Acta Pædiatrica, 2005; 94: 132–137

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REVIEW ARTICLE

Physiological and pathological aspects of GSH metabolism

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Abstract

The antioxidant glutathione is found in low levels in diseases in which increasing evidence implicate oxidative stress in the development of the disease, for example retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, patent ductus arteriosus and asthma. Glutathione is metabolized in the γ-glutamyl cycle, which involves six different enzymes. The synthesis of glutathione is a two-step process in which the first step is catalysed by γ-glutamylcysteine synthetase and the second step by glutathione synthetase. Glutathione synthetase deficiency is an autosomal recessive disease and the most common inborn error of the γ-glutamyl cycle. Approximately 25% of patients with hereditary glutathione synthetase deficiency die during childhood. Patients present with a clinical picture ranging from compensated haemolytic anaemia to a complex disorder with additional symptoms like 5-oxoprolinuria, metabolic acidosis and central nervous system impairment. Even though the correlation between phenotype and genotype in these patients is complex, an indication of the phenotype can be based on the type of mutation involved. Also, there is a correlation between the glutathione synthetase activity and the level of glutathione in cultured fibroblasts. Inborn errors have also been described in three additional steps of the γ-glutamyl cycle, namely γ-glutamyl-transpeptidase, 5-oxoprolinase and γ-glutamylcysteine synthetase.

Conclusion: The range of disorders in patients with inborn errors in the metabolism of glutathione illustrates the intricate metabolism of glutathione and its involvement in numerous essential processes in the cell. By studying these patients, further insight into the functions and metabolism of glutathione can be achieved.

Key Words: *Glutathione, glutathione synthetase deficiency, 5-oxoprolinase, metabolic acidosis, haemolytic anaemia*

Introduction

Premature newborns are subjected to increased oxidative stress because of limited intracellular oxidative defence, exposure to high concentration of inhaled oxygen, and increased oxidative stress as a result of inflammations and infections. An increasing body of evidence indicates that free radicals are involved in several diseases primarily affecting premature newborns. Such conditions, collectively called "oxygen radical disease of newborn", include retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and patent ductus arteriosus [1].

One major antioxidant is the tripeptide glutathione (*L*-γ-glytamyl-*L*-cysteinylglycine). Glutathione functions as a redox buffer, e.g. by removing toxic peroxides via reactions catalysed by GSH peroxidase. The ratio between the reduced (GSH) and oxidized (GSSG) forms of glutathione is often used as an indicator of the cellular redox state [2], reflecting the balance between the capacity of the defence response for regeneration of GSH and the extent of neutralization by oxidants. Glutathione is metabolized via the γ-glutamyl cycle (Figure 1). The cycle involves six enzymes, and the synthesis of GSH consists of two consecutive steps catalysed by γ-glutamylcysteine synthetase (γ-GCS) and GSH synthetase (GS). In the first, rate-limiting

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(Received 28 May 2004; revised 24 August 2004; accepted 27 September 2004)

ISSN 0803-5253 print/ISSN 1651-2227 online
DOI: 10.1080/08035250410025285