Glycogenosis / question and case reports

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Questions

1. Glycogen biosynthesis
   - A - requires inorganic phosphate as one of the substrates
   - B - involves the formation of α-1 → 6 branches by glucan unit transfer from α-1 → 4 bonds
   - C - includes synthesis of UDP-glucose directly from uridine triphosphate and glucose-6-phosphate
   - D - involves the transfer of glucose residue in UDP-glucose to the reduced end of the "primer" of glycogen
2. Glucagon acts by:
   - A - inhibits cAMP-dependent protein kinase in the liver
   - B - stimulates glycolysis in the liver
   - C - stimulates gluconeogenesis in muscles
   - D - stimulates glycogen phosphorylase phosphorylation in the liver
   - E - stimulates glycogen synthase dephosphorylation in the liver
3. Type I glycogenosis (Gierke's disease) is caused by:
   - A - hepatic glucose-6-phosphate dehydrogenase deficiency
   - B - glucose-6-phosphatase deficiency in the liver and kidneys
   - C - abnormal structure of liver glycogen
   - D - amylo-1 → 6-glucosidase deficiency in the liver and muscles
   - E - hepatic phosphorylase deficiency
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     Question 1.
     - A - Wrong. Glycogen formation starts from glucose-1-phosphate and does not require the presence of inorganic phosphate; it is needed to phosphorylate glucose to glucose-6-phosphate.
     - B - Wrong. The branching of the glycogen chain [1 → 6] by the α-glycosidic bond does not occur by transfer of the glucan unit from the [1 → 4] α-glycosidic bond. This is done using a "branching enzyme" (amylo [1 → 4] → [1 → 6] -transglucosidase).
     - C - Wrong. This reaction is not based on glucose-6-phosphate, but on glucose-1-phosphate.
     - D - Right. Glucose-1-phosphate reacts with uridine diphosphate glucose (catalyzed by UDP-glupyrophosphorylase). Glycogen synthase causes a glycosidic bond between carbons C1 and C4 of the active nucleotide (UDP-glu). The condition for the formation of the polysaccharide skeleton is the presence of a small amount of "glycogen primer". Question 2.
     - A - Wrong. Glucagon, on the other hand, induces a sequence of reactions leading to the activation of cAMP-dependent protein kinase in the liver.
     - B - Wrong. Glucagon does not stimulate glycolysis in the liver, but insulin. Glucagon has an inhibitory effect on glycolysis enzymes (phosphofructokinase and pyruvate kinase).
     - C - Wrong. Gluconeogenesis takes place mainly in the liver ev. in the kidney, not in skeletal muscle. It is a lactate producer, but it is metabolized to glucose in the liver (Cori cycle).
     - D - Right. Glucagon in the liver (similar to adrenaline in the liver and muscle) first induces increased cAMP production in the cell ("second messenger"), which activates cAMP-dependent protein kinase, which activates the enzyme phosphorylase kinase b to active phosphorylase kinase a; this in turn activates phosphorylase b to active phosphorylase a. This enzyme initiates glycogenolysis. Question 3.
     - A - Wrong. Glucose-6-phosphate dehydrogenase deficiency prevents glucose metabolism in the pentose cycle .
     - B - Correct. Type I glycogenosis is caused by glucose-6-phosphatase deficiency in the liver and kidneys.
     - C - Wrong. Type I glycogenosis does not lie in an abnormal glycogen structure. This is for type IIIa, IIIb, IV.
     - D - Wrong. A– [1 → 4] –glucosidase deficiency causes type IIa glycogenosis (Pompe disease).
     - E - Wrong. Hepatic phosphorylase deficiency causes type VIa glycogenosis (Hers).

Case reports

Newborn slightly hypotrophic, with cyanosis and marked hypoglycemia edit source]

It is a newborn born in the 38th week of gestation, 2,100 g (adequate weight: 3,300 g), length 47 cm, slightly cyanotic (for hypoxia), with tachycardia (35 / min). Glycaemia: 0.8 mmol / l (lower limit for newborns: 2.5 mmol / l). Mother 35 years. In the last trimester, she had mild hypertension and recurrent urinary tract infections, vomiting and eating very little.

Questions:

1. What is the cause of such low levels in the newborn?
2. How is the energy metabolism of a fetus different from a newborn?
   1. Glycogen deficiency in the newborn's liver. In the last 9-10 weeks of gestation, glucose from the mother's

blood (passing through the placental barrier into the fetal circulation) is also stored in the fetal liver in the form of glycogen. This is due to the predominant effect of insulin during this period. After childbirth, when the mother's glucose supply suddenly stops, the source of glucose in the first hours is glycogen stored in the liver. If the mother does not eat enough in the last weeks before giving birth, a sufficient supply of glycogen cannot be created in the fetal liver, because hypoglycemia inhibits glycogen synthase activation.

2. The only source of energy for the fetus in the uterus is the continuous supply of glucose from the maternal circulation. Fetal blood glucose levels are about 75% of maternal blood glucose. In terms of energy metabolism, fetal tissues are under the dominant hormonal effect of insulin, which supports fetal growth. In the last 10 weeks of pregnancy, the energy supply for the first hours after birth begins to form in the form of liver glycogen. The birth of the mother's circulating glucose ends in childbirth, and the source of glucose before the first meal is hepatic glycogenolysis. The newborn must adapt to an intermittent supply of nutrients (fat, glucose and galactose from lactose in milk). The glucose requirement in the newborn is relatively greater than in the adult, because the weight of the brain tissue is greater than the weight of the liver. Therefore, the newborn is more difficult to maintain glucose homeostasis and can easily fall into hypoglycemia under heavy load. With umbilical cord occlusion, the newborn must cope very quickly with the predominant fetal hyperinsulinism. This is made possible by the secretion of "counterhormones": adrenaline and glucagon, which prevent the progressive fall of glycaemia by stimulating glycogenolysis and gluconeogenesis.

Infant with recurrent hypoglycaemia edit source]

An infant with recurrent hypoglycemia from birth was tested with glucagon and 1 hour after a carbohydrate diet. Glycaemia rose from 3.9 mmol / l to 6.1 mmol / l. 3 hours later, the blood glucose dropped to 2.5 mmol / l. However, no increase in blood glucose was observed after further glucagon administration.

Question: What is the cause of this form of glucagon response?

- A - Deficiency of hepatic glycogen phosphorylase or glycogen "mediator"
- B - Glucose-6-phosphatase deficiency.
- C - Defect in the glucagon receptor.
- D - Inability to secrete an adequate amount of glucagon.
- E - The problem in gluconeogenesis.

This is only a problem in gluconeogenesis. The patient responds rapidly with an adequate increase in blood glucose after carbohydrate delivery and a further increase in blood glucose 1 hour after glucagon administration. This means that it is able to produce and break down liver glycogen normally. Its glucose-6-phosphatase also releases glucose from glucose-6-phosphate in the hepatocyte. The glucagon receptor and protein kinase a must also be functional. However, fasting glucose levels fall rapidly to below normal levels. Glycogen stores are unable to maintain normal blood glucose levels for extended periods of time, even though glucagon is functioning properly. The error is therefore in the alternative source of glucose - in gluconeogenesis. It may be a deficiency of one of the key enzymes of gluconeogenesis, e.g. pyruvate dehydrogenase, pyruvate carboxylase, phosphoenolpyruvate carboxykinase or fructose-1,6-bisphosphatase, glucose-6-phosphatase is fine.

Patient with type V glycogenosis (McArdle's disease) and patient with type VI glycogenosis (Hers' disease) [edit | edit source]

Both conditions are caused by an inherited deficiency of a key glycogen degradation enzyme: glycogen phosphorylase.

Question:

1. Which of these types has more severe clinical symptoms and why?
    1. Liver and muscle glycogen phosphorylase are genetically distinct forms. *Hepatic glycogen phosphorylase* deficiency is clinically manifested as Hers' disease. The main symptom is hypoglycaemia during fasting because liver glycogenolysis does not work. If gluconeogenesis from other sources is OK, hypoglycemia is usually mild. However, it can be fatal if this glucose source does not work. In contrast, deficiency of *muscle glycogen phosphorylase* (McArdle's disease) manifests itself only with increased muscle strain (muscle fatigue, muscle cramps, myoglobinuria and leaching of creatine kinase into the blood plasma). At rest, the patient is virtually asymptomatic.

Links

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- Glycogenosis
- Disorders of glucose metabolism and thematic issues and case reports
- Characteristics of the neonatal period

Other chapters from the book MASOPUST, J., PRŮŠA, R .: Pathobiochemistry of metabolic pathways : [show]

Source

- MASOPUST, Jaroslav and Richard PRŮŠA. *Pathobiochemistry of metabolic pathways.* 1st edition. Prague: Charles University, 1999. 182 pp. 38- 40. ISBN 80-238-4589-6 .