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Galactosemia unsolved

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Abstract Classic galactosemia is an enigmatic disorder that presents the challenge of unraveling the basis of the long-term complications of mental disability, speech defects, ovarian failure and neurologic syndromes which occur despite a galactose-restricted diet. A complete understanding of the pathobiochemistry and molecular genetics, and evaluation of the present theories for the poor long-term outcome, continuous intoxication, critical metabolite depletion and in utero damage is needed in order to design new therapeutic strategies. Answering this urgent question of how to treat galactosemic patients mandates enhanced clinical and basic research efforts.

Key words Chronic intoxication · Complications · Endogenous galactose · Galactose metabolism

Abbreviations *GALT* galactose-1-phosphate uridyltransferase · *Gal-1-P* galactose-1-phosphate · *Glc-1-P* glucose-1-phosphate

Introduction

It is the aim of this paper to reflect on a disorder that has become an enigma. Galactose restriction has been the basis of therapy of congenital galactosemia due to galactose-1-phosphate uridyltransferase (GALT) deficiency since Mason and Turner [45] in 1935 described how removing galactose from the diet elminated the acute toxicity syndrome. The clinical picture of a galactosemic infant with severe inanition, cataracts, hepatomegaly and jaundice can be readily changed to a thriving child with regression of these symptoms and signs within a short time after a galactose-free diet is started. This marked improvement has caused many to feel that early diagnosis and institution of stringent dietary therapy would result in normal children. This appears not to be the case.

Despite early diagnosis and institution of a galactose-free diet a number of clinical observations have suggested that mental disability and speech impairment may occur [14, 41]. Ovarian failure was observed in afflicted females [36, 70], and reports appeared of an ataxia syndrome in some well-treated patients [16, 44]. A poor outcome has been highlighted in the recent retrospective survey of over 350 patients by Waggoner et al. [76], where developmental delay, speech impairment, ovarian dysfunction and growth retardation were found in a number of patients seemingly independent of the time that dietary restriction was begun. The high incidence of patients with such sequelae did not differ regardless of whether the patient had a normal neonatal history and treatment before the onset of symptoms or of whether the treatment ensued after symptoms were observed. It was apparent that the complications in later childhood seemed to be unrelated to the time treatment began within the first 2 months. These disturbing findings on the outcome of well-treated patients and those published by Schweitzer et al. [60], and reported by Naughton [47] and Bakker [2] form the enigma of galactosemia. The question is when galactose is eliminated from the diet on the 1st day of extrauterine life or from the mother during pregnancy, why are we not able to produce a normal individual?

The galactose metabolic pathway

Before detailing several theories which attempt to explain the poor retrospective outcome of dietary therapy, it is essential to review the galactose metabolic pathways and develop an understanding of the metabolic schema. An in depth description of galactose metabolism can be found in the publication by Segal [63]. A simplified version is presented here. As shown in Fig. 1, galactose is phosphorylated by galactokinase with ATP to form galactose-1-phosphate (gal-1-P). Gal-1-P reacts with UDPglucose to produce two products, UDPgalactose and glucose-1-phosphate (glc-1-P). The block in galactosemia due to GALT deficiency occurs at this point. The glc-1-P produced can be converted to glucose; by normal liver, about 80% of galactose can be converted to glucose within a short time [4, 65]. The UDPgalactose formed in the reaction is converted to UDPglucose by epimerase [46]. UDPglucose thus formed can then enter the reaction again in a cyclical fashion until all of the galactose coming into the pathway may be converted to glucose via glc-1-P. Some of the UDPglucose formed from galactose can serve as the glucose precursor of glycogen synthesis.

In the absence of GALT activity, gal-1-P, and galactose accumulate behind the block. With the accumulation of galactose two alternate pathways come into play: in the first, the aldehyde group of galactose is reduced to form a sugar alcohol, galactitol [73], and in the second an oxidation reaction converts the carbonyl group of galactose to a carboxyl group to form the sugar acid galactonate [8]. Both compounds accumulate in tissues [22, 53, 55] of galactosemic patients and have been identified in their urine [3, 58]. Animals fed a high galactose diet also accumulate these substances in their tissues [52, 75]. Galactitol is an end product of metabolism and has osmotic properties that are considered a major factor in cataract formation [39]. Galactonate can be further metabolized to xylulose. This pathway accounts for about 50% of the oxidation of galactose by galactosemic patients [66].

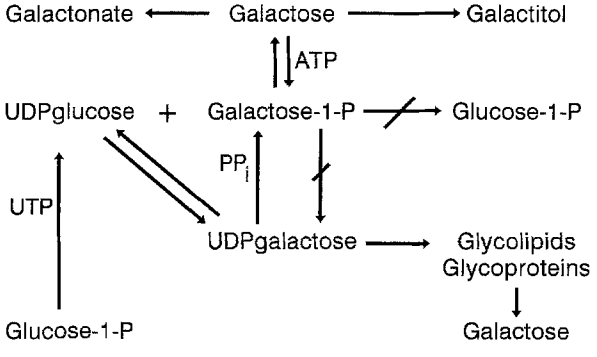

Fig. 1 An abbreviated scheme of galactose metabolism. The *diagonal lines* across the *arrows* indicate the site of the metabolic block in classic galactosemia

UDPgalactose plays an important role since it is a donor of galactose in the formation of complex glycoproteins and glycolipids. These complex substances turn over in cells with liberation of free galactose which can re-enter the pathway of galactose metabolism. In the galactosemic, however, the liberated galactose can only be converted as far as gal-1-P or enter the alternate pathways.

Several important facts deserve emphasis. First, when no galactose moves through the pathway either because an enzymatic block exists or none is ingested, there is a mechanism for the formation of such a key substance as UDPgalactose. This comes from the interaction of glc-1-P with UTP via UDPglucose pyrophosphorylase activity to give UDPglucose which then undergoes epimerization to form UDPgalactose. The epimerase reaction is in equilibrium in nearly all cells with a ratio of UDPglucose to UDPgalactose of about 3:1 [46, 72].

Second, even though external galactose may not be provided there is a mechanism for the formation of gal-1-P and galactose via a pyrophosphorylitic cleavage of UDPgalactose [18]. Thus, there can be continuous production of gal-1-P even though no galactose might be entering the cell. It is obvious that if lactose restricted diets do not prevent the poor long-term outcome, an explanation must be sought in alterations of the internal environment of cells as a metabolic consequence of GALT deficiency. In this regard, three key metabolites of galactose deserve careful scrutiny, gal-1-P, galactitol and UDPgalactose which are discussed by Gitzelmann [19], Jakobs [34] and Segal [63].

Theories explaining dietary inefficacy

There are three principal reasons that have been proposed for the far from optimal outcome expected from restriction of dietary galactose. The first is chronic intoxication with galactose, the sugar being produced endogenously by the breakdown of UDPgalactose or obtained exogenously from the diet which, though formulated for treatment, is not sufficiently low in galactose. The second is a

Table 1 The chronic intoxication theory

Evidence for toxin production
Galactose-1-phosphate
Urinary galactitol excretion
Urinary galactonate excretion
Sources of galactose and metabolites
Endogenous
From UDPgalactose formed from UDPglucose
From glycoprotein and galactolipid turnover
Exogenous
Free galactose in vegetables and fruits
Galactans and complex carbohydrates

metabolite depletion. These metabolites include the cyclic polyol, inositol whose concentration diminishes with the accumulation of galactitol and nucleotide sugars, reportedly mainly UDPgalactose. The third is in utero toxicity, possibly by the mechanisms just cited.

The first theory, summarized in Table 1, is that of Gitzelmann and his colleagues who have been proponents of chronic intoxication [18, 20, 23]. There is good evidence for toxin production even in the best treated galactosemics. Chronic tenfold elevation of red cell gal-1-P occurs even on the best diets [10]. Urinary excretion of galactitol by patients on lactose-free diets is increased up to 20-fold [3, 58], and galactonate excretion is in excess [3]. The question is what are the sources of the gal-1-P and the abnormal metabolites that are seen in well treated galactosemics? Gitzelmann et al. [20, 23], propose that there is endogenous self-intoxication. This could stem from the continuous formation of gal-1-P by cleavage of UDPgalactose [20] which is normally formed from glucose via UDPglucose. The other endogenous source, is the turnover of glycoproteins and galactolipids. The extent of galactose production and the body burden which occurs via the turnover of these ubiquitous compounds is unknown and should be of principal concern.

There have been others, such as Gross and Acosta [26], who have felt that the intoxication may be exogenous, due to ingestion of galactose from hidden sources. The basis for this is the considerable amount of free galactose in vegetables and fruits and the possibility that galactose can be released from ingested galactans and complex carbohydrates. It is practically impossible to have a patient on a totally galactose-free diet. Indeed, Berry et al. [6] have shown in a dietary analysis of patients on lactose-free diets that nearly all the galactose ingested could be accounted for by fruits and vegetables containing the free sugar. However, after quantitating urinary galactitol of galactosemics in whom galactose ingestion was increased from the lowest level possible by supplementing 200 mg of the sugar per day they estimated that much of the urinary galactitol was derived from endogenous production of galactose [6].

The second hypothesis involves metabolite depletion. Low levels of inositol, the cyclic polyol, have been observed in lens and peripheral nerve of experimentally galactose-intoxicated animals [71]. This could result in abnormal metabolism of phosphatidylinositol and impairment of intracellular signalling. Another group of metabolites considered are the sugar nucleotides. Ng et al. [48] have reported low levels of UDPgalactose in red blood cells, cultured fibroblasts and liver of galactosemic patients. They postulated that the decreased formation of cellular UDPgalactose due to defective GALT results in the impairment of glycoprotein and galactolipid synthesis. This was based on the fact that UDPgalactose is the required donor of galactose to these complex substances. The use of more accurate methods of measuring UDP-galactose, however, have indicated that the erythrocyte levels of the compound are low in only a small number of galactosemic patients compared to normal subjects [5, 38], but that the ratio of UDPglucose to UDPgalactose is abnormal in many [6]. These findings are presented in more detail [63]. With regard to abnormal galactosylation there is, indeed, mounting evidence that there is defective galactosylation of glycoconjugates in affected cells [9, 49].

Table 2 Evidence for in utero toxicity

Neonatal Abnormalities
Fetal cataracts
Early liver dysfunction
Metabolite Accumulation
Amniotic fluid galactitol
Cord blood and tissue galactose-1-phosphate
Experimental Toxicity in Pregnant Rats
Newborn cataracts
Low brain weight, protein, DNA in offspring
Decreased oocytes in female offspring
Abnormal brain inositol metabolism

Table 2 presents observations which support the possibility of in utero toxicity. These are summarised by Holton [31] and Gibson [17]. Abnormalities are observed at birth. On slit lamp ophthalmologic examination fetal or embryonal cataracts have been found. Metabolite accumulation is another piece of evidence. Even when the mother of a galactosemic fetus is placed on a galactose-restricted diet there are abnormal levels of amniotic fluid galactitol [35] indicating that this substance is being formed in the developing fetus. In addition, there is elevated gal-1-P in the fetus [33]. Both of these observations are consistent with exposure of the fetus to galactose and abnormal prenatal metabolism. Further evidence for possible in utero toxicity comes from the experimental abnormalities produced in the offspring of pregnant rats who have been fed high galactose diet. In this case, the galactose readily crosses the placenta to produce fetal plasma levels which overwhelm the normal pathway of galactose metabolism. The findings include newborn cataracts [64], low brain weight and brain DNA in the offspring [27], decreased number of oocytes in the ovaries of females later in life [7], increased galactitol content in nerve endings [77] and evidence for abnormal brain inositol metabolism [78].

An examination of the phenotype of the various enzyme deficiencies related to galactose metabolism may shed some light on the metabolic problem. The abnormalities observed in galactokinase, GALT and epimerase deficiencies described in depth by Segal [62], are summarized in Table 3. In GALT deficiency there are abnormalities in lens, liver, brain, ovary and there is a high incidence of *Escherichia coli* sepsis. These occur, as noted

Table 3 The phenotype of enzyme deficiencies

	Galactokinase	Uridyltransferase	Epimerase
Lens	+	+	±
Liver	–	+	+
Kidney	–	+	+
Brain	±	+	+
Ovary	–	+	–
Sepsis	–	+	±

previously, in association with the high red cell gal-1-P, high urinary galactitol excretion and a tendency to lower RBC levels of UDPgalactose. On the other hand, galactokinase deficiency has the principal finding of cataracts without liver, kidney and ovarian dysfunction and no indication of sepsis. With regard to the brain, there are infants reported to have pseudotumor cerebri [43], and two patients with mental retardation [69], but there are too few reports to be sure of neurologic involvement. In contrast to GALT deficient patients, those with defective galactokinase form large amounts of galactitol [1, 21] without high cell levels of gal-1-P. The implication, after contrasting these two entities is that GALT-deficient patients suffer from the consequences of cellular gal-1-P accumulation.

There are only two cases of symptomatic severe UDP-galactose-4′-epimerase deficiency [29, 59]. One had cataracts, one had sepsis but both have liver, kidney and brain abnormalities including a new finding of neurosensory deafness. There appears to be no ovarian dysfunction [30]. In epimerase deficiency, when dietary galactose is low, elevated red blood cell gal-1-P may be reduced to normal but UDPgalactose stays elevated. Despite the many phenotypic similarities between GALT and epimerase deficiency, the latter is characterized by elevated red cell UDPgalactose even with modest galactose intake. The absence of ovarian dysfunction suggests that elevated UDPgalactose may protect the ovary from the damage observed in GALT deficiency. Again, the formation of gal-1-P is implicated as an important element in the poor outcome observed in other aspects of epimerase deficient patients.

Most of the preceding comments serve to highlight the unknown aspects of the pathobiochemistry of galactosemia. The sources of urinary galactitol and galactonate and RBC gal-1-P are unknown, and there are no data about their production rates. No information is available for the dietary and other factors that influence cell nucleotide sugar concentrations. Little has been learned about the metabolic flux of galactose in galactosemic cells or the rates of galactose production resulting from glycoconjugate synthesis and turnover.

Molecular genetics of galactosemia

Knowledge of molecular genetic defects has rapidly accumulated with the human GALT cDNA being cloned [54] characterized [15] and the gene structure sequenced [42]. A number of sequence changes have been observed [55, 56], the most frequent being a change at amino acid codon position 188 in which an arginine is substituted for glutamine, the so called Q188R mutation [42, 55]. The Q188R sequence change in exon 6 is significant since its location is two amino acids away from the histidine-proline-histidine binding sequence thought to be the active catalytic site [13]. The genetic information should allow us to make genotype-phenotype correlations, determine GALT structure-function relationships and examine factors regulating gene expression. They should permit construction of much needed genetic animal models of GALT deficiency and stimulate a beginning exploration of gene therapy. Molecular genetic defects are highlighted by Elsas [12] and gene expression by Heidenreich [28].

The dilemma of treatment

The comment on gene therapy leads emphasizes the dilemma of how to treat galactosemic patients. Should there be an attempt to stimulate residual GALT activity? Many patients have some GALT activity and there are observations that pharmacological doses of folic acid [58] or progesterone [50] may enhance this residual activity. Black galactosemics with 10% residual activity in liver [68] can metabolize significant amounts of galactose [61, 67]. If flux through the pathway were increased it would be possible to decrease gal-1-P in tissues and at the same time elevate UDPgalactose thereby normalizing factors which may be the basis of complications of galactosemia.

Should there be the stimulation of alternate metabolic pathways? Increasing the formation of galactonate, an oxidizable metabolite [8], could be helpful. Methods for accomplishing such a feat are, as yet, unknown. Should alternate pathways be interrupted. Much is known about the production of galactitol and it is possible to reduce the formation of this substance with aldose reductase inhibitors. Prevention of galactitol formation has been able to correct the observed toxicity of galactose in various animal models [40, 74].

Should the replacement of depleted metabolites be considered. One possibility is to give high doses of inositol to correct the depletion described in some experimental situations [24, 25]. Another would be to increase the level of nucleotide sugars. This has been advocated by the California group who are carrying out a study involving the administration of uridine to increase red cell UDP-galactose content [37]. Another possibility, of course, is gene therapy and the replacement of the defective GALT

gene. The sequence of the cDNA and the entire GALT gene are known [42]. The use of this information is important in devising gene transfer techniques by vectors to appropriate tissues. One of the key questions is whether replacement in liver would be sufficient or most replacement be made in other tissues, especially the brain and ovary, to prevent the disruption of their functions.

Those interested in galactosemia face a serious challenge. The "Clouds over Galactosaemia" announced in a commentary in the Lancet [11] over a decade ago have darkened. There is now a great urgency to find a solution of what to do to effectively treat galactosemic patients. It is clear that acute toxic manifestations of galactose in the newborn period can be prevented with elimination of galactose from the diet, but long-term complications still occur. The challenge should not be taken lightly. It is imperative that future strategies be considered to solve the galactosemia dilemma.

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