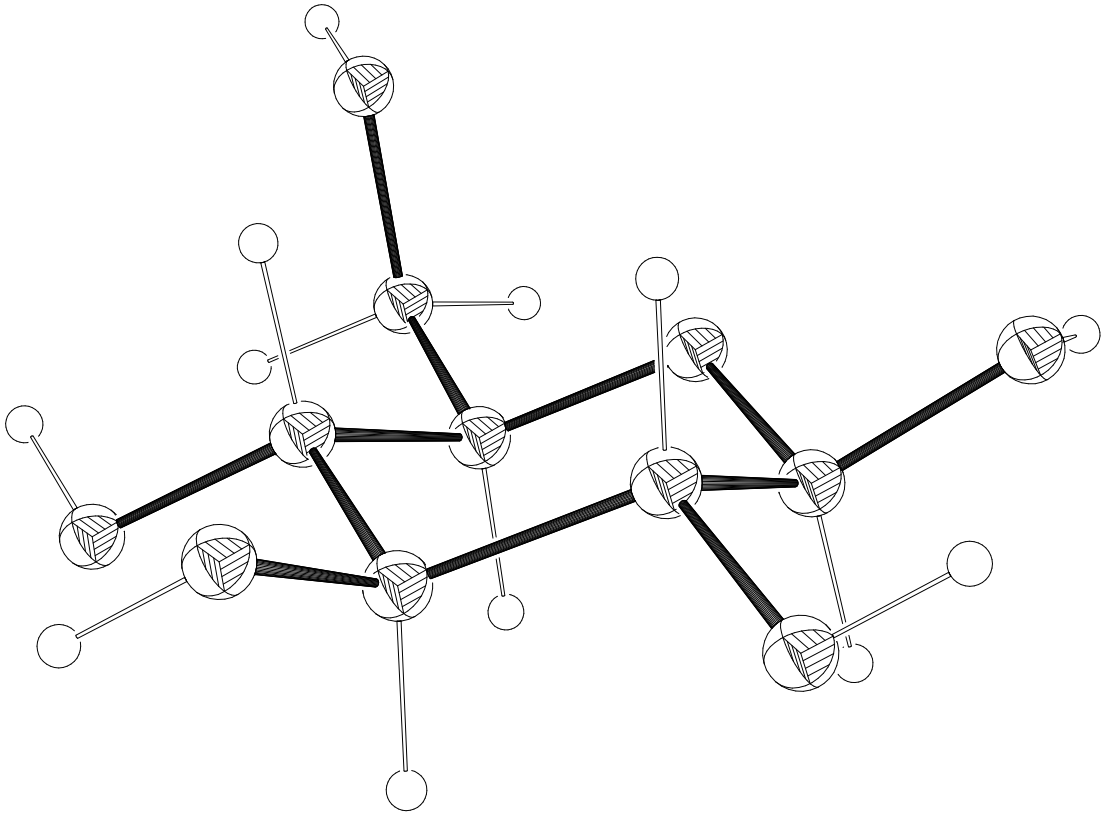
Glucose in blood. Diabetes mellitus

Seminar No. 4

What is glucose?

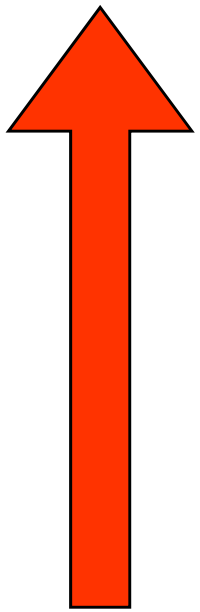


- the most common monosaccharide / aldohexose
- $C_6H_{12}O_6$ (M_r 180)
- synonyms: grape sugar, blood sugar, dextrose
- the most important sugar in the human body
- the source of chemical energy (17 kJ/g)
- metabolic nutrient for most tissues
- prominent fuel for the brain and RBC

Q. 1

A.1a) Free glucose in food is rare

Food	Glucose (%)[a]
Glukopur[b]	100
Raisins	50
Honey[c]	30
Grapes	6-10
Other fresh fruits	1-5



[a] mass percentage, average values

[b] pure crystalline glucose, Czech made, sold in pharmacy

[c] about 30 % glucose, 40 % fructose, 10 % oligosaccharides, 20 % water

A.1 b) Glucose chemically bound

- **Starch** (polysaccharide from glucose: amylose + amylopectin)

  cereals, bread, rolls, pastry, cakes, biscuits, dumplings, rice, pasta, semolina, legumes, potatoes, banana ...

- **Sugar** (table sugar, **sucrose**, disaccharide: glucose + fructose)

  commercially available in 100% purity

- **Lactose** (disaccharide: galactose + glucose) – milk

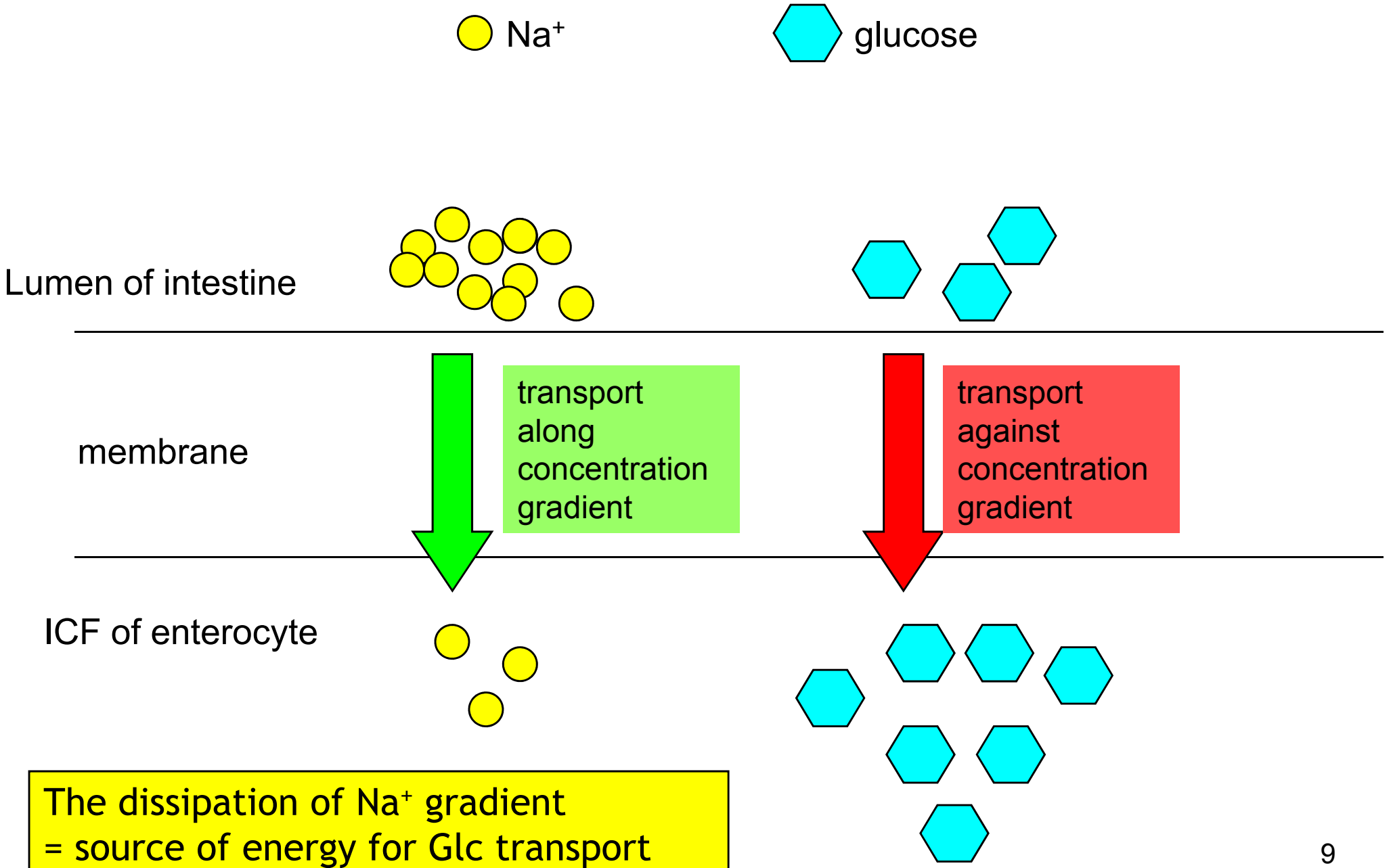
Q. 2

A. 2 Symport (co-transport) with Na^+ ions

- transporter binds together Glc and Na^+ (secondary active transport) – see also Harper (27th ed., p. 436)
- Na^+ ions move from high conc. space to low conc. space
- Glc is expelled from enterocyte *via* GLUT2 (facilitated diffusion)
- Na^+ ions are expelled from cell *via* Na^+,K^+-ATPase pump

What is the metabolic fuel for enterocyte itself ?

Symport of Glucose with Na^+

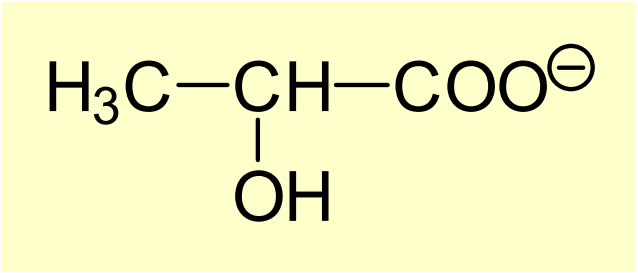


The dissipation of Na^+ gradient
= source of energy for Glc transport

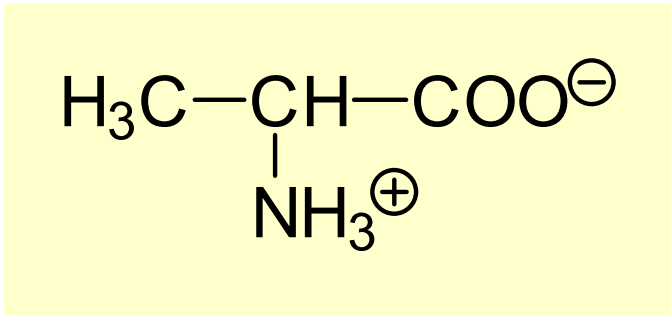
Q. 4 + 5

A. 4, 5

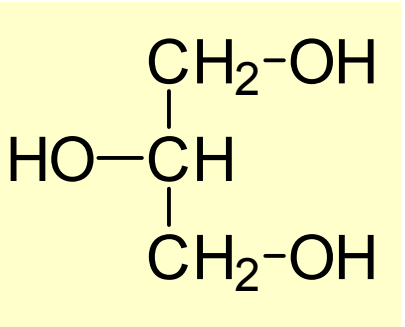
Lactate (60 %)



Alanine + other glucogenic AA (30 %)



Glycerol (10 %)

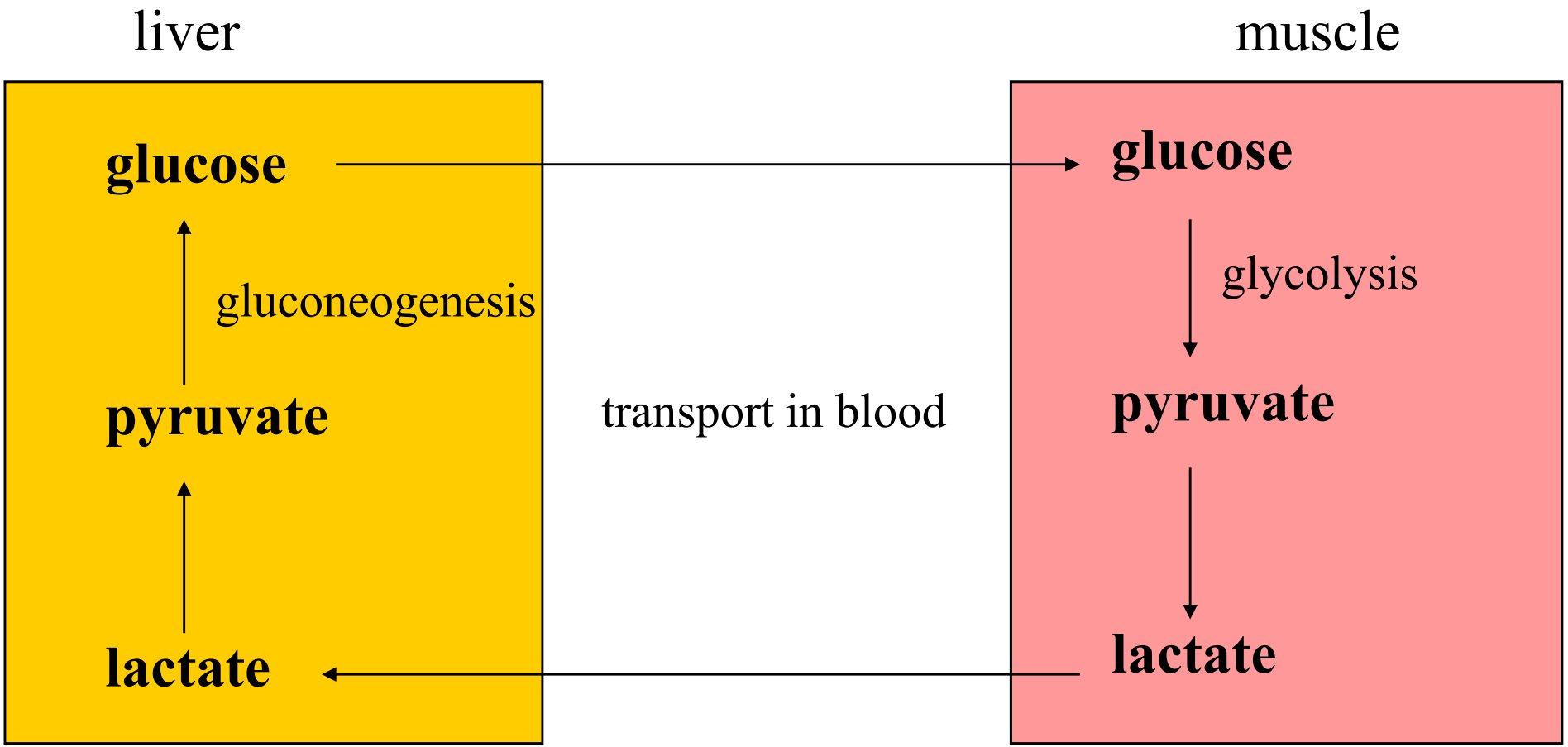


gluconeogenesis

occurs in liver

Q. 7

A. 7 Cori cycle



Q. 8

A. 8

- **Liver glycogen** is degraded by phosphate (phosphorolysis)

$$\text{glycogen} \xrightarrow{P_i} \text{Glc-1-P} \rightarrow \text{Glc-6-P} \rightarrow \text{glucose in blood}$$

- Phosphorylase – phosphoglucomutase – glc-6-phosphatase

Q. 9 + 10

A. 9 + 10 (Harper, p. 173)

- Glucose is highly polar compound, does not pass freely across hydrophobic cell membranes
- Requires specific protein transporters
- GLUT = glucose transporter

GLUT 1	most cells, brain, erythrocytes
GLUT 2	liver, pancreas, kidney
GLUT 3	brain, kidney
GLUT 4	muscle, adip. tissues – **insulin dependent**
GLUT 5	small intestine
SGLT 1	small intestine, kidney (Na^+ coupled active transport)

Insulin-independent transporters

- In most tissues (liver, CNS, Ery)
- Passive transport – facilitated diffusion
- Transporter – integral protein
- After binding Glc it changes conformation and releases glucose into ICF

Passive transport – no energy required

Insulin-dependent transporters

- In muscles, adipose tissue
- After binding Glc it changes conformation and releases glucose into ICF
- Free transporters are then transferred inside the cell by endocytosis
- **Insulin stimulates their incorporation into cell membrane when necessary**

Passive transport – no energy required

Q. 12

A. 12

- night fasting – liver glycogen
- one-day fasting - liver glycogen + gluconeogenesis
- three-day fasting - gluconeogenesis

Five stages of glucose homeostasis

Feature	I	II	III	IV	V
Stage description	well-fed	post resorption	early starvation	prolonged starvation	extreme starvation
Time interval[a]	0-4 h	4-16 h	16-30 h	2-24 d	over 24 d
Origin of Glc in blood	food	liver glycogen gluconeogenesis	gluconeogenesis liver glycogen	gluconeogenesis	gluconeogenesis
Utilization of Glc	all tissues	all tissues[b] muscle, ad.t. limited	all tissues[b] muscle, ad.t. limited	brain, Ercs, kidney	Ercs, kidney, brain - limited
Energy for brain	Glc	Glc	Glc	Glc, ketone bodies	ketone bodies, Glc

[a] Approximate values, time 0 = any main meal (e.g. lunch).

[b] Except of liver.

Five stages of glucose homeostasis

- Stage I – glucose comes from food (mainly starch)
- Stage II – glycogenolysis in liver
- Stage III – gluconeogenesis in liver starts to work
- Stage IV – in addition to liver, kidney starts to make Glc
- Stage V – liver and kidney gluconeogenesis diminishes, energy needs of most tissues are met by FA + KB

Hormonal regulation of Glc metabolism

- insulin, glucagon
- stress hormones: adrenalin, cortisol

Q. 16

Harper, 27th ed., Ch. 20, p. 170

Q. 17

A.17

a) glucose ↓

b) FFA ↓

Q. 18

Glucagon (fasting)

- Low blood glucose level is the signal for glucagon secretion
- Glucagon stimulates:
- breakdown of glycogen in liver (**not in muscles**)
- gluconeogenesis in liver (from lactate and AA)
- lipolysis in adip. tissues

Glucagon is **inducer** of key enzymes of gluconeogenesis

Q. 19

Insulin (after meal) stimulates

- in liver: glycolysis + synthesis of glycogen
- in adip. tissue: synthesis of TAG
- in muscles: synthesis of proteins

Insulin is generally anabolic hormone

Insulin is **inducer** of key enzymes of glycolysis and glycogenesis

Q. 20

A. 20

- Glc phosphorylation (hexokinase, glucokinase)
- Glc-1-P isomeration
- Fru-6-P isomeration

Q. 21

A. 21 Glycogenolysis

liver

- cca 4-6 % of liver mass
- Glycogenolysis affords **free glucose** - for other tissues
- After about 18 h of fasting exhausted

muscle

- cca 1 % of muscle mass
- Glycogenolysis affords **Glc-6-P** for muscle only
- Storage lasts longer

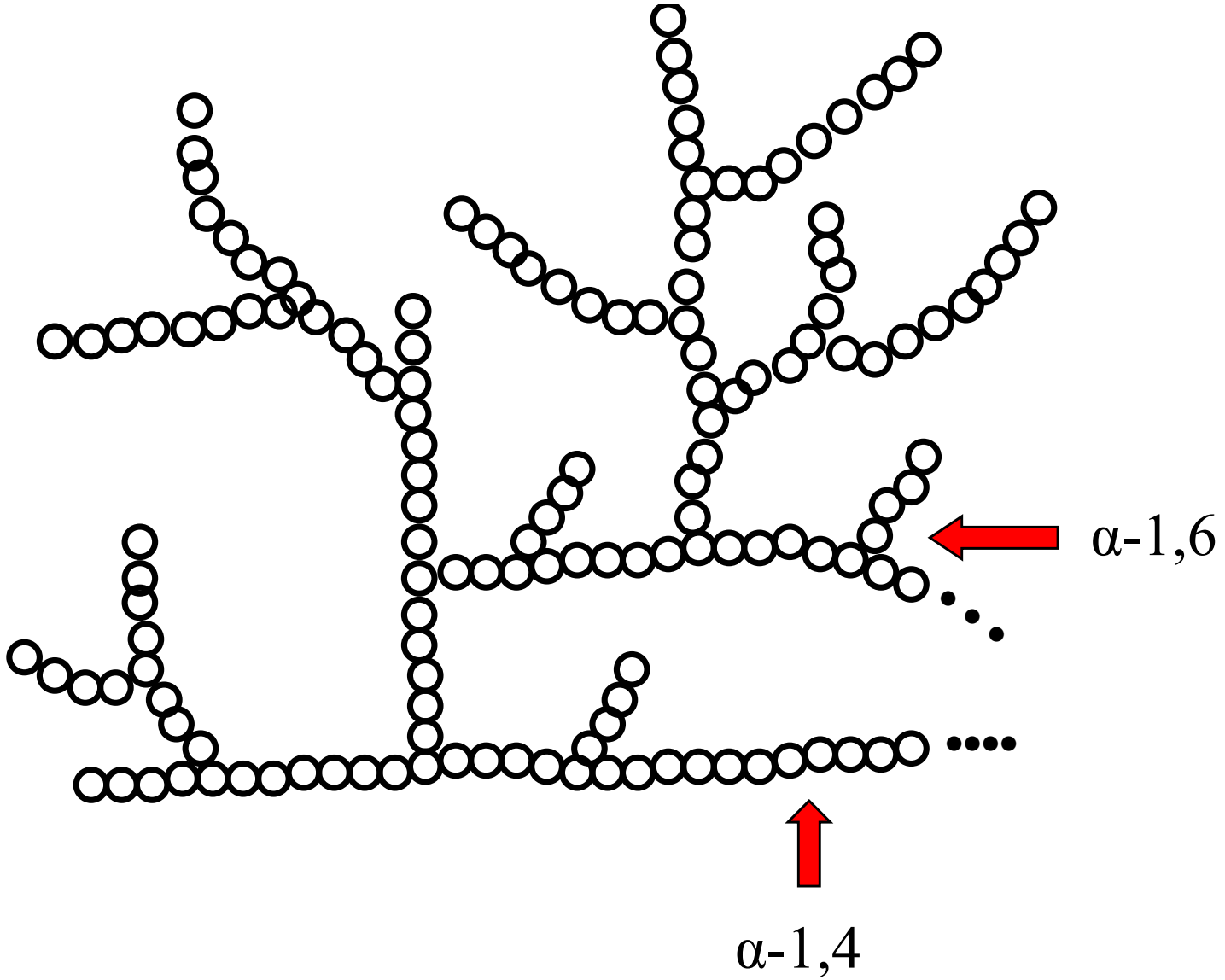
Q. 22

A. 22

- Liver: glucagon, adrenalin
- Muscle: adrenalin

Q.23

A. 23



Q. 24

A. 24

glycogen $\rightarrow$ Glc-1-P $\rightarrow$ Glc-6-P $\rightarrow$ glucose in blood

Q. 25

A. 25

glucose-6-phosphatase

$$\text{Glc-6-P} + H_2O \rightarrow \text{Glc} + P_i$$

occurs in liver, kidney, intestine but **not in muscles**

Q. 26

A. 26

- Glc is the source of **energy** (aerobic glycolysis)
- Glc is the source of **NADPH +H^+** for FA synthesis (pentose cycle)
- Glc is the source of **glycerol-3-P** for TAG synthesis

glycerol-3-P → 1-acylglycerol-3-P → 1,2-diacylglycerol-3-P →

1,2-diacylglycerol → **TAG**

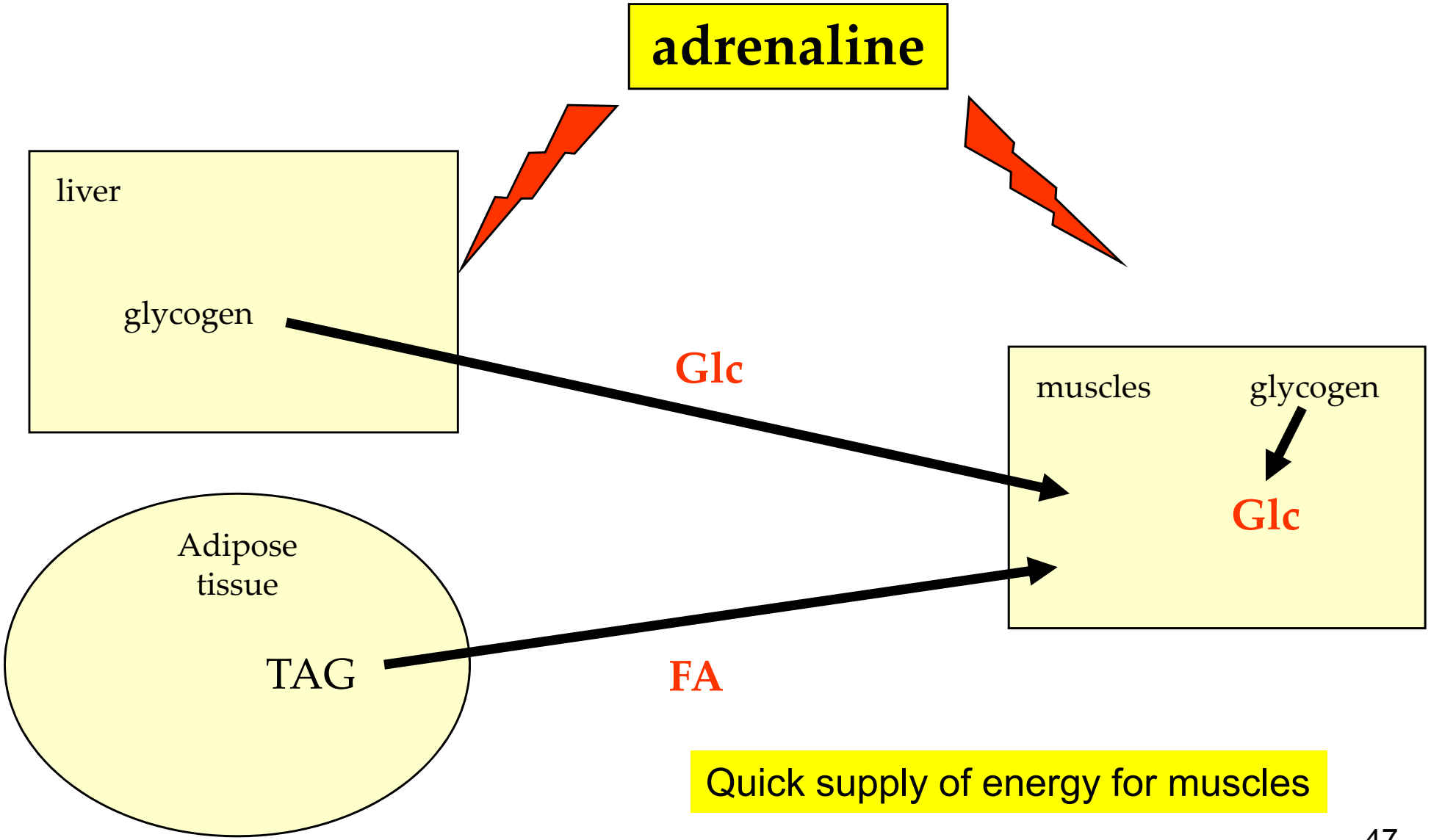
Adrenaline – acute stress

- Signal that energy is needed immediately
- Very quick action
- Stimulates the breakdown of glycogen (in liver and muscles) and TAG (In adipos. tissue)

Cortisol – adaptation to stress

- Stimulates proteolysis in muscles
- Released AA are substrates for gluconeogenesis
- Inducer of key enzymes of gluconeogenesis

Adrenaline action in fight-or-flight situation



Metabolic Features of Diabetes (Type I)

metabolic processes occur **under influence of glucagon**

Q. 30

Process	Change	Consequence
Transport of glucose to muscle + ad.t.		
Glycolysis in liver		
Gluconeogenesis in liver		
Lipolysis in adipocytes		
β-Oxidation of FA in liver		
Capacity CAC, lack of oxaloacetate		
Production of ketone bodies		

A. 30

Process	Change	Consequence
Transport of glucose to muscle + ad.t.	⇩	elevated blood glucose
Glycolysis in liver	⇩	elevated blood glucose
Gluconeogenesis in liver	⇧	elevated blood glucose
Lipolysis in adipocytes	⇧	elevated blood fatty acids
β-Oxidation of FA in liver	⇧	↑ production of acetyl-CoA
Capacity CAC, lack of oxaloacetate	⇩	↑ amount of acetyl-CoA
Production of ketone bodies	⇧	elevated blood KB, acidosis

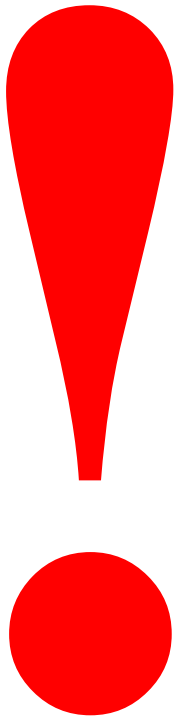
Q. 31

Elevated: glucose

FFA

TG

KB



A. 31 – elevated Glc

- **The lack of insulin** ⇒ few GLUT4 ⇒ Glc cannot enter adipose and muscle cells ⇒ elevated blood Glc
- **The lack of insulin** ⇒ decreased glycolysis in liver
- **The excess of glucagon** ⇒ glycogenolysis ⇒ elevated blood glucose
- **The excess of glucagon** ⇒ increased liver gluconeogenesis

A. 31 – elevated FFA

The excess of glucagon $\Rightarrow$ lipolysis $\Rightarrow$

elevated blood FFA (bound to albumin)

A. 31 – elevated TG

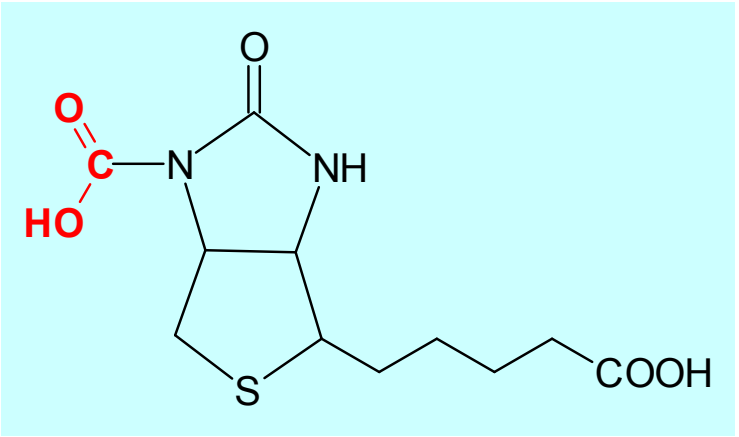
- **The lack of insulin** ⇒ not enough LPL (insulin is the inducer of its synthesis) ⇒ elevated blood TG (CM + VLDL)

A. 31 – elevated KB

- **The excess of FA** from lipolysis ⇒ excess of acetyl-CoA (over CAC capacity) ⇒ synthesis of KB ⇒ elevated blood KB
- **Limited glycolysis in liver** ⇒ not enough pyruvate ⇒ **not enough oxaloacetate** to run CAC ⇒ excess of acetyl-CoA (over CAC capacity) ⇒ synthesis of KB ⇒ elevated blood KB

Q. 32

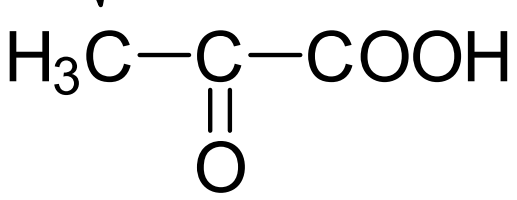
A. 32



Biotin—COOH

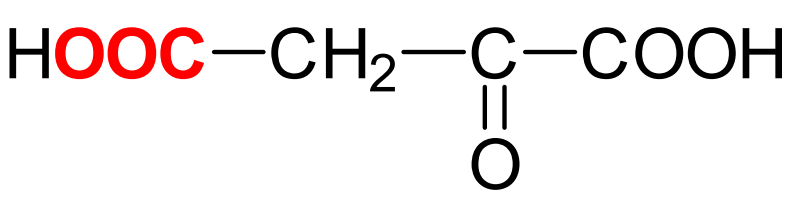
Biotin—H

Pyruvate carboxylase



pyruvate

+



oxaloacetate

Q. 33

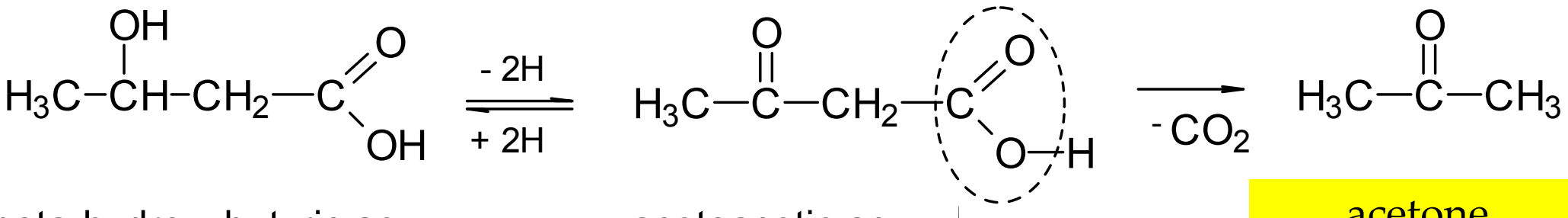
A. 33

1. The lack of insulin ⇒ decreased glycolysis ⇒ the shortage of pyruvate ⇒ the shortage of oxaloacetate

2. The excess of glucagon ⇒ increased utilization of oxaloacetate for gluconeogenesis

Q. 34

A. 34



beta-hydroxybutyric ac. acetoacetic ac.

acetone

non-electrolyte

Acid	**pK_A**
Acetoacetic	3.52
β-Hydroxybutyric	4.70

Complications of diabetes

Acute

- ketoacidosis (pH of blood $<$ 7.36)
- hyperosmolarity of blood plasma (> 310 mmol/l)

Long-term

- non-enzymatic glycation of proteins
- AGE production (advanced glycation endproducts)
- activation of sorbitol (glucitol) production

Q. 35

A. 35

A) Increased lipolysis, elevated FFA-albumin in blood

B) Shortage of LPL because of the lack of insulin $\Rightarrow$ elevated plasma TG (CM and VLDL)

C) Increased production of KB and VLDL

Glycated hemoglobin HbA_{1c}

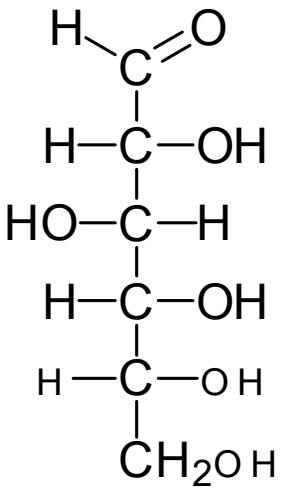
- glycation is **non-enzymatic** and **irrevesible**
- reaction of globin NH_2-groups with aldehyde group of glucose
- **the concentration of HbA_{1c} depends on:**

  concentration of glucose in blood

  duration of hyperglycemia

  concentration of hemoglobin (less important factor)
- normal values: 2.8 – 4.0 %
- **the value of HBA_{1c} gives cumulative information on glucose level in recent 4-8 weeks**

Glycation of proteins



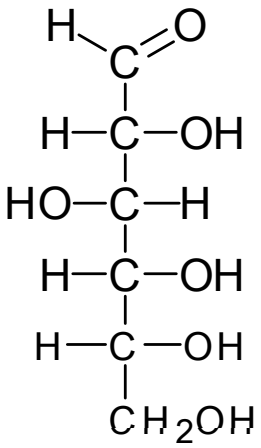
glucose
aldehyde form

+ H_2N-PROTEIN ⟶

- H_2O

which -NH_2 groups in globin are nucleophilic?

Glycation of proteins

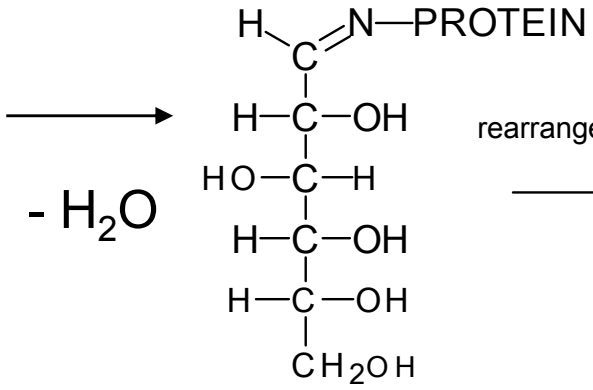


+ H_2N-PROTEIN

N-terminal

or

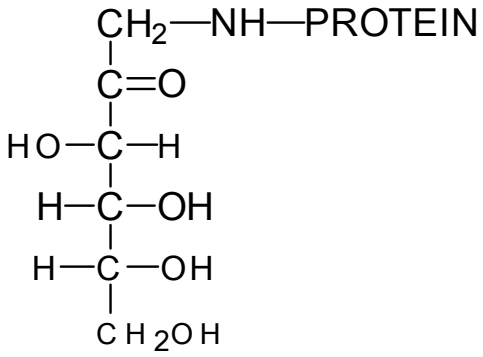
Lysine side chain



aldimine

Schiff's base

unstable



ketoamine

glycated protein

AGE