to the presence of malformations detected early after delivery. There is some reports of ultrasonographic prenatal detection of these abnormalities (Witt et al., 1991). Common findings include dysmorphic features, cystic renal dysplasia, and neuronal migration defects. Postmortem examination variably reveals cystic dysplasia, polymicrogyria, glial heterotopias, and hemorrhages. The pathologic findings in these patients are similar to those observed in a subset of patients with a severe deficiency of electron flavoprotein-ubiquinone oxidoreductase (ETF:QO) resulting in impaired mitochondrial FAO.

The "symptom-free interval" between birth and onset of the acute metabolic symptoms ranges from a few hours to 4 days of life. Respiratory distress, hypoglycemia with seizures and hepatomegaly, heart involvement presenting as cardiomegaly associated with rhythm and conduction disorders, are constant features. Metabolic acidosis and marked hyperammonemia (up to 1800 μM) are commonly found. All patients died shortly after birth (D0-D34) apart from one patient who recovered after initial ressuscitation (Smeitink et al., 1998).

2.2. Pathogenesis

2.2.1. CPT1-A deficiency

Deficiency of CPT1-A in the liver results in a failure of acylcarnitine formation and hence little or no entry of LCFA into mitochondria for oxidative metabolism. Hepatic FAO physiologically increases the neoglucogenic flux by providing acetyl-CoA and reducing equivalents required for gluconeogenesis. Therefore, the inability of CPT1-deficient patients to maintain normoglycemia during prolonged starvation appeared to be caused by an impaired glucose production secondary to a "functional" deficiency of gluconeogenesis. The low capacity for hepatic FAO also explains the concomitant hypoketonemia. In these patients, the usual absence of muscle involvement is in agreement with the finding of two tissue-specific CPT1

isoforms, one expressed in liver while the other is predominantly expressed in skeletal muscle. The occasional finding of transient cardiac manifestations in affected neonates should be considered by taking into account data found in animals: a mitochondrial CPT1 isoform switching has been established in the developing rat heart so that, while CPT1-A represents a very minor constituent of the CPT complex in the adult heart, its contribution is much greater in the newborn animal. Should this prove to be the case in human, CPT1-A-deficient patients should be systematically regarded as at risk for cardiac insult during young infancy. The common occurrence of renal tubular acidosis in these patients is in agreement with the fact that FAO is an important source of energy for kidney and, supports the hypothesis that the CPT1 isoform predominantly expressed in the human kidney CPT1-A, as previously established in rat (McGarry and Brown, 1997). Finally, elevated levels of plasma carnitine are accompanied by an unusually high threshold for free carnitine suggesting a secondary increase in carnitine transport (Stanley et al., 1992).

2.2.2. CPT2 deficiencies

In these disorders, long-chain acylcarnitines are translocated across the inner mitochondrial membrane but are not efficiently converted to acyl-CoAs. The accumulating acylcarnitines may be transported out of mitochondria as suggested by the prominent long-chain acylcarnitine species seen in plasma. In the adult form of CPT2 deficiency, the triggering circumstances of myolysis attacks are consistent with the fact that LCFA are the main energy source for skeletal muscle during fasting or prolonged exercise. Ubiquitous expression of CPT2 is in agreement with the generalized expression of the clinical symptomatology in CPT2-deficient infants or neonates, predominating in organs highly dependent upon FAO (e.g., liver, heart, skeletal muscle) for energy homeostasis. It has been speculated that increased concentrations of long-chain acylcarnitines in patients with the severe form of CPT2 deficiency may promote cardiac arrythmia (Demaugre et al., 1991), as described in a cat heart model (Corr et al., 1989).

Why the two clinical presentations of CPT2 deficiency (mild adult form vs severe infantile/neonatal type) differ both in age of onset and tissue expression pattern remains puzzling. It has been speculated that the severity of the disease could be related to the impact of the enzymatic defect on LCFA oxidation in a given tissue. As an example, fibroblast LCFA oxidation is usually normal or at least over 50% of controls in ''muscular'' patients with a residual CPT2 activity over 15% of controls, while it is below 10% of control values in ''hepatocardiomuscular'' patients with a residual activity below the 15% threshold value. This hypothesis additionally implies that the level of residual CPT2 activity sufficient to prevent impairment of LCFA oxidation varies among tissues (Thuillier et al., 2003). Others have proposed that CPT2 may form a physical association with distal components of the β-oxidation machinery such that mutations at different sites in the protein result in variable efficiency of the overall system (Taroni et al., 1993).

Finally, the occasional association of the neonatal form of CPT2 deficiency with dysmorphic features and cystic dysplasia of the brain and kidney is poorly understood. The striking similarity of these malformative features with those observed in

other metabolic disorders such as glutaric aciduria type II, Zellweger syndrome and other disorders in which peroxisomal β-oxidation is impaired, raised the possibility that disruption of FAO is responsible for this abnormal organogenesis (Gellera et al., 1994).

2.3. Diagnosis

2.3.1. In vivo metabolic investigations

In both L-CPT1 and infantile-type CPT2 deficient patients, a carefully monitored fasting test shows decline of blood glucose concentration and low plasma ketone body values. In such patients, long chain triglyceride loading fails to enhance ketogenesis (Bonnefont et al., 1999) while serum ketones significantly increase after administration of medium-chain fatty acids which bypass the enzymatic block for entering the mitochondria. Such a metabolic profile points to a FAO disorder involving LCFA specifically. In most adult-type CPT2-deficient patients, a prolonged fast induces an insufficient or delayed rise in ketone bodies (as observed after a long-chain triglyceride loading test), while serum CK markedly increases. Plasma glucose remains constantly normal in these patients.

2.3.2. In vitro metabolic investigations

The overall oxidation of radiolabelled LCFA is constantly reduced to 5–25% of control values in fresh lymphocytes and cultured fibroblasts from both L-CPT1 and infantile/neonatal-type CPT2-deficient patients. Conversely, the rate of LCFA oxidation is frequently normal or over 50% of control values in fibroblasts and lymphocytes from adult-type CPT2-deficient patients (Demaugre et al., 1988; Slama et al., 1996).

The accumulation of β-oxidation intermediates may be detected in cells incubated with a labelled LCFA. For example, radio-high-pressure liquid chromatography analysis of fibroblasts incubated with [U-^{14}C] palmitate demonstrates the accumulation of large amounts of either palmitoyl-CoA in CPT1-deficient cells or palmitoylcarnitine in CPT2-deficient cells (Schaefer et al., 1997). Tandem-mass spectrometry can demonstrate the accumulation of palmitoylcarnitine in CPT2-deficient fibroblasts incubated with deuterated linoleate and L-carnitine (Nada et al., 1995).

The acylcarnitine profile may be determined from blood using tandem-mass spectrometry (Gempel et al., 2002; Albers et al., 2001). A prominent peak of C16 species is found in infantile/neonatal-type CPT2-deficient patients. A characteristic profile of blood acylcarnitines has also been reported in CPT1-A deficiency (Fingerhut et al., 2001; Sim et al., 2001).

A number of different assays and assays conditions for CPT have been reported to date. All assays are based on the reaction: palmitoyl-CoA + carnitine $\Longleftrightarrow$ palmitoylcarnitine + CoA-SH. The "forward" assay measures either the incorporation of carnitine into palmitoylcarnitine (Bremer, 1963; Demaugre et al., 1988) or the release of CoA-SH from palmitoyl-CoA (Yates and Garland, 1970; Bieber et al., 1972), or the decrease of palmitoyl-CoA in the assay medium (Fritz et al., 1963; Fritz and Marquis, 1985). The "backward" assay determines either the release of carnitine

from palmitoylcarnitine or the formation of palmitoyl-CoA (Kopec and Fritz, 1971; Crabtree and Newsholme, 1972). The "isotope exchange" assay measures the incorporation of carnitine into a pool of palmitoylcarnitine via its transfer on palmitoyl-CoA formed through the reaction of Coenzyme A with palmitoylcarnitine (Norum, 1964). Due to the reversibility of reactions catalyzed by CPT1 and CPT2, either assay may be used for measurement of either activity (Demaugre et al., 1988). Assay of CPT2 activity on skeletal muscle using mass tandem spectrometry has recently been reported (Rettinger et al., 2002).

The CPT1 activity is measured in non-detergent conditions, as checked by simultaneous assays of interface membrane and matrix enzyme activities, and is identified by its sensitivity to inhibition by malonyl-CoA. The CPT2 activity is measured after disruption of mitochondrial membranes using a detergent (e.g.: Triton X-100 or octylglucoside) which is supposed to fully inhibit CPT1 activity (Woeltje et al., 1987). CPT2 fraction of the total CPT activity can be specifically studied using L-amino carnitine, a specific inhibitor of CPT2 activity (Hertel et al., 1999). The use of permeabilized cells, rather than gently sonicated cells, has been proposed for assaying CPT activities (Schaefer et al., 1997).

The CPT1 activity measured in fibroblasts from CPT1-deficient patients ranges from 5% to 20% of control values while it is normal in CPT2-deficient patients. The lack of CPT1 deficiency in skeletal muscle samples from 2 patients with typical features of CPT1-A deficiency is in agreement with the finding of 2 separate "liver" and "muscle" isoforms of CPT1 (Tein et al., 1989). The CPT2 activity measured in fibroblasts or lymphocytes from CPT2-deficient patients ranges from 5% to 25% of control values while it is normal in CPT1-deficient patients. In CPT2-deficient patients, the CPT2 deficiency is found in all tissues tested (liver, heart, skeletal muscle, kidney) irrespective of the severity of the clinical picture. This point is in agreement with the fact that CPT2 is an ubiquitous enzyme. It has been shown that residual CPT2 activity varies among tissues of a given CPT2-deficient individual when measured using identical assay conditions (Taroni et al., 1993; Hug et al., 1991, and unpublished personal data).Whether some degree of correlation exists between the severity of the phenotype and the residual CPT2 activity remains under debate. In our experience, the mean value of the fibroblast residual CPT2 activity is markedly lower in a subset of neonatal/infantile-type CPT2-deficient patients ($n = 7$) than in a subset of adult-type CPT2 deficient patients ($n = 12$) (Bonnefont et al., 1996; Thuillier et al., 2003). However, in several studies, there was a significant overlap of residual CPT2 activities between adult-type and infantile-type patients (Taroni et al., 1993; Wataya et al., 1998). More data are required to clarify this point. Finally, assay of CPT2 activity on skeletal muscle using mass tandem spectrometry has recently been reported (Rettinger et al., 2002).

2.4. Molecular pathology and genotype/phenotype correlations

2.4.1. CPT1 deficiency

In human, the first CPT1-A mutation has been identified in 1998 (Ijlst et al., 1998). These authors reported a homozygous 1361A > G transition (D454G) in the

CPT1-A gene of a typical CPT1-A-deficient patient. A recent study revealed the molecular defect in several CPT1-A-deficient patients belonging to an extended inbred Hutterite kindred, namely a homozygous 2129G > A transition predicting a G710D substitution (Prip-Buus et al., 2001; Prasad et al., 2001). To date, 24 mutations of the CPT1-A gene have been reported (Ijlst et al., 1998; Prip-Buus et al., 2001; Brown et al., 2001; Gobin et al., 2002, 2003; Ogawa et al., 2002; Bennett et al., 2004). Most of these mutations are private mutations distributed throughout the entire sequence of the gene. 21 of them are point mutations, of which 5 are nonsense mutations [Y32X (exon 2), Q100X (exon 4), R160X (exon 5), W475X (exon 12), Y498X (exon 13)], the remaining ones being missense mutations [R123C (exon 4), A275T (exon 8), C304W and R316G (exon 9), F343V, R357W, and E360G (exon 10), A414V (exon 11), D454G, G465W, P479L, and L484P (exon 12), Y498C (exon 13), G709E and G710E (exon 17)] and a splice mutation [1876-1G > A (intron 15)]. 4 mutations are either small in frame-[del 1183_1185 (exon 11) resulting in loss of Arg395] or frameshift deletions [2028 + 2delAAGT (exon 16)], and one is a 8-kb deletion encompassing intron 14 to exon 17 of the gene. In vitro functional expression of some of the missense mutants has shown that they fall into two categories, depending on whether they affect directly (functional determinant) or indirectly the active site of the enzyme (structural determinant) (Gobin et al., 2003). It has to be emphasized that this marked genetic heterogeneity generates in fact a somewhat phenotypic homogeneity.

2.4.2. CPT2 deficiency

To date, more than 40 mutations have been characterized in patients with the adult, infantile, or neonatal form of CPT2 deficiency (Taroni et al., 1997; Vladutiu et al., 2000; Olpin et al., 2003; Wieser et al., 2003; Thuillier et al., 2003). Two of them, 338C > T [S113L, allele frequency 60% in European subjects (Taroni et al., 1993)] and 149C > A [P50H, allele frequency 6.5% (Verderio et al., 1995)], are regarded as common mutations in the subset of CPT2-deficient patients with the adult form of the disease. While some CPT2 mutations, e.g., 1238-1239delAG [Q413fs (Taggart et al., 1999)], 1342T > C[F448L (Wieser et al., 1997; Taggart et al., 1999)], 1883A > C [Y628S (Bonnefont et al., 1996, Martinez et al., 1997; Merinero et al., 1998)], 1891C > T [R631C (Taroni et al., 1992, Toscano et al., 1996)], are recurrent, the remaining ones are private mutations. Both 1238-1239delAG and 1342T > C mutations seem to be in strong association disequilibrium.

An update of all CPT2 mutations reported to date is given in Table 1. These 40 mutations are distributed throughout the entire coding sequence of the gene. Apart from the prevalent S113L (exon 3), exons 4 and 5 are hot spots of mutations. Thirty of the 40 mutations (77%) are missense mutations while the nine remaining ones are predicted to truncate the protein. With respect to the relation between genotypes and clinical phenotypes, these 40 mutations can be partitioned into three genotyping subsets, consisting of mutations associated either with the "adult" phenotype only (subset 1), with the "infantile" phenotype only (subset 2), or with both forms of the disease (subset 3). Subset one includes seventeen mutations, of which only three have been reported in a homozygous state ("mild" mutations P50H, S113L, R161W). The

Table 1
Human CPT2 mutations update

Exon	Nucleotide[a]	Amino acid	References
1	109Ins GC		Martin et al. (2000)
	112-113 Ins GC	S38fs[c]	Martin et al. (2000)
	149C > A	P50H[b]	Verderio et al. (1995)
2	216G > C/T	L72F	Ijlst et al. (1998)
3	338C > T	S113L[b]	Taroni et al. (1993)
	IVS3 + 5G > A[d]	del179_113	Deschauer et al. (2003)
4	359A > G	Y120C	Martin et al. (1999, 2000)
	370C > T	R124X	Yang et al. (1998a)
	371G > A	R124Q	Thuillier et al. (2003)
	437A > C	N146T	Thuillier et al. (2003)
	452G > A	R151Q	Yang et al. (1998b)
	481C > T	R161W	Thuillier et al. (2003)
	490A > T	K164X	Ijlst et al. (1998)
	520G > A	E174 K[b]	Yamamoto et al. (1996)
	533-534insT; 534-558 del	L178 F; N179-I186 del	Yang et al. (1998b)
	628T > G	Y210D	Ijlst et al. (1998)
	641T > C	M214T	Wieser et al. (1997)
	680C > T	P227L	Taroni et al. (1994)
	821A > T	K274M	Ijlst et al. (1998)
	890C > A/G	Y290X	Ijlst et al. (1998)
	906C > T	R296X	Ijlst et al. (1998)
	907G > A	R296Q	Ijlst et al. (1998)
	907-918ins	L302fs[c]	Gellera et al. (1994)
	983A > G	D328G	Thuillier et al. (2003)
	1145G > A	R382K	Yang et al. (1997)
	1148T > A	F383Y[b]	Yamamoto et al. (1996)
	1238-1239delAG	Q413fs[c]	Taggart et al. (1999)
	1342T > C	F448L	Wieser et al. (1997)
	1436A > T	Y479F	Wieser et al. (1997)
	1459G > A	E487K	Bruno et al. (2000)
	1507C > T	R503C	Taggart et al. (1999)
	1543-1546delGCCT	515del4	Deschauer et al. (2002)
	1646G > A	G549D	Taggart et al. (1999)
5	1649A > G	Q550R	Yang et al. (1998b)
	1657G > A	D553N[b]	Verderio et al. (1995)
	1798G > A	G600R	Ijlst et al. (1998)
	1810C > T	P604S	Yang et al. (1998b)
	1823G > C	D608H	Thuillier et al. (2003)
	1883A > C	Y628S[b]	Bonnefont et al. (1996)
	1891C > T	R631C[b]	Taroni et al. (1992)

[a] Nucleotide 1: A from the initiator ATG.
[b] Mutations expressed in cos-1 cells.
[c] fs: reading frame shift.
[d] Intron 3.

fourteen others are predominantly located in exon 4, and all are associated with S113L (exon 3) or P50H (exon 1) in compound heterozygous patients. Subset two consists of eight mutations, five of which have been reported at a homozygous state ("severe" mutations R151Q, P227L, D328G, R382K, F383Y). All eight mutations are located in exons 4 or 5. While six of these mutations have also been identified in compound heterozygous patients, it is noteworthy that the second mutation (most often not identified) never is S113L or P50H, in complete opposition to the genotypic status observed in compound heterozygous adult-onset patients. *It can therefore be inferred that S113L and P50H would have some protective effect against occurrence of a severe infantile phenotype*. Subset three includes 6 mutations lying in exon 4 or 5. Two of them, Q413delAG and F448L, have been found on a same chromosome (cis-association) (Taggart et al., 1999). Five of these six mutations have been identified in compound heterozygous individuals. Association of any of these five mutations to S113L or P50H constantly results in a "mild" phenotype, as observed in subset one, while their association to another mutation results in a "severe" form of the disease as observed in subset two. Only one mutation, R631C, has been shown to cause either a severe or a mild disease when present in a homozygous state, suggesting that, at least in this specific case, an additional factor is involved in the disease phenotype. *Altogether, these data emphasize that, in most patients with the adult form of the disease, at least one mutation lies in exons 1 to 3 (except for R161W and R631C), while both mutations are constantly located in exons 4 or 5 in all patients with the early form of CPT2 deficiency.*

Taking into account ethnical origins of CPT2-deficient patients, it is noteworthy that Q413delG + F448L, F383Y, Y628S and D328G have been detected in Ashkenazi Jews (Q413delG + F448L: 6 mutants alleles, [Taggart et al., 1999; Thuillier et al., 2003]), Asian (F383Y: 3 mutants alleles [Wataya et al., 1998; Thuillier et al., 2003]) and North African individuals (Y628S: 3 mutant alleles [Bonnefont et al., 1996; Thuillier et al., 1999]; D328G: 4 mutant alleles [Thuillier et al., 2003]), respectively.

Finally, three polymorphisms have also been described, that by themselves do not cause CPT II deficiency but appear to contribute to further reduction in enzyme activity when combined with CPT2 mutations (Taroni et al., 1992; Wataya et al., 1998). Association between polymorphisms and some mutations have been described. Both 1102G > A (V368I) and 1939A > G (M647V) polymorphisms are constantly associated with the 338C > T (S113L) mutation. Allelic frequencies of V368I ($V1 = 0.49$, $V2 = 0.51$) and M647V ($M1 = 0.75$, $M2 = 0.25$) have been reported in Southern European populations (Verderio et al., 1995, Verderio et al., 1993). The 1055T > G (F352C) polymorphism was not observed among Caucasians, appearing to be uniquely present in the Japanese population (Wataya et al., 1998).

Difference in clinical severity between the two distinct presentations of the disease also correlates in some extent with enzymatic and functional data. Taking into account the residual CPT2 activity, we showed that the mean value is lower in the "infantile" subset than in the "adult" subset of patients (Thuillier et al., 2003). However, upper values of infantile-type CPT2 activities overlap with lower values of

adult-type CPT2 activities in lymphocytes and fibroblasts as well. Comparison of these data with those of the literature is not easy since most reports focus on only one presentation of the disease, and furthermore, enzymatic assay conditions markedly vary among the different reports. However, measurement of CPT2 activities (Taroni et al., 1992, 1993; Merinero et al., 1998; Gellera et al., 1994; Verderio et al., 1995; Yamamoto et al., 1996) using similar assay conditions in adult or infantile onset disease are in agreement with our conclusion that *the predictive value of the residual enzymatic activity for severity of the disease is questionable*. When attempting at matching CPT2 genotypes with enzymatic data, it appears that the range of residual CPT2 activities is rather narrow (12–16%) in adult and patients carrying at least one S113L allele. These data are in agreement with results of cos-1 cells expression of S113L, showing residual activity (around 30%) markedly higher than the activity observed after expression of six other mutations (Wataya et al., 1998). It is difficult to draw significant conclusion with respect to genotype-CPT2 activity relationship in infantile type patients due to their low enzyme activities. It is however noteworthy that three mutations namely D328G, R382K, and F383Y are located in CPT2 domains that could be part of the catalytic core of the enzyme by reference to recent reports showing that the homologous domains of rat CPT1-A are important for catalytic activity.

Conversely, it has been shown that *the residual level of LCFA oxidation would strongly correlate with the severity of the disease* (Bonnefont et al., 1996; Thuillier et al., 1999; Thuillier et al., 2003). The residual levels of LCFA oxidation are significantly lower in the infantile form than in the adult form of the disease, without any overlap between the borderlines values of the respective ranges. However, regarding LCFA oxidation, all cell lines from infantile onset patients display quite similar values irrespective of the type of CPT2 mutations while these FAO values markedly differ between 2 adult-onset patients with the same CPT2 genotype (Thuillier et al., 2003). These data suggest that one or several unknown genetic actors additional to the type of CPT2 mutation, modulate the FAO flux, this effect being unmasked only when the residual CPT2 activity is sufficient to preserve a significant residual FAO. Identifying such factors might contribute improving the clinical condition in CPT2-deficient patient with the adult form of the disease.

2.5. Prenatal diagnosis

To date, there is no report on prenatal diagnosis of CPT1-A deficiency.

Very few data are available regarding the prenatal diagnosis of infantile/neonatal type-CPT2 deficiency in at 1/4 risk families. CPT2 deficiency was prenatally established by ultrasonography revealing enlarged echogenic kidneys in one fetus (Witt et al., 1991). We have carried out a prenatal diagnosis in six unrelated families at risk for the severe form of CPT2 deficiency by molecular analysis (mutation detection and haplotyping studies using polymorphic markers linked to the CPT2 gene locus) and/or by enzymatic assay on either a chorionic villous sampling or cultured amniocytes, occasionally coupled to FAO studies on amniocytes (Brivet et al., 1999; Thuillier et al., 1999; Vekemans et al., 2003).

2.6. Treatment

The main goal is to provide sufficient glucose supply to prevent adipose tissue lipolysis (Saudubray et al., 1999). During the neonatal period and in acute metabolic attacks (L-CPT1 and severe CPT2 deficiencies), glucose solutions are IV infused to maintain high to normal levels of plasma glucose. Continuous nasogastric drip feeding may also be implemented. Carnitine supply might be useful in severe CPT2 deficiencies. In one neonatal-onset case (Smeitink et al., 1998), glucose plus insulin infusion in combination with repeated exchange transfusions resulted in a spectacular clinical improvement.

Long-term dietary therapy is aimed at preventing any period of fasting. Restriction of long-chain fat intake along with medium-chain triglyceride supplementation is recommended. In the muscular form of CPT2 deficiency, preventive therapy of rhabdomyolysis attacks is based on frequent meals with carbohydrate extra-intake before and during prolonged exercise.

It has to be kept in mind that some drugs, such as valproïc acid, (Kottlors et al., 2001) diazepam, ibuprofen can trigger attacks of rhabdomyolysis in CPT2-deficient patients.

Two promising therapeutic approaches are currently under investigation: supply with anaplerotic odd-chain triglycerides has been successfully used to treat cardiomyopathy and rhabdomyolysis in long-chain fatty acid disorders (Roe et al., 2002). Finally, agonists of PPAR alpha such as bezafibrate have been shown to restore both CPT2 activity and long-chain fatty acid oxidation in fibroblasts from patients with the adult form of CPT2 deficiency (Djouadi et al., 2003).

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