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Review

Peroxisomes, lipid metabolism and lipotoxicity

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ABSTRACT

Peroxisomes play an essential role in cellular lipid metabolism as exemplified by the existence of a number of genetic diseases in humans caused by the impaired function of one of the peroxisomal enzymes involved in lipid metabolism. Key pathways in which peroxisomes are involved include: (1.) fatty acid beta-oxidation; (2.) etherphospholipid biosynthesis, and (3.) fatty acid alpha-oxidation. In this paper we will describe these different pathways in some detail and will provide an overview of peroxisomal disorders of metabolism and in addition discuss the toxicity of the intermediates of peroxisomal metabolism as they accumulate in the different peroxisomal deficiencies.

1. Introduction

Although originally underrated as organelles of relatively little physiological significance, peroxisomes are now known to play a crucial role in human physiology. The best evidence in support of this conclusion comes from the fact that a genetically determined inability to synthesize peroxisomes gives rise to severe clinical abnormalities with multiple aberrations and early death. Indeed, patients suffering from the cerebro-hepato-renal syndrome of Zellweger (in short: Zellweger syndrome), show a wide range of abnormalities, including neurological, craniofacial, ocular, hepatological and other aberrations. Zellweger patients lack peroxisomes in all body cells leading to a generalized loss of peroxisomal functions.

The first evidence that peroxisomes are involved in lipid metabolism came in the early 1980s when two key observations were published. The first paper documented the accumulation of very-long-chain fatty acids (VLCFA) in plasma from Zellweger patients [1], whereas in the second publication the complete deficiency of plasmalogens in tissues of Zellweger patients was described [2]. Soon after these seminal papers by Brown et al. [1] and Heijmans et al. [2], Poulos et al. [3] reported the accumulation of phytanic acid in plasma from Zellweger patients. Phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) is a branched-chain fatty acid, which because of the presence of a methyl-group at the 3-position cannot be beta-oxidized and instead undergoes one cycle of alpha-oxidation. The finding that phytanic acid accumulates in Zellweger patients [3], was the first indication pointing to a key role of peroxisomes in fatty acid (FA) alpha-oxidation. In this paper, we will 1) describe the peroxisomal lipid pathways in some detail, 2) give an overview of peroxisomal disorders of lipid metabolism and 3) focus on the toxicity of the intermediates of peroxisomal lipid metabolism as they accumulate in the different peroxisomal deficiencies.

1.1. Peroxisomal fatty acid beta-oxidation

At present, three different types of fatty acids are known to rely fully on peroxisomes for beta-oxidation. These include: (1.) VLCFA like C24:0, and C26:0; (2.) the 2-methyl branched-chain fatty acid pristanic acid (2,6,10,14-tetramethylpentadecanoic acid), and (3.) the bile acid synthesis intermediates dihydroxycholestanoic acid (DHCA) and trihydroxycholestanoic acid (THCA). In addition to these exclusive peroxisomal substrates, there are other fatty acids, which can be beta-oxidized in both mitochondria and peroxisomes, whereas some fatty acids can only be oxidized in mitochondria, including short-chain fatty acids and 4,8-dimethylnonanoic acid, an intermediate in pristanic acid beta-oxidation [4].

Peroxisomes contain the full enzymatic machinery to beta-oxidize fatty acids, although oxidation does not go to completion. This has

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most firmly been established for pristanic acid, which undergoes three cycles of beta-oxidation in peroxisomes [5] to produce propionyl-CoA (2×), acetyl-CoA and 4,8-dimethylnonanoyl-CoA. Subsequently, 4,8-dimethylnonanoyl-CoA is transported out of peroxisomes to the mitochondria for full oxidation to CO_2 and H_2O (Fig. 1). In principle there are two mechanisms by which these end products of peroxisomal pristanic acid beta-oxidation can be shuttled to mitochondria. The first mechanism involves 4 steps: 1) hydrolysis of the different CoA-esters to produce propionic acid, acetic acid, and 4,8-dimethylnonanoic acid, 2) transfer across the peroxisomal and mitochondrial membrane probably in protonated form, 3) activation to the corresponding CoA-esters in the mitochondrion, and 4) further oxidation. The second mechanism involves 1) conversion of the CoA-esters into their corresponding carnitine-esters within peroxisomes, 2) transfer across the peroxisomal membrane, probably via a yet unidentified carrier, and 3) import into to mitochondrial matrix. This final step is mediated by the mitochondrial carnitine/acylcarnitine carrier (CACT), as demonstrated convincingly in yeast [6] and human fibroblasts [7]. Once inside the mitochondrion the carnitine-esters can be reconverted into the CoA-esters, which can then undergo further oxidation. For VLCFA like C26:0, it has not been established definitively how many cycles of beta-oxidation take place in the peroxisome (Fig. 1).

In liver, the bile acid intermediates DHCA and THCA only undergo one cycle of beta-oxidation in peroxisomes, with choloyl-CoA and chenodeoxycholoyl-CoA as end products, respectively. These two CoA-esters are then conjugated with either taurine or glycine within peroxisomes (Fig. 1). Subsequently, the taurine- and glycine-esters are transported out of the peroxisome into the cytosolic space, followed by transport across the canalicular membrane via the bile salt efflux pump, i.e. BSEP (ABCB11), to end up in bile [8,9].

In general, the architecture of the peroxisomal beta-oxidation system is comparable to that of mitochondria and consists of subsequent steps of: dehydrogenation, hydration, dehydrogenation again and thiolytic cleavage (Fig. 2). In mitochondria the first step in beta-oxidation is catalyzed by acyl-CoA dehydrogenases (ACADs), which are flavoproteins. They are directly coupled to the mitochondrial respiratory chain via the ETF/ETF-dehydrogenase system so that the electrons, coming from the ACADs in their reduced form ultimately enter the respiratory chain at the level of coenzyme Q. In contrast, in peroxisomes the first step is catalyzed by acyl-CoA oxidases (ACOX) which are also flavoproteins. These enzymes, however, interact directly with molecular oxygen generating H_2O_2 as product. In humans at least, there are two acyl-CoA oxidases (ACOX1 and ACOX2) (Fig. 2). ACOX1 is specific for VLCFA-CoA, whereas ACOX2 preferentially reacts with the CoA-esters of 2-methyl branched-chain fatty acids, including pristanoyl-CoA and DHC-CoA and THC-CoA [10]. The next two steps in peroxisomal beta-oxidation are catalyzed by one of two so-called *bifunctional proteins* harboring two separate enzymatic functions: enoyl-CoA hydratase and 3-hydroxy-acyl-CoA dehydrogenase activity. Interestingly, the first of these two bifunctional proteins, named L-bifunctional protein (LBP: alternatively called MFP-1 or MFE-1) generates 3-ketoacyl-CoAs via an L-3-OH-acyl-CoA intermediate, whereas the other bifunctional protein, named D-bifunctional protein (DBP: alternative name: MFP-2, or MFE-2) has a D-3-OH-acyl-CoA-ester as intermediate. Both in humans [11] and mice [12], DBP has been demonstrated to be the dominant enzyme involved in the oxidation of VLCFA, pristanic acid, as well as DHCA and THCA [13]. Indeed, in case of D-bifunctional protein deficiency in man, the oxidation of both VLCFA, pristanic acid, and the bile acid intermediates is deficient [11], whereas loss of LBP function in the LBP knockout mouse does not affect oxidation of these fatty acids [14] (Table 1).

Finally, human peroxisomes contain two thiolases (Fig. 2). These include a straight-chain 3-oxoacyl-CoA thiolase (ACAA1) and sterol carrier protein X (SCPx), the 58 kDa protein with thiolase activity [15]. SCPx is reactive with the 3-keto-acyl-CoA-esters of pristanic acid and DHCA and THCA, whereas ACAA1 only accepts the 3-keto-acyl-CoA-esters of VLCFA [15]. The importance of SCPx is emphasized by the existence of SCPx deficiency in humans, as described later [16].

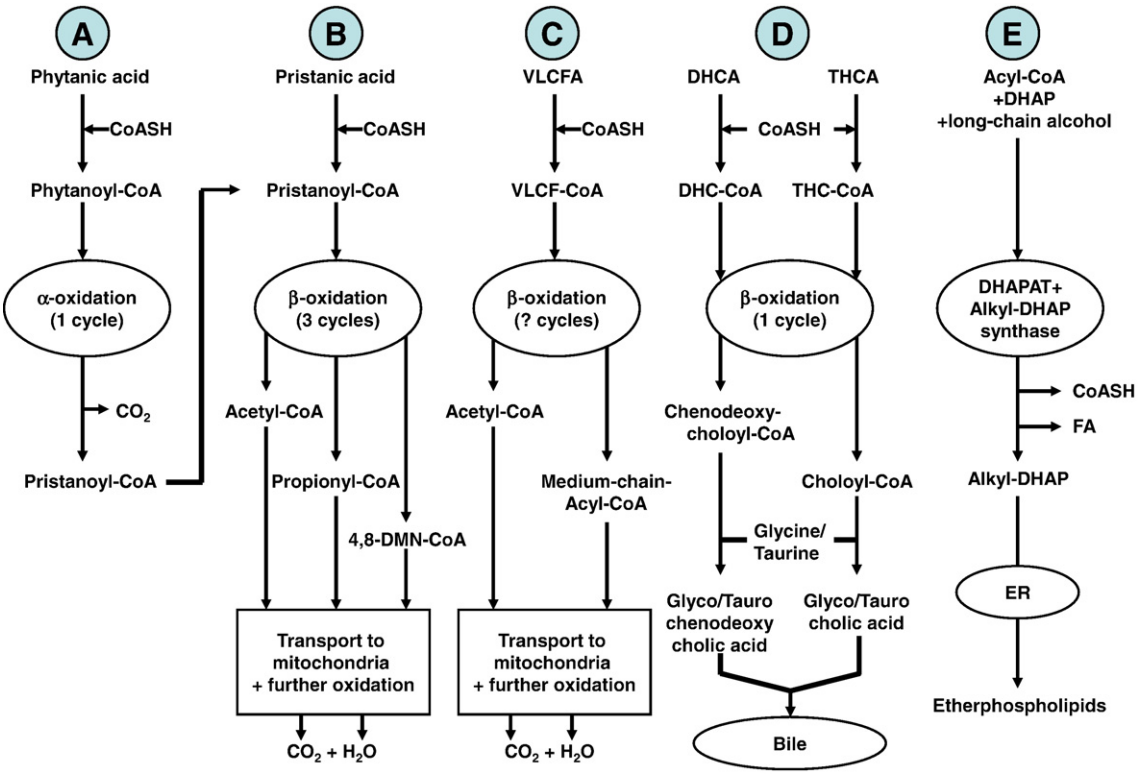

Fig. 1. A schematic representation of the pathways of lipid metabolism in peroxisomes.