

Comments in Biochemistry

The Galactose Metabolic Pathway

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THE GALACTOSE METABOLIC PATHWAY involves the following set of biochemical reactions:

- 1) Lactose + H₂O → galactose + glucose
- 2) Galactose + ATP → galactose-1-phosphate + ADP
- 3) Galactose-1-phosphate + uridine diphosphoglucose ⇌ uridine diphosphogalactose + glucose-1-phosphate
- 4) Galactose-1-phosphate + UTP ⇌ uridine diphosphogalactose + UDP
- 5) Uridine diphosphogalactose ⇌ uridine diphosphoglucose
- 6) Uridine diphosphoglucose + PP_i ⇌ glucose-1-phosphate + UTP

Reaction 1 is mediated by the enzyme lactase or beta-galactosidase in the small intestine. A deficiency of lactase leads to diarrhea after the ingestion of lactose-containing foods, notably milk (1). *Reaction 2* is mediated by the enzyme galactokinase which requires Mg⁺⁺. A deficiency of this enzyme has been described in one patient who was presumed to have galactosemia (2, 3). However, the enzyme galactose-1-phosphate uridyl transferase was normal and the patient's red blood cell galactose-1-phosphate content was very low. The pa-

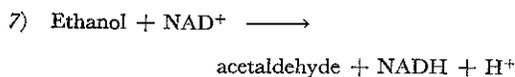
tient had cataracts and coincident neurofibromatosis.

Reaction 3 is the major pathway for galactose and is mediated by galactose-1-phosphate uridyl transferase. A deficiency of this enzyme leads to the inability to metabolize galactose further, and galactose-1-phosphate accumulates, resulting in the clinical condition of galactosemia. This can be a very serious disease resulting in cataracts, cirrhosis, renal disease with proteinuria and aminoaciduria, mental retardation, anorexia, vomiting, diarrhea, osteoporosis, failure to gain weight, coma, and death (4-7). The accumulated galactose-1-phosphate may inhibit various enzymes (8-12) which may account for the pathogenesis of the disease. The possibility that galactitol formation from galactose may accumulate to toxic levels must also be considered (2, 13-15). A decreased level of galactose-1-phosphate uridyl transferase has been described in the red blood cells of people from nongalactosemic families. This form of galactose-1-phosphate uridyl transferase deficiency has been called the Duarte variant (16). An increased level of this enzyme has been reported in children with Down's syndrome (trisomy 21) suggesting that galactose-1-phosphate uridyl transferase is localized to chromosome 21 (17).

Reaction 4 is a minor pathway which may handle an increased portion of the galactose in some of the patients with galactosemia as they grow older (18). The enzyme for this reaction is uridine diphosphogalactose pyrophosphorylase.

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Reaction 5 is carried out by the enzyme uridine diphosphogalactose 4-epimerase. This is a NAD⁺-dependent enzyme (19). The reaction is inhibited by NADH (20) which can be generated in the liver from ethanol by ethanol dehydrogenase:



Galactose tolerance is impaired after alcohol ingestion and this may be due to the inhibition of *reaction 5* by NADH (21).

Reaction 6, mediated by uridine diphosphoglucose pyrophosphorylase, brings the transformed galactose molecule to the Embden-Meyerhof pathway. From uridine diphosphoglucose the galactose may enter into glycogen or be transformed into uridine diphosphoglucuronic acid and thereby enter into the uronic acid pathway. It has been reported that uridine diphosphogalactose inhibits uridine diphosphoglucose dehydrogenase (22). If this is so then lactose ingestion might decrease glucosiduronide formation of various substances by blocking the formation of uridine diphosphoglucuronic acid.

It should be noted that uridine diphosphoglucose is required for the metabolism of galactose-1-phosphate so that glucose must be present to provide the uridine diphosphoglucose before galactose can be fully metabolized. However, once galactose-1-phosphate reacts with uridine diphosphoglucose to form uridine diphosphogalactose, glucose-1-phosphate is formed, which can then react with UTP to form uridine diphosphoglucose to keep the reaction going. In view of these considerations one would expect that galactose metabolism in the starving individual would be impaired and that a large load of lactose ingested by a starving person might lead to transient illness.

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