Pathophysiology of fatty acid oxidation disorders and resultant phenotypic variability

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Abstract  Fatty acids are a major fuel for the body and fatty acid oxidation is particularly important during fasting, sustained aerobic exercise and stress. The myocardium and resting skeletal muscle utilise long-chain fatty acids as a major source of energy. Inherited disorders affecting fatty acid oxidation seriously compromise the function of muscle and other highly energy-dependent tissues such as brain, nerve, heart, kidney and liver. Such defects encompass a wide spectrum of clinical disease, presenting in the neonatal period or infancy with recurrent hypoketotic hypoglycaemic encephalopathy, liver dysfunction, hyperammonaemia and often cardiac dysfunction. In older children, adolescence or adults there is often exercise intolerance with episodic myalgia or rhabdomyolysis in association with prolonged aerobic exercise or other exacerbating factors. Some disorders are particularly associated with toxic metabolites that may contribute to encephalopathy, polyneuropathy, axonopathy and pigmentary retinopathy. The phenotypic diversity encountered in defects of fat oxidation is partly explained by genotype/phenotype correlation and certain identifiable environmental factors but there remain many unresolved questions regarding the complex interaction of genetic, epigenetic and environmental influences that dictate phenotypic expression. It is becoming increasingly clear that the view that most inherited disorders are purely monogenic diseases is a naive concept. In the future our approach to understanding the phenotypic diversity and management of patients will be more realistically achieved from a polygenic perspective.

Abbreviations
AFLP acute fatty liver of pregnancy
CTD OCTN2 transporter deficiency
CPT1 carnitine palmitoyltransferase type 1 deficiency
CATR carnitine-acylcarnitine translocase deficiency
CPT2 carnitine palmitoyltransferase type 2 deficiency
FAD flavin adenine dinucleotide
FAO fatty acid oxidation
HELLP haemolysis elevated liver enzymes, low platelets
LCHAD long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
MTP mitochondrial trifunctional protein deficiency
MCAD medium chain acyl-CoA dehydrogenase deficiency
MADD multiple acyl-CoA dehydrogenase deficiency
RR-MADD riboflavin responsive multiple acyl-CoA dehydrogenase deficiency
SCHAD short chain 3-hydroxyacyl-CoA dehydrogenase deficiency
VLCAD very long-chain acyl-CoA dehydrogenase deficiency

Introduction
The oxidation of fatty acids plays a major role in energy production and during fasting provides up to 80% of the total energy requirement. The major metabolic flux of long-chain fatty acids is through the beta-oxidation system of the mitochondria present in all cells except the mature erythrocyte (Kunau et al 1995). Long chain fatty acids act as an important
source of respiratory fuel for many tissues especially skeletal and cardiac muscle. The brain is generally dependent on glucose for energy production and the “glucose sparing” effect of ketones during short term fasting is particularly important in infants. However in keto-adapted individuals the brain switches to utilise ketone bodies as its major energy source (Phinney 1983a).

Inherited disorders of fatty acid oxidation FAO result in a wide spectrum of clinical disease resulting from the interaction of genetic and numerous environmental factors that act together to produce the phenotype. The factors that conspire together to give rise to the diverse phenotypes will be discussed and a number of specific fatty acid oxidation disorders will be explored in some detail to illustrate the interplay of factors that may act together to produce such diverse phenotypes.

**Inherited disorders of fatty acid oxidation**

Inherited defects in 17 proteins directly affecting either carnitine dependent transport of long chain fatty acids or the process of \(\beta\)-oxidation itself have so far been described (Bennett et al 2000; Wanders et al 1999; Rinaldo et al 2002; Wanders et al 2010; Spiekerkoetter 2010; Houten and Wanders 2010). Several long chain acyl-CoA dehydrogenases involved in fatty acid oxidation including ACAD9, ACAD10 and ACAD11 have also been described but their role in the pathophysiology of human disease is not fully elucidated (Ensenaur et al 2005; Oey et al 2005, 2006; He et al 2011).

The biochemical consequences of a defect affecting the process of FAO can be categorized as follows:

1. Inadequate supply of energy.
2. Accumulation of toxic metabolites.
3. Sequestration or loss of vital components.
4. Altered production of enzyme product, e.g. lack of surfactant in LCHAD/MTP/LCAD.
5. Loss of protein-protein interaction, e.g. SCHAD deficiency.

Inadequate supply of energy

Fatty acids are mobilised from adipose tissue in the fasted state and used for hepatic generation of ketone bodies which act as vital fuel to extra hepatic tissue with the additional effect of “sparing” glucose for other vital tissues, especially the brain. This “glucose sparing effect” is particularly important in infants where there is high proportional glucose utilisation in cerebral tissue. Hypoglycaemia is the inevitable consequence of an inability of the body to maintain normoglycaemia, as glycogen levels become exhausted and gluconeogenic pathways fail in the face of an inadequate supply of ketones.

In the fasting state hepatic gluconeogenesis and ketone body generation act synergistically to provide energy for both hepatic and extra hepatic tissues. Amino acids are the major substrates for hepatic gluconeogenesis which in turn relies on a steady supply of acetyl-CoA, NADH+H\(^+\) and ATP from fat oxidation to sustain this process. In the absence of a steady supply of these metabolites gluconeogenesis is compromised and hypoglycaemia follows (Fig. 1).

**Fig. 1** Interaction of \(\beta\)-oxidation and gluconeogenesis. \(\beta\)-oxidation generates ATP, NADH+ and acetyl-CoA and these stimulate pyruvate carboxylase PC and inhibit pyruvate dehydrogenase PDH. Mobilisation of alanine from muscle, and lactate produced, for example from anaerobic glycolysis in the red cell, are the major sources of pyruvate during catabolic stress. The conversion of pyruvate to oxaloacetate is a crucial step in the process of gluconeogenesis which is mediated through pyruvate carboxylase PC. Acetyl-CoA is the primary activator of this enzyme, which converts pyruvate to oxaloacetate. The equilibrium of the mitochondrial malate dehydrogenase MDH is displaced to favour the reduction of oxaloacetate to malate. ATP is used as a co-substrate for PC and phosphoenolpyruvate carboxykinase PEPCK. Consequently in defects of fat oxidation this crucial early step of gluconeogenesis is compromised and this also contributes significantly to hypoglycaemia.

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Skeletal and cardiac muscle derive a significant proportion of their energy, even in the fed state, from \( \beta \)-oxidation of long chain fatty acids. Myocardial fat oxidation is severely reduced in patients with long-chain defects and these fatty acids are likely shunted into a slow-turnover compartment, predominantly reflecting esterification to triglycerides. The forced increased reliance of the myocardium on glucose appears in the long term to bring about a profound but poorly understood remodelling, mediated by major shifts in gene expression and resulting in hypertrophy of the myocardium (Ritchie and Delbridge 2006).

Reduced energy supply to skeletal muscle results in chronic hypotonia, muscle weakness and exercise intolerance. Similarly reduction of hepatic ATP availability for the vital and varied metabolic processes occurring within the hepatocyte frequently results in hyperammonaemia and resultant encephalopathy due to a failing urea cycle.

**Accumulation of toxic metabolites**

Approximately two thirds of all identified disease-associated gene variations are of the missense type with the potential to produce abnormal protein conformations due to misfolding. The fate of abnormal protein will, depending on a number of factors within the cell result in variable toxic effects within the putative fatty acid oxidation metabolone (Gregersen et al 2008; 2010a, b).

The potential toxicity effects are best divided up into those that affect the carnitine shuttle and those defects within the \( \beta \)-oxidation spiral itself.

*Carnitine shuttle* The nature of the defects in primary carnitine transporter deficiency CTD (OCTN2, SLC22A5) and carnitine palmitoyltransferase type 1 (CPT1A) deficiency dictates that toxic metabolites are not produced within the mitochondria.

In severe carnitine acyl-carnitine translocase CACT and carnitine palmitoyl transferase type 2 (CPT2) deficiency the majority of tissue and plasma carnitine is ultimately as long-chain acylcarnitine species.

*\( \beta \)-oxidation* Defects within the \( \beta \)-oxidation spiral generate, depending on the defect, a range of short, medium and long-chain acyl-CoA intermediates within the mitochondrial compartment, some of which are reported to be particularly toxic, e.g. octanoyl-CoA in medium chain acyl-CoA dehydrogenase deficiency MCADD. These intermediates once transported back out of the mitochondria, undergo peroxisomal \( \beta \)-oxidation and/or \( \omega \)-oxidation to produce a range of C4-C16 carboxylic and C4-C10 dicarboxylic acids including some unsaturated species. Short and medium chain carboxylic and dicarboxylic acids can re-enter the mitochondria where they can be oxidised in the normal way. However some carboxylic acid derivatives particularly C8-C10 and 3-hydroxy C12-C16 are reported to be toxic (Table 1).

Sequestration of vital components

Coenzyme A does not cross the mitochondrial membrane and there is a finite pool of coenzyme A within the mitochondria. Defects of \( \beta \)-oxidation lead to sequestration of coenzyme A in the form of acyl-CoA intermediates.

Primary defects of fatty acid oxidation, with the exception of CPT1 deficiency, invariably result in a reduction in total plasma L-carnitine concentration and/or an increase in the acyl: free L-carnitine ratio. Free L-carnitine facilitates the removal of unmetabolised acyl groups from the mitochondria with the freeing up of coenzyme A. Acylcarnitines is excreted by the kidneys with reduction in total L-carnitine. Acylcarnitines inhibit the carrier-mediated reabsorption of L-carnitine from the renal tubule, thus exacerbating L-carnitine depletion (Tein 2003).

In general it is difficult to evaluate the contribution of toxic metabolites in the context of human fatty acid oxidation defects to the overall pathology of disease, as in many fatty acid oxidation disorders there is a combination of energy deficit, potentially toxic metabolites and sequestration of vital components.

Altered enzyme product

Acute respiratory distress syndrome ARDS in both neonates and older patients has been described in both isolated long chain 3-hydroxyacyl-CoA dehydrogenase deficiency LCHADD and mitochondrial trifunctional protein MTP deficiency (Lundy et al 2003; Olpin et al 2005). Long chain acyl-CoA dehydrogenase LCAD and the MTP complex are expressed in human lung (Oey et al 2005). Surfactant abnormalities and mitochondrial dysfunction are two potential mechanisms by which MTP/LCHAD defects might predispose to ARDS. Accumulating fatty acid metabolites in patients with LCHAD/MTP defects might well alter the phospholipid components of surfactant and impair its function. A single case of respiratory distress has been linked to LCAD deficiency (Suhrie et al 2011). This might suggest a role for LCAD and MTP protein in substrate modification for the production of surfactant which contains several lipid components including palmitoylemyristoylphosphatidylcholine (Bernhard et al 2001; Ridsdale et al 2005). Synthesis of myristic acid would imply a need for fatty acid chain shortening.

Loss of protein-protein interaction

Patients with short chain 3-hydroxyacyl-CoA dehydrogenase SCHAD deficiency have been shown to present with
| Disorder   | Metabolite(s)                      | Toxicity effect                                                                 | Clinical consequence                                                                 | Reference |
|------------|-----------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------|
| MCAD       | Octanoic acid                     | Inhibition of choroid plexus organic anion transport                           | Cerebral accumulation of fatty acids with disruption of mitochondrial function       | Kim et al 1992 |
|            | Decanoic acid                     | Uncouple oxidative phosphorylation Inhibition of complexes I-III, II-III, IV in liver (rat) | Encephalopathy                                                                      | Schuck et al 2009 |
| MCAD       | Octanoyl-CoA                       | ↑acyl-CoA:free CoA ratio                                                      | Inhibition of gluconeogenesis and intermediary metabolism liver dysfunction - Reye-like presentation | Sauer et al 2008 |
| MCAD       | cis-4-decenolic acid               | Elicit oxidative damage/reduce glutathione reserves inhibit cytochrome c oxidase activity un couples oxidative phosphorylation (rat brain) | encephalopathy                                                                      | Schuck et al 2010 |
| Defects affecting ETF or ETFDH | Short and medium chain carboxylic acids C4-C10 | Increased ROS generation                                                      | Eencephalopathy                                                                      | Scaini et al 2012 |
|            | Ethylmalonic acid (derived from butyryl-CoA) | Inhibition of respiratory chain Inhibit mitochondrial creatine kinase in cerebral cortex (rats) | Muscle weakness                                                                      | Leipnitz et al 2003 |
| LCHAD/MTP  | 3-hydroxydodecanoic acid          | Uncouple oxidative phosphorylation                                            | Hepatic cholestasis, fibrosis, cirrhosis HELLP                                         | Tyni et al 1996 |
|            | 3-hydroxytetradecanoic acid       |                                                                                 |                                                                                      | Ventura et al 1996 |
|            | 3-hydroxypalmitic acid            |                                                                                 |                                                                                      | Ibdah et al 2000 |
|            | LCHAD/MTP                         | 3-hydroxydodecanoic acid                                                      | Chorioretinopathy polyneuropathy, demyelination Rhabdomyolysis                         | Tyni et al 1996 |
|            | 3-hydroxytetradecanoic acid       | Interference with DHA metabolism in retinal pigment epithelium/neural membranes |                                                                                      | Tein et al 1999 |
|            | 3-hydroxypalmitic acid            | Inhibition of respiratory chain                                               |                                                                                      | Tyni et al 2002 |
|            | CPT2/CACT/VLCAD                   | Long chain acylcarnitines                                                     | Inhibition of N-acetylglutamate synthase Generate ROS/lipid peroxidation Uncouple oxidative phosphorylation | Ventura et al 1996 |
|            |                                  |                                   | Hyperammonaemia Cardiac arrhythmias                                                | Ibdah et al 1998 |
|            |                                  |                                   |                                                                                      | Spiekerkoetter et al 2004a |
|            |                                  |                                   |                                                                                      | Tyni et al 2004 |
|            |                                  |                                   |                                                                                      | Mak et al 1986 |
|            |                                  |                                   |                                                                                      | Sparagna et al 2000 |
|            |                                  |                                   |                                                                                      | Corr and Yamanda 1995 |
|            | CPT2/CACT/VLCAD                   | Long chain acyl-CoA’s                                                         | Detergent-like properties on sarcolemma                                               | Ventura et al 2005 |
|            |                                  |                                   | Inhibition of ADP/ATP carrier                                                      |                                                                      |
|            |                                  |                                   | Inhibition of oxidative phosphorylation                                            | Ventura et al 2007 |

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DHA docosahexaenoic acid
VLCAD very long-chain acyl-CoA dehydrogenase deficiency
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hypoglycaemia precipitated by hyperinsulinaemia. This has been shown to be due to loss of inhibition of glutamate dehydrogenase by the SCHAD protein. This is an unusual example of a protein exhibiting dual function both as an enzyme and also through direct protein-protein interaction (Li et al 2010).

Phenotypic diversity in fatty acid oxidation disorders

Disorders of fatty acid oxidation result in a wide spectrum of clinical disease (Table 2). Even patients with the same mutation may present in entirely different ways, e.g. homozygous c.985A > G MCADD presenting as neonatal ketoacidosis with encephalopathy (personal observation), hypoketotic hypoglycaemia in infancy or absence of history of any related clinical disease in adults. The precise mechanisms underlying this diversity remain unclear, although recent advances in our knowledge of multiple gene expression which dictates the metabolome are providing some clues (Homuth et al 2012). Some FAOD’s do show significant genotype/phenotype correlation particularly with regard to the severe, as compared to the milder phenotypes of, e.g. CPT2, very long chain acyl-CoA dehydrogenase VLCAD and multiple acyl-CoA dehydrogenase MAD deficiency (Bonnefont et al 1996; Andresen et al 1999; Olsen et al 2003) see Table 3. However in many disorders there is a much poorer or virtually absent correlation, e.g. MCADD, CTD. Certainly there are many factors that are known to influence the phenotype such as frequency and duration of fasting, intercurrent infections, type of energy substrate, e.g. fat vs. carbohydrate, the extent and duration of exercise, exposure to certain drugs and protection by anti-oxidants and co-factors (Lucas et al 2011). However we still remain unable to explain why for example even relatively well controlled LCHADD (homozygous c.1528G>C) patients exhibit significant morbidity, develop chorioretinopathy and often neuropathy while a few reach adulthood with minimal retinal changes as the only manifestation of clinical disease (den Boer et al 2002; Olpin et al 2005).

There is an increasing understanding of the influence of single nucleotide polymorphisms (SNPs) on the variation in functional activity of many of the genes involved in intermediary metabolism. Recent description of the peroxisome

Table 2 Clinical features of fatty acid oxidation defects as presenting in various tissue/organs

| Tissue/organ   | Disorder                        | Nature of clinical feature                                                                 |
|----------------|--------------------------------|------------------------------------------------------------------------------------------|
| CNS            | CTD, CPT1, CACT, CPT2, VLCAD, LCHAD/MTP, MCAD, MADD | Reye-like encephalopathy, seizures, coma, death                                            |
| Liver          | CTD, CPT1, CACT, CPT2, VLCAD, LCHAD/MTP, MCAD, MADD | Hepatic dysfunction hyperammonaemia, increased liver enzymes, hepatosteatosis              |
| Liver          | CPT1                            | Cholestatic jaundice, hyperlipidaemia,                                                    |
| Liver          | LCHAD/MTP                       | Cholestatic jaundice, cirrhosis/fibrosis, maternal HELLP/AFLP                             |
| Heart          | CTD, CPT2, CACT, VLCAD, LCHAD/MTP, MADD | Arrhythmias (anything from tachycardia to complete heart block), cardiomyopathy - dilated or hypertrophic |
| Skeletal muscle| CTD, CACT, CPT2, VLCAD, RR-MADD, MADD | Hypotonia, lipid deposition, weakness, exercise intolerance, myalgia, rhabdomyolysis     |
| Nerves         | LCHAD/MTP                       | Sensori-motor neuropathy, chorioretinopathy, axonopathy, demyelination, peripheral neuropathy |
| Lungs          | LCHAD/MTP                       | Acute respiratory distress, respiratory failure                                            |
| Parathyroid    | LCHAD/MTP                       | Hypoparathyroidism – hypocalcaemia, hyperphosphataemia, low PTH                           |
| Kindney        | CPT2, MADD (severe)             | Renal cystic dysplasia                                                                    |
| Kidney         | CPT1                            | Renal tubular acidosis                                                                    |

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AFLP acute fatty liver of pregnancy
proliferators-activated receptor gamma-Co-activator-1α (PGC-1α) transcriptional complexes regulated through silent information regulator; ortholog of mammalian sirtuin (SIRT1) pathways may help to explain some of the regulatory processes that influence this phenotypic diversity (Abbott 2009; Rodgers et al 2008; Dominy et al 2011).

Table 3 Disorders of fatty acid oxidation divided according to the presence or absence of significant residual protein function. Biochemical consequences of each defect with manifestation of clinical disease

| Severe fatty acid oxidation defects | Minimal/no functional protein/null mutations | Clinical disease |
|-----------------------------------|---------------------------------------------|-----------------|
| Disorder                          | Biochemical consequence                     | Reye-like presentation, encephalopathy, seizures, coma, death. Moderate/severe hyperammonaemia, abnormal liver function |
| CTD, MCAD, CPT1                   | Non/hypoketotic hypoglycaemia               | Hepatic failure, severe hypotonia/rhabdomyolysis, cardiomyopathy/arythmias, encephalopathy, seizures, coma, death |
| CPT2, CACT, VLCAD, MADD, LCHAD/MTP | Non-ketotic hypoglycaemia, inhibition of gluconeogenesis | Severe metabolic acidosis, hyperammonaemia, production of toxic metabolites, sequestration of Coenzyme A and carnitine |
| CPT2, MADD                        | Severely reduced ATP production, toxic metabolites | Congenital abnormalities due to disruption of intrauterine growth - renal cystic dysplasia, facial dysmorphism, rocker-bottom feet, muscular defects of anterior abdominal wall and abnormal genitalia (hypospadias and chordoe) |
| LCHAD/MTP                         | Toxic 3-hydroxyacyl-metabolites              | Maternal HELLP and acute fatty liver of pregnancy AFLP (affected foetus). |

“Milder” disorder with reduced fatty acid oxidation

Significant residual protein function – many (not all) missense mutations

| Disorder                          | Biochemical consequence                     | Clinical disease |
|-----------------------------------|---------------------------------------------|-----------------|
| VLCAD                             | Hypoketotic hypoglycaemia                   | Reye-like episodes with seizures/encephalopathy |
| MADD                              | mild/moderate hyperammonaemia               | Exercise intolerance, myalgia, muscle weakness, rhabdomyolysis - triggered by prolonged exercise, cold/heat stress or infection |
| VLCAD                             | Reduced aerobic energy                      | Sensori-motor peripheral neuropathy (mainly lower limbs), chorioretinopathy, axonopathy, demyelination, episodic rhabdomyolysis, respiratory failure |
| CPT2                              | production from long chain fat oxidation    | Chronic hypotonia – weakness of neck, shoulder, hip, diaphragm/respiratory muscles. Progressive exercise intolerance, episodic rhabdomyolysis. |
| MTP                               | Chronic production of toxic 3-hydroxyacyl metabolites/reduced energy production | Cyclical vomiting, loss of appetite, weight loss. Acute confusion/encephalopathy |
| RR-MADD                           | Toxicity of multiple medium chain metabolites/reduced energy production – hypocarnitinaemia, ketoacidosis, secondary Coenzyme Q deficiency and reduced activity of respiratory chain complexes I, II-III and IV | |

CTD OCTN2 transporter deficiency

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VLCAD very long-chain acyl-CoA dehydrogenase deficiency

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MTP mitochondrial trifunctional protein deficiency

MCAD medium chain acyl-CoA dehydrogenase deficiency

MADD multiple acyl-CoA dehydrogenase deficiency

RR-MADD riboflavin responsive multiple acyl-CoA dehydrogenase deficiency
is becoming increasingly clear that the view that most inherited disorders are purely monogenic diseases is a naive concept. In future our approach to understanding the phenotypic diversity and management of patients will be more realistically achieved from a polygenic perspective (Rocha et al 2011a, b).

**Individual disorders of fatty acid oxidation**

Primary carnitine deficiency

CTD is a potentially lethal, autosomal recessive disorder characterised by early childhood onset cardiomyopathy, with or without weakness and hypotonia, recurrent hypoglycaemic hypoketotic seizures and/or coma, failure to thrive, and extremely low plasma and tissue carnitine concentrations (Tein et al 1990; Stanley et al 1991; Tein 2003). There is phenotypic variability in this disorder, many patients present during the first few years of life either with symptomatic cardiomyopathy and/or with repeated hypoglycaemic hypoketotic episodes (Reye-like episodes). Some infants may present initially with relatively mild symptoms of muscle hypotonia, mild developmental delay, failure to thrive, delayed walking, repeated infections and poor growth. Other patients may present much later in childhood (4–12 years) with isolated cardiomyopathy which can present as sudden death. Occasionally older subjects have been described with mild ventricular fibrillation or adult onset lipid storage myopathy (Rijlaarsdam et al 2004; Vielhaber et al 2004). Both silent and symptomatic individuals have been described within the same pedigree (Spiekerkoetter et al 2003a) and asymptomatic adults are now well described (Vijay et al 2006). There is evidence to suggest that asymptomatic patients tend to have slightly higher residual carnitine transporter activity than clinically presenting patients (Rose et al 2011).

Clinical disease is generally explained by reduced energy production from long-chain fatty acids. Variability of the clinical phenotype however, is not fully understood although factors such as duration of fasting, composition of diet, infection, rates of endogenous carnitine synthesis and other environmental stressors such as drugs and cold exposure must play an important part (Rasmussen et al 2013). It is suggested that carriers of a single OCTN2 mutation may be at risk of clinical disease given sufficient stress, e.g. hypertension, valproic acid (Tein et al 1995; Tein 2003).

Carnitine palmitoyltransferase type 1 deficiency (CPT1A)

Carnitine palmitoyltransferase type 1 (CPT1) is an enzyme of the outer mitochondrial membrane that converts long chain fatty acyl molecules to their corresponding acylcarnitines which are then transported across the inner mitochondrial membrane for β-oxidation in the mitochondrial matrix. There are three genes in the human genome that are known to encode related carnitine acyltransferases: CPT1A encodes the liver isoform of CPT1, CPT1B encodes muscle-type CPT1 and CPT1C, encoding CPT1 related protein expressed in brain (Price et al 2002). CPT1A is expressed in liver, kidney, lung, spleen, intestine, pancreas, ovary and fibroblasts. Only liver-type CPT1A deficiency has been recognised so far (Demaugre et al 1988; Falik-Borenstein et al 1992; Haworth et al 1992; Bergman et al 1994; Olpin et al 2001). Deficiency of CPT1A prevents the formation of long-chain acylcarnitines and the absence of these species, which are potent inhibitors of renal tubular free carnitine transport, results in a higher renal threshold for free carnitine (Stanley et al 1991). Patients often have characteristically high total plasma carnitine concentrations with more than 90 % in the free form. Patients with CPT1 deficiency usually present in infancy with recurrent episodes of hypoglycemic hypoketotic acidosis with raised transaminases, hepatomegaly, hepatosteatosis and mild to moderate hyperammonemia. Cholestatic jaundice has recently been described (Morris et al 2013). Acute fatty liver of pregnancy AFLP has also been reported in an Inuit female (Innes et al 2000). Death may occur during an acute presentation but surviving infants may suffer with severe developmental delay and intellectual impairment as a result of cerebral bioenergetic failure.

A range of cardiac abnormalities including tachycardia, bradycardia, arrhythmias, right bundle branch block and sudden cardiac arrest have been reported in neonates. Expression of CPT1A in fetal myocardium with persistence of expression into the neonatal period is proposed as an explanation (Weis et al 1994). Renal tubular acidosis has also been reported in a number of patients and this is explained by the expression of CPT1A in renal tubular epithelium with reliance on fat oxidation to power the high energy transport processes. Renal tubular acidosis appears to respond to medium chain triglyceride MCT supplementation but not to a low fat diet per se (Falik-Borenstein et al 1992; Olpin et al 2001). Hyperlipidaemia with raised triglycerides and/or cholesterol is also a feature of CPT1A deficiency, although hyperlipidaemia is rarely reported in other fat oxidation disorders (Falik-Borenstein et al 1992; Olpin et al 2001). The nature of a block on the outer mitochondrial membrane may specifically favour hepatic very low density lipoprotein synthesis with resultant hyperlipidaemia. Clinical presentation is explained primarily by lack of energy production from long chain fatty acids but with metabolic disturbance confined to the tissues where CPT1A is expressed.

A common CPT1A p.P479L (c.1436C>T) variant is prevalent in many Inuit populations and is present in its homozygous state in up to 65 % of the Inuit population in some Arctic coastal areas. This indicates that this variant is unlikely to be clinically disadvantageous for most individuals, although it has been shown that the variant significantly reduces CPT1A
activity and renders the enzyme partially insensitive to
malonyl-CoA inhibition (Brown et al 2001; Morillas et al
2001; Greenberg et al 2009). It has been postulated that this
variant may represent a selectively advantageous adaptation to
a high marine fat diet and to a state of permanent keto-
adaptation (Greenberg et al 2009).

Recent research suggests that the P479L variant in its
homozygous state may increase the risk of hypoglycaemic
events in neonates living a less traditional life-style on a
more “westernised” diet, and to at least partially account for
the higher infant mortality seen in these First Nations peo-

dles. A reduced capacity to generate ketones as observed in
patients with more “severe” mutations in the CPT1 gene is
postulated as precipitating hypoglycaemia in these infants
(Gessner et al 2010; Gillingham et al 2011).

Carnitine palmitoyltransferase type 2 (CPT2) deficiency

CPT2 is associated with the inner mitochondrial membrane
and has a single ubiquitously expressed isoform. CPT2
deficiency has three phenotypes, a fatal neonatal-onset form
with congenital abnormalities, a severe neonatal hepato-
cardio-muscular form, and a mild myopathic adult form.
The lethal neonatal form is characterised by non-ketotic
hypoglycaemia, liver disease, hypotonia, cardiomyopathy
and congenital abnormalities (Hug et al 1991). The infantile
form with or without cardiac disease presents with liver, and
skeletal muscle involvement with episodes of decompensa-
tion, primarily as non-ketotic hypoglycaemia occurring with
fasting and/or intercurrent infection (Demaugre et al 1988).

There is good correlation between the biochemical measures
of enzyme activity, genotype and phenotype in severe in-
fantile disease as compared to “mild” adult-onset myopathic
presentation. However there is no such correlation within
the myopathic group, despite significant phenotypic vari-
ability (Olpin et al 2003).

Mutation analysis in CPT2 deficiency has revealed
numerous mutations but the common S113L mutation
accounts for ~50 % of myopathic disease (Taroni et al
1992; Verderio et al 1995; Taggart et al 1999;
Deschauer et al 2005). Hypoglycaemia and cardiac in-
volvement are generally not features of “mild” CPT2
deficiency.

A thermolabile CPT2 mutant SNP variant [p. Phe352Cys]
(1055 T>G/F352C) has been recently described in the
Japanese population and shown to be closely correlated with
influenza associated encephalopathy (IEA), low blood ATP
and predisposition to brain vascular invasion by virus (Kubota
et al 2012; Yao et al 2011).

Very long-chain acyl-CoA dehydrogenase (VLCADD)

Very long-chain acyl-CoA dehydrogenase catalyses the ini-
tial rate-limiting step in mitochondrial long-chain fatty acid
β-oxidation. Very long-chain acyl-CoA dehydrogenase de-

ficiency is a clinically heterogeneous disease, and as with
CPT2 deficiency there are three major phenotypes: a late
onset myopathic form, a milder childhood form, usually
with hypoketotic hypoglycaemia as the main presenting
feature but often with exercise intolerance and rhabdomyo-
ysis as a significant feature particularly in older children and
young adults. There is also a severe infantile form, with
early onset non-ketotic hypoglycaemia, high mortality, and
high incidence of cardiomyopathy. However unlike the fatal
neonatal-onset form of severe CPT2 deficiency where de-
velopmental abnormalities are often present (see Table 3),
these are not reported in severe neonatal VLCADD. It is
hypothesised that in fetal tissues the role of VLCADD is
replaced by other ACAD’s thus permitting normal in utero
development (He et al 2011). Overall VLCADD is one of
the commonest fatty acid oxidation disorders that we en-
counter, second only to MCADD (Fig. 2). There is a good

Fig. 2 Fatty acid oxidation flux measured in fibroblasts at 37°C
using [9,10-H3] myristate, palmitate and olate as substrates in myopathic and
infantile VLCADD as compared to controls. Each plotted value represents the
mean result for individual patient or control cell lines assayed in duplicate in 2-5
separate assays. There is overlap between the infantile and milder myopathic
phenotypes but all VLCADD cell lines are clearly separated from the controls

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Defects of the mitochondrial trifunctional protein MTP

The MTP protein is a hetero-octameric (α4β4) enzyme complex which catalyses the last three steps in β-oxidation of long chain fatty acids. The common c.1528G>C HADHA mutation results in isolated LCHADD whereas other mutations in the HADHA or HADHB result in deficiency of all three enzymes (Spiekerkoetter et al 2004b; Spiekerkoetter et al 2003b; Spiekerkoetter and Wood 2010).

Patients with MTP deficiency exhibit a wide clinical spectrum of disease with severe neonatal manifestation including cardiomyopathy and death, through moderate/severe infantile presentation with hepatic manifestations to mild peripheral polyneuropathy, episodic rhabdomyolysis and pigmentary retinopathy (Tyni et al 1998; Spiekerkoetter et al 2003b; Spiekerkoetter et al 2004a, b; Schaefer et al 1996; Chakrapani et al 2000). Hypoparathyroidism is a rare complication of both LCHADD and MTP deficiency (Tyni et al 1997).

Mild MTP deficiency is rare with an unusual phenotype having features in common with the hereditary sensory-motor neuropathies HMSN and spinal muscular atrophy SMA (Spiekerkoetter et al 2004a; Olpin et al 2005). There is a progressive peripheral polyneuropathy from infancy or early childhood affecting predominantly the lower limbs, but also symmetric weakness in wrist and finger extensors. There may be exercise intolerance, gait abnormalities with bilateral Achilles tendon contractures, planovalus deformities and loss of vibrational sense. Some patients may develop respiratory failure often in association with an acute decompensation. Nerve conduction studies and sural nerve biopsy frequently show evidence of axonal degeneration and loss of normal myelin (Spiekerkoetter et al 2004a).

There may be pigmented retinopathy. Episodic rhabdomyolysis in association with exercise, illness or fasting, is usually encountered in this condition but this may not appear until many years after the initial neurological presentation (Spiekerkoetter et al 2004a, Olpin et al 2005). It has been proposed that the neuropathy and rhabdomyolysis seen in mild trifunctional protein deficiency is due to the specific toxic nature of the 3-hydroxacyl metabolites (Ibdah et al 1998; Schaefer et al 1996; Spiekerkoetter et al 2003b).

Riboflavin responsive multiple acyl-CoA dehydrogenase deficiency RR-MADD

Multiple acyl-CoA dehydrogenation deficiency (MADD) is a disorder of fatty acid, amino acid and choline oxidation caused by defects in any one of two flavoproteins, electron transfer flavoprotein (ETF) or ETF:ubiquinone oxidoreductase (ETF-QO) which affect some 14 dehydrogenases (Fig. 3). Patients are categorised into severe (MADD:S) or milder (MADD:M) forms depending on the nature of the defects in the genes (ETF, ETFB and ETFDH) (Goodman...
et al 2002; Olsen et al 2003). Most patients do not respond to riboflavin supplementation. However a sub-set of MADD patients have been recently characterised who respond to pharmacological doses of riboflavin both clinically and biochemically (RR-MADD). These RR-MADD patients for the most part have been shown to have mutations in ETFQO and most mutations are situated around the ubiquinone binding pocket. (Olsen et al 2007; Gempel et al 2007). Riboflavin is the precursor of FAD, and riboflavin responsiveness results from the ability of FAD to act as a chemical chaperone that promotes folding of certain misfolded ETF-QO proteins, and thereby ameliorate or normalise disease symptoms (Cornelius et al 2012). Patients may present with cyclical vomiting, loss of appetite, progressive proximal muscle weakness particularly affecting neck, shoulder, hip and/or respiratory muscles but also chronic leg weakness and exercise intolerance with occasional rhabdomyolysis. Some patients may present with acute encephalopathy. There is also frequently an associated muscle ubiquinone deficiency with low respiratory chain complexes I, II/III and IV (Olsen et al 2007; Gempel et al 2007). The clinical response to pharmacological doses of riboflavin is usually rapid and striking. Most patients present as adolescents or young adults with an increased female: male ratio. Riboflavin intake in many diets often falls below the recommended daily intake and this may be particularly true for adolescent females (Gregory and Lowe 2000). RR-MADD may be considered as an example of the interaction of micronutrient availability and genetic predisposition.

Fig. 3 Fibroblast fatty acid oxidation flux using palmitate in 9 myopathic CPT2 deficient cell lines and 3 neonatal CPT2 deficient cell lines grown and assayed at 37°C and 41°C. The lower fatty acid oxidation flux in all the myopathic cell lines demonstrates the thermal instability of the CPT2 mutant protein at higher temperature. Neonatal “severe” CPT2 deficient cell lines show barely detectable flux at both temperatures. (Olpin et al 2003)

Fig. 4 Mitochondrial FAD dependent pathways. FAD co-factor dependent acyl-CoA dehydrogenases, ETF, ETFDH and other FAD containing proteins including complexes I and II of the respiratory chain. Relationship of fatty acid oxidation, amino acid degradation and the respiratory chain. FMN flavin mononucleotide. FAD flavin adenine dinucleotide. ETF electron transfer flavoprotein. SCAD short chain acyl-CoA dehydrogenase. MCAD medium chain acyl-CoA dehydrogenase. LCAD long chain acyl-CoA dehydrogenase. VLCAD very long chain acyl-CoA dehydrogenase. ACAD9 acyl-CoA dehydrogenase 9. ACAD10/11 acyl-CoA dehydrogenase 10/11. GCD glutaryl-CoA dehydrogenase. D-2-HGD D-2-hydroxyglutaryl-CoA dehydrogenase. IVD isovaleryl-CoA dehydrogenase. SBCAD short branched chain acyl-CoA dehydrogenase. IBD isobutyryl-CoA dehydrogenase. DMGD dimethylglycine dehydrogenase. SARD sarcosine dehydrogenase.
More recent aspects of defects affecting fatty acid oxidation

Mutant proteins and future therapeutic options

The effect of increased temperature on fibroblast fatty acid oxidation flux can be demonstrated in both mild CPT2 (Fig. 4) and VLCAD deficiency (Olpin et al 2012). Several thermolabile CPT2 mutant SNP variants including [p. Phe352Cys] p. Val368Ile (V368I) has been recently described in the Japanese and Chinese population and shown to confer high susceptibility to influenza associated encephalopathy (IEA), low blood ATP and predisposition to brain vascular invasion by virus (Chen et al 2005; Kubota et al 2012; Yao et al 2011; Mak et al 2011). Treating fibroblasts with bezafibrate has been shown to upregulate ATP levels and may possibly offer a therapeutic option in patients infected with IEA (Yao et al 2011). The presence of the V368I variant was also reported as being overrepresented in myopathic CPT2 patients in the UK population (Olpin et al 2003). Bezafibrate also upregulates VLCAD mutant mRNA production and restores fat oxidation in VLCAD deficient cell lines (Gobin-Limballe et al 2007). Similarly bezafibrate has been shown to upregulate CPT2 activity in CPT2 deficient cells, both in vitro and in vivo, with improved clinical outcome (Djouadi et al 2005; Bonnefont et al 2010). Resveratrol and its synthetic analogues have been recently shown to offer great potential for the upregulation of mutant protein mediated through PGC-1α and SIRT1 pathways (Bastin et al 2011). This unstable nature of mutant protein is by no means confined to these disorders and is a well recognised feature of many mutant proteins (Gregersen et al 2008, 2010a, b; Yao et al 2011; Furuki et al 2006). As previously mentioned over two thirds of mutations are missense mutations many of which will result in unstable folding mutants but with potential for residual enzyme function. Studies using PTC124 and gentamicin have demonstrated the potential for the use of such compounds to promote readthrough and to increase functional activity of nonsense mutations (Tan et al 2011).

In general mutant proteins are recognised by molecular chaperones involved in cellular quality control and rapidly targeted for proteasomal degradation. If they can be rescued prior to being degraded by the cell there is potential for preserving enzyme function. A combination of upregulation of mutant protein, induction of readthrough mechanisms and enhanced protection by increasing either natural or artificial chaperones (e.g. riboflavin/FAD in ETFDH mutants) offers great potential for future therapeutic intervention in a wide range of inherited disorders.

Conclusion

Disorders of fatty acid oxidation exhibit a wide clinical spectrum of disease which are partly explained by genotype/phenotype correlation and identifiable environmental factors. However there remain many unresolved questions regarding the precise mechanisms that conspire to produce the phenotypic diversity that we encounter. Increased understanding of the gene regulatory mechanisms will hopefully improve our understanding of these disorders and these together with the environmental factors that influence the metabolome will serve to answer many of these unresolved questions. In time this will allow us to manage patients more effectively by tailoring therapies to achieve up or down regulation of metabolic pathways and to maximise mutant protein function.

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