The Inborn Errors of Peroxisomal \(\beta\)-Oxidation: A Review

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Summary: In recent years a growing number of inherited diseases in man have been recognized in which there is an impairment in peroxisomal \(\beta\)-oxidation. In some diseases this is due to the (virtual) absence of peroxisomes leading to a generalized loss of peroxisomal functions including peroxisomal \(\beta\)-oxidation. In most inborn errors of peroxisomal \(\beta\)-oxidation, however, peroxisomes are normally present and the impairment in peroxisomal \(\beta\)-oxidation is due to the single or multiple loss of peroxisomal \(\beta\)-oxidation enzyme activities. In all these disorders there is accumulation of very-long-chain fatty acids in plasma, which allows biochemical diagnosis of patients affected by an inborn error of peroxisomal \(\beta\)-oxidation to be done via gas-chromatographic analysis of plasma very-long-chain fatty acids. Subsequent enzymic and immunological investigations are required to identify the precise enzymic defects in these patients. In all inborn errors of peroxisomal \(\beta\)-oxidation known today there are multiple abnormalities, especially neurological with death usually occurring in the first decade of life. Prenatal diagnosis of these disorders has recently become possible.

INTRODUCTION

In 1976 Lazarow and de Duve described the presence of a fatty acid \(\beta\)-oxidation system in rat liver peroxisomes. Their study was inspired by earlier work from Cooper and Beevers (1969) who found that glyoxysomes, organelles closely related to peroxisomes, are capable of oxidizing fatty acids. Until then it was generally believed that mitochondria were the sole site of fatty acid degradation. Present knowledge indicates that non-mitochondrial \(\beta\)-oxidation is in fact much more widely distributed in nature than \(\beta\)-oxidation in mitochondria, which is mainly restricted to the animal kingdom (see Kunau et al., 1987).

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The functional significance of a separate peroxisomal \( \beta \)-oxidation system remained obscure for some time. In recent years, however, it has become clear that the peroxisomal system is not just a functional duplication of the mitochondrial system but is involved in the \( \beta \)-oxidative chain-shortening of a distinct set of compounds. The recognition of a number of inherited diseases in man, caused by a dysfunction in peroxisomal \( \beta \)-oxidation, stresses the importance of this system. In the last few years our knowledge about peroxisomal \( \beta \)-oxidation has progressed enormously. New developments include the recognition of several inborn errors of metabolism in which peroxisomal \( \beta \)-oxidation is impaired, the identification of the primary defects in these disorders, the discovery of novel functions for peroxisomes and the further characterization of the peroxisomal \( \beta \)-oxidation system. These developments will be described in this review.

**ENZYMIC ORGANIZATION OF THE MITOCHONDRIAL AND PEROXISOMAL \( \beta \)-OXIDATION SYSTEMS**

Fatty acids are transported between organs either in the form of unesterified fatty acids complexed to albumin or in the form of triacylglycerols which are subsequently hydrolysed. Following their uptake into cells via a mechanism which is not well understood, long-chain fatty acids are activated to the corresponding CoA esters.

**Mitochondrial \( \beta \)-oxidation**

The acyl-CoA thioesters are carried across the mitochondrial inner membrane by a concerted mechanism involving L-carnitine, carnitine palmitoyltransferase I (CPT I), the carnitine : acylcarnitine translocator and carnitine palmitoyltransferase II (CPT II). Short-chain and medium-chain fatty acids with ten carbon atoms or less are taken up by mitochondria as free fatty acids independently of carnitine; this is followed by their activation in the mitochondrial matrix (see Bremer and Osmundsen, 1984 for further information).

Once inside the mitochondrion the acyl-CoA esters are oxidized via sequential steps of dehydrogenation, hydration, dehydrogenation and thiolytic cleavage (for review see Bremer and Osmundsen, 1984; Schulz, 1985 and Vianey-Liaud et al., 1987). Three different acyl-CoA dehydrogenases catalyse the conversion of short-chain, medium-chain or long-chain thioesters, respectively, to the corresponding 2-trans-enoyl-CoA esters. In addition to these three enzymes, there are two acyl-CoA dehydrogenases involved in dehydrogenation of isovaleryl-CoA and 2-methyl-branched-chain acyl-CoA esters, respectively. In all these dehydrogenases, tightly bound FAD is the prosthetic group. Enzyme-bound FADH\(_2\) is re-oxidized by transfer of electrons to a second flavoprotein named electron-transferring flavoprotein (ETF)