MINI-REVIEW

Refsum’s disease: a peroxisomal disorder affecting phytanic acid α-oxidation

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Abstract

Refsum’s disease (hereditary motor sensory neuropathy type IV, heredopathia atactica polyneuritiformis) is an autosomal recessive disorder the clinical features of which include retinitis pigmentosa, blindness, anosmia, deafness, sensory neuropathy, ataxia and accumulation of phytanic acid in plasma- and lipid-containing tissues. The transport and biochemical pathways of phytanic acid metabolism have recently been defined with the cloning of two key enzymes, phytanoyl-CoA 2-hydroxylase (PAHX) and 2-hydroxyphytanoyl-CoA lyase, together with the confirmation of their localization in peroxisomes. PAHX, an iron(II) and 2-oxoglutarate-dependent oxygenase is located on chromosome 10p13. Mutant forms of PAHX have been shown to be responsible for some, but not all, cases of Refsum’s disease. Certain cases have been shown to be atypical mild variants of rhizomelic chondrodysplasia punctata type 1a. Other atypical cases with low-plasma phytanic acid may be caused by α-methylacyl-CoA racemase deficiency. A sterol-carrier protein-2 (SCP-2) knockout mouse model shares a similar clinical phenotype to Refsum’s disease, but no mutations in SCP-2 have been described to-date in man. This review describes the clinical, biochemical and metabolic features of Refsum’s disease and shows how the biochemistry of the α-oxidation pathway may be linked to the regulation of metabolic pathways controlled by isoprenoid lipids, involving calcineurin or the peroxisomal proliferator activating α-receptor.

Keywords: oxygenase, peroxisomes, phytanic acid, Refsum’s disease, review.


Peroxisomes are cellular organelles involved in biosynthetic and degradative functions (Titorenko and Rachubinski 2001) which, like mitochondria, may have originated from ancient commensal bacteria. Anabolic functions of peroxisomes include the biosynthesis of cholesterol and plasmalogens for cell and neuronal membranes (Moser 1987; Singh 1997; Wanders 2000; Parsons et al. 2001). Their degradative functions include the metabolism of unsaturated and aromatic fatty acids including bile acids. Peroxisomes also contain an analogous fatty acid β-oxidation pathway to that found in mitochondria and also specific enzymes for the α-oxidation of 3-methyl branched fatty acids including phytic acid (Moser 2000; Moser 1999; Wanders 2000; Parsons et al. 2001).

Refsum’s disease – a disorder of fatty acid α-oxidation

The symptoms of adult Refsum’s disease (ARD; OMIM 266510; on-line Mendelian inheritance in man, http://www.ncbi.nlm.nih.gov), also called heredopathia atactica polyneuritiformis and hereditary sensory motor neuropathy type IV, were first described in 1945 (Refsum 1945; Wanders et al. 2001). He described a constellation of signs comprising...
retinitis pigmentosa, anosmia, deafness, ataxia and polyneuropathy allied with raised levels of CSF protein. The biochemical defect was identified in 1963 by Kenke and Kahlke, who noticed the presence of excess phytanic acid in the plasma of affected patients (Kenke and Kahlke 1963). Phytanic acid cannot be degraded by β-oxidation because of the presence of a 3-methyl group; instead it undergoes one round of α-oxidation that shortens phytanic acid by one carbon atom to give pristanic acid. Steinberg et al. postulated that ARD results from a deficiency in the enzyme responsible for α-oxidation of phytanic acid (Steinberg et al. 1967).

The pathophysiology of ARD remained obscure, although cell complementation analyses assigned it to complementation group 14 of the peroxisomal diseases (Moser et al., 1995). This proposal was disputed as the enzyme activity in rats was apparently localized to mitochondria. Recent work has completely revised the major pathway involved in the metabolism of phytanic acid, and has confirmed its subcellular localization as peroxisomal and has identified the mutated gene responsible for some cases of ARD (Mannaerts et al. 2000; Verhoeven and Jakobs 2001).

**Clinical signs and symptoms**

In contrast to Zellweger’s syndrome (OMIM 214100), neonatal adrenoleukodystrophy (OMIM 202370), infantile Refsum’s disease (IRD; OMIM 266500) and rhizomelic chondrodysplasia (RCDP; OMIM 601757) (Singh 1997), ARD usually presents in late childhood with progressive deterioration of night vision, the occurrence of progressive retinitis pigmentosa and anosmia. After 10–15 years, deafness, ataxia, polyneuropathy (sometimes termed hereditary sensory motor neuropathy type IV), ichthyosis and cardiac arrhythmias can occur (Fig. 1) (Gibberd and Wierzbicki 2000). Short metacarpals or metatarsals are also found in around 30% of patients (Plant et al. 1990). Rare findings include psychiatric disturbance and proteinuria (Pabico et al. 1981). Premature death can occur either from cardiac arrhythmias caused by an acute release of a labile phytanic pool from the liver following infection or rarely as a result of stress-induced catecholamine release during plasmapheresis (Wanders et al. 2001).

The pathognomic finding of ARD on serum analysis is a highly raised phytic acid level (> 200 μmol/L; normal < 30 μmol/L), in contrast to other peroxisomal disorders where levels are usually lower and other metabolic abnormalities are also present (Gibberd and Wierzbicki 2000; Wanders et al. 2001). Unlike in RCDP or the peroxisomal biogenesis disorders, no intellectual defects are seen, bone abnormalities are mild (if at all present) and there is no defect in plasmalogen synthesis. In IRD, which is a mild clinical variant of the peroxisomal biogenesis disorder encompassing Zellweger’s disease as its most severe form, numerous subtle peroxisomal defects are present and the condition presents from birth (Wanders 2000). The age at which symptoms first present in ARD can be variable, with cases described with an onset at age 2 years whilst others do not present until age 40–50 (Gibberd and Wierzbicki 2000). In addition the classical presentation with phytic acidemia may not be exclusive, as one family with offspring affected with a ‘Refsum–like’ syndrome has been described in which other subjects had signs of leukodystrophy, intellectual impairment and the co-occurrence of pipecolic academia (OMIM 600964) (Tranchant et al. 1993). The disease is treated symptomatically by the restriction of phytic acid intake in the diet or by its elimination by plasmapheresis or lipid apheresis (Gibberd et al. 1979; Moser et al. 1980; Gutsche et al. 1996). These regimes reduce plasma phytic acid levels by 50–70% to values typically around 100–300 μmol/L. Treatment successfully resolves symptoms of ichthyosis, sensory neuropathy and ataxia in approximately that order. However, it has uncertain effects on the progression of the retinitis pigmentosa, anosmia or deafness (Gibberd and Wierzbicki 2000; Wanders et al. 2001).

**Clinical enzymology**

Phytic acid (3R,S,7R,11R,15-tetramethylhexadecanoic acid) (1a; Fig. 2) is an isoprenoid lipid derived from the phytol side-chain of chlorophylls by bacterial degradation in ruminants, invertebrates or pelagic fish. High levels of phytic acid in mutton were described in New Zealand in 1959 but the clinical significance of this was not appreciated at the time. The average human daily dietary intake of phytic acid in Western societies is 50–100 mg, of which around 50% is absorbed and metabolized (Dhopheshwarkar 1980; Coppack et al. 1988; Brown et al. 1993).

Phytic acid is transported in plasma allied to very-low-density lipoprotein (VLDL) and later in low-density
lipoprotein (LDL) (Wierzbicki et al. 1999), with its elimination from tissue stores occurring by mechanisms associated with reverse cholesterol transport (high-density lipoprotein; HDL). It also condenses to form triglycerides, but apparently only occupies the 1 or 3 positions because of steric constraints (Wanders et al. 2001). Phytanoyl-glycerides are also resistant to plasma lipases, which limits their metabolism in plasma. Phytic acid is preferentially taken up by the liver and may account for up to 50% of the free fatty acid pool in hepatocytes. This pool is labile and can be acutely mobilized by stress, infection or starvation resulting in rapid phytic acid release (Britton et al. 1989). Phytanoyl-glycerides are also resistant to plasma lipases, which limits their metabolism in plasma. Phytic acid is preferentially taken up by the liver and may account for up to 50% of the free fatty acid pool in hepatocytes. This pool is labile and can be acutely mobilized by stress, infection or starvation resulting in rapid phytic acid release (Britton et al. 1989).

Phytic acid cannot be metabolized by this route because of the presence of a β-methyl group. Instead, phytic acid (1a) is metabolized either by α-oxidation to pristane acid (5a) or by α-oxidation from the other end of the molecule. Using radiolabelled [14C]phytanic acid as a substrate, an enzyme activity responsible for the α-oxidation of phytanic acid (1a) in cell lysates was described in 1967 (Steinberg et al. 1967; Herndon et al. 1969). This activity was eventually localized within peroxisomes and after 30 years the pathway responsible for α-oxidation has been clarified (Verhoeven et al. 1998).

Patients with ARD are unable to detoxify phytic acid (1a) by α-oxidation, and so the α-oxidation pathway is the only metabolic pathway available for phytic acid degradation. This pathway produces 3-methyladipic acid as the final metabolite, which is excreted in the urine (Wanders et al. 2001). Activity of the α-oxidation pathway is approximately doubled in ARD patients compared with normal levels (Wierzbicki, unpublished data).
Metabolism of phytanic acid

Most metabolism of phytanic acid seems to occur in the liver and kidney, although skin fibroblasts are used for clinical diagnostic purposes (Wanders et al. 2001). Phytanic acid from plasma enters the peroxisome in association with the sterol carrier protein-2 (SCP2) and is metabolized by a four-step initial α-oxidation pathway (Fig. 2). Unusually, it appears this pathway can equally well metabolize two stereoisomers of its substrate, i.e. both the (3R)- and (3S)-epimers of phytanic acid. Initially, phytanic acid (1a) is thioesterified with coenzyme A (CoA) to give phytanoyl-CoA (1b), which is then hydroxylated to give 2-hydroxy-phytanoyl-CoA (2b). One carbon atom is then removed from the latter in a lyase reaction to give epimeric pristanal (3) and formyl-CoA (4b). Pristanal (3) is then oxidized to pristanic acid (5a). Pristanic acid is then thioesterified with CoA to give the epimeric (2R,S)-mixture. The action of a α-methyl-acyl-CoA 'racemase' converts the (2R)- epimer to the (2S)- epimer. Further degradation of (2S)-pristanic acid by the stereospecific β-oxidation pathway then occurs, with the release of propionyl and acetyl-CoA units (Ferdinandusse et al. 2000). Further β-oxidation reactions (including epimerization) are required to generate the dimethylundecanoic (6), dimethylnonanoic (7) and methyl-heptanoic acid derivatives, which are finally exported for mitochondrial β-oxidation (Ferdinandusse et al. 1999).

The enzyme responsible for esterification of phytic acid with CoA has not been unequivocally identified. Candidates, based on cell extract studies, include a non-specific long chain fatty acyl (LCFA)-CoA synthetase (Watkins et al. 1996) and a specific enzyme, which has not been cloned (Pahan et al. 1993). Completion of the pathway requires thioesterification of pristanic acid by LCFA-CoA synthetase, the product of the α-oxidation pathway, before β-oxidation can take place.

The second (hydroxylation) step is catalysed by phytanoyl-CoA 2-hydroxylase (PAHX; Jansen et al. 1997; Mihalik et al. 1997). In many regards this enzyme appears to be a typical member of the family of non-haem, iron(II) and oxygenases (Hegg 1997). The enzyme can apparently utilize both epimers of phytanoyl-CoA as substrates (Kershaw et al. 2001; Mukherji et al. 2001a), and it contains the 2-His-1-carboxylate (HXD) iron(II)-binding motif (amino acids 175–177) typical of these oxygenases (Hegg 1997). The enzyme exists in two active forms, a pro-protein containing the PTS-2 signal, and a mature (peroxisomal) protein in which this signal is removed. The enzyme can apparently utilize both epimers of phytanoyl-CoA as substrates (Kershaw et al. 2001; Mukherji et al. 2001a). In addition to its role in the α-oxidation pathway, recent results indicate that PAHX might play other roles in the cell, including cell signalling and blood coagulation (Chambraud et al. 1999; Chen et al. 2001). These putative roles are unconnected with its role in the α-oxidation pathway.

The third (cleavage) step is performed by 2-hydroxyphytanoyl-CoA lyase (2HPCL) (Foulon et al. 1999). The reaction requires thiamine pyrophosphate (TPP) as a cofactor, and presumably its mechanism proceeds via the addition of TPP to the thioester followed by the rupture of the C-1, C-2 bond of (2b). The products of the reaction are formyl-CoA (4b), which is subsequently converted to formate (4a) (Croes et al. 1996), and pristanal (3) (Verhoeven et al. 1997). Formate (4a) may be further metabolized via one-carbon pathways outside the peroxisome. Other hydroxylated CoA derivatives can also be utilized as substrates by this enzyme (Foulon et al. 1999; Jansen et al. 2001). However, high-level expression of 2-hydroxy acid oxidases (HAOXs) in the liver, of which HAOX-2 shows the highest ability to metabolize 2-hydroxy-palmitate, suggests that these enzymes may have a role in metabolism of 2-hydroxy-phytanoyl-CoA through a 2-keto derivative (Jones et al. 2000). The substrate specificity of these enzymes with 2-hydroxy-phytanoyl-CoA has not been investigated.

The fourth (oxidation) step from pristanal (3) to pristanic acid (5a) has been shown to be a NAD+-dependent reaction in liver peroxisomal extracts, although little is known about the enzyme (Jansen et al. 2001). It has been suggested that the dehydrogenase responsible is identical to the deficient enzyme in Sjögren–Larsson syndrome (OMIM 270200) (Verhoeven et al. 1997; Sillen et al. 1998) although other data does not support this identification (Jansen et al. 2001).

Molecular genetics

Two groups identified the gene for PAHX simultaneously in 1997. One group employed molecular cloning using the N-terminal sequence information from the purified native enzyme (Jansen et al. 1997). The other identified PAHX via a homologous cloning strategy for enzymes with a PSHT-2 recognition site similar to that found in 3-ketoacyl-CoA thiolase (Mihalik et al. 1997). The human PAHX gene has been localized to chromosome 10p13 in the region between D10S196 and D10S547 by three groups (Nadal et al. 1995; Mihalik et al. 1997; Wierzbicki et al. 2000a).

The PAHX gene includes nine exons and codes for a 338 amino acid protein including the 30 amino acid signal domain, which is cleaved on entry into the peroxisome (Jansen et al. 2000).

Like all PHS-2-containing proteins, PAHX is transported into peroxisomes by the protein transporter peroxin 7 (Pex 7). Deficiency in this transporter is responsible for type-1 RCDP (Purdue et al. 1999). The peroxisomal transport process is complex, and it is interesting to note that PAHX is a ligand for the tacrolimus-binding protein FKBP52, given the occurrence of renal disease in some patients with ARD. This rotamase or peptidyl-prolyl isomerase corresponds to the mouse lupus nephritis antigen LN1. These findings imply that PAHX may have a role in...
cytosolic calcineurin-dependent cell signalling pathways, and also may be processed by FKBP52 on entry to the peroxisome (Chambraud et al. 1999).

PAHX is an iron(II) and 2-oxoglutarate-dependent oxygenase with little overall sequence similarity to other human oxygenases including prolyl hydroxylase, lysyl hydroxylase, γ-butyrobetaine or N,N′,N″-trimethyl-lysine hydroxylase (Prescott and Lloyd 2000). Numerous mutations in the PAHX have now been described in ARD patients, many of which affect 2-oxoglutarate conversion. Some of the mutations affecting 2-oxoglutarate binding can be rescued in vitro by the use of alternative 2-oxoacids as 2-oxoglutarate analogues (Table 1), and this has led to insight into their molecular effects (Mukherji et al. 2001a,b). Other mutations probably disrupt the 8-chain β-barrel core of the enzyme (Mukherji et al. 2001a).

Despite the new data on PAHX mutations and their consequences, some biochemical aspects of ARD variants remain to be elucidated. Phenotypic variants exist for ARD including one family with concurrent piquecolic academia, which has been found to colocalize to the chromosome 10p13 PAHX locus by heterozygosity mapping (Tranchant et al. 1993; Nadal et al. 1995). Another atypical ARD family has been identified with piquecolic acidemia and an abnormal catalase distribution, which was associated with a frame-shift mutation in PAHX (Baumgartner et al. 2000). This suggests that PAHX may have a role in the peroxisomal metabolism of lysine metabolites, and it is notable that piquecolic acid oxidase deficiency is a feature of Zellweger’s disease. As many as 20% of patients with Refsum’s disease may exhibit mildly elevated levels of piquecolic acid (Wierzbicki, unpublished data), and this may be associated with defects in 2-oxoglutarate utilization by PAHX.

Genetic mapping studies of a cohort of 17 patients with ARD has shown that only 45% of cases with classical ARD map to chromosome 10 (Wierzbicki et al. 2000a). Recent work has localized the locus for the second form of ARD to chromosome 6q22–24 (Wierzbicki et al. 2000b). Biochemical studies of fibroblasts from patients with ARD, but lacking mutations in PAHX, have established that these patients have subtle deficiencies of PTS-2-dependent enzyme functions (plasmalogen synthesis) consistent with it being a mild variant of RCDP (van den Brink et al. 2001). A report has previously described a patient with ARD whose complementation group was similar to that found for patients with RCDP (Moser et al. 1995). This indicates that Refsum’s ‘disease’ is actually a syndrome with mutations to more than one gene responsible for producing the clinical phenotypes. The recent description of the ‘Refsum-like’ α-methylacyl-CoA racemase (AMACR) deficiency (OMIM 604489), the symptoms of which include adult onset retinitis pigmentosa and sensory neuropathy with a minor elevation in phytanic

Table 1 Proposed structure-function relationship of mutations to PAHX causing Refsum’s disease

<table>
<thead>
<tr>
<th>Report</th>
<th>Type</th>
<th>Number of patients</th>
<th>Mutation Genomic</th>
<th>Protein</th>
<th>Functional effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumgartner et al. (2000)</td>
<td>Frameshift</td>
<td>1</td>
<td>376delGG</td>
<td>E127R D127X</td>
<td>loss of enzyme</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 2</td>
<td>2</td>
<td>C85T</td>
<td>P29S</td>
<td>mislocalization to cytosol?</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 2</td>
<td>2</td>
<td>C517T</td>
<td>P173S</td>
<td>β-2 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Frameshift</td>
<td>1</td>
<td>C526A</td>
<td>Q176X</td>
<td>loss of enzyme</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 6</td>
<td>6</td>
<td>A530G</td>
<td>D177G</td>
<td>loss of iron binding</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 2</td>
<td>2</td>
<td>T577C</td>
<td>W193R</td>
<td>β-3 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 1</td>
<td>1</td>
<td>G589C</td>
<td>E197Q</td>
<td>β-3 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 1</td>
<td>1</td>
<td>A595T</td>
<td>I199F</td>
<td>β-3 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 2</td>
<td>2</td>
<td>G610A</td>
<td>G204S</td>
<td>β-4 strand core disruption, uncoupling</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
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<td>1</td>
<td>C658T</td>
<td>H220Y</td>
<td>?</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
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<td>6</td>
<td>G734A</td>
<td>R245Q</td>
<td>β-5 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Point 3</td>
<td>3</td>
<td>T770C</td>
<td>F257S</td>
<td>β-6 strand core disruption</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
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<td>1</td>
<td>A805C</td>
<td>N269H</td>
<td>uncoupling</td>
</tr>
<tr>
<td>Chahal et al. (1998)</td>
<td>Point 7</td>
<td>7</td>
<td>C823T</td>
<td>R275W</td>
<td>loss of 2-oxoglutarate binding</td>
</tr>
<tr>
<td>Mihalik et al. (1997)</td>
<td>Point 3</td>
<td>3</td>
<td>G824A</td>
<td>R275Q</td>
<td>loss of 2-oxoglutarate binding</td>
</tr>
<tr>
<td>Jansen et al. (2000)</td>
<td>Splice 8</td>
<td>8</td>
<td>IVS2–2 A G</td>
<td>ΔY46-R82</td>
<td>β-1 strand core disruption</td>
</tr>
</tbody>
</table>

Mutations in phytanoyl-CoA 2-hydroxylase (PAHX) giving rise to adult Refsum’s disease. PAHX is a member of the 2-oxoglutarate- and non-haem ferrous-dependent oxygenase family. The effects of mutations are based on primary sequence alignments, secondary structure predictions and known motifs from the crystal structures of other oxygenases (modified from Mukherji et al. 2001a). X = frameshift mutations leading to truncated PAHX. Uncoupling indicates that 2-oxoglutarate conversion does not always lead to phytanoyl-CoA oxidation.

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acid levels but gross pristanic acidaemia, also favours this hypothesis (Ferdinandusse et al. 2000).

No PAHX-deficient animal model has been produced to date. However, a clinical phenotype broadly similar to human ARD can be generated in mice by the deletion of the SCP-2 gene (Seedorf et al. 2000). These mice develop ataxia when fed diets rich in phytanic acid and are prone to die in utero of cardiac arrhythmias. However, they seem to lack the ocular features of ARD, which would be expected if the pathway was inducible by phytanic acid (Zomer et al. 2000a). Their biochemical phenotype includes elevations in both phytanic and pristanic acid and possibly subtle defects in steroid hormone synthesis (Ellinghaus et al. 1999). In man, the SCP-2 gene is located on chromosome 2 and mapping has excluded this region as a candidate area for ARD (Wierzbicki AS, unpublished data).

Unanswered questions

The exact mechanism of the toxicity of phytanic acid to neuronal, cardiac and bone tissue remains obscure. Some studies have indicated that it is directly toxic to ciliary ganglion cells and induces calcium-driven apoptosis in Purkinje cells (Powers et al. 1999). Structural homology between phytanic acid and vitamin A (11-cis-retinol), vitamin E (β-tocopherol), geranyl-pyrophosphate (GPP) and farnesyl pyrophosphate (FPP) has been noted (Wanders et al. 2001), but little work has been completed to investigate whether they are metabolized via the β-oxidation pathway. Phytanic acid may also have a role in the regulation of isoprenoid metabolism and protein prenylation, if it does compete for receptor binding with other isoprenoids of similar structure. Reduction of intracellular levels of the isoprenoids FPP and GPP is a key non-lipid lowering action of cholesterol-lowering drugs: the statins (HMG-CoA reductase inhibitors), which are used to treat atherosclerosis (Torra et al. 2001). The effects of phytanic acid on isoprenoid levels has not been investigated though cholesterol, and phytic acid transport and metabolism are closely linked.

Whether the neurological and ophthalmological symptoms of ARD are directly caused by the toxic effects of the phytanic acid itself, or by the dysfunction of calcineurin or isoprenoid-controlled metabolism, remains to be determined. LCFA-CoA synthetase is promiscuous with regard to substrates and non-heme oxygenases are often able to oxidize alternative substrates. Thus, the possibility exists that the β-oxidation pathway may be involved in the degradation of many branched-chain lipids, of which phytic acid is only one.

The identity of the other genes involved in producing the ARD phenotype is becoming clearer with the identification of a second locus for Refsum’s disease (Wierzbicki et al. 2000b) and the identification of substantial phenotypic heterogeneity in RCDP (van den Brink et al. 2001). Although the 2-hydroxyphytanoyl-CoA lyase gene has been recently cloned, no mutations in it have yet been identified and there is no record of any patient with excess 2-hydroxyphytanic acid in plasma. The clinical phenotype of lyase deficiency would be predicted to share many features with RCDP and ARD.

Long-term prospects for treatment (at least some forms) of ARD are good as it is one of the few inherited disorders of metabolism with an exogenous precipitating cause, and an in vivo gene therapy approach has been successful in restoring enzyme activity (Chahal et al. 1998). Reduction of dietary phytanic acid is already successful in ameliorating some symptoms, but newer more efficacious therapies are still required to fully reverse the progression of this disease.

The wider significance of phytanic acid metabolism

Refsum’s disease and associated disorders would be considered biochemical curiosities with little wider relevance to human disease if it were not for the fact that phytanic acid seems to play a key role in the regulation of peroxisomal number and activity. PPARs are involved in the regulation of lipid and glucose metabolism, obesity, inflammation, atherosclerosis and carcinogenesis, whereas peroxisomal enzyme deficiencies are clearly associated with neurological disease (Torra et al. 2001). Phytanic acid in rodents is a ligand for the PPAR-α receptor (Ellinghaus et al. 1999; Gelman et al. 1999), which is the target for the fibrate groups of drugs (Staels et al. 1998). However, differences in sterol metabolism between humans and mice suggest that the intracellular role of phytanic acid may differ substantially between rodents and man. In rodents, phytanic acid regulates nuclear retinoid-X receptors (RXR) (Kitareewan et al. 1996; Lemotte et al. 1996; Seedorf et al. 1998), PPAR-α (Ellinghaus et al. 1999), and the expression of liver fatty acid binding protein (Wolfrum et al. 1999). This suggests that phytanic acid may be the natural ligand for the ‘orphan’ PPAR-α receptor in rodents and that the β-oxidation pathway is the mechanism for inactivating this signal. However, in human cell lines phytic acid regulates PAHX expression independently of its effects on PPAR-α or RXR (Zomer et al. 2000b). This implies that an alternative pathway exists in man to control the metabolism of isoprenoid lipids, and that other lipids may be the principal PPAR-α ligands in humans. The differences in the regulatory functions may also explain the differences in presentation between the SCP-2(-) mouse and human ARD or AMACR deficiency, and the relatively slow onset of the major clinical features in man compared with mouse. Additionally the possible non-peroxisomal roles of PAHX in regulation of tacrolimus binding-proteins and in the control of the levels of clotting factor VIII imply this enzyme may have other unidentified roles in metabolism (Chambrad et al. 1999; Chen et al. 2001).

The role of phytanic acid metabolism in common human neurodegenerative diseases remains to be determined.
However, the close relationship of peroxisomes to neurological disease and lipid metabolism to stroke, vascular dementia, and Alzheimer's disease, mean that it is likely to be significant.

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