

16.1 Introduction

The cellular uptake and release of glucose and other monosaccharides is a protein-mediated process. Such proteins are embedded into the cell membrane and can be regarded as hydrophilic pores within the hydrophobic lipid bilayer. Monosaccharide transporters are substrate specific and stereospecific; their action is saturable and can be inhibited by specific competitors. Like an enzymatic reaction, the kinetic characteristics can be described by affinity constants and the number of transporter protein molecules determines maximal transport velocity (v_{\max}).

Two classes of monosaccharide transporters exist. The SGLT (sodium-dependent *glucose transporter*) family is characterized by the fact that glucose transport is coupled to sodium transport. Since the driving force for this type of transport is the electrochemical gradient for sodium (produced by the cellular Na^+/K^+ -ATPase system), glucose can be (“actively”) transported against its own gradient.

The second family, the GLUT (*glucose transporter*) proteins, mediates so-called facilitative diffusion along an existing glucose gradient and in the past members of this family have been considered to function as “passive” transporters. However, GLUT proteins are hormonally and substrate regulated; thus, they play a pivotal role in the regulation of carbohydrate metabolism. For example, one of the key functions of insulin is the translocation of GLUT4-bearing vesicles to the cell membrane of muscle cells and adipocytes allowing glucose influx.

The genes of the growing number of members of both the SGLT and the GLUT family have been identified during recent years. This was a key step in the study of the function of these proteins, of their tissue-specific expression and in the identification of genetic defects.

Knowledge of the tissue-specific expression of monosaccharide transporter proteins helps to define the clinical picture of the different disease entities. Many tissues carry more than one type of transporter and many members of the two monosaccharide transporter families are expressed in more than one tissue. Therefore, congenital disorders of different isoforms of monosaccharide transporters may present with a complex clinical picture

and will involve different organ systems. Well characterized disease entities are congenital glucose/galactose malabsorption (*SGLT1* defect), the glucose transporter protein syndrome (*GLUT1* defect), and the Fanconi-Bickel syndrome (*GLUT2* defect). In contrast, due to the high solubility of glucose, renal glucosuria (*SGLT2* defect) is not accompanied by specific clinical symptoms and, like some of the amino acid transporter defects, it can be classified as a “non-disease”. This condition is therefore only of biochemical, pathophysiological, molecular-genetic and differential-diagnostic interest.

■ 16.1.1 Congenital Glucose/Galactose Malabsorption (Synonym: *SGLT1* Defect)

Congenital glucose/galactose malabsorption is an autosomal recessive disorder. Clinical symptoms begin with the introduction of a glucose and galactose containing diet shortly after birth. Since *SGLT1* is responsible for glucose and galactose transport across the apical membrane of enterocytes, treatment attempts to avoid the osmotic effects of these malabsorbed monosaccharides by replacing them with fructose, which uses other transporter proteins. *SGLT1* could not be detected in human kidney; the fact, however, that patients with an *SGLT1* defect show mild glucosuria points to a physiological role of *SGLT1* in renal glucose reabsorption. Probably due to different kinetic characteristics, the main renal glucose transporter, *SGLT2*, cannot compensate for an impaired *SGLT1* function [1].

■ 16.1.2 Renal Glucosuria (Synonym: *SGLT2* Defect)

Renal glucosuria is a benign condition defined by isolated glucosuria in the presence of normoglycemia. A tubular transport defect has long been suspected and severe types (with a glucose excretion of up to $>100 \text{ g}/1.73 \text{ m}^2/\text{d}$ and recessive inheritance) and milder types (with a glucose excretion of $0.4\text{--}5 \text{ g}/1.73 \text{ m}^2/\text{d}$ and dominant inheritance) have been differentiated. Recently, it could be demonstrated that the different types of renal glucosuria can be caused by homozygosity (or compound heterozygosity) and heterozygosity for *SGLT2* mutations, respectively [2]. No treatment is necessary.

■ 16.1.3 Glucose Transporter Protein Syndrome (Synonyms: *GLUT1* Defect, DeVivo Syndrome)

Hypoglycorrachia (low CSF glucose) is the hallmark of this condition. In order to reach the CSF from small cerebral blood vessels, glucose has to cross the blood-brain barrier. The blood-brain barrier is characterized by impermeable tight junctions of endothelial cells which limit paracellular

transport. Glucose has to be transported across endothelial cells by facilitative diffusion along its gradient. Haplo-insufficiency of *GLUT1* (i.e. in most cases a de novo mutation or in rare families a dominantly inherited mutation on one chromosome) is sufficient to cause infantile convulsions, developmental delay, microcephaly, and movement disorders with a broad range of severity. Acute clinical symptoms may be triggered by fasting, and symptoms may be inversely related to the concentration of ketone bodies in blood. The fact that these alternate substrates are transported by other carriers is the rationale for therapeutic trials of a ketogenic diet [3, 4].

■ 16.1.4 Fanconi-Bickel Syndrome (Synonyms: *GLUT2* Defect, Glycogenosis with Fanconi Syndrome, “Glycogenosis Type XI”)

Fanconi-Bickel syndrome shows autosomal recessive inheritance. It is clinically characterized by the combination of hepatic glycogen storage and a generalized renal tubular dysfunction with disproportionately severe glucosuria. This combination of symptoms together with fasting hypoglycemia and glucose and galactose intolerance can be explained by the tissue-specific expression of *GLUT2* and the fact that *GLUT2* is both a glucose and a galactose transporter [5, 6].

16.2 Nomenclature

No.	Disorder	Tissue distribution	Chromosomal localisation	MIM
16.1	Congenital glucose/galactose malabsorption (<i>SGLT1</i> defect)	Intestine (kidney)	22q13.1	(*182380)
16.2	Renal glucosuria (<i>SGLT2</i> defect)	Kidney	16p11.2	233100 (*182381)
16.3	Glucose transporter protein syndrome (<i>GLUT1</i> defect)	Blood brain barrier (erythrocytes, many other tissues)	1p35–31.3	(*138140)
16.4	Fanconi-Bickel syndrome (<i>GLUT2</i> defect) (<i>see also 15.17</i>)	Liver, kidney, pancreatic β cells, intestine	3q26	227810 (*138160)

16.3 Metabolic Pathway

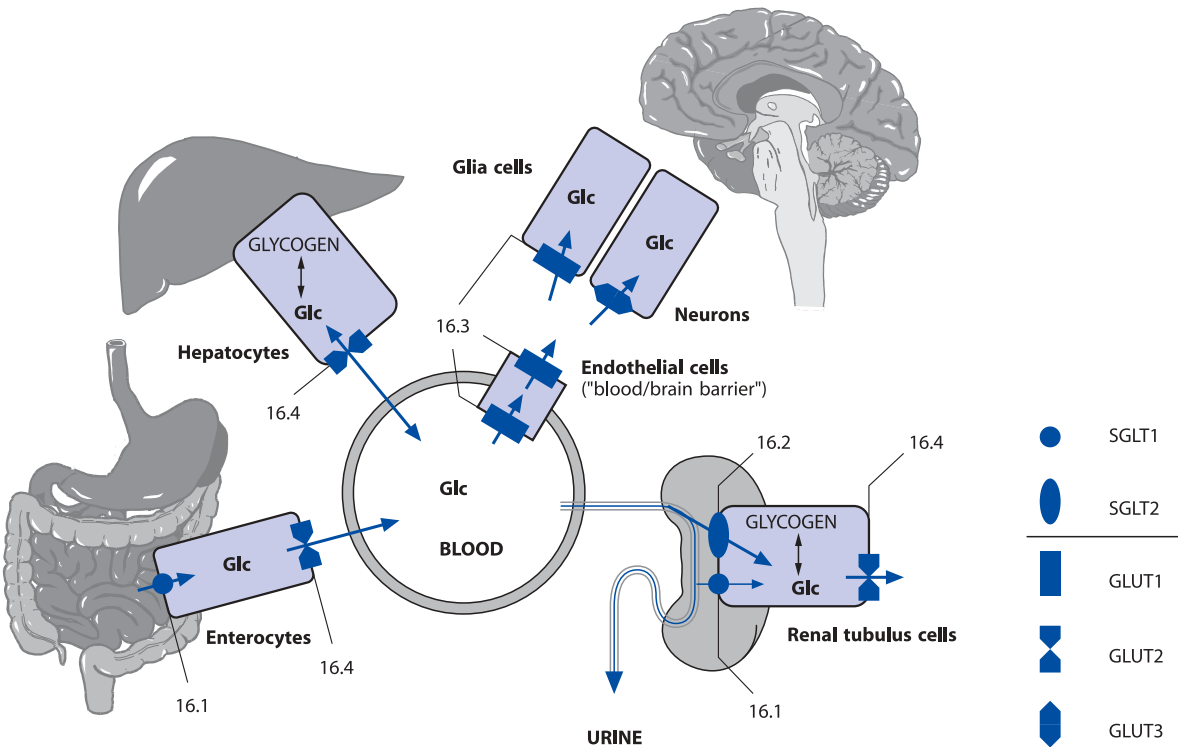


Fig. 16.1. Metabolic pathway

16.4 Signs and Symptoms

Table 16.1. Congenital glucose/galactose malabsorption (*SGLT1* defect) (approx. 40 patients reported)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Profuse osmotic diarrhea ^a	+++	+++	++	++	++
	Dehydration ^a	+++	+++	++	++	++
	Hypovolemic shock ^a	+	+	+	+	+
Routine laboratory	Na ⁺ (P) ^a	n-↑	n-↑	n-↑	n-↑	n-↑
	Glucose (U)	↑	↑	↑	↑	↑
Special laboratory	Reducing sugars (stool) ^a	+	+	+	+	+
	Pathological results on					
	oral glucose loading test	+	+	+	+	+
	oral galactose loading test	+	+	+	+	+
	oral fructose loading test	N	N	N	N	N
	Glucose, galactose uptake by enterocytes	↓	↓	↓	↓	↓
Kidney	Mild glucosuria	+	+	+	+	+

^a On a glucose- and/or galactose-containing diet.

Table 16.2. Renal glucosuria (*SGLT2* defect) (severe defects rare, approx. 20 cases; mild defects are frequent)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Isolated glucosuria (normal blood glucose)	+	+	+	+	+
Routine laboratory	Glucose (U)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
Special laboratory	None					

Table 16.3. Glucose transporter protein syndrome (*GLUT1* defect) (approx. 25 cases in literature)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Microcephaly		±	±	±	±
	Mental retardation		±	±	±	±
	Seizures		±	±	±	±
	Ataxia		±	±	±	±
	Muscular hypotonia		±	±	±	±
Routine laboratory ^a	Glucose (CSF)	↓	↓	↓	↓	↓
	Lactate (CSF)	n-↓	n-↓	n-↓	n-↓	n-↓
Special laboratory	Glucose uptake by erythrocytes	↓	↓	↓	↓	↓
	GLUT1 in erythrocytes (Western blot)	↓	↓	↓	↓	↓

^a Do not misinterpret the results of random, eventually postictal lumbar punctures that can give false-high glucose concentrations. In case of a clinical suspicion perform determination of CSF/plasma glucose ratio in samples drawn after at least 4 h of fasting.

Table 16.4. Fanconi-Bickel syndrome (*GLUT2* defect) (approx. 120 cases reported)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Hepatomegaly	n	n-++	++	+	+
	Hypoglycemic symptoms	±	±			
	Generalized renal tubulopathy (renal Fanconi syndrome)	+	+	+	+	+
	Rickets		±	±	±	±
	Short stature		++	++	++	++
Routine laboratory	Glucose-fasted (P)	n-↓	n-↓	n-↓	n-↓	n-↓
	Glucose-fed (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	Galactose (P)	n-↑	n-↑	n-↑	n-↑	n-↑
	ASAT/ALAT (P)	↑	↑	↑	↑	n-↑
	Triglycerides, cholesterol (P)	↑	↑	↑	↑	↑
	Uric acid (P)	↑	↑	↑	↑	↑
	Glucose (U)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Galactose (U)	↑	↑	n-↑	n-↑	n-↑
	Galactitol (U)	↑	↑	↑	↑	↑
	Sorbitol (U)	↑	↑	↑	↑	↑
	Lactate (U)	↑	↑	↑	↑	↑
	Amino acids (U)	↑	↑	↑	↑	↑
	Calcium, phosphorus (U)	↑	↑	↑	↑	↑
Special laboratory	Glycogen (L)	↑	↑	↑	↑	↑
	Glycogenolytic enzymes (all tissues)	N	N	N	N	N
GI	Loose stools, malabsorption	±	±			
Renal	Nephromegaly	+	+	+	+	+
	Hyperfiltration, renal failure				±	±
Eye	Cataract		±			

16.5 Normal and Pathological Values

The reference values for metabolites whose concentrations are altered in congenital disorders of glucose transport are shown in Table 16.4. Due to variable assay conditions, results of measuring monosaccharide transport into various cell types have to be interpreted in comparison to laboratory-specific reference values. Diagnostic values of monosaccharide uptake by enterocytes in SGLT1 deficiency (an autosomal recessive condition) usually fall below 10% of normal; diagnostic values of glucose uptake by erythrocytes in GLUT1 deficiency (an autosomal dominant condition) have been reported to be $46 \pm 8\%$ of controls.

Metabolite		Age group	Normal values	Pathological values
Glucose (P)	Fasting	1 d	2.2–3.3 mmol/l (40–60 mg/dl)	
		>1 d	2.8–5.0 mmol/l (50–90 mg/dl)	
		Child	3.3–5.5 mmol/l (60–100 mg/dl)	
		Adult	3.9–5.8 mmol/l (70–105 mg/dl)	
Glucose (CSF)	1 h after ingestion	Adult	6.6–9.4 mmol/l (120–170 mg/dl)	
	Fasting	Child	1.7–3.7 mmol/l (32–68 mg/dl)	
Glucose (CSF/P ratio)		Child	65–85%	<50%
Glucose (U)			<0.8 mmol/l (<15 mg/dl)	>0.8 mmol/l (>15 mg/dl)
			0.13–0.32 g/1.73 m ² /d	>0.32 g/1.73 m ² /d
Reducing substances (stool)			negative	positive
Galactose (P)	Fasting		0–0.03 mmol/l (0–0.5 mg/dl)	
	After milk ingestion	Newborn	<1.1 mmol/l (<20 mg/dl)	>1.1 mmol/l (>20 mg/dl)
		Child	<0.5 mmol/l (<9 mg/dl)	>0.5 mmol/l (>9 mg/dl)
		Adult	<0.24 mmol/l (<4.3 mg/dl)	>0.24 mmol/l (>4.3 mg/dl)
Galactose (U)			<377 mmol/mol creat	>631 mmol/mol creat
Galactitol (U)			2–5 mmol/mol creat	>30 mmol/mol creat
Sorbitol (U)			2–26 mmol/mol creat	
Lactic acid (P)	Fasting	Child	0.6–2.4 mmol/l	>3.0 mmol/l
Lactic acid (CSF)		Child	1.1–2.6 mmol/l	>3.0 mmol/l
Lactic acid (U)		Child	<200 mmol/mol creat	>300 mmol/mol creat
Glycogen (L)			<5.0 g/100 g wet tissue	>5.0 g/100 g wet tissue

16.6 Loading Tests

■ Oral Glucose Loading Test

Indication:

1. To test for impaired intestinal uptake in SGLT1 deficiency.
2. To test for glucose intolerance (decreased hepatic uptake, decreased β -cell insulin secretion (?)) in Fanconi-Bickel syndrome.

Fasting state: 4 to 12 h (depending on age).

Glucose dose: 2 g/kg as 10% solution or as an equivalent amount of oligo-saccharides (maximum dose 50 g) given by mouth within 5–7 min.

Criteria:

1. Clinical signs, abdominal pain, diarrhea, reducing substances in stool, H₂ breath test and glucose (P) determination at baseline and every 30 min for 3 h;
2. Glucose (P) and lactic acid (P) determinations at baseline and every 30 min for 3 h.

Caution: hypovolemia may develop in SGLT1 deficiency.

Interpretation: pathologic increase of H_2 (breath test) and diminished increase of glucose (P) in SGLT1 deficiency. Glucose low or normal and lactate high or normal at baseline, exaggerated increase of glucose and decrease of lactate after glucose load in Fanconi-Bickel syndrome.

■ Oral Galactose Loading Test

Indication:

1. To test for impaired intestinal uptake in SGLT1 deficiency.
2. To test for galactose intolerance (decreased hepatic uptake) in Fanconi-Bickel syndrome.

Fasting state: 4 to 12 h (depending on age).

Galactose dose: 1 g/kg as 20% solution given by mouth within 5–7 min.

Criteria:

1. Clinical signs, abdominal pain, diarrhea, reducing substances in stool, H_2 breath test and glucose (P) determination at baseline and every 30 min for 3 h;
2. Glucose (P), galactose (P) and lactic acid (P) determinations at baseline and every 30 min for 3 h.

Caution: hypovolemia may develop in SGLT1 deficiency.

Interpretation: pathologic increase of H_2 (breath test) and diminished increase of glucose (P) in SGLT1 deficiency. Glucose low or normal and lactate high or normal at baseline, exaggerated increase of galactose after galactose load in Fanconi-Bickel syndrome.

■ Oral Fructose Loading Test

Indication: while dangerous and obsolete in the diagnosis of HFI, the *oral* fructose loading test serves as a reference test in the diagnosis of SGLT1 deficiency.

Fasting state: 4 to 12 h (depending on age).

Fructose dose: 1 g/kg as 20% solution given by mouth within 5–7 min.

Criteria: clinical signs, abdominal pain, diarrhea, reducing substances in stool, H_2 breath test and glucose (P) determination at baseline and every 30 min for 2 h.

Interpretation: no increase of H_2 (breath test) and normal increase of glucose (P) in SGLT1 deficiency.

16.7 Specimen Collection

Test	Preconditions	Material	Handling	Pitfalls
Metabolites				
Glucose	Fasted/non-fasted	P	NaF tubes	Bacterial contamination ^a
Glucose	Fasted (!) ^b	CSF		Bacterial contamination ^a Pleocytosis
Glucose		U		Bacterial contamination ^a
Reducing substances		Stool		Bacterial contamination ^a
Galactose	Fasted/non-fasted	P	Perchloric acid extract	
Galactose		U		Bacterial contamination ^a
Galactitol		U		Bacterial contamination ^a
Sorbitol		U		Bacterial contamination ^a
Lactic acid	Fasted/non-fasted	P	NaF tubes or perchloric acid extract	Hypoxia ^a
Lactic acid	Fasted (!) ^b	CSF	NaF tubes or perchloric acid extract	^a
Glycogen		Liver	Freeze immediately	
Monosaccharide transport assays				
SGLT1		Intestinal biopsy	^c	
GLUT1		Erythrocytes	^c	

^a Always store samples at -20°C if immediate processing is not possible.

^b Always use fasted samples and a concomitantly drawn plasma sample for determination of CSF/P ratio.

^c Since assay conditions may vary with time and with different reference laboratories you are encouraged to contact these laboratories before obtaining specimens.

16.8 Prenatal Diagnosis

Disorder	Material	Timing, trimester
16.1 Congenital glucose/galactose malabsorption (<i>SGLT1</i> defect)	CV, AFC	I, II
16.2 Renal glucosuria (<i>SGLT2</i> defect)		
16.3 Glucose transporter protein syndrome (<i>GLUT1</i> defect)	CV, AFC	I, II
16.4 Fanconi-Bickel syndrome (<i>GLUT2</i> defect)	CV, AFC	I, II

16.9 DNA Analysis

Disorder	Material	Method
16.1 Congenital glucose/galactose malabsorption (SGLT1 defect)	Genomic	Sequencing
16.2 Renal glucosuria (SGLT2 defect)	Genomic	Sequencing
– Severe type	Genomic	Sequencing
– Mild type	Genomic	Sequencing
16.3 Glucose transporter protein syndrome (GLUT1 defect)	Genomic	Sequencing FISH
16.4 Fanconi-Bickel syndrome (GLUT2 defect)	Genomic	Sequencing RFLP analysis

16.10 Initial Treatment (Management while Awaiting Results)

■ 16.10.1 Congenital Glucose/Galactose Malabsorption

Patients completely recover after replacement of oral feedings by total parenteral nutrition. A diet containing fructose as the only carbohydrate is well tolerated (hereditary fructose intolerance must be excluded).

■ 16.10.2 Renal Glucosuria

None! Renal glucosuria should not be confused with any types of diabetes mellitus.

■ 16.10.3 Glucose Transporter Protein Syndrome

Early introduction of a strict ketogenic diet provides an alternate energy source for the brain. It has been shown that it may have a dramatic effect on seizure frequency which suggests a long-term effect on brain development.

■ 16.10.4 Fanconi-Bickel Syndrome

Gluconeogenesis should be suppressed in order to avoid glycogen accumulation; this can be accomplished by a constant supply of slow release carbohydrates (frequent feeds, corn starch, nasogastric oligosaccharide drip feeding). Symptomatic replacement of water, electrolytes, alkali, calcium, phosphorus, vitamin D. Galactose restriction depending on galactose (P) and galactose-1-phosphate (erythrocytes) concentration.

16.11 Summary/Comments

Congenital disorders of glucose transport present with a broad spectrum of clinical symptoms depending on which tissue-specific isoform is affected. Although clinical signs of some of the transporter defects have been known for a while, the description of the molecular genetic bases during the last few years has helped in our understanding of the etiology and the pathophysiology of these conditions. Except renal glucosuria (a non-disease yet important differential diagnosis) all known defects of glucose transporter proteins are treatable inborn errors of metabolism that respond well to dietary measures.

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