Ministry of Public Health of Ukraine
Poltava State Medical University

Carbohydrate metabolism – 2. Metabolism of glycogen; gluconeogenesis. Regulation and pathology of carbohydrate metabolism. Diabetis mellitus.

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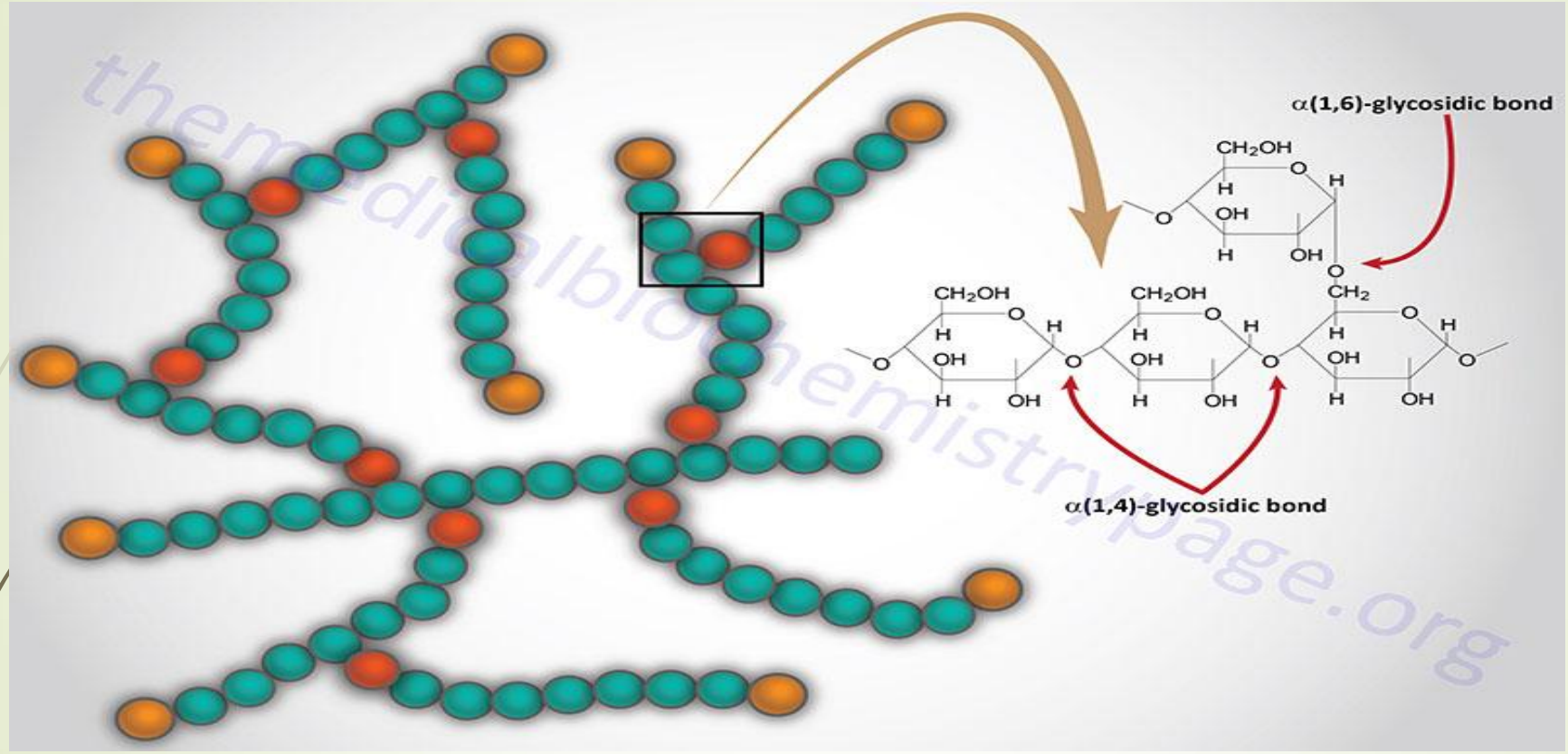
Lecture plan

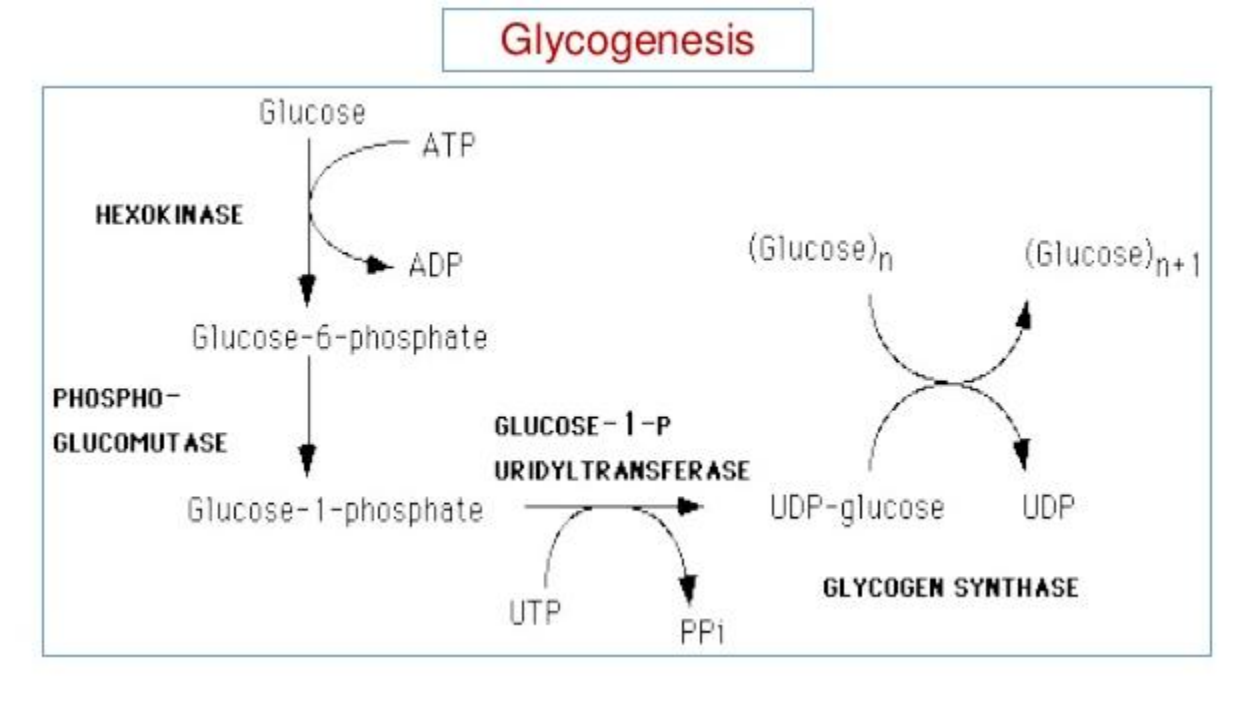
- Synthesis of glycogen.
- Catabolism of glycogen.
- Regulation of glycogen metabolism.
- Gluconeogenesis.
- Glucosemia
- Hormonal regulation of glucose blood concentration.
- Diabetes mellitus.

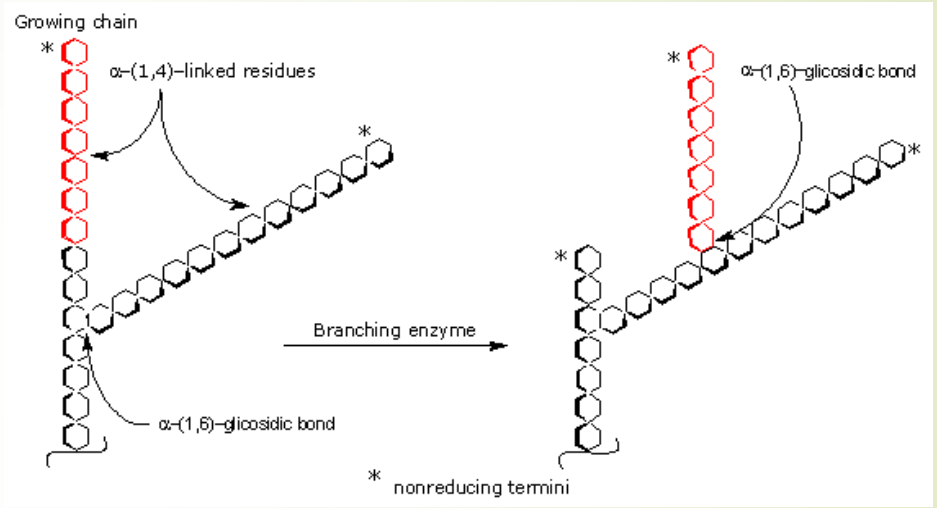
Structure of glycogen



https://themedicalbiochemistrypage.org/glycogen-metabolism/

Glycogen synthesis





https://laboratoryinfo.com/glycogenesis/

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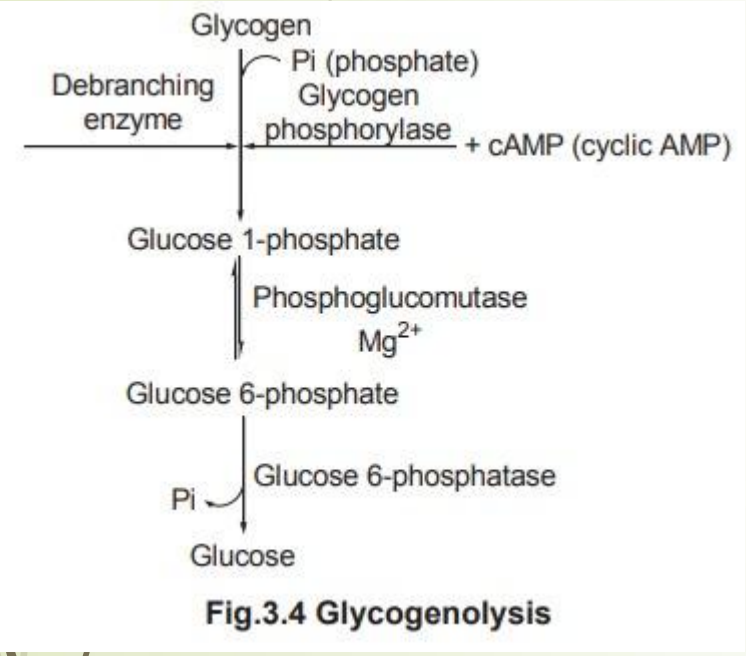


Fig.3.4 Glycogenolysis

Glycogenolysis

Glycogenolysis : Degradation of stored glycogen, termed glycogenolysis

Different pathways of glycogen breakdown

- In muscle: Glycogen → glucose-6-phosphate (G6P) → glycolysis
- In liver: Glycogen → G6P → glucose → bloodstream → various cells → glycolysis

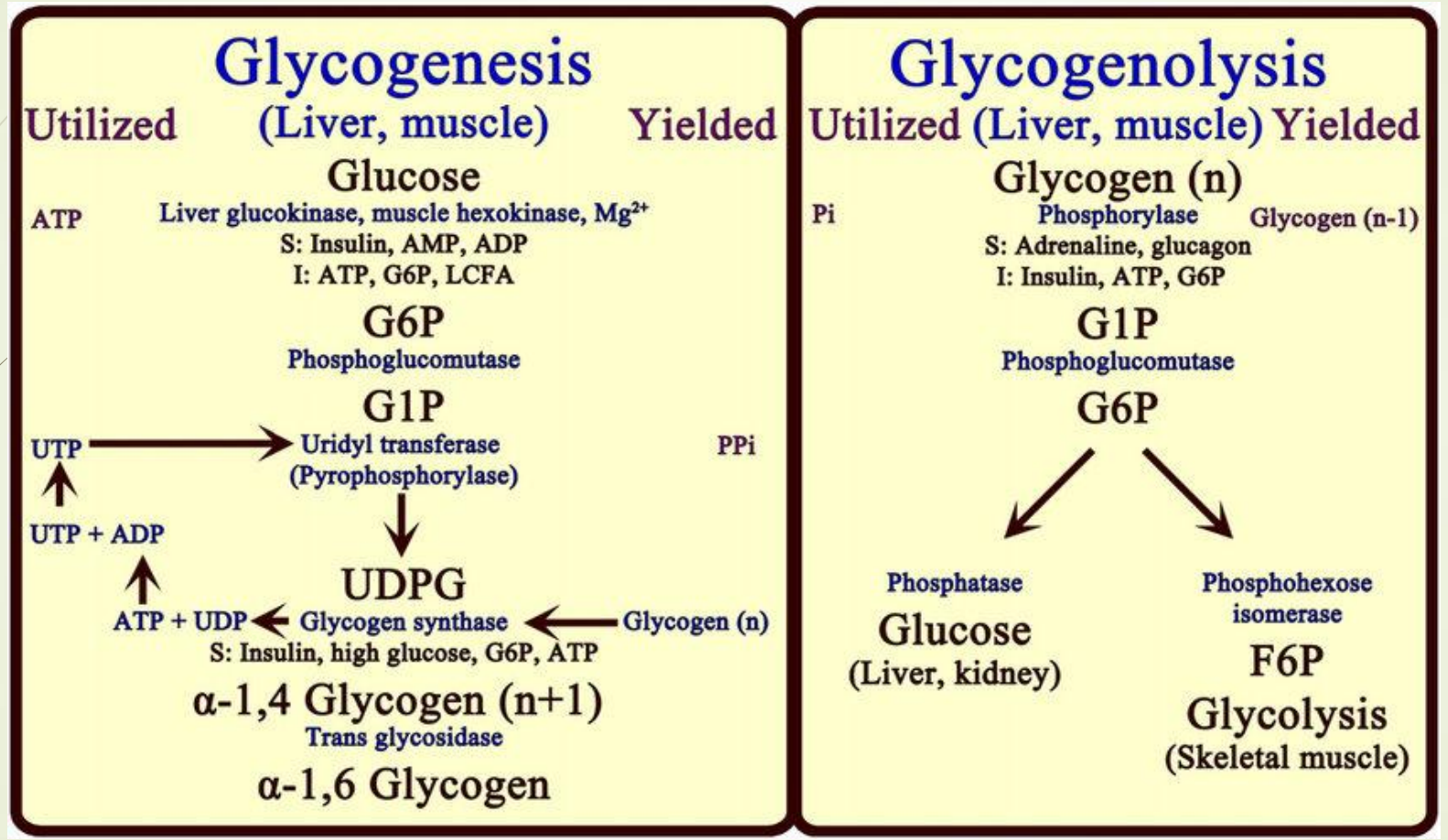
Because the muscle cells mainly consume glucose molecules whereas the liver cells mainly store the glucose molecules.

Glycogen degradation consists of three steps:

- The release of glucose 1- phosphate from glycogen.
- The remodeling of the glycogen substrate to permit further degradation
- The conversion of glucose 1- P to glucose 6-P.

http://www.brainkart.com/article/Degradation-of-glycogen-(Glycogenolysis)_26680/

https://slideplayer.com/slide/13277354/



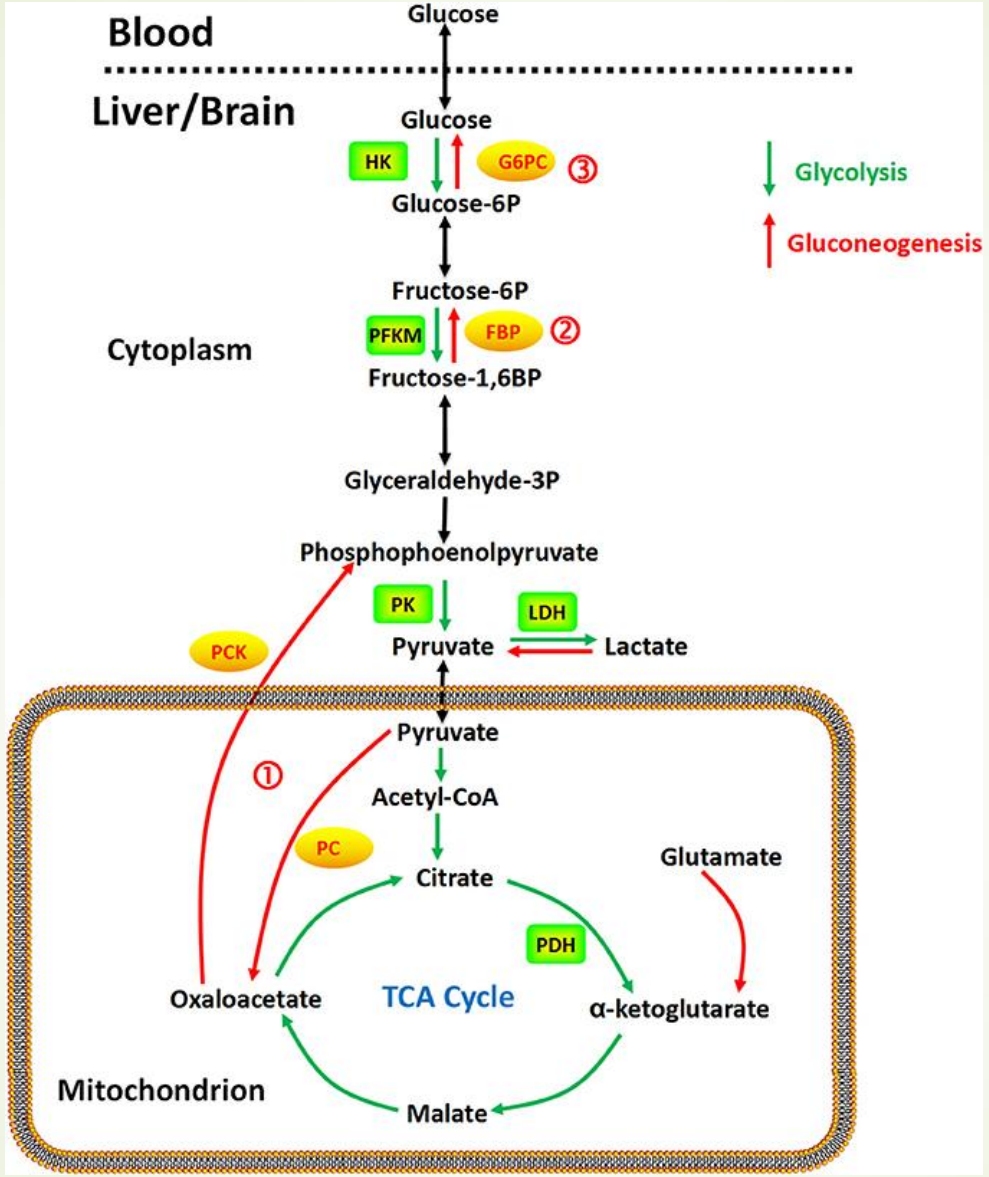
https://www.researchgate.net/figure/Glycogenesis-and-glycogenolysis-Regulation-of-blood-glucose-is-in-close-association-with_fig10_236914625

Gluconeogenesis

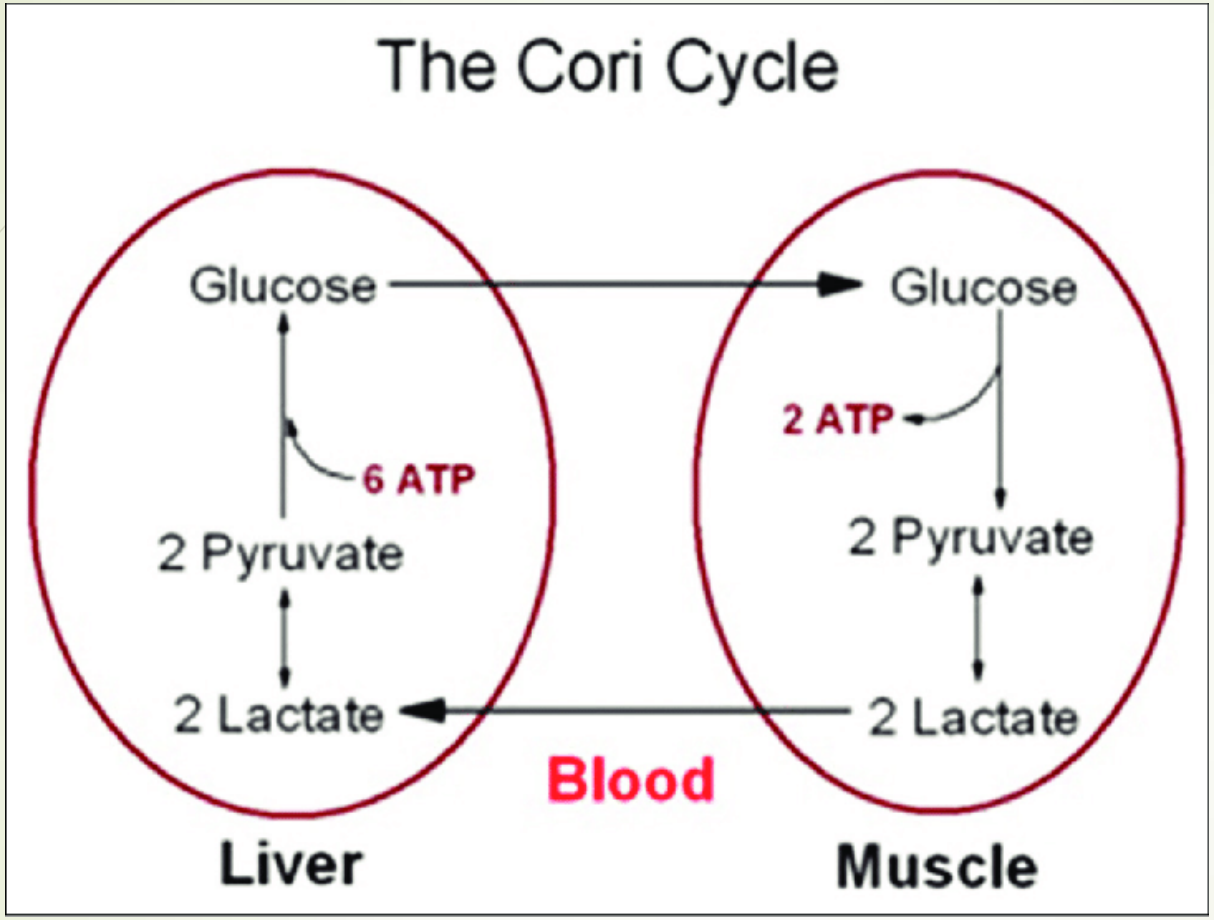
- Gluconeogenesis is the metabolic process that results in the generation of glucose from certain non-carbohydrate carbon substrates (pyruvate, lactate, glucogenic amino acids, glycerol). This process occurs in the liver, kidney.
- The process occurs during periods of fasting, starvation, low-carbohydrate diets, or intense exercise.

Gluconeogenesis is much like glycolysis only the process occurs in reverse. However, there are exceptions. In glycolysis there are three highly exergonic steps (steps 1,3,10). These are also regulatory steps which include the enzymes hexokinase, phosphofructokinase, and pyruvate kinase. Biological reactions can occur in both the forward and reverse direction. If the reaction occurs in the reverse direction the energy normally released in that reaction is now required. If gluconeogenesis were to simply occur in reverse the reaction would require too much energy to be profitable to that particular organism. In order to overcome this problem, nature has evolved three other enzymes to replace the glycolysis enzymes hexokinase, phosphofructokinase, and pyruvate kinase when going through the process of gluconeogenesis:

- The first step in gluconeogenesis is the conversion of pyruvate to phosphoenolpyruvic acid (PEP). In order to convert pyruvate to PEP there are several steps and several enzymes required. Pyruvate carboxylase, PEP carboxykinase and malate dehydrogenase are the three enzymes responsible for this conversion. Pyruvate carboxylase is found on the mitochondria and converts pyruvate into oxaloacetate. Because oxaloacetate cannot pass through the mitochondria membranes it must be first converted into malate by malate dehydrogenase. Malate can then cross the mitochondria membrane into the cytoplasm where it is then converted back into oxaloacetate with another malate dehydrogenase. Lastly, oxaloacetate is converted into PEP via PEP carboxykinase. The next several steps are exactly the same as glycolysis only the process is in reverse.
- The second step that differs from glycolysis is the conversion of fructose-1,6-bP to fructose-6-P with the use of the enzyme fructose-1,6-phosphatase. The conversion of fructose-6-P to glucose-6-P uses the same enzyme as glycolysis, phosphoglucoisomerase.
- The last step that differs from glycolysis is the conversion of glucose-6-P to glucose with the enzyme glucose-6-phosphatase. This enzyme is located in the endoplasmic reticulum.



https://www.frontiersin.org/articles/10.3389/fphar.2016.00521/full



https://www.researchgate.net/figure/Schematic-diagram-of-Cori-Cycle_fig1_331736228

Glucose blood concentration

- Normoglycemia - 3,3-5,5 mmol/l
- Hypoglycemia - ↓ 2,5 mmol/l
- Hyperglycemia - ↑ 6 mmol/l

Causes and consequences of hypoglycemia

Causes:
Insulin intake
Postprandial
Caused by alcohol
Primary enzymopathy:
galactosemia, intolerance to disaccharides , fructose intolerance
Glycogenosis (hepatic)
Insuloma (hyperinsulinism)
Adrenal insufficiency (Addison's disease)
Pituitary insufficiency
Septicemia
Renal glucosuria
Gastrointestinal diseases (malabsorption of monoses)
Transient hypoglycemia of newborns

Cosequences:
•Sweating
•Shakiness, dizziness, weakness
•Anxiety
•Rapid pulse
•Irritability (if you’re “hangry” – ‘hungry’ and ‘angry’ – chances are your blood sugar is low)
•Headache
•Fatigue

•Terminal complication of hypoglycemia – hypoglycemic coma, due to energy deficiency of neurons.

Causes and consequences of hyperglycemia

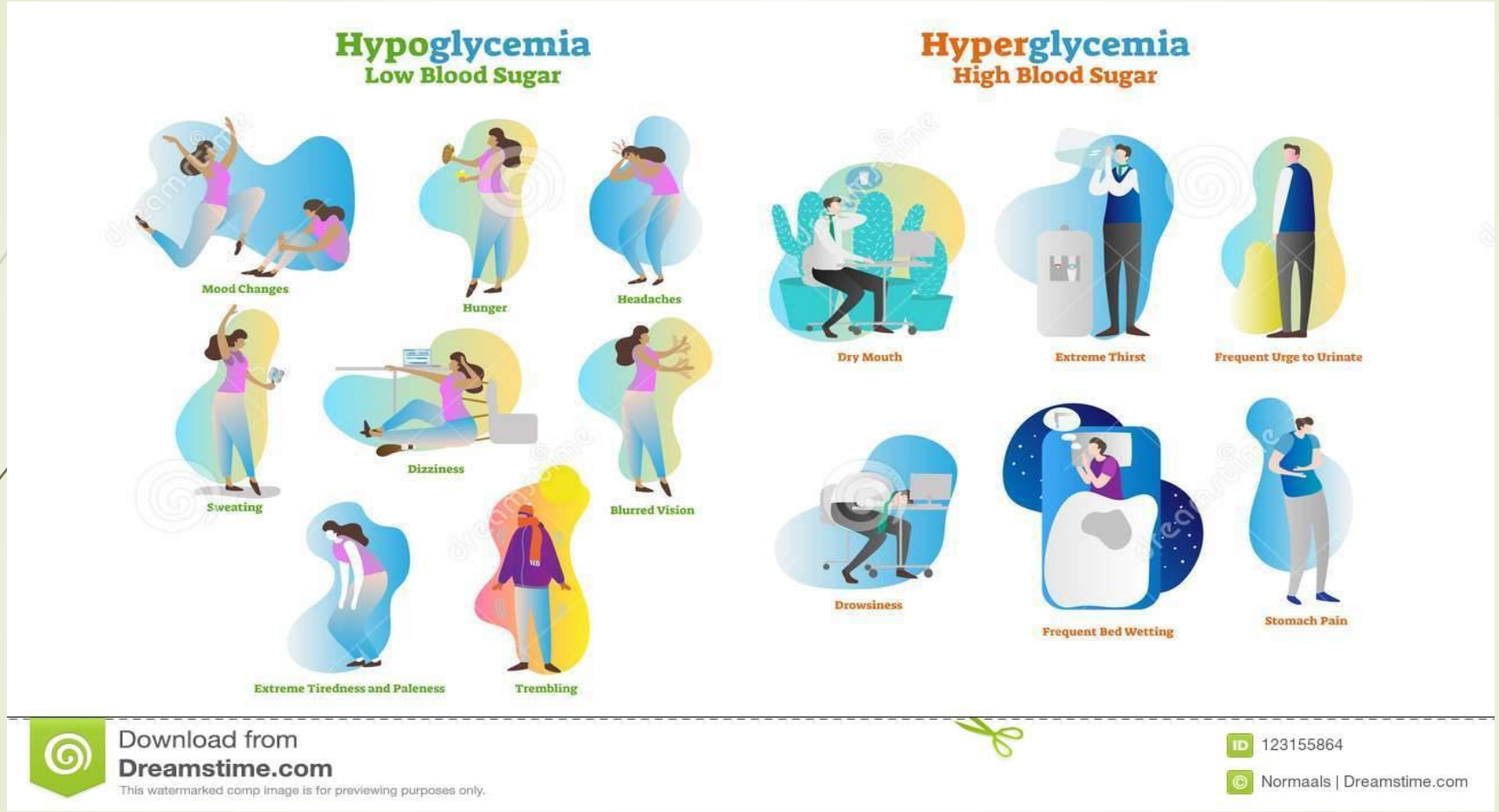
Causes:

Alimentary (physiological)
Stressful
Injury of central nervous system
Hepatic failure (cirrhosis)
Endocrine:
Cushing syndrome (hypercorticism)
Glucagonoma
Pheochromocytoma
Pituitary gigantism
Hyperthyroidism

Cosequences:

The following symptoms may be associated with acute or chronic hyperglycemia, with the first three composing the classic hyperglycemic triad:
Polyphagia– frequent hunger, especially pronounced hunger
Polydipsia – frequent thirst, especially excessive thirst
Polyuria – increased volume of urination (*not* an increased frequency, although it is a common consequence)
Blurred vision
Fatigue
Restlessness
Weight loss
Poor wound healing (cuts, scrapes, etc.)
Dry mouth
Dry or itchy skin
Tingling in feet or heels
Erectile dysfunction
Recurrent infections, external ear infections (swimmer's ear)
Cardiac arrhythmia
Stupor

Terminal complication of hyperglycemia – hyperketonemic coma (occurs due to ketosis) or hyperosmolar coma (occurs due to disturbance of water-electrolyte balance due to the increasing of osmoactive glucose (more than 20 mmol/l) in the serum, which causes of neurons dehydration. Not accompanied by ketoacidosis).



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Hormonal regulation of blood glucose concentration

- **Decreased blood glucose:**

INSULIN

- **Increased blood glucose:**

Glucagon
Epinephrine
Cortisol
ACTH
Somatotropin
Thyroxine

Endocrine Regulation of Blood Glucose Concentration

PANCREATIC HORMONES

	Liver	Muscle	Adipose tissue
Insulin	+ glycogen synthesis + glycolysis - glycogenolysis - gluconeogenesis - ketogenesis	+ glucose uptake + amino acid uptake - proteolysis	+ glucose uptake + free fatty acid uptake - lipolysis
Glucagon	+ glycogenolysis + gluconeogenesis + ketogenesis	minimal action	minimal action
Cortisol	+ glycogenolysis + gluconeogenesis	- amino acid uptake + proteolysis - insulin action	+ lipolysis - insulin action
Growth hormone	+ gluconeogenesis + IGFs/IGFBP	+ amino acid uptake - glucose uptake	+ lipolysis - glucose uptake
Epinephrine	+ glycogenolysis + gluconeogenesis + ketogenesis	+ glycogenolysis - insulin action	+ lipolysis - insulin action
Thyroid hormones	+ gluconeogenesis	+ proteolysis	+ lipolysis

* stimulates - inhibits Abbreviations: IGFs, insulin like growth factors; IGFBP, IGF binding protein

https://quizlet.com/234936744/physio-pancreatic-hormones-and-glucose-homeostasis-taylor-flash-cards/

Diabetes mellitus

- Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM). It used to be called juvenile-onset diabetes, because it often begins in childhood. It is results from the pancreas's failure to produce enough insulin due to loss of beta cells. It is an autoimmune condition.

- Type 2 diabetes (non-insulin-dependent, NIDDM, adult-onset diabetes). But it’s become more common in children and teens over the past 20 years, largely because more young people are overweight or obese. About 90% of people with diabetes have type 2. Type 2 diabetes mellitus begins with insulin resistance, a condition in which cells fail to respond to insulin properly. The most common cause is a combination of excessive body weight and insufficient exercise.

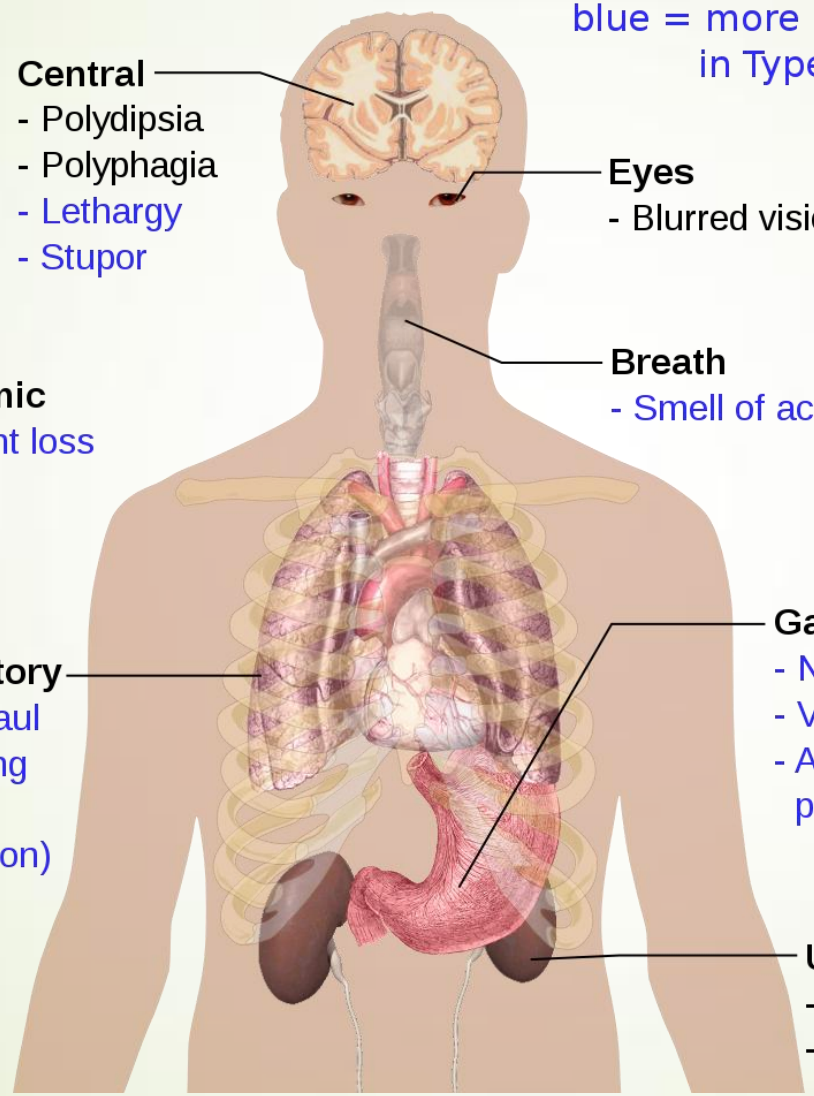
Comparison of type 1 and 2 diabetes		
Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Any age (mostly young)	Mostly in adults
Body habitus	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	Less prevalent	More prevalent - 90 to 95% of U.S. diabetics

https://www.diffen.com/difference/Type_1_Diabetes_vs_Type_2_Diabetes

Main symptoms of

Diabetes

blue = more common in Type 1



Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes
- Blurred vision

Breath
- Smell of acetone

Systemic
- Weight loss

Respiratory
- Kussmaul breathing (hyper-ventilation)

Gastric
- Nausea
- Vomiting
- Abdominal pain

Urinary
- Polyuria
- Glycosuria

https://en.wikipedia.org/wiki/Diabetes

Biochemical diagnosis of diabetes mellitus

Blood test

- Glycated (glycosylated) hemoglobin (Hb A1c) not more than 5% (8% - subcompensated DM, ≤ 12% - decompensated ЦД)
- Fasting glucose - 3,3-5,5 mmol/l
- C-peptide 0,9-4 ng/ml
- Ketone bodies 0,034–0,43 mmol/l
- Glucose tolerance test

Urine test

Absence or presence of glucosuria, ketonuria.

Glucosuria

- **Glycosuria** is the excretion of glucose into the urine. Ordinarily, urine contains no glucose because the kidneys are able to reabsorb all of the filtered glucose from the tubular fluid back into the bloodstream. Glycosuria is nearly always caused by elevated blood glucose levels.

- When the blood glucose level exceeds about 8.9-10 mmol/L (160–180 mg/dL), the proximal tubule becomes overwhelmed and begins to excrete glucose in the urine. 8.9-10 mmol/L is called the renal threshold for glucose.

Glucose tolerance test (Oral glucose tolerance test, OGTT)

The patient should not eat for
10-16 hours immediately before the test.
The test should be performed in the morning.
First, fasting blood glucose is determined.
After that, at the rate of 1 g of glucose per 1 kg of body weight,
but not more than 100 g, drink dissolved in 250 ml of water.
After 2 hours, the blood glucose level is determined.

Table 1. Interpretation of OGTT

	Fasting	2 hour	Implications
No diabetes	≤6.0	<7.8	No excess micro- nor macro-vascular risk
Prediabetes	6.1–6.9	7.8–11.0	Excess macro- but not micro-vascular risk
Diabetes	≥7.0	≥11.1	Excess macro- and micro-vascular risk

Sources of information

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