Methylglyoxal, glyoxalases and the development of diabetic complications

Review Article

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Summary. The formation of the reactive α,β-dicarbonyl metabolite, methylglyoxal, is increased during hyperglycaemia associated with diabetes mellitus. Methylglyoxal is metabolised to S-D-lactoylglutathione and D-lactate by the glyoxalase system and to hydroxyacetone (95%) and D-lactaldehyde by aldose reductase. Methylglyoxal and hydroxyacetone bind and modify protein, producing fluorescent products. Red blood cell activities of glyoxalase enzymes are risk factors for the development of clinical complications of diabetes. Aldose reductase inhibitors decrease the concentration of methylglyoxal in experimental diabetic rats to normal levels, aminoguanidine and L-arginine scavenge methylglyoxal; these effects may be involved in their prospective preventive therapy of diabetic complications. Biochemical and clinical evidence suggests that the metabolism of methylglyoxal in diabetes mellitus is linked to the development of diabetic complications. A causal relationship may involve modification of protein by methylglyoxal and hydroxyacetone.

Keywords: Amino acids – Methylglyoxal – Glyoxalase – Hydroxyacetone – Aldose reductase – Aminoguanidine – Diabetic complications

Introduction

Methylglyoxal (2-oxopropanal) is a reactive α,β-dicarbonyl metabolite. It is formed from glyceraldehyde-3-phosphate and dihydroxyacetonephosphate by non-enzymatic elimination of phosphate (Phillips and Thornalley, 1993a; Richard, 1991), and enzymatically from dihydroxyacetonephosphate by methylglyoxal synthase in some mammalian tissues (Ray & Ray, 1984) and leakage of the active site-bound phospho-enediolate intermediate of triosephosphate isomerase (Pompliano et al., 1990). It is also formed from aminoacetone in the
Fig. 1. Metabolic pathways for the formation of methylglyoxal. Abbreviations: G-6-P, glucose-6-phosphate; F-1-P, fructose-1-phosphate; F-1,6-bis-P, fructose-1,6-bis-phosphate; F-6-P, fructose-6-phosphate; DHAP, dihydroxyacetonephosphate; G3P, glyceraldehyde-3-phosphate; TPI, triosephosphate isomerase; GA, D-glyceraldehyde.

catabolism of threonine (Ray and Ray, 1987) and from hydroxyacetone in the metabolism of acetone (Reichard et al., 1986) (Fig. 1).

Methylglyoxal is the physiological substrate of the glyoxalase system, a cytosolic metabolic pathway which catalyses the conversion of methylglyoxal to D-lactate via the intermediate S-D-lactoylglutathione. The glyoxalase system comprises two enzymes, glyoxalase I and glyoxalase II, and a catalytic amount of reduced glutathione. Glyoxalase I (EC 4.4.1.5) catalyses the formation of S-D-lactoylglutathione from the hemithioacetal formed non-enzymatically from methylglyoxal and reduced glutathione.

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\text{MeCOCHO} + \text{GSH} \rightleftharpoons \text{MeCOCH(OH)} \text{Glyoxalase I} \rightarrow \text{MeCH(OH)CO} \text{Glyoxalase II (EC 3.1.2.6) catalyses the hydrolysis of S-D-lactoylglutathione to D-lactate, reforming the reduced glutathione consumed in the glyoxalase I-catalysed reaction.}
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\text{MeCH(OH)CO} + \text{H}_2\text{O} \text{Glyoxalase II} \rightarrow \text{MeCH(OH)CO}_2^- + \text{GSH} + \text{H}^+ \]

D-Lactate is metabolised in mammalian tissues by 2-hydroxyacid dehydrogenase, an FAD-dependent mitochondrial enzyme, to pyruvate. The function of