Lactic acidosis in long-chain fatty acid β-oxidation disorders

F. V. Ventura1,2, J. P. N. Ruiter1, L. IJlst1, I. Tavares de Almeida2 and R. J. A. Wanders1*

1 Departments of Clinical Chemistry and Pediatrics, Academic Medical Centre, Amsterdam, The Netherlands; 2 Centro de Patogénese Molecular, Fac. Farmácia da Universidade de Lisboa, Lisbon, Portugal

* Correspondence: Department of Clinical Biochemistry, University Hospital Amsterdam, A.M.C., Meibergdreef 9 (F0-224), 1105 AZ Amsterdam, The Netherlands

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Summary: Among the many disorders of fatty acid β-oxidation known today, the disorders of long-chain fatty acid oxidation are the most severe and life-threatening. One remarkable abnormality, not observed in, for instance, medium-chain acyl-CoA dehydrogenase deficiency, is the moderate to severe lactic acidaemia in long-chain fatty acid β-oxidation-deficient patients, suggesting that oxidation of pyruvate is also compromised. In order to understand the underlying basis of the lactic acidaemia in these patients, we have studied the formation of L-lactate and pyruvate in cultured skin fibroblasts incubated with D-glucose. All long-chain fatty acid β-oxidation-deficient cell lines studied were found to show a moderate elevation of lactate when compared with control and medium-chain acyl-CoA dehydrogenase-deficient fibroblasts. Interestingly, differences were found between cells deficient in long-chain 3-hydroxyacyl-CoA dehydrogenase and very-long-chain acyl-CoA dehydrogenase, suggesting that saturated acyl-CoA esters and their 3-hydroxyacyl-CoA derivatives affect pyruvate metabolism differently.

Over the past twenty years, an increasing number of disorders have been identified in which there is a defect in one or more of the multiple enzymes and proteins essential for mitochondrial fatty acid transport and β-oxidation processes (Roe and Coates 1995). Mitochondrial fatty acid β-oxidation disorders share a range of signs and symptoms including early age at onset, hypoketotic hypoglycaemia, Reye-like syndrome and multiorgan involvement, with the development of fatty liver, dilated or hypertrophic cardiomyopathy and skeletal myopathy. Coma and sudden unexplained death in the first two years of life, are frequently observed in such patients (Brackett et al 1995). As a consequence of a defect in fatty acid oxidation, there is
intracellular accumulation of a series of fatty acids and fatty acid derivatives including the fatty acyl-CoA intermediates. The types of acyl-CoA esters which accumulate depend upon the nature of the enzyme block (Jackson et al. 1992; Pourfarzam et al. 1994).

Among the disorders of mitochondrial fatty acid β-oxidation identified so far, the ones in which long-chain fatty acid β-oxidation is impaired are by far the most severe and life-threatening, even when diagnosed early and treated immediately. In contrast, when properly diagnosed and appropriately treated, medium-chain acyl-CoA dehydrogenase (MCAD)-deficient patients are able to lead a normal and asymptomatic life (Iafolla et al. 1994). Among the differences in the clinical presentation of long- and medium-chain fatty acid β-oxidation-deficient patients, one frequent finding in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (Bertini et al. 1992; Duran et al. 1991; Jackson et al. 1991; Moore et al. 1993; Treem et al. 1994; Tyni et al. 1997) and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (Aoyama et al. 1995; Largilliè re et al. 1995; Parini et al. 1991; Treem et al. 1991), but not in MCAD deficiency, is a moderate to severe lactic acidosis.

Although the lactic acidaemia observed in some of the patients described above might be secondary to anoxia or poor tissue haemoperfusion caused, for instance, by vomiting and seizures (e.g. Bertini et al. 1992; Moore et al. 1993; patients 9 and 11 from Tyni et al. 1997), lactic acidosis has also been described in LCHAD- and VLCAD-deficient patients with no signs of anoxia and with good tissue perfusion (see patient 1 from Aoyama et al. 1995; Treem et al. 1994; patient 2 from Duran et al. 1991 (before gastroenteritis); patient 8 from Tyni et al. 1997). In these latter cases the lactic acidosis may well be due to a disturbance in the oxidative phosphorylation system and/or any other step in pyruvate oxidation. The underlying basis for the striking difference in clinical presentation of long-chain and medium-chain fatty acid oxidation-deficient patients may well reside in the toxic properties of the different acyl-CoA esters. Using digitonin-permeabilized human skin fibroblasts, we have previously shown (Ventura et al. 1995a) that ATP synthesis is progressively inhibited by increasing concentrations of long-chain acyl-CoA esters, with chain length of 14–20 carbon atoms, while medium-chain acyl-CoA esters are much less inhibitory. If the inhibition of oxidative phosphorylation by long-chain acyl-CoA esters is also occurring under in vivo conditions, this may well explain some of the findings, including the lactic acidosis, observed in patients with these kinds of disorders.

Cultured skin fibroblasts are a useful model system for studying the function and dysfunction of mitochondrial (and peroxisomal) β-oxidation and its interactions with other metabolic pathways. With the aim of reproducing the lactic acidosis observed in long-chain fatty acid β-oxidation-deficient patients, and to reinforce the hypothesis that the intramitochondrial accumulation of acyl-CoA intermediates may be at the basis of these pathological findings, we studied the formation of lactate and pyruvate from glucose in cells from control individuals and from patients with established β-oxidation enzyme deficiencies. The results are described in this paper.