Peroxisomal β-Oxidation Enzymes*

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The enzymes involved in β-oxidation spiral are schematically classified into two groups. The first group consists of palmitoyl-CoA oxidase, the L-bifunctional protein, which has been called as the bifunctional protein, and 3-ketoacyl-CoA thiolase. The second group consists of the newly confirmed enzymes, branched chain oxidase, the D-bifunctional protein, and sterol carrier protein x. The enzymes of the first group are inducible and act on the straight chain acyl-CoA substrates. But the enzymes of the second group are non-inducible and act on branched chain acyl-CoAs. Accordingly, bile acid formation and oxidation of pristanic acid derived from phytol are catalyzed by the enzymes of the second group but not by those of the first group. The functions of the peroxisomal system and methods of analysis of the enzymes are briefly summarized.

KEY WORDS: β-oxidation; fatty acids; bile acids; peroxisomes; mitochondria.

INTRODUCTION

The β-oxidation hypothesis for fatty acid oxidation was proposed early in this century. Enzymological studies were begun in the 1950’s, when the structure of coenzyme A was elucidated, and intracellular localization of this metabolic system in mitochondria was shown. The presence of a fatty acid β-oxidation system outside the mitochondrial compartment was first noted in glyoxysomes in germinating castor bean seeds in 1969. Very similar system to the glyoxysomal one was found in rat liver peroxisomes by Lazarow and de Duve in 1976 (1). This finding attracted attention because a complete metabolic sequence was found in peroxisomes of higher animals. It is now clear that, in animals, both the mitochondrial and peroxisomal fatty acid oxidation systems are present in the same cell and these two important systems play functionally different roles.

The peroxisomal system consists of unique enzymes differing from the mitochondrial enzymes. Specialties of the peroxisomal and mitochondrial systems are established by the studies on the peroxisomal and mitochondrial fatty acid oxidation defects. The mitochondrial fatty acid oxidation is one of the main energy-yielding processes. The peroxisomal system oxidizes not only long-chain fatty acids but also very-long-chain fatty acids, eicosanoids, pristanic acid, bile acid intermediates, and side-chains of xenobiotics which are not metabolized by mitochondria.

It is believed that almost all of the cells in humans, except erythrocytes, have peroxisomes and peroxisomal fatty acid oxidation system. But, it is not yet confirmed whether all of the cells have all of the peroxisomal fatty acid oxidation enzymes described below at similar ratios and oxidize various substances described above, or that cells are different in the peroxisomal oxidation function due to cell-specific expression of the enzymes.

Outline of Peroxisomal and Mitochondrial Fatty Acid Oxidation Systems

As shown in Fig. 1, the chemical changes of fatty acid moieties in the two β-oxidation systems are the
In mitochondria, long-chain fatty acids are activated by long-chain acyl-CoA synthetase on the mitochondrial outer membrane and acyl groups of the CoA esters are transported into the matrix by the carnitine palmitoyltransferase/carnitine translocase system located in the inner membrane, which are then oxidized by the \( \beta \)-oxidation cycle. Therefore, oxidation of long-chain fatty acids is carnitine-dependent. But, oxidation of medium-chain fatty acids is carnitine-independent, since these fatty acids are imported into the mitochondrial matrix, activated by another activation enzyme, and then oxidized.

The mitochondrial \( \beta \)-oxidation cycle consists of four reactions. Long-chain fatty acyl-CoAs are first oxidized by the two new inner membrane-associated enzymes: one is a very-long-chain acyl-CoA dehydrogenase (2) and the other is enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase trifunctional protein (3). The resulting carbon-chain shortened fatty acyl-CoAs are then completely oxidized by the well-known classical enzymes: long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases, enoyl-CoA hydratase (or crotonase), 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase.

In peroxisomes, fatty acids are activated by acyl-CoA synthetase on the peroxisomal membrane (4–6). Peroxisomes have both long-chain and very-long-chain acyl-CoA synthetases. Carnitine octanoyltransferase is present in the peroxisomal matrix (7), but its role is obscure because the peroxisomal fatty acid oxidation is independent of carnitine (4,8).

Three enzymes of the peroxisomal \( \beta \)-oxidation cycle were first purified around 1980: palmitoyl-CoA oxidase, enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase bifunctional protein (L-bifunctional protein; this abbreviation is explained below), and 3-ketoacyl-CoA thiolase (see Ref. 9–12). Recently, the presence of other enzymes involved in the peroxisomal fatty acid oxidation has been revealed. Other oxidases named as pristanoyl-CoA oxidase and trihydroxycoprostanoyl-CoA oxidase (13,14) react on 2-methyl-branched fatty acyl-CoA and the precursors of bile acid formation. A new bifunctional enzyme catalyzing the second and third reactions was found. The names of the L- and D-bifunctional proteins are used for the old and new en-