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Research article

"Role of peroxisomes in human lipid metabolism and its importance for neurological development"

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ABSTRACT

Peroxisomes play a crucial role in normal neurological development as exemplified by the devastating neurological consequences of a defect in the biogenesis of peroxisomes as in Zellweger syndrome. The underlying basis for the important role of peroxisomes in neurological development resides in the fact that peroxisomes catalyze a number of physiological functions, notably involving the metabolism of different lipids. Indeed, peroxisomes catalyse the beta-oxidative breakdown of certain fatty acids including: (1.) the very long-chain fatty acids C22:0, C24:0, and C26:0; (2.) pristanic acid and (3.) the bile acid intermediates di- and trihydroxycholestanoic acid which cannot be oxidized in mitochondria. Furthermore, peroxisomes catalyze the synthesis of a particular type of lipids, i.e. ether-linked phospholipids, which are highly abundant in brain, especially in myelin. The current state of knowledge with respect to the metabolic role of peroxisomes will be described in this paper with particular emphasis on the role of peroxisomes in brain.

1. Introduction

Peroxisomes are subcellular organelles present in virtually all eukaryotic cells except the mature erythrocyte. Although long underrated as organelles of doubtful physiological significance, studies over the last three decades have shown that peroxisomes are in fact indispensable organelles which catalyze a range of different metabolic functions unique to this organelle. The importance of peroxisomes for human health and development is immediately clear if it is realized that a genetic defect in the biogenesis of peroxisomes which results in the absence of morphologically identifiable peroxisomes in cells, has severe consequences for human health as exemplified by the devastating clinical signs and symptoms observed in the cerebro-hepato-renal syndrome, better known as Zellweger syndrome (ZS). Indeed, ZS patients manifest a wide range of abnormalities affecting multiple tissues which include developmental defects, cranial facial dysmorphia, psychomotor delay, seizures, retinopathy, cataracts, impaired hearing, hepatomegaly, renal cysts, adrenal insufficiency and skeletal aberrations. The neurological and developmental abnormalities are pronounced and include impaired neuronal migration, affecting the cerebral hemispheres, cerebellum and inferior olivary complex, abnormal Purkinje cell arborisation and white matter abnormalities [1].

With respect to the metabolic functions of peroxisomes in humans, it all started with the discovery of Brown et al. [2] which revealed greatly increased levels of certain fatty acids (FAs), notably the very long-chain fatty acids (VLCFAs) tetracosanoic acid (C24:0) and hexacosanoic acid (C26:0), in plasma from ZS patients whereas the levels of long-chain FAs, including oleate and palmitate, were normal. This suggested that oxidation of VLCFAs required the active participation of peroxisomes. At that time, peroxisomes were already known to contain a fatty acid beta-oxidation machinery. Until then, however, the general notion was that peroxisomal beta-oxidation was just an auxiliary system assisting mitochondrial beta-oxidation in times of fatty acid overload [3]. The seminal observation by Brown et al. [2] was soon followed by subsequent reports documenting the accumulation of additional FAs in plasma from Zellweger patients including pristanic acid (2,6,10,14-tetramethylpentadecanoic acid) which turned out to be an exclusive substrate for peroxisomal beta-oxidation [4]. Furthermore, the identification by Hanson et al. [5] of increased levels of the bile acid intermediates di- and trihydroxycholestanoic acid (DHCA and THCA) in plasma from ZS patients which were originally thought to be due to the mitochondrial abnormalities in ZS,

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could now be reinterpreted and properly assigned to the direct involvement of peroxisomes in the degradation of these bile acid intermediates. Indeed, work by Pedersen and co-workers (see [6] for review) has shown that the beta-oxidative cleavage of di- and trihydroxycholestanoic acid to generate chenodeoxycholic acid and cholic acid, respectively, occurs solely in peroxisomes.

Parallel to the work done by Moser et al., Heymans et al. reported the deficiency of plasmalogens in 1983, which indicated that peroxisomes also play a key role in the formation of etherphospholipids [7]. Similarly, the discovery that peroxisomes also catalyze the alpha-oxidation of fatty acids was based on the finding of greatly increased levels of phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) in plasma from Zellweger patients [8]. Apart from the role of peroxisomes in lipid metabolism, including etherphospholipid biosynthesis, fatty acid alpha-oxidation and fatty acid beta-oxidation as reviewed in more detail below, peroxisomes also play a role in several non-lipid metabolic pathways not described here. Below, we will briefly describe the major metabolic pathways in peroxisomes related to lipid metabolism followed by description of the human disorders in which peroxisomal lipid metabolism is impaired.

1.1. Peroxisomal fatty acid beta-oxidation

Isolated peroxisomes can handle a large variety of fatty acids for beta-oxidation including saturated FAs, mono- and poly-unsaturated FAs, 2- and 3-methyl branched-chain FAs, hydroxylated FAs notably 2-hydroxy-FAs, dicarboxylic FAs and others (see [9] for review). There are only a few fatty acid substrates which can be beta-oxidized by peroxisomes only. These include: (1.) the very long-chain fatty acids, notably C22:0, C24:0 and C26:0; (2.) the 2-methyl branched-chain FA pristanic acid (2,6,10,14-tetramethylpentadecanoic acid); (3.) di- and trihydroxycholestanoic acid; (4.) the poly-unsaturated FA tetracosahexaenoic acid (C24:6n-3); (5.) long-chain dicarboxylic acids; (6.) 2-hydroxy-FAs, and (7.) a number of prostanoids. The prostanoids that are currently known to require peroxisomal beta-oxidation for side-chain cleavage include PGF2-alpha [10], 8-iso-PGF2-alpha [11], thromboxane-B2 [12,13], monohydroxy-eicosatrienoic acid (12-HETE, 15-HETE) [14], leukotriene-B4 [15,16], and the cysteinyl leukotriene LTE4 [17] (see [18] for review). In this way prostanoids are inactivated by cleavage of their carboxy-side chains.

The general theme of peroxisomal beta-oxidation is that peroxisomes perform one or more cycles of beta-oxidation and release the products to the cytosol for subsequent metabolism. In some cases peroxisomes catalyse a single cycle of beta-oxidation. This is true for the bile acid intermediates di- and trihydroxycholestanoic acid which undergo a single cycle of beta-oxidation generating cholic acid and chenodeoxycholic acid in their CoA-ester form. For most other FAs, including the VLCFAs C22:0, C24:0 and C26:0, the number of cycles of beta-oxidation in peroxisomes remains to be established definitively, although the general notion is that beta-oxidation in peroxisomes continues until a C8- or C6-medium-chain acyl-CoA has been generated. Exceptions to this rule are: (1.) pristanic acid which undergoes three cycles of beta-oxidation in peroxisomes to produce one unit of acetyl-CoA, two propionyl-CoA units plus 4,8-dimethylnonanoyl-CoA [19], and (2.) some of the prostanoids like PGF2-alpha and 8-iso-PGF2-alpha which undergo one or two cycles of beta-oxidation to produce the corresponding dinor and/or tetranor compounds.

In humans, the four steps of peroxisomal beta-oxidation are catalysed by two different acyl-CoA oxidases, two distinct bifunctional proteins and two different thiolases. The physiological roles of the two acyl-CoA oxidases, and to a lesser extent for the two bifunctional proteins and two thiolases has been resolved in recent years. The identification of patients with acyl-CoA oxidase 1 (ACOX1) deficiency already in 1988 [20] in whom there was only accumulation of very long-chain fatty acids but not of pristanic acid and di- and trihydroxycholestanoic acid, indicated that there had to be a different oxidase with specificity for 2-methyl branched-chain acyl-CoAs. This enzyme was identified, purified and cloned a few years later by Vanhove et al. [21]. Although so far no patients with a deficiency of branched-chain acyl-CoA oxidase (ACOX2) have been described and no mouse model with branched-chain acyl-CoA oxidase deficiency has been generated, the generally accepted view is that ACOX1 is the principal enzyme handling saturated acyl-CoAs including C22:0-CoA, C24:0-CoA, and C26:0-CoA whereas ACOX2 is the prime oxidase dehydrogenating pristanoyl-CoA and di- and trihydroxycholestanoyL-CoA. It should be mentioned that there is also a third peroxisomal oxidase with high specificity for pristanoyl-CoA which is highly expressed in rat liver but not in human liver. Interestingly, it has been shown that ACOX3 mRNA expression is upregulated in prostate and breast cancer [22]. With respect to the two bifunctional proteins which have different names ranging from multifunctional proteins-1 and 2 (MFP1 and MFP2), multifunctional enzymes-1 and -2 (MFE-1 and MFE-2) and the L- and D-bifunctional proteins (LBP and DBP), it is clear that the D-specific enzyme plays an obligatory role in the beta-oxidation of very long-chain fatty acids, pristanic acid and the bile acid intermediates. This is concluded from studies in patients suffering from D-bifunctional protein deficiency [23,24] and DBP-deficient mice [25]. Recent work from our laboratory has shown that the L-specific enzyme is the major enzyme involved in the beta-oxidation of long-chain dicarboxylic acids [26]. Earlier work in peroxisome-deficient fibroblasts had already shown that oxidation of long-chain dicarboxylic acids is primary peroxisomal [27]. Finally, with respect to the two thiolases in human peroxisomes, the physiological role of the branched-chain specific thiolase has been elucidated again as a corollary of the identification of a human deficiency of this enzyme [28] and a mutant mouse model generated by Seedorf et al. [29]. The thiolase involved is called sterol carrier protein X (SCPx) because it also contains a sterol-carrier-binding unit, and is able to cleave the 3-keto-acyl-CoA esters of pristanic acid and di- and trihydroxycholestanoic acid. SCPx thus plays a central role in the beta-oxidation of these FAs. Straight-chain FAs are handled both by SCPx and the other peroxisomal thiolase, called 3-ketoacyl-CoA thiolase [9].

For the beta-oxidation of mono- and poly-unsaturated FAs auxiliary enzymes are required, which include different isomerases and di-enoyl-CoA reductases [9,18]. In contrast to the detailed knowledge about the enzymes of the peroxisomal beta-oxidation machinery itself less information is available on the identity and catalytic properties of the latter enzymes.

1.2. Etherphospholipid biosynthesis

Peroxisomes play a crucial role in the synthesis of etherphospholipids since the first part of the biosynthetic pathway is solely peroxisomal. This includes the enzyme alkyldihydroxyacetone phosphate synthase (ADHAPS) encoded by *AGPS* which is responsible for the generation of the characteristic ether-bond. The two substrates required in the ADHAPS enzyme reaction, i.e. a long-chain alcohol and acyldihydroxyacetone phosphate (acyl-DHAP) are also synthesized by peroxisomes via the enzymes acyl-CoA: NADPH oxidoreductase and dihydroxyacetone phosphate acyltransferase (DHAPAT), respectively. DHAPAT and ADHAPS form a complex bound to the inner face of the peroxisomal membrane [30]. The end products of the ADHAPS reaction, i.e. alkyl-DHAP is converted into alkylglycerol-3-phosphate (alkylG3P) either within peroxisomes or at the ER membrane [31]. All the subsequent steps