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Mini-review

# Metabolic functions of peroxisomes in health and disease

Ronald J.A. Wanders*

*University of Amsterdam, Academic Medical Center, Departments of Clinical Chemistry and Pediatrics, Emma Children's Hospital, Laboratory Genetic Metabolic Diseases, Room F0-226, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

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ABSTRACT

Peroxisomes are subcellular organelles which are present in virtually every eukaryotic cell and catalyze a large number of metabolic functions. The importance of peroxisomes for humans is stressed by the existence of a large group of genetic diseases in which either the biogenesis of peroxisomes is impaired or one of its metabolic functions. Thanks to the work on Zellweger syndrome which is the prototype of the group of peroxisomal disorders, much has been learned about the metabolism and biogenesis of peroxisomes in humans. These metabolic functions include: (1.) fatty acid beta-oxidation; (2.) ether-phospholipid biosynthesis; (3.) fatty acid alpha-oxidation, and (4.) glyoxylate detoxification. Since peroxisomes lack a citric acid cycle and a respiratory chain, peroxisomes are relatively helpless organelles which rely heavily on their cross-talk with other subcellular organelles in order to metabolize the end products of metabolism as generated in peroxisomes. The metabolic functions of peroxisomes in humans will be briefly described in this review with emphasis on the cross-talk with other subcellular organelles as well as the peroxisomal disorders in which one or more peroxisomal functions are impaired.



## 1. Introduction

Peroxisomes are subcellular organelles bounded by a single membrane, which are present in all major groups of eukaryotes, and involved in a variety of physiological processes which differ among species. Following their morphological identification by Rhodin in 1954 [1] during his thesis work on proximal tubule cells from mouse kidney, peroxisomes were first isolated and characterized biochemically by De Duve and coworkers [2] using differential and density gradient centrifugation techniques. The identification of several enzymes producing hydrogen peroxide together with catalase in this newly identified organelle prompted De Duve to introduce the name "*peroxisome*". In subsequent years peroxisomes have been isolated from different organisms which has revealed that the enzymatic properties of peroxisomes may vary among organisms and even between organs from the same organism. The metabolic pathway which is virtually ubiquitous among all species, is the beta-oxidation of fatty acids. Other metabolic pathways may only be present in peroxisomes from some species. This is true for the glycolytic pathway which is only present in peroxisomes from kinetoplastids including the trypanosomatids of the genera *Trypanosoma* and *Leishmania*. Interestingly, in general these peroxisomes appear to lack catalase.

The diversity in enzymatic properties of peroxisomes has long created confusion with respect to the question whether organelles like glycosomes and glyoxysomes belong to the peroxisome family. This issue was only resolved when the principal features of peroxisome biogenesis were beginning to be identified which includes the discovery of the first peroxisome targeting signal made up of a set of three amino acids at the carboxy terminal end of peroxisomal proteins [3].

The identification of the proteins required for the biosynthesis of peroxisomes (*peroxins*) and the corresponding genes, has also contributed greatly to our current understanding of the evolutionary origin of peroxisomes. Initially, peroxisomes were thought to have an endosymbiont origin just like mitochondria do. This concept have changed drastically and current evidence holds that peroxisomes are ER-derived organelles of the endomembrane system (for review see Refs. [4–6]).

Elucidation of the metabolic role of peroxisomes in humans is tightly coupled to research on a rare genetic disease called Zellweger syndrome (ZS) in which morphologically identifiable peroxisomes were shown to be absent by Goldfischer and co-workers, already in 1973 [7]. It took until the early 1980s when two key observations were published providing convincing evidence for a key role of peroxisomes in metabolism. The first clue came from work from Moser and co-workers [8], who discovered the accumulation of very long-chain fatty acids, but not long-chain fatty acids in plasma and tissues from Zellweger patients. Secondly, we

* Tel.: +31 (0)20 5665958/5664197; fax: +31 (0)20 6962596.
*E-mail address:* r.j.wanders@amc.uva.nl.

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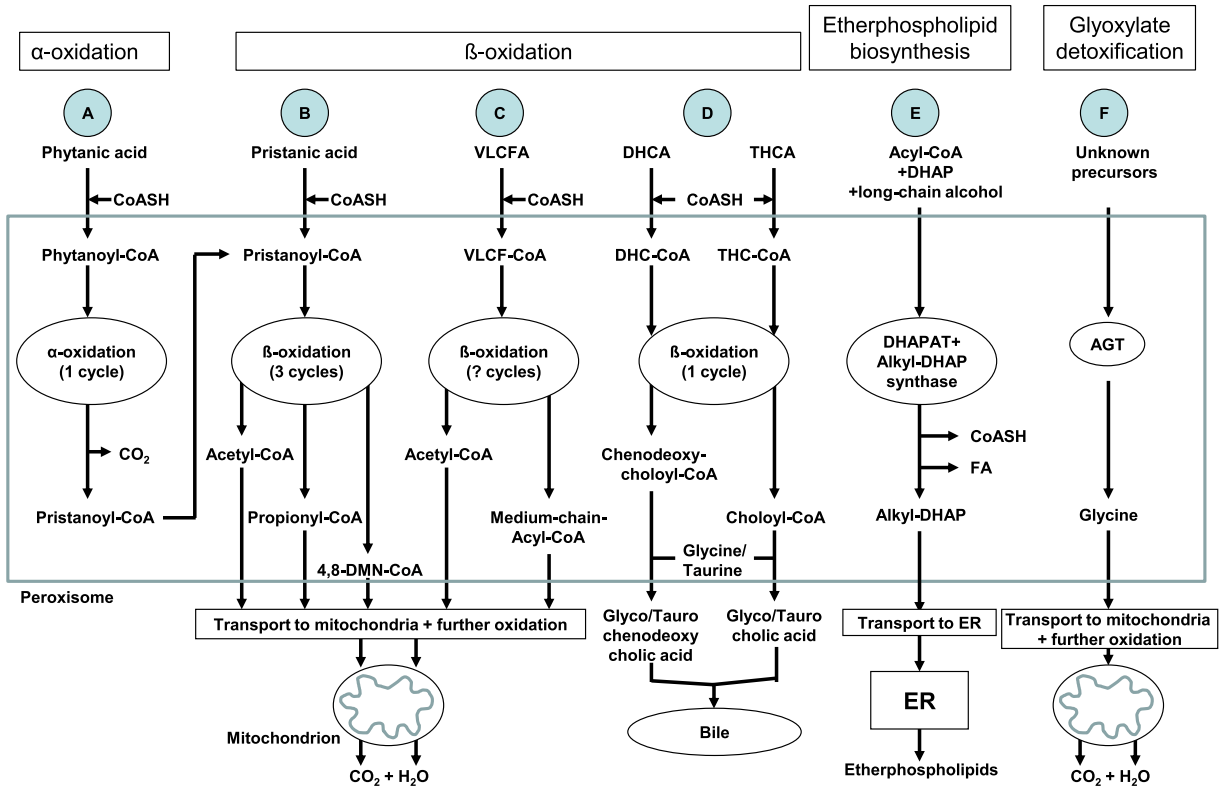


**Fig. 1.** Metabolic functions of peroxisomes in humans and the cross-talk between peroxisomes and other subcellular organelles, notably mitochondria and the endoplasmic reticulum. See text for background information. Abbreviations used: 4,8-DMN-CoA = 4,8-dimethylnonanoyl-CoA; ER = endoplasmic reticulum; AGT = alanine glyoxylate aminotransferase.

in Amsterdam discovered the deficiency of a specific class of phospholipids, called plasmalogens, in tissues and erythrocytes from Zellweger patients [9]. These two findings prompted a renewed interest in peroxisomes and have set the stage for detailed studies, aimed to resolve the metabolic functions and biogenesis of peroxisomes. In this review we will discuss the current state of knowledge with respect to the metabolic functions of peroxisomes and their cross-talk with other organelles, notably mitochondria and the endoplasmic reticulum (ER).

## 2. Metabolic functions of peroxisomes

Peroxisomes catalyze a number of essential metabolic functions. Below we will review the current state of knowledge with respect to metabolic functions as relevant for human disease.

(1). Peroxisomal fatty acid beta-oxidation

Isolated peroxisomes are able to catalyze the beta-oxidation of a large range of different fatty acids including medium and long-chain fatty acids. Nevertheless, under normal conditions oxidation of medium and long-chain fatty acids is primarily handled by the mitochondrial beta-oxidation system and there is only little contribution from the peroxisomal system. On the other hand a number of metabolites have been identified whose oxidation is strictly dependent upon the activity of the peroxisomal beta-oxidation system. These include:

- *Very long-chain fatty acids (VLCFAs)*: it is generally agreed that certain VLCFAs, including C22:0, C24:0 and C26:0 can only be oxidized in peroxisomes and not in mitochondria. At least one reason for this phenomenon is that these VLCFAs are no substrates for carnitine palmitoyltransferase 1 (CPT1) which essentially eliminates their entry into mitochondria. Since peroxisomes lack a citric acid cycle and respiratory chain, the end products of beta-oxidation in peroxisomes which include acetyl-CoA, propionyl-CoA and other acyl-CoAs, but also NADH, need to be shuttled from peroxisomes to mitochondria for full oxidation to $CO_2$ and $H_2O$ in case of acetyl-CoA, propionyl-CoA and the other acyl-CoAs and reoxidation of NADH back to $NAD^+$ (see Fig. 1). This will be discussed later in this review.
- *Pristanic acid (2,6,10,14-tetramethylpentadecanoic acid)*: this FA is primarily derived from phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) after one round of alpha-oxidation but is also derived directly from dietary sources. Work by Verhoeven et al. [10] has shown that pristanic acid undergoes three rounds of beta-oxidation in peroxisomes to produce 4,8-dimethylnonanoyl-CoA plus two units of propionyl-CoA and one unit of acetyl-CoA which are transported from the peroxisome as carnitine ester or in their free acid form followed by uptake into mitochondria for full oxidation to $CO_2$ and $H_2O$ [10] (see Fig. 1).
- *Di and trihydroxycholestanoic acid (DHCA and THCA)*: these FAs are produced from cholesterol in the liver and are the immediate precursors of the primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA). Formation of CA and CDCA first involves formation of the CoA esters of DHCA and THCA at the endoplasmic reticulum membrane after which the CoA esters enter the peroxisome, possibly mediated by the peroxisomal half-ABC transporter PMP70, to undergo beta-oxidation in peroxisomes to produce choloyl-CoA and chenodeoxycholoyl-CoA. Peroxisomes also contain an enzyme named BAAT (bile acid-CoA: amino acid N-acyltransferase) which can convert the CoA esters of CA and CDCA into the taurine and glycine

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