Disorders of Galactose Metabolism*

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ABSTRACT

Galactose metabolism occupies a central position in modern biology through its relationship to cell surface antigenicity and its metabolic function as a component of glycolipids and glycoproteins. Disturbances in three fundamental reaction sequences of this hexose have led to a delineation of pathways of the chemistry resulting in the understanding of its metabolic fate. These inherited disorders of metabolism are prototypes for the application of nutritional therapy of biochemical genetic defects.

Primates and guinea pigs lack the synthetic pathway to convert glucuronyl and galacturonyl residues to ascorbate. Ingestion of nutrients rich in this vitamin ablates the deleterious consequences of this mutation. In the absence of adequate intake, scurvy occurs,—a consequence of an inborn error of metabolism in man. The realization that environmental manipulation can neutralize the effects of biochemical genetic defects represents the first approach to treatment of genetic diseases.

A prototype for the successful application of such considerations to human disease is the disorders of galactose metabolism. In the past two decades mutations in three components of the galactose metabolic pathway have been described: (1) galactose-1-phosphate uridyl transferase, (2) galactokinase and (3) galactose epimerase. Variability of pathology and differences in therapy are

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predictable as a consequence of the de-
lineation of galactose metabolism in man.

Classical Galactosemia

The clinical manifestations of this au-
tosomal recessively inherited disorder
consist of the tetrad: hepatosplen-
omegaly, cataracts, mental retardation
and failure to thrive. The homozygous
infant usually appears normal after birth;
however, following the ingestion of
galactose-containing foods, non-specific
symptoms of gastrointestinal disease en-
sue. The appearance of icterus late in the
neonatal course and the progressive de-
velopment of hepatomegaly connote the
development of hepatocellular disease.

In jaundice, with or without significant
liver enlargement, the absence of
hemolysis mandates examination of
biologic fluids for galactosemia and
galactosuria. Initially, the liver shows
fatty infiltration which readily proceeds
to cirrhosis if milk ingestion persists. In-
duction of galactosemia by milk (lactose)
ingestion for four to eight weeks leads to
the development of cataracts which is fol-
lowed by subsequent development of
central nervous system disease. Variable
disease manifestations between affected
individuals are apparent and less pro-
nounced symptoms, disturbances of
growth, liver function or central nervous
system may not attract attention for
weeks or months.

Clinical deficits in patients may in-
clude hypoglucoemia, lethargy and
hypotonia. Anorexia or food apathy is ap-
parent in infants as a consequence of milk
tolerance. Persistence of galactosemia
and galactosuria may lead to renal tubular
dysfunction with resultant amino
aciduria of neutral amino acids. This ab-
normality occurs only in the presence of
galactosuria and remits with correction of
sacchariduria.

From 1950 to 1958 the association of
increased blood levels of galactose in
conjunction with Laennec's cirrhosis,22,29
cataracts and mental dysfunction2 were
solidly established. Kalckar and Issel-
bacher et al,1,3,9 based on the accumula-
tion of galactose and galactose-1-
phosphate in liver and erythrocytes,
postulated and experimentally estab-
lished a deficiency of the sugar nu-
clotide transferase in this disease.

The conversion of galactose via the
Leloir pathway is dependent upon the
following metabolic conversions:

1. \[ \text{Galactose} + \text{ATP} \xrightarrow{\text{Kinase}} \alpha\text{-galactose-1-phosphate} + \text{ADP} \]

2. \[ \alpha\text{-Galactose-1-phosphate} + \text{UDP} \xrightarrow{\alpha\text{-glucose-1-phosphate + UDP}} \text{Galactose-1-phosphate uridyl transferase} \]

3. \[ \text{UDP galactose} \xrightarrow{\text{Epimerase} (\text{NAD}^+)} \text{UDP glucose} \]

The pathogenesis of symptoms is as a
consequence of a mutation in production
of the enzyme galactose-1-phosphate
uridyl transferase (Gal-1-P uridyl trans-
ferase). Recently, considerations of acces-
sory metabolic pathways have been
shown to contribute to the pathology of
this autosomal recessive disorder.

4. \[ \text{UDP glucose} + \text{PP}_1 \xrightarrow{\text{pyrophosphorylase}} \text{UTP} + \text{Glucose-1-phosphate} \]

5. \[ \text{Galactose-1-phosphate} + \text{UTP} \xrightarrow{\text{UDP Galactose pyrophosphorylase}} \text{UDP Gal} + \text{PP}_1 \]
(6) Galactose + NADPH

\[
\text{Aldose Reductase} \xrightarrow{[\text{H}^+]} \text{Galactitol} + \text{NADP}^+
\]

In patients with classical galactosemia, administration of galactose resulted in the accumulation of galactose-1-phosphate as well as galactose in erythrocytes. Shortly thereafter, the in vitro corollary to this clinical loading test was accomplished with isolated erythrocytes. These observations, in addition to the demonstration by Holzel and co-workers, supported the postulation that the biochemical defect resided in the uridyl transferase enzyme. However, whether galactose, galactose-1-phosphate or their metabolic derivatives produced cirrhosis, cataracts or brain damage, could not be resolved. The unequivocal demonstration of the molecular defect in erythrocyte hemolysates was by Kalckar and associates.

One of the most devastating clinical features of galactosemia is the development of irreversible brain damage which occurs if institution of appropriate therapy is delayed beyond the second or third month of life. Similarly, significant visceral morbidity occurs when therapy is not instituted,—the development of cirrhosis. Data on patients and experimental models do not allow a precise delineation of the molecular pathophysiology of these lesions. In erythrocytes and liver specimens from patients, reduced concentrations of adenosine triphosphate (ATP), phosphocreatine, glucose and glucolytic intermediates have been observed. In addition, abnormal increases in the concentration of galactose, galactose-1-phosphate and galactitol are reported.

The reduced concentrations of ATP, phosphocreatine and diphosphoglyceric acid are thought to be the wasteful consequences of the “idle” phosphorylation of galactose leading to reduced energy reserves and generating capacities—thus, comprised cell function. The accumulation of galactose-1-phosphate, galactitol and galactose further compromise cellular function. Galactose-1-phosphate has been shown to inhibit phosphoglucomutase, UDP glucose pyrophosphorylase and UDP Gal epimerase. These changes not only reduce intracellular energy production but also lead to diminished synthesis of glycoproteins and glycolipids by virtue of reducing the sugar nucleotide pools, thus limiting the developing nervous system of the infant.

Further evidence for the primary toxic role of galactose-1-phosphate is the demonstration of cytotoxicity to tissue cultured HeLa cells and galactosemic cultured skin fibroblasts. These cells, when grown in the presence of galactose, exhibit increased levels of galactose-1-phosphate as well as degeneration and dilation of the rough endoplasmic reticulum and cell death. This sequence of events may occur in vivo in brain and liver. Further evidence of the cyto- and neurotoxic effects of galactose-1-phosphate indicates it interferes with ribonucleic acid (RNA) metabolism and protein synthesis. It may make galactosyl linkages with the epsilon-amino groups of proteins, thus modulating their physiologic activity.

Accumulation of galactose leads to the accumulation of galactitol via the path catalyzed by aldose reductase. Changes in myoinositol and phosphatidyl inositol occur either through action as a metabolic inhibitor or owing to its capacity to penetrate biological membranes effectively leading to changes in intracellular osmotic pressure and, thus, intracellular edema. It is likely that a combination of these factors in vivo leads to deranged hepatic and nervous system function.
Galactosemia, that is, the disorder characterized by increased concentrations of galactose in blood and deficiency of galactose-1-phosphate uridyl transferase, is a genetically heterogeneous group. This entity, when associated with the classical clinical picture, is usually associated with a structural mutation. Variability in the clinical manifestations as well as the residual enzyme activity present in homozygous individuals has resulted in the identification of at least two additional genetic groups: the Duarte variant and a variant with decreased activity and electrophoretic mobility. Elegant investigations attesting to genetic heterogeneity have employed the complementation test with fibroblast cultures.

Potential genetic heterogeneity, as well as variability of clinical expression, resulted in the recognition of a second disease characterized by high levels of blood galactose, galactosuria and cataracts, but without apparent involvement of brain and liver—an entity subsequently shown to be due to a different inborn error of metabolism. Classical galactosemia (GAL-1-P uridyl transferase deficiency) and galactokinase deficiency can readily be differentiated on the basis of enzymological study of erythrocyte hemolysates.

**Galactokinase Deficiency**

The occurrence of cataracts during the first or second decade of life without other symptoms should alert the attending physician to a possible diagnosis of galactokinase deficiency. Mental retardation, hepatosplenomegaly and impairment of growth are not symptoms of this disorder. This disease is transmitted in an autosomal recessive fashion. In Gitzelmann's original description of one patient, a 44-year old man who had cataracts diagnosed during childhood, the only persisting symptoms were increased galactose concentrations in blood and abnormally excreted quantities of galactose and galactitol in urine. In addition to the demonstration of deficient galactokinase activity in erythrocytes, these pioneering studies indicated that significant quantities of galactose were converted to galactitol and the ratio of their daily excretion is galactose/galactitol = 4.

Subsequent reports have further attested to the absence of hepatic and CNS disease in this entity. Most recently, Litman and associates reported on the occurrence of pseudotumor cerebri in association with galactokinase deficiency. These findings of cerebral cellular swelling are ascribed to osmotic changes following the accumulation of galactose and galactitol. The relatively benign nature of this disorder is suspect because of two reported patients, one of whom had mental retardation and the other who had seizures and deteriorating neurologic function.

In this syndrome, phosphorylated galactose clearly can not have a role in the pathophysiology of aberrant function. To explore further which noxious galactose metabolite is significant, close scrutiny of the development of galactokinase-deficiency-cataracts is appropriate.

Maintenance of young rats on a diet containing 35 to 50 percent galactose results in the development of vacuolar lens lesions and nuclear opacities within two to three weeks. The sensitivity of various model systems to galactose-toxic effects varies between animal species, notably, humans tolerate proportionately larger doses. The earliest lens pathology is the appearance of hydropic lens fibers,—individual lens fibers swollen with accumulated fluid. In 1959 Van Heyningen demonstrated accumulation of galactitol in the lens of galactose-fed
animals. Subsequent investigations established that increased concentrations of galactitol with associated increases in osmotic pressure were sufficient to account for lens swelling. Extensive studies on galactose metabolite effects indicate that the changes in lens concentrations of amino acids and electrolytes are due to primary osmotic effects.12,13

This sequence of events leading to the formation of lens opacities and the more recent reports suggesting more systemic pathologic effects in galactokinase deficiency imply that every case of childhood and early adult onset of cataracts should be evaluated for disorders of galactose metabolism.

In 1965, Kalckar wrote an article entitled "Galactose Metabolism and Cell Sociology"10 suggesting that the relationship of galactose to living cells exemplified one of the freaks of nature illustrating the extravagances of nature. He pointed out that the hexose galactose is important for cell surface properties, antigeneity, blood group substance structure and molecular structure of brain galactolipids. Seven years prior to the elucidation of the epimerase deficiency, Kalckar hypothesized a science fiction patient with epimerase deficiency. Symptoms of "glucolipid brain with intelligence lower than a mermaid's or as high as one of Szilard's dolphins ... milk sugar composed of glucose or cellubose ... complete or partial loss of blood groups A, B ..." Point to abnormal tissues with regard to transplant characteristics and susceptible to virus infections.

Most recently, Gitzelmann identified a third metabolic derangement of galactose chemistry, namely, an erythrocyte epimerase defect.6 The conversion of galactose to a metabolizable form involves activation by phosphorylation with ATP and subsequent conversion to a sugar nucleotide. The inborn errors of this metabolic sequence have been reviewed. The successful therapy of these conditions is dependent upon the fact that man is capable of synthesizing UDP galactose independent of exogenous supplies of this hexose by enzymatic conversion of UDP glucose to UDP galactose. In 1972, Gitzelmann6 described a mutation in the UDP galactose epimerase reaction functionally resulting in conversion to a galactose auxotroph. The predicted sequellae of such a defect would be defective synthesis of glycoproteins and glycolipids in the absence of exogenous supplies of galactose and thus, abnormal synthesis of cell walls, brain lipids, etc.

Significantly, in the patient reported by Gitzelmann, the features of import were good health, normal psychomotor development and the presence of galactosemia on a normal diet. Thus, subsequent queries in terms of possible pathophysiology are: (1) is this defect present in tissue other than the erythrocyte; (2) will dietary galactose deprivation produce disease; and (3) will such a female patient synthesize a galactose-containing milk during lactation. No data exist at present to resolve these questions.

The search for an understanding of disease, its treatment and prevention, as well as understanding of processes functional in the maintenance of health, are all exemplified by the investigations oriented to a definition of galactose metabolism in man. It is as described in "The Yellow Emperor's Classic of Internal Medicine":31 "I, your humble servant, hear that not to forget dangers at times of security, and not to forget decline or fall at times of safe existence, constituted the most important duties of the early sages. I hear that to search for ailments of people and to sympathize with the distress of the people repre-
sented the profound humaneness of the superior rulers.”

References


