Connecticut Children's MEDICAL CENTER

Glycogen Storage Disease Program

FAROE ISLAND RESEARCH TEAM

Landssjúkrahúsið
National Hospital of the Faroe Islands

Ketotic GSDs (type 0, III, VI and IX) - basics -

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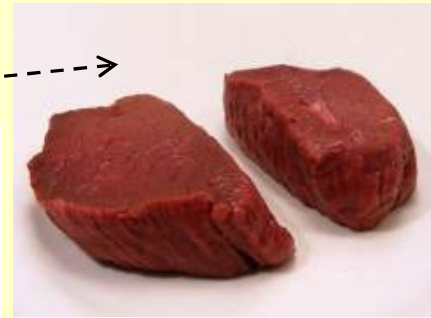
Sources of energy

Carbohydrates (sugars)

Fats

Protein



Major functions of different nutrient

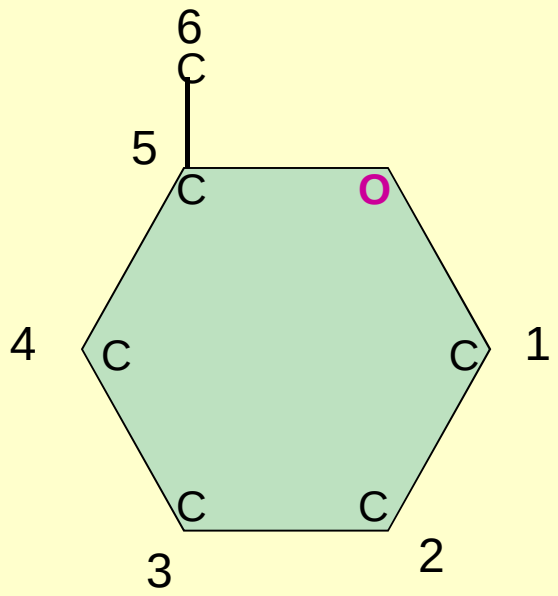
- sugars / carbohydrates:

  nutrition for brain; sugar = “fast” fuel
- fat:

  fuel for muscle; transport of vitamins
- protein:

  growth, major component of muscles,
  2nd line energy-source
  (via gluconeogenesis = transformation of non-sugars into glucose)

Glucose, the “prototype” of sugars



Glucose is formed as a hexagon, 5 corners are constituted by a carbon (C) atom, in the sixth corner an oxygen (O) atom is located. At the corner no. 5 a branch is positioned with the sixth carbon atom in the end.

Different sugars

act at different speeds: for some of them it takes more time to get blood sugar up, for others less

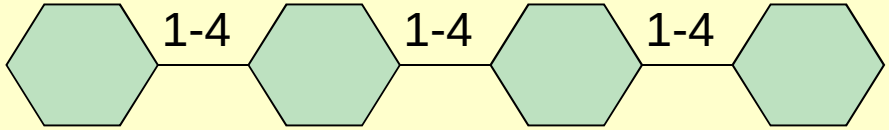
- “Short”/”fast” or simple sugars/disaccharides:
  - glucose (grapes)
  - fructose (fruits)
  - sucrose/ saccharide (cane sugar)
  - lactose (milk)
- “Delayed” sugars or oligosaccharides (maltodextrin)
- “Slow” carbohydrates or starch/glycogen

  (from corn, in potatoes, in carrots, in grain)

Why is sugar stored as glycogen?

- To avoid too high blood sugars after meals
- Sugar would be used immediately for energy production
- More “space” for storage: “one item into one drawer”

Oligosaccharide and Glycogen
are composed of glucose molecules

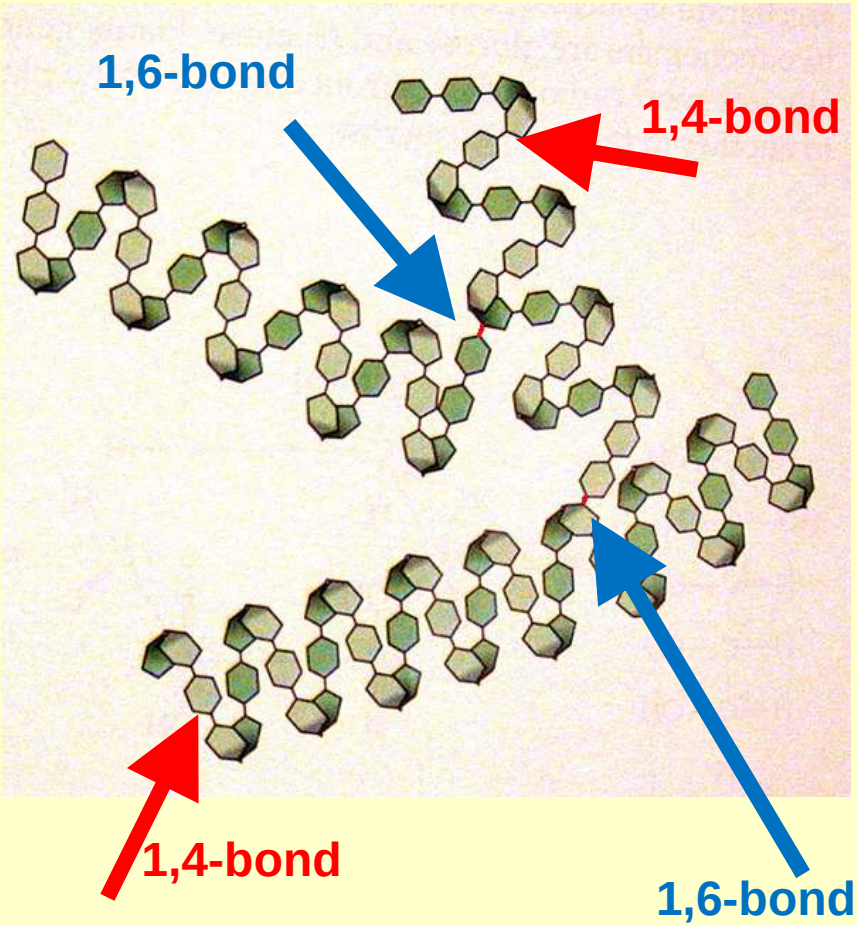


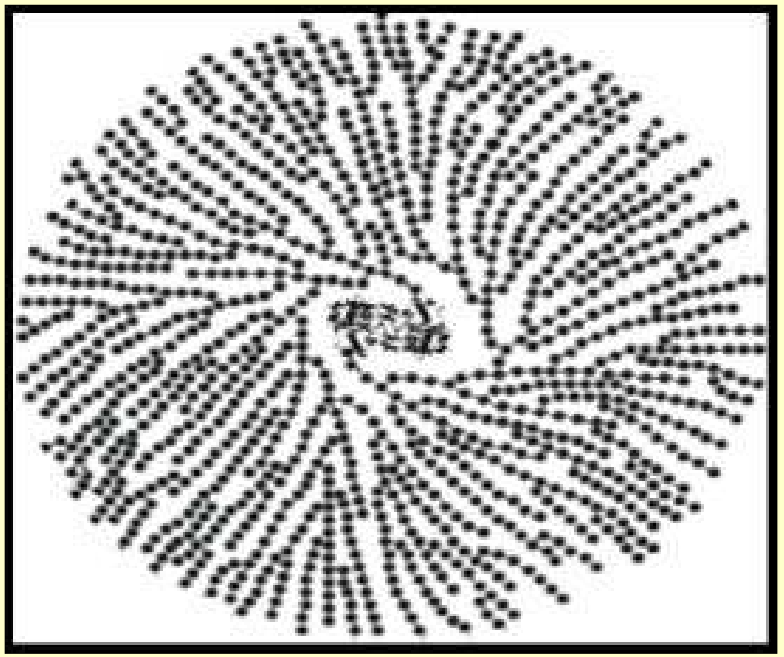
Maltodextrin / Fantomalt (=oligosaccharide):
3-20 glycosyl-[=sugar-] residues; 1,4-bond

Structure of glycogen

- Straight chain of **1,4-bonds**.
- After 12 to 16 glucosyl-residues have been added, a branching enzyme transfers a block of about six residues to yield a new branch starting with a **1,6-bond**.

Structure of glycogen

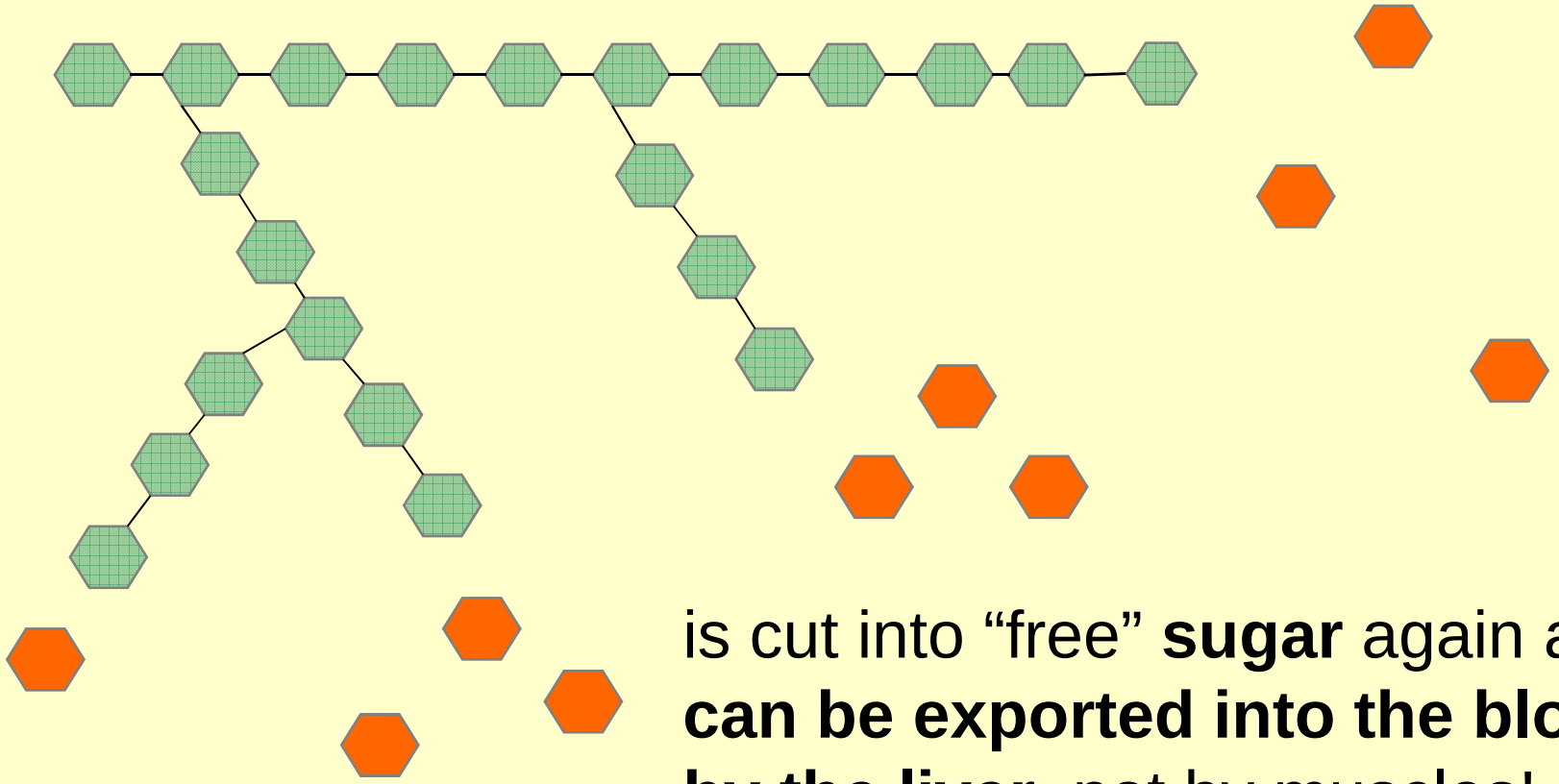




Up to 30.000 glucose molecules in one glycogen molecule! Glycogen is mainly stored in liver and muscles.

Glycogen → Glucose

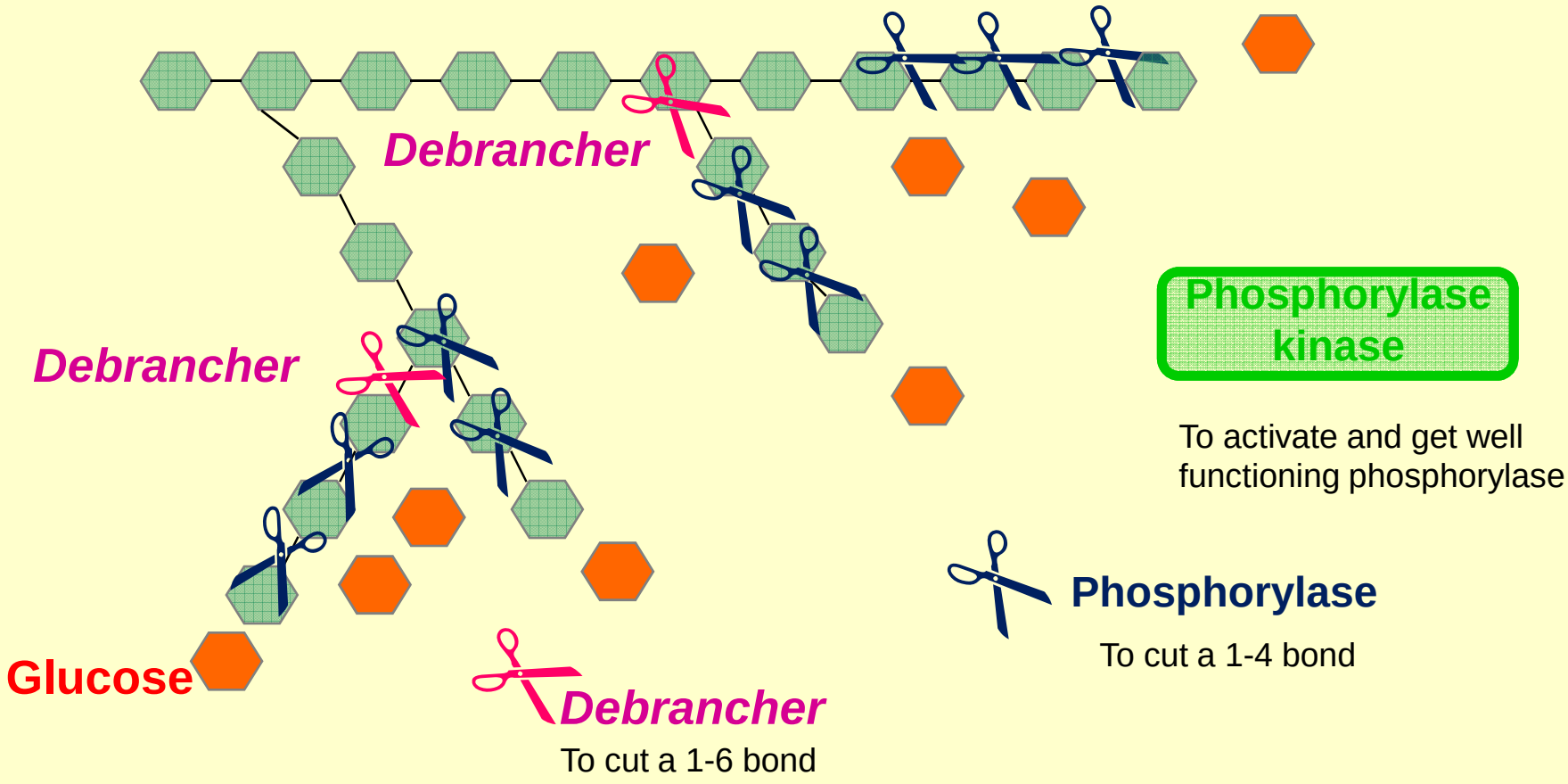
When blood sugar falls low, **glycogen**



is cut into “free” **sugar** again and **can be exported into the blood by the liver**, not by muscles!

Glycogen → Glucose

To cut down glycogen into glucose, different enzymes (=scissors) are required.



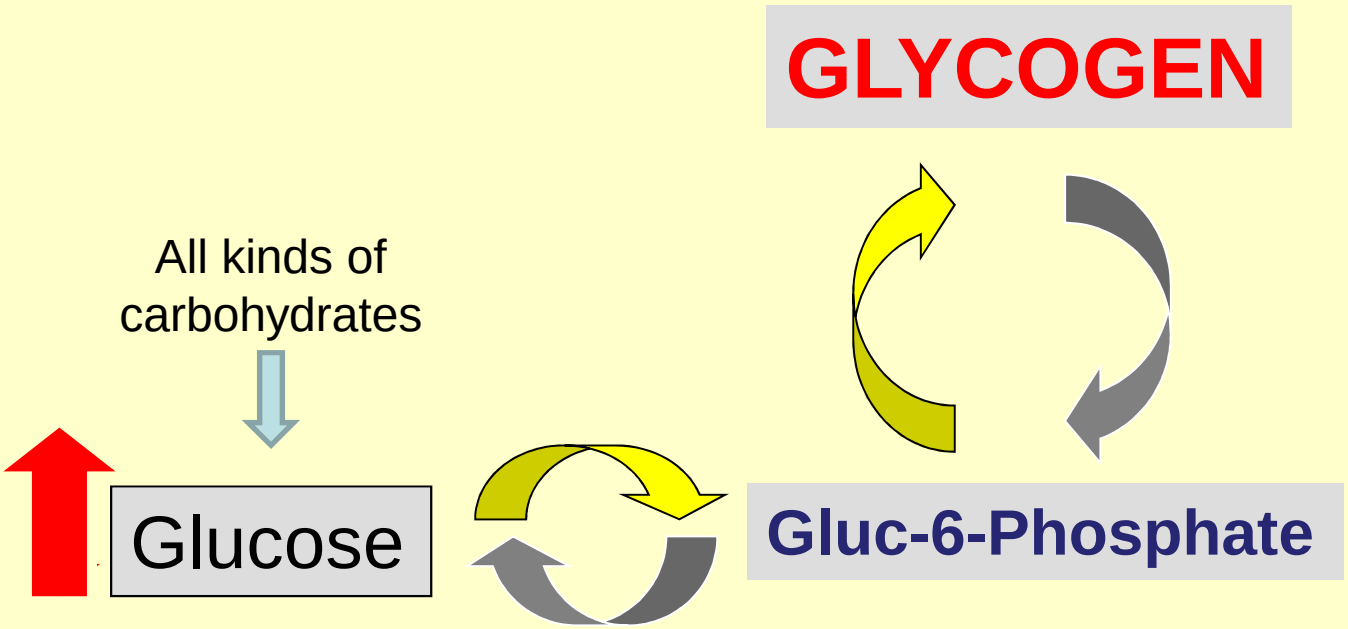
Glycogen → Glucose: some defects

Sometimes one or several of the enzyme that are required for cutting glycogen into glucose don't function correctly; this is caused by mutation(s) [mistakes] in the genes (blueprints) of these enzymes.

	defect enzyme/scissor
GSD type III	***Debrancher***
GSD type VI	**Phosphorylase**
GSD type IX	**Phosphorylase kinase** (= activator of phosphorylase)

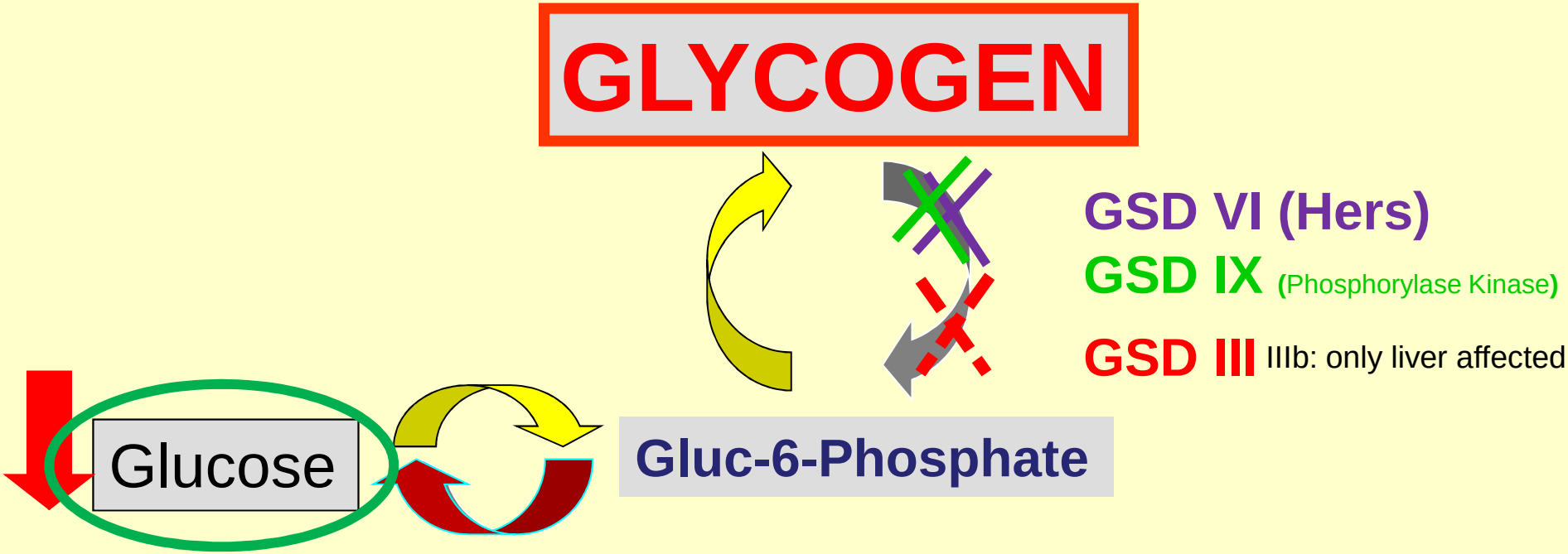
In GSD III, VI and IX glycogen cannot completely be broken down to sugar/glucose.

Stabilization of blood sugar level with the “help” of glycogen



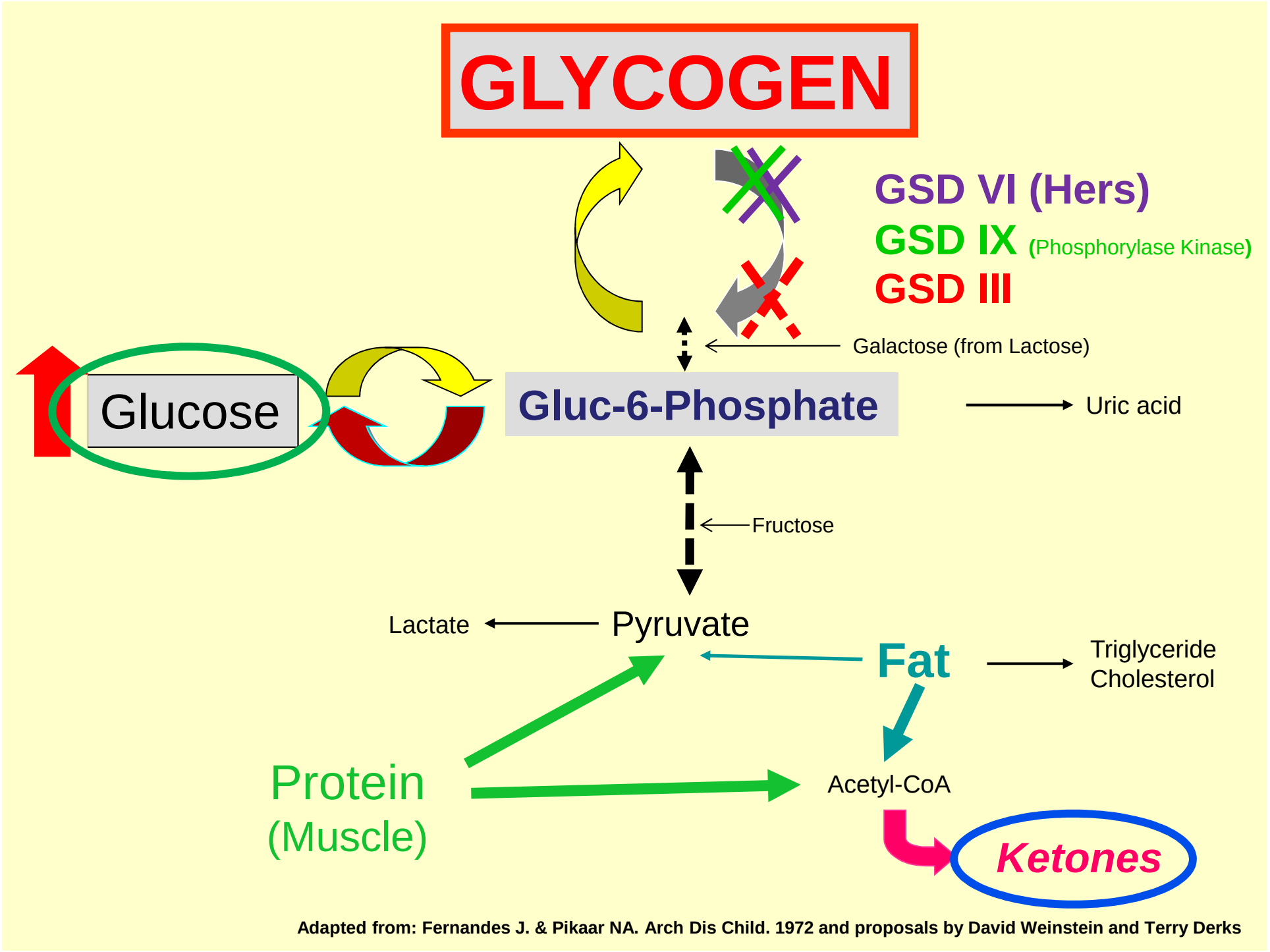
Normal situation: all kinds of carbohydrates are broken down into simple sugars in the intestine and in the liver; then they can be stored as glycogen (mostly in liver and muscles, but, too, in many other cells). If blood sugar is falling, glycogen is transformed back into sugar. But only the liver (and to a small degree the kidneys) is able to set this sugar free into the blood. The other organs will use “their” sugar.

Adapted from: Fernandes J. & Pikaar NA. Arch Dis Child. 1972 and proposals by David Weinstein and Terry Derks



Buildup of glycogen is normal in GSD III, VI and IX. It‘s the breakdown that is hampered/ impaired. During the time more and more glycogen is stored. Sugar/glucose from blood is used by the body. Thus, blood sugar will fall but cannot be corrected by breakdown of glycogen. So, a counter regulation is activated (see figure on **next slide**):

Protein can be transformed via pyruvate into glucose (some protein will be converted into acetyl-CoA and ketones). Thus blood sugar gets up again.
At the same time fat gets mobilized from fatty tissue, is transported into the liver and transformed into ketone bodies. And if you don’t measure ketones, you might miss the fact that your blood sugar has been low and that your body had to use (muscle) protein to provide sugar which is the first line energy source for the brain.
Sugar from fruits (fructose) and milk (lactose = galactose and glucose) can be metabolized into glucose, too!



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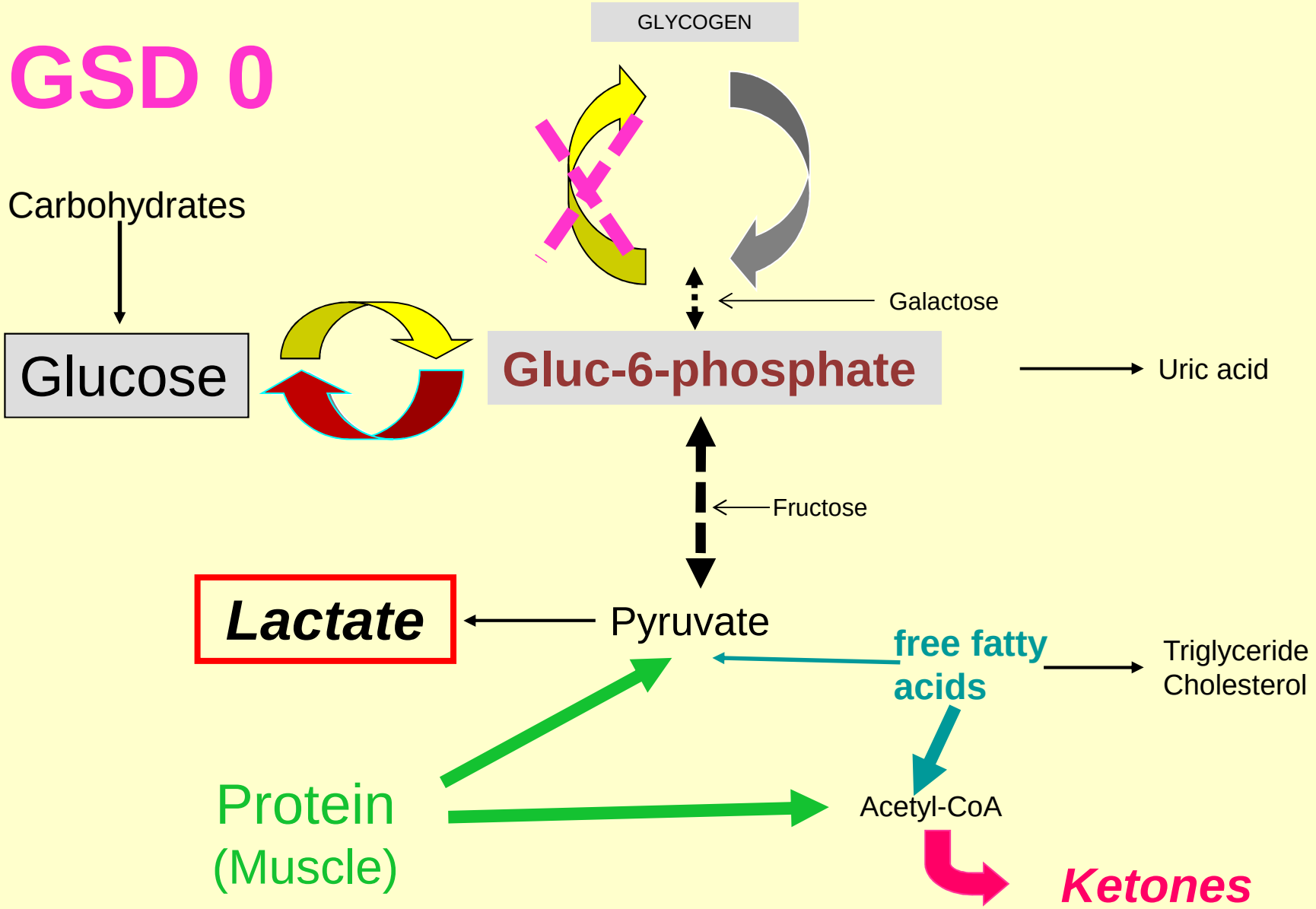
GSD 0



In GSD type 0, ***BUILD-UP*** of glycogen is impaired. Glucose is shunted from Glucose-6-Phosphate via Pyruvate to Lactate after meals. When blood sugar falls low again, the body uses the same mechanism as in type III, VI and IX (see slide above) to transform protein into sugar.

Effects of incomplete breakdown of glycogen in GSD type III, VI and IX

- Storage of partially broken down glycogen
- This abnormal glycogen irritates (liver) cells
- Incomplete breakdown of glycogen leads to lack of energy/sugar during fast and exercise
- Therefore, other sources have to be used for survival/normal function of brain and muscles

Ketotic GSDs

GSDs type 0, III, VI and IX present

in ***FASTING*** state with

- **Elevated** ketones
- Normo- or hypoglycemia
- Normal lactate

Therefore these types are called the

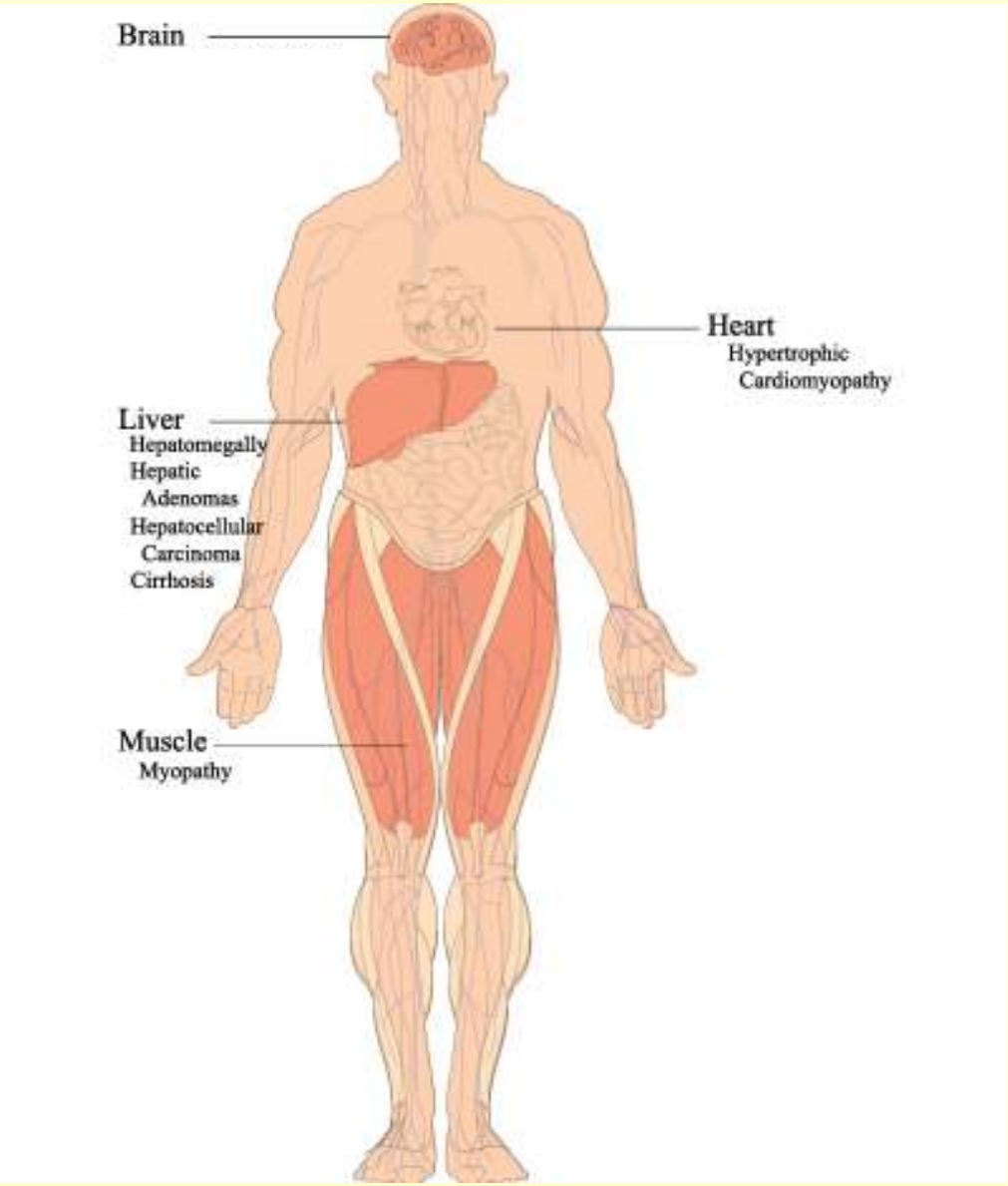
“ketotic GSDs”

Some details about the different types of ketotic GSDs

GSD IIIa: Symptoms in children

- enormously enlarged liver
- protruded abdomen
- truncal obesity and doll face
- hypoglycemia
- hyperlipidemia/hypercholesterinemia
- muscle hypotonia
- reduced physical endurance/stamina
- cardiomyopathy
- delayed motor development
- retarded growth/short stature
- normal mental development

Common complications in adults with GSD IIIa who have not been treated optimally (1)



Common complications in adults with GSD IIIa who have not been treated optimally (2)

- myopathy (up to 100%): weakness and wasting
- mildly enlarged liver, cirrhosis (*alcohol and smoking!*), sometimes adenomas or even cancer
- cardiomyopathy (up to 50%)
- type 2 diabetes mellitus
- osteoporosis (poor calcium intake, vitamin D deficiency, lack of muscle effects, increased cortisol, high ketones)
- neuropathy / encephalopathy
- early atherosclerosis / early coronary artery disease?

Symptoms in type VI and IX

Type VI (Hers)

- Hepatomegaly
- Poor growth
- Delayed puberty
- Hypoglycemia
  (esp. in the morning with elevated ketones)
- Hepatic adenomas, cirrhosis
- Cardiomyopathy?

Type IX (PHK-def)

(Phosphorylase-Kinase)

- Hepatomegaly
- Poor growth
- ADHD
- Delayed puberty
- Fasting ketosis
- Liver fibrosis/cirrhosis

Symptoms in type 0

Caused by deficient glycogen synthase

- Hyperglycemia AFTER meals
- Hyperlactatemia (=high lactate) AFTER meals
- Fasting ketotic hypoglycemia
- Lethargy, morning drowsiness, pallor, nausea, vomiting, seizures following overnight fasting
- Sometimes mild hepatomegaly from fatty liver
- Poor growth

Prognosis for ketotic GSDs with optimal treatment

- With good metabolic control
  - All labs can become completely normal
  - All persons with ketotic GSDs can have a great life
- In some adults type IIIa a mild non-debilitating myopathy might develop

Goals of intervention/treatment

- blood sugar 4.2-5.0mmol/L (75-90mg/dL)
- low/negative ketones (0.0-0.2mmol/L)
  after puberty ketones up to 0.5mmol/l are ok as long as liver function tests are fine
- normal growth
- (nearly) normal strength and endurance
- normal life / good life quality

Treatment of GSD Type 0, III, VI and IX

Goal: Provide enough energy without provoking over-storing of glucose as glycogen, but on the other hand being sufficient to prevent muscle breakdown/damage

Minimum amount of cornstarch or carbohydrates to avoid hypoglycemia

High protein diet with 3-3.5 (-4) grams/kg/day

in type 0, VI and IX: 2-2.5 (-3)g/kg/day

Adjust dose based upon blood glucose,
blood ketone,
and urine myoglobin monitoring

Principles of diet in GSD 0, III, VI and IX

- ✓ Frequent small meals (every 3-4 hours)
- ✓ Max 15g of carbohydrates per main meal (5g per snack)
- ✓ Max 5g of simple sugar per main meal (2.5g per snack)
- ✓ High protein food

  protein intake for type IIIa: **3-4g/kg** bodyweight/day, resp. **2-2.5g/kg** in type 0, IIIb, VI, IX
- ✓ Bedtime snack
- ✓ Uncooked cornstarch UCCS
- ✓ Supplements (vitamins, calcium, iron)
- ✓ Probiotics for those who use cornstarch

For details see: Diet and treatment in ketotic GSDs