Overview of nutrient metabolism? The organ relations

First law of thermodynamics

$$\Delta U = \Delta W + \Delta Q = \textbf{work} + \textbf{heat}$$

Energy can not be created nor destroyed, it can only be changed from one form of energy to another.

Transformation of energy in human body

Income of E | **Cost of E**

Chemical E of nutrient = **work** + **heat**

E of nutrient = **BM + physical activity + reserves** + **heat**

Every work needs- ATP

chemical: synthesis of proteins.. ...

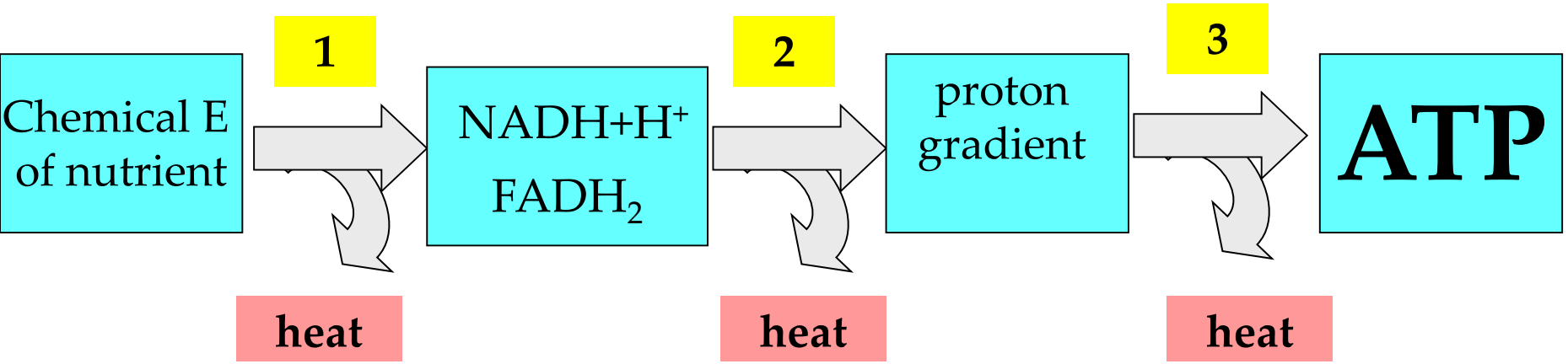
osmotical: transport of ions ...

mechanical: muscle contraction ...

BM = basal methabolism

reserves = adipose tissue, glycogéne

Transformation of E – production of heat



1 ..... metabolically dehydrogenation

2 ..... RCH = oxidation of reduced cofactors and reduction of O_2 to H_2O

3 ..... Aerobic phosphorylation

..... High energetic system

Nutrients and E

nutrient	E (kJ/g)	Thermogenesis	Source of E/day
Lipids	38	4 %	≤ 30 % SAFA 5 %, MUFA 20 %, PUFA 5 %
CH + sugars	17	6 %	55 - 60 %
Proteins	17	30 %	10 - 15 %

Chemical energy nutrients and thermogenesis

Nutrient	Energy (kJ/g)	Thermogenesis
Fat	**38**	4 %
Carbohydrates	17	6 %
Proteins	17	**30 %**

Thermogenesis is the generation of heat (generally after energy expenditure) 3-5 hours after intake of nutrients. Expressed in % received power for a given nutrient. Thermogenesis is related to digestion, absorption, transport and metabolism of nutrients.

Two ways to produce ATP in the cell

95% of the ATP formed **aerobic phosphorylation (in the presence of O_2):**

ADP + Pi + H^+gradient energy $\rightarrow$ ATP

5 % of the ATP formed by **substrate phosphorylation:**

ADP + macroergic-P* $\rightarrow$ ATP + second product

* 1,3-bisphosphoglycerate (glycolysis)

phosphoenolpyruvate (glycolysis)

succinyl-CoA + P_i $\rightarrow$ succinylP, succinate (CC)

Basal metabolism (BM)

Even in utter calm the body must expend some

basic (basal) amount of energy to the activity of the CNS, heart, constancy of the internal environment, transport through membranes,

biosynthesis etc.

Estimated level of BM: 0,1 MJ/kg/day

Man, 70 kg $\Rightarrow$ BM = 0,1 . 70 = 7 MJ/day

Basal metabolism depend on

- gender (female about 10% less)
- age (age decreases)
- body temperature (a temperature increase of 1 °C BM is increased by about 12%)
- ambient temperature - stay in a cold environment increases BM
- thyroxine hormones, adrenalin - increase BM
- prolonged fasting - BM decreases (slimming diets, anorexia)

Recommended Nutrient

nutrient	% income of energy/day
Carboh.	55 – 60 %
Lipids	≤ 30 %
Proteins	10-15 %

SAFA ≈ 5 %

MUFA ≈ 20 % *

PUFA ≈ 5 %

Essential FA: linoleic acid, α-linolenic
Conditionally essence. FA: arachidonic
Essential AA: Phe, Trp, Val, Leu, Ile, Met, Thr, Lys
Conditionally essence. AA: His, Arg (childhood), Ala, Gln (Metab. Stress)

* 67 % lipids

The supply of nutrients in the body (male, 70 kg)

Nutrient	Location	weight (g)	Energy (MJ)
Glycogen	liver	70	1,2
Glycogen	muscle	120	2,0
Glucose	ECT	20	0,3
Lipids	Adipose t	15 000	**570**
Proteins	muscle	6 000	102/3 = 34

- The largest reserve of energy forms fat

  The amount of total body fat is 10-30% (men, women)

  It is useful about ⅓ muscle mass without compromising the integrity of the organism

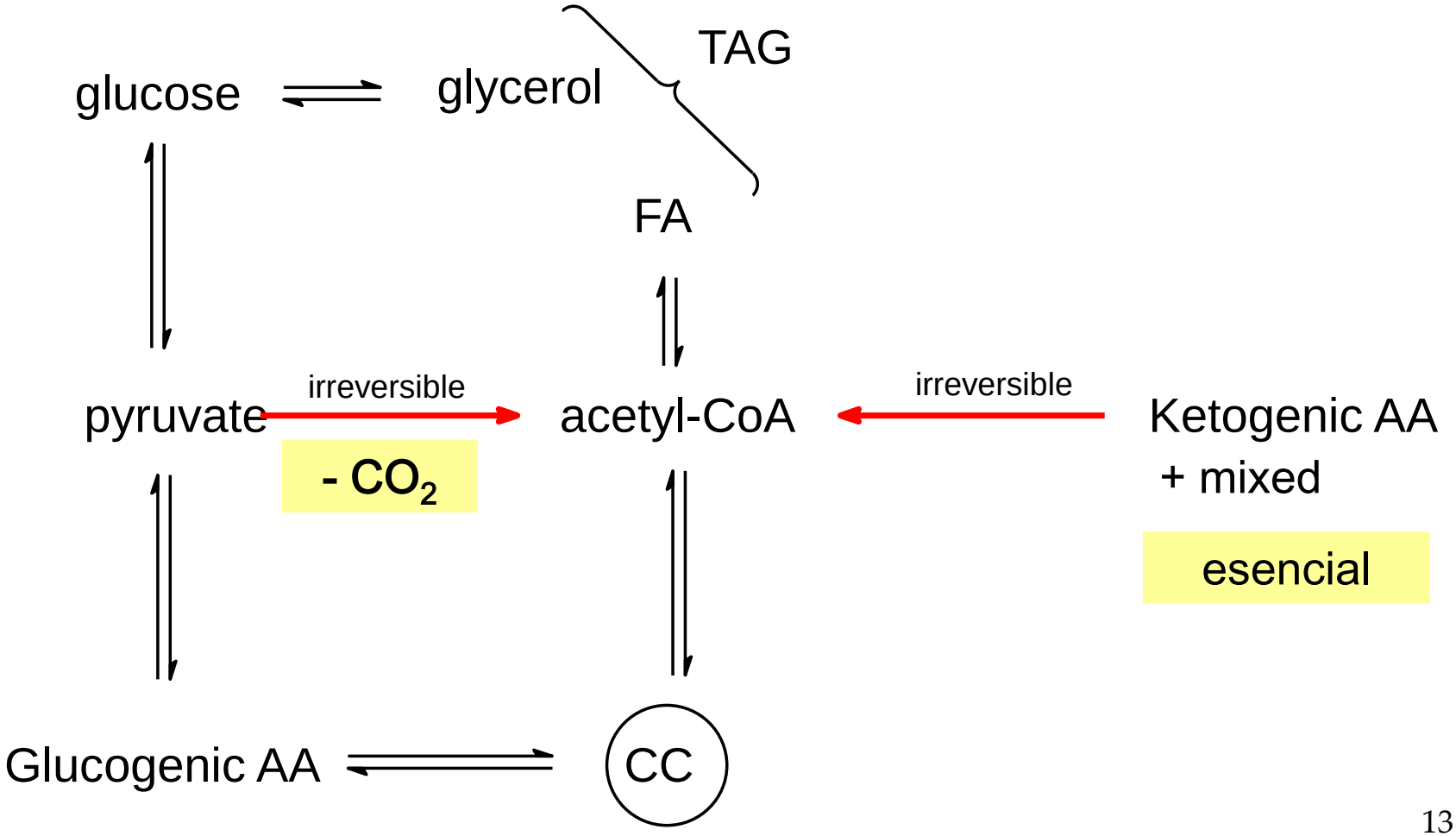
  Liver glycogen lasts about 24 hours

  Muscle glycogen - only for muscles (lack of glucose-6-phosphatase)

Basic facts about metabolism

- ATP is the immediate and universal source of chemical energy for cellular processes
- ATP is generated as a result of oxidation of nutrients
- nutrients → acetyl-CoA→ CC → RCh → ATP
- **The organism requires a constant level of ATP and glucose**
- Glucose is essential for brain and erythrocytes
- **Glucose is essential for the use of energy from fat** = for the course of CC(Glc → pyruvate → oxalacetate → CC)
- **Glucose can not be synthesized from fats**

Metabolic intermediates and their relationships



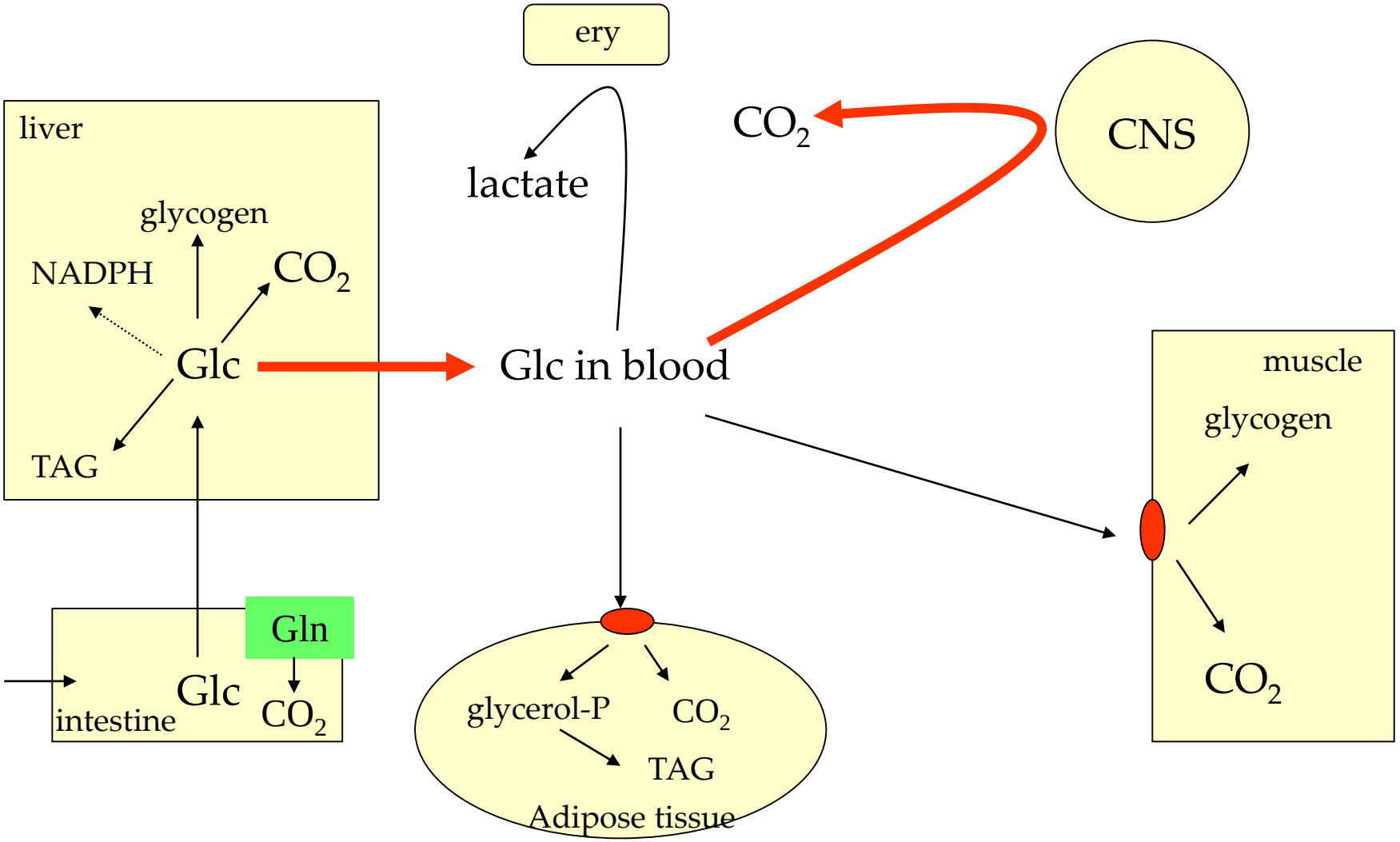
Interconversion of nutrients

Conversion	**Comments**
Carbohydrates → lipids	Easy and quick
Lipids ~~→~~ glucose	Not possible Pyruvatedehydrogenation is irreversible
Amino acids → glucose	Majority of AA is glucogenic
Glucose → amino acids	Pyruvate and intermediate of CC give carbon sceleton for AA synthesis
Amino acids → lipids	In case excess proteins in diet
Lipids ~~→~~ amino acids	Pyruvatedehydrogenation reaction is irreversible ketogenic + mixed AA are essential

Metabolism in resorptive phase

- After meal
- Enough nutrients, it is not necessary to save
- Chemical energy is stored in reserves
- Hormonal regulation - Insulin

Carbohydrates in the resorptive phase (insulin)



GLUT4 dependent on insulite

Metabolism of glucose in the liver (after meal)

- glucose **at this stage is rarely** used as metabolic fuel for the liver
- Insulin increases glycolysis (induces the synthesis of glucokinase)
- Part of glucose is converted to hepatic glycogen
- In excess glucose, there are synthesize TAG as VLDL → adipose tissue –obesity
- part of glucose in the blood passes through the liver
- a small proportion of glucose provides specialized products (pentose cycle - NADPH and ribose, galactose, glucuronate)

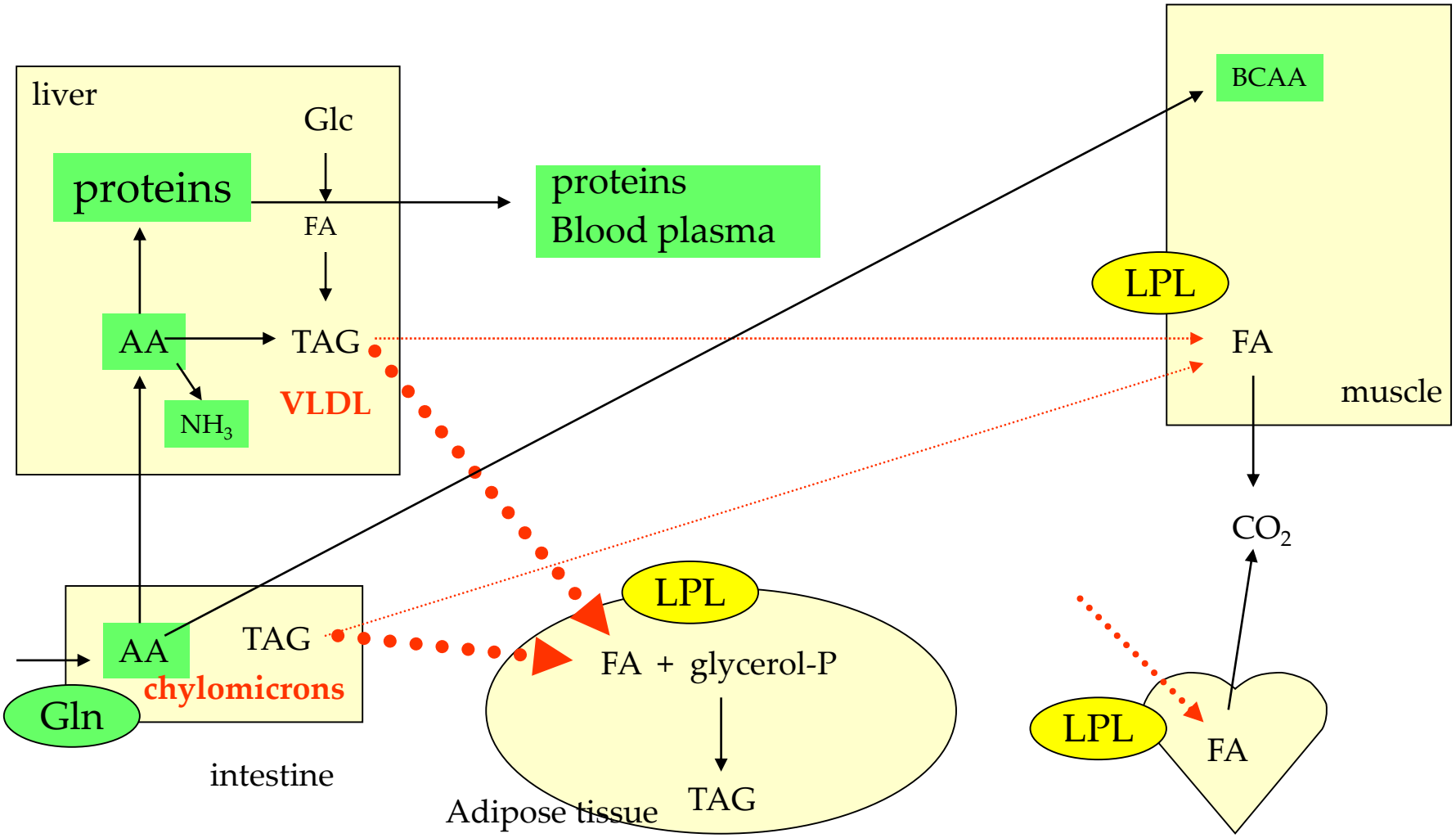
Extrahepatic glucose utilization

- a single power source for erythrocytes (anaerobic glycolysis)
- prominent energy source for the CNS (aerobic glycolysis)
- main source of energy for **muscles at rest** (aerobic glycolysis), muscle glycogen synthesis (limited capacity)
- power source, glycerol-3-P and NADPH + H + for TAG in adipose tissue

Glc $\rightarrow \rightarrow$ glyceraldehyd-3-P + dihydroxyaceton-P

glycerol-3-P

Lipids and proteins in the resorption phase (insulin)



Lipids in resorptive phase

- exogenous TAG are hydrolyzed in the intestine, in enterocytes are resynthesized and built into chylomicrons
- endogenous TAG formed in the liver as VLDL
- lipoproteins are directed mainly in adipose tissue (raised in adipose tissue LPL)
- FA secondary uses are also in muscle (primary glucose) and other tissues (myocardium, kidneys ad.)
- FA $\rightarrow$ acetyl-CoA $\rightarrow$ CC $\rightarrow$ CO_2 + energy

Amino acids in the resorptive phase

- AA are partially metabolized in enterocytes (Gln)
- part is utilized by the liver to synthesize proteins
- from excess amino acids are formed FA and TAG
- Val, Leu, Ile (= BCAA) **are not** utilized in the liver

  (missing aminotransferase) utilized by the muscles, CNS

Summary of reactions in the resorptive phase (insulin)

Liver	• increased phosphorylation of glucose → Glc-6-P (glukokinase) • Glc-6-P → CO_2 + energy (exceptionally metabolic fuel for the liver) •Glc-6-P → glycogen (supply of glucose to other organs) • Glc-6-P → → $NADPH+H^+$ (pentos. cycle) → → MK → → TAG → VLDL • AK → liver proteins + blood plasma proteins • AA in excess→ carbon skeleton (oxidation) + ammonia → → urea
Tuková tkáň	• increased glucose influx (GLUT4 / insulin) • increased glycolysis→ energy + glycerol-3-P (for lipogenesis) • increased pentose cycle→ → MK (synthesis of FA *de novo* is not important) • influx FA z CM + VLDL (LPL) → TAG (llipogenesis)
Adipose tissue	• increased glucose influx (GLUT4 / insulin) • glucose → CO_2 + energy • increased glycogen synthesis (need for muscle) • income of AA (esp. BCAA) → protein synthesis (+ AA oxidation)
Brain	• glucose → CO_2 + energy
Kidneys	• glucose / FA / glutamine → CO_2 + energy

Insulin

- After a meal, insulin is released from pancreatic β-cells
- Decreases in blood glucose concentration by
- A) increases the transport of glucose into muscle and fat. tissue
- B) stimulates the synthesis of glycogen (liver, muscle)
- C) inhibits glycogenolysis and gluconeogenesis
- D) supports glycolysis in tissues (liver, muscles ...)
- At the same time promotes the synthesis of TAG (tt, liver) and proteins (non-specifically)

Inzulin is anabolic hormon

Supports the construction of storage compounds and cellular glucose utilization

Fatty Acids ⟶ TAG

CO_2 ⟵ (glycolysis) glucose ⟶ glycogen

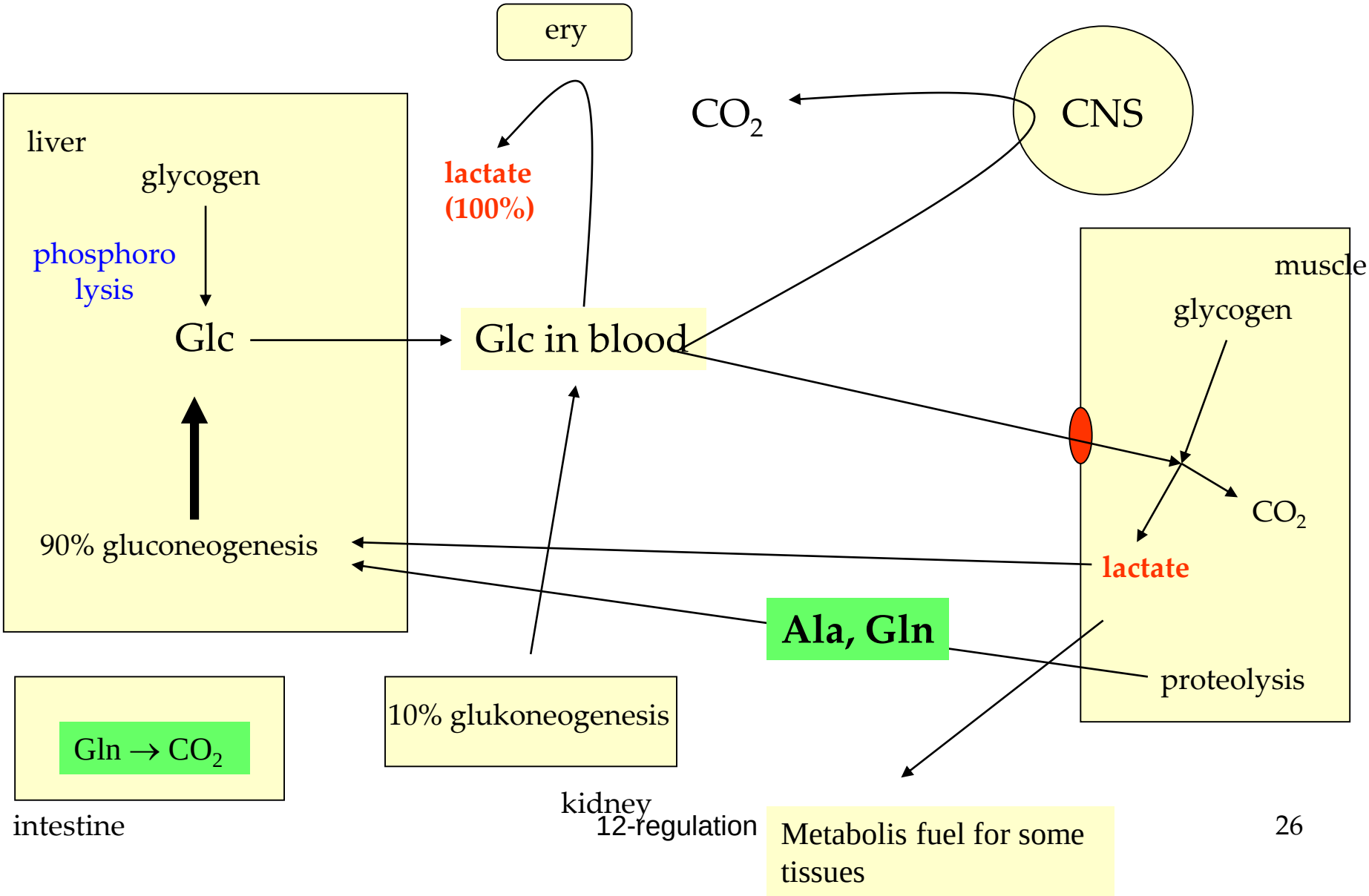
Amino Acids ⟶ proteins

Insulin induces the synthesis of key enzymes of glycolysis (glucokinase, phosphofructokinase, pyruvate kinase), and glycogenesis

Post resorptive phase

- Fasting (first feelings of hunger)
- About 10-12 hours after the last meal (before breakfast)
- Hormonal regulation – glucagon

Carbohydrates and proteins in Post resorptive phase (glucagon)



Glucose in post resorptive phase (glucagon)

glucose in blood is controlled by two processes:

(1) hepatic glycogenolysis (phosphorolysis) $(Glc)_n + P_i \rightarrow (Glc)_{n-1} + Glc\text{-}1\text{-}P$

phosphorylase is activated by glucagon and adrenalin

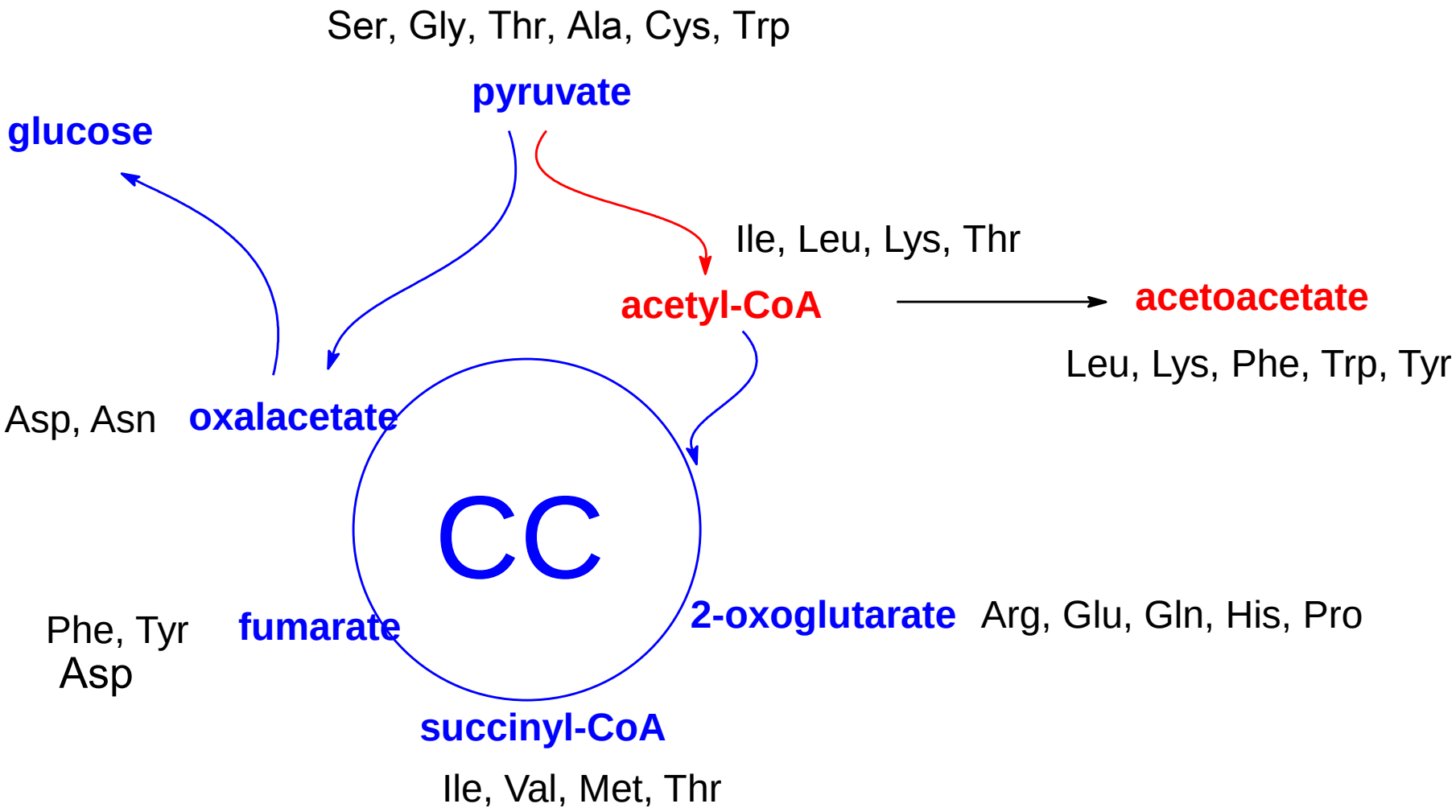
Glc-6-P $\rightarrow$ free Glc

(2) The hepatic gluconeogenesis from non-sugar precursors

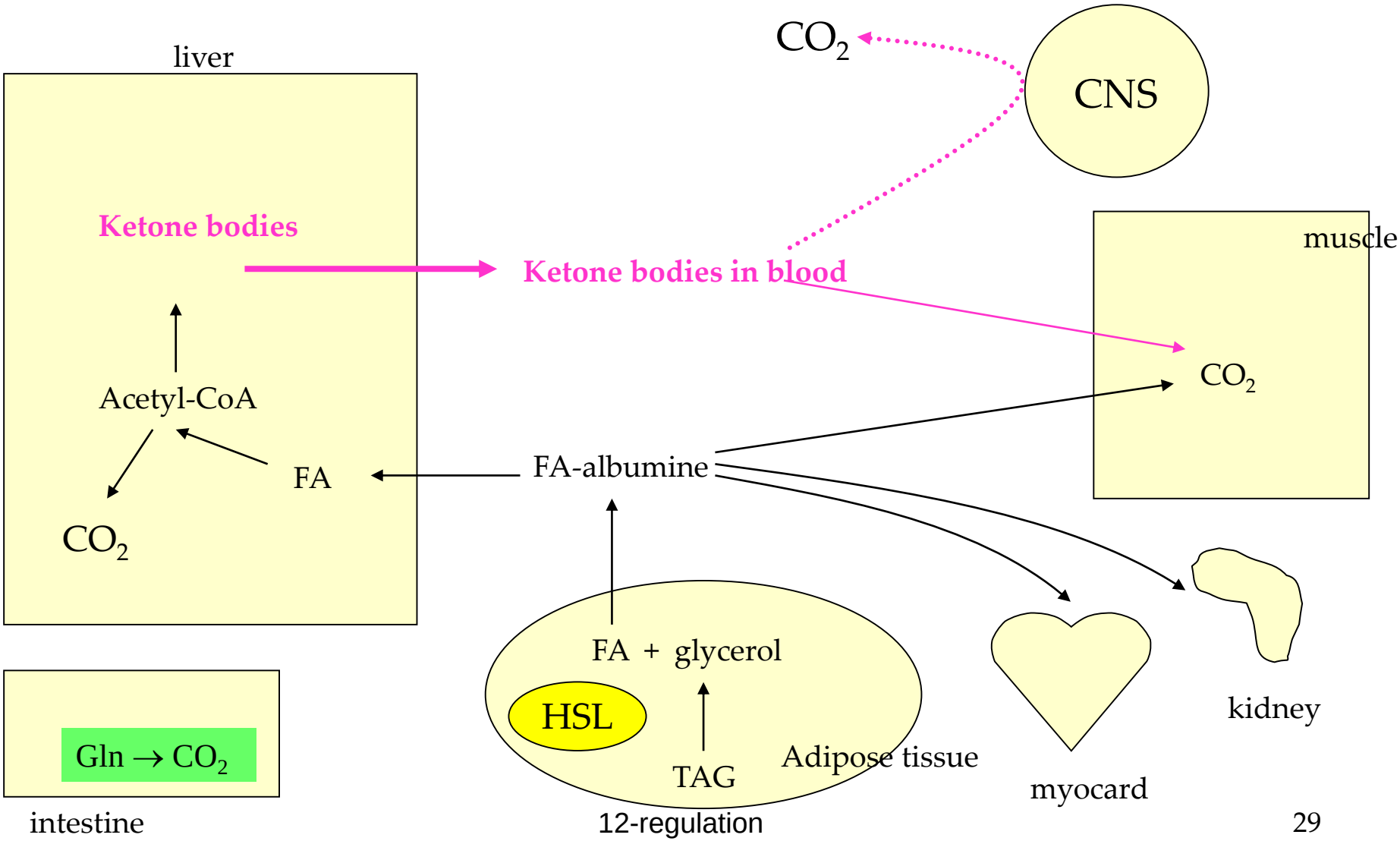
alanine, more glucogenic AK, glycerol, lactate

glucagon induces synthesis of three key enzymes:
fosfoenolpyruvátkarboxykinasa (PEPCK)
fructose-1,6-bisfosfatasa
glucose-6-phosphatase

Most (14) amino acids are glucogenic



Lipids in the post resorptive phase (glucagon)



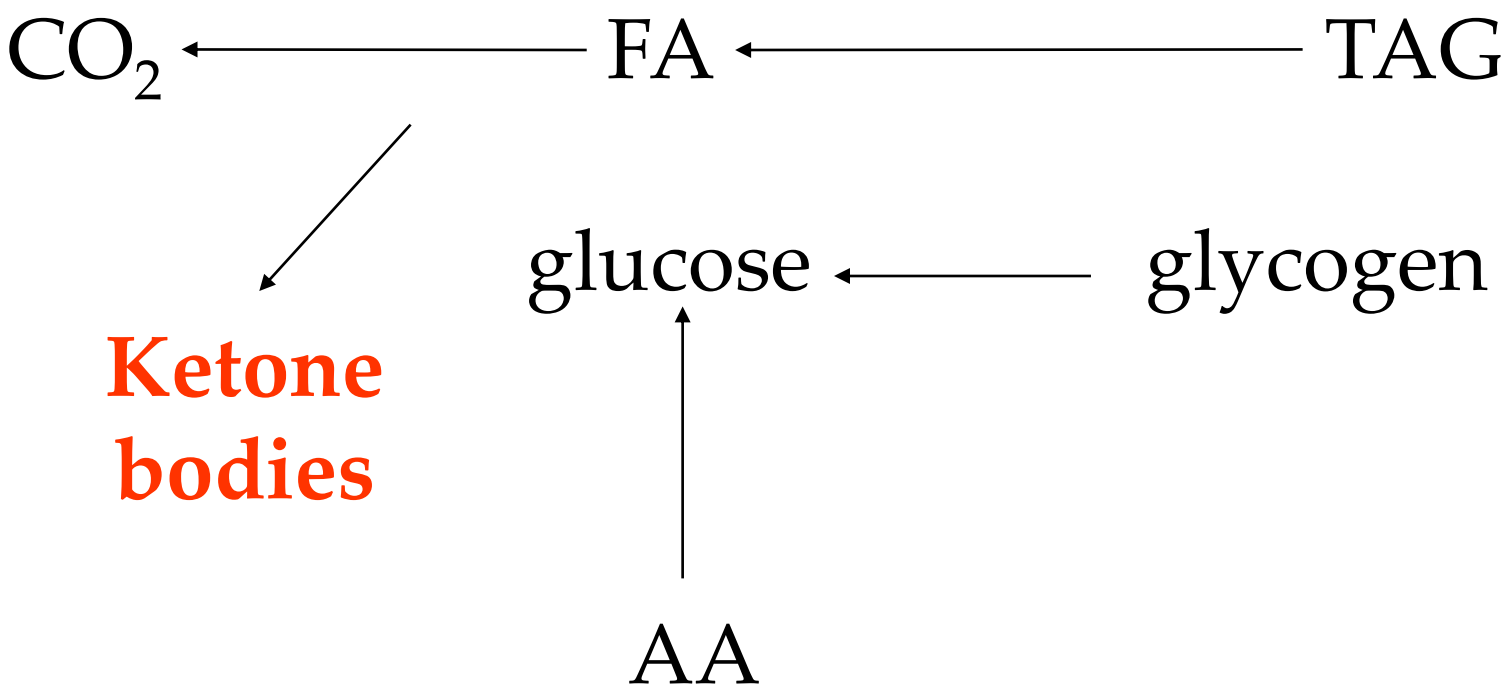
Lipids in the post resorptive phase

- In adipose tissue lipolysis occurs (hormone sensitive lipase)
- FA are transported in the ECT, in relation to the albumin
- FA are an energy source for the liver, muscles and myocardium
- Ketone bodies are used in the muscles and partly in the CNS

Glucagon is antagonist of insuline

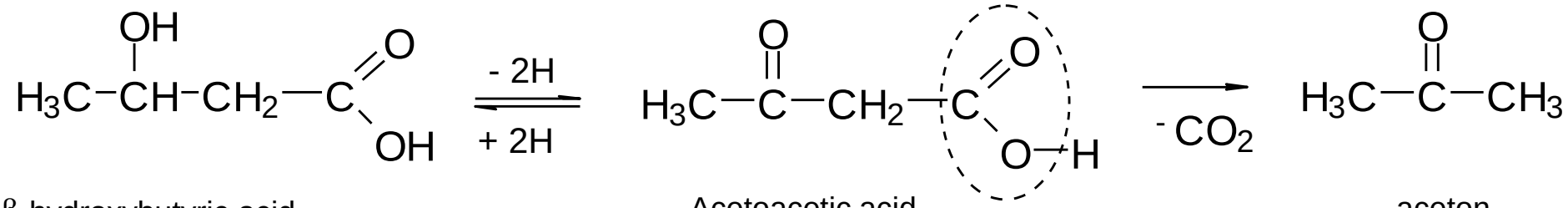
- Second messenger cAMP
- Promotes degradation of storage substances: glycogen (liver), TAG (a.t.) and proteins (liver)
- Promotes gluconeogenesis from lactate and AA
- It inhibits glycogen synthesis, and protein TAG
- acts on liver and fat. tissue (not muscle)

Glucagon is the antagonist of insulin (Ketogenic hormone)



Glucagon induces synthesis of three key enzymes of gluconeogenesis:
PEPKC, Fru-1,6-bisfosfatasu, glc-6-phosphatase

ketone bodies



β-hydroxybutyric acid

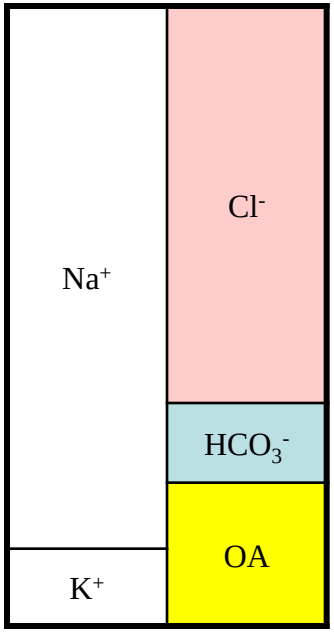
Acetoacetic acid

aceton

anion

anion

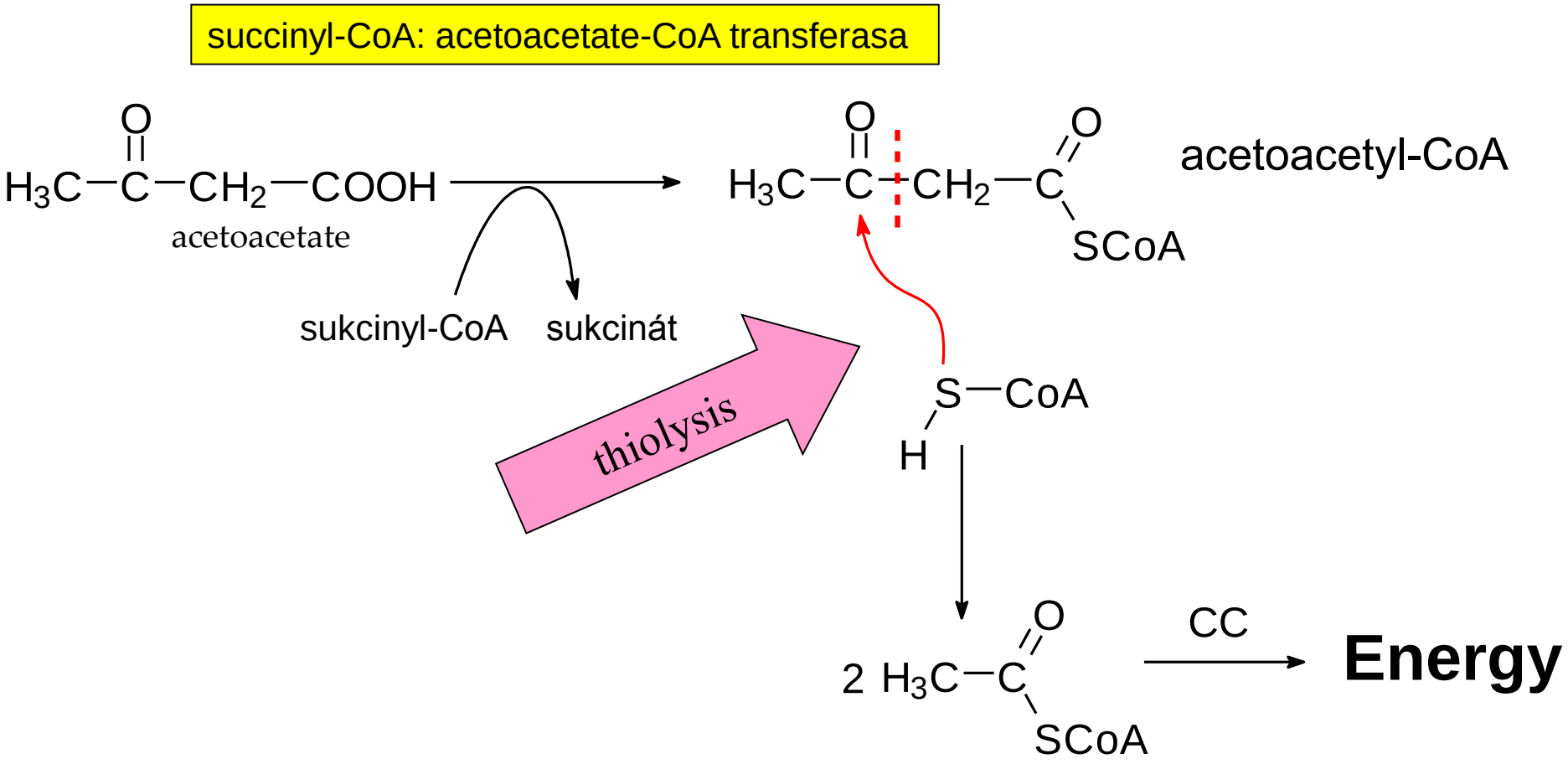
No electrolyte



acetone, acetoacetic acid, and *beta*-hydroxybutyric acid

Ketone bodies are three water-soluble molecules that are produced by the liver from fatty acids during periods of low food intake (fasting) or carbohydrate restriction for cells of the body to use as energy instead of glucose. Two of the three are used as a source of energy in the heart and brain while the third (acetone) is a degradation breakdown product of acetoacetic acid.

Ketone bodies as source of energy

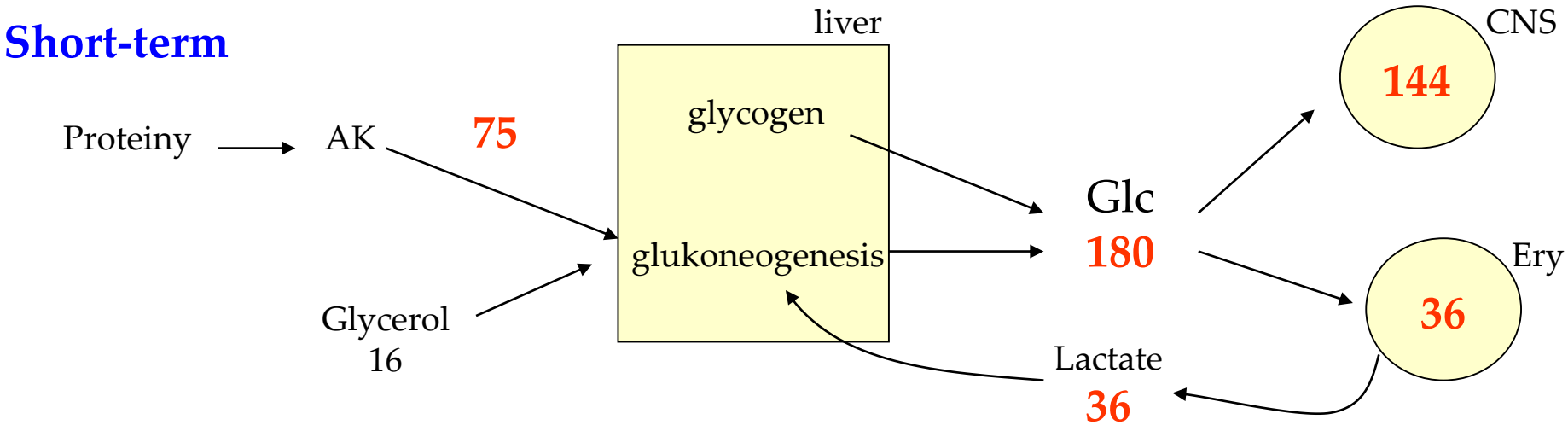


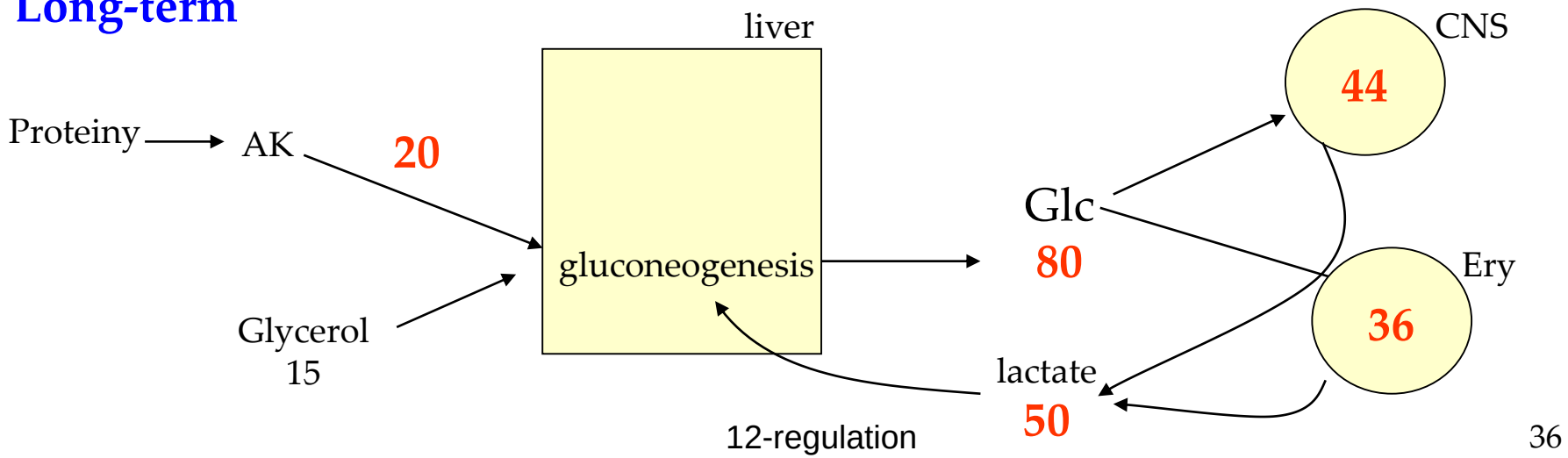
A summary reactions in post resorptive phase (glucagon)

Liver	• increased glycogenolysis • gluconeogenesis (from Ala, AA, lactate/pyruvate, glycerol) • increased β-oxidation FA → acetyl-CoA → → ketone bodies → export KB
Adipose tissue	• increased lipolysis (HSL / glukagon, adrenalin) → FA + glycerol • increased export FA to blood
Muscle	• FA (from AT) + ketonebodies (from liver) → CO_2 + energy • long fasting – FA only oxidated • proteolysis → AA (mainly Ala, Gln – for liver gluconeogenesis) / kortisol
Brain	• glucose → CO_2 + energy • ketone bodies → CO_2 + energy (long fasting)
kidney	• glucose / FA / ketone bodies / glutamin → CO_2 + energy • gluconeogenesis (for kidney and others) • compensation of keto acidosis : Gln/Glu → NH_3 + H^+ → NH_4^+ (excretion to urine)

glucosa-6-phosphatase

Carbohydrate metabolic turnover during starvation (g/d)

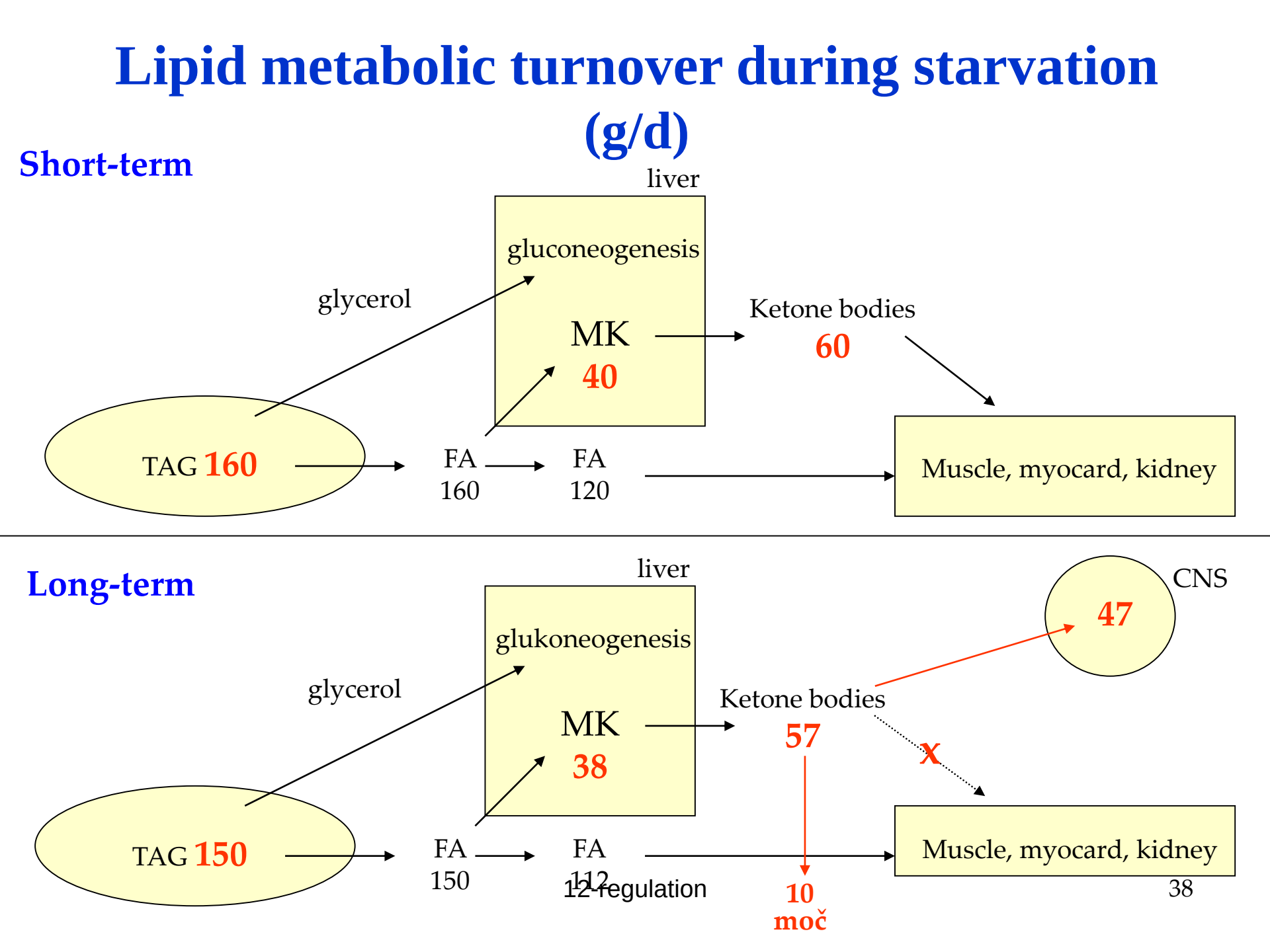




Carbohydrate metabolic turnover during starvation

- Gluconeogenesis in the liver gradually decreases
- muscle proteolysis gradually decreases
- Substrates for gluconeogenesis are unchanged (lactate, AA, glycerol)
- CNS decreases glucose utilization
- Proportion Ery Glc consumption remains constant (36 g / d), which during prolonged fasting can be up to 45% of production Glc

Lipid metabolic turnover during starvation (g/d)



Lipid metabolic turnover during starvation

- The extent of lipolysis in adipose tissue remains roughly the same
- Production of ketone bodies is also roughly equal (acidosis)
- Muscles cease to use ketone bodies
- The brain gradually adapts to ketone bodies

The main priorities of the body during starvation

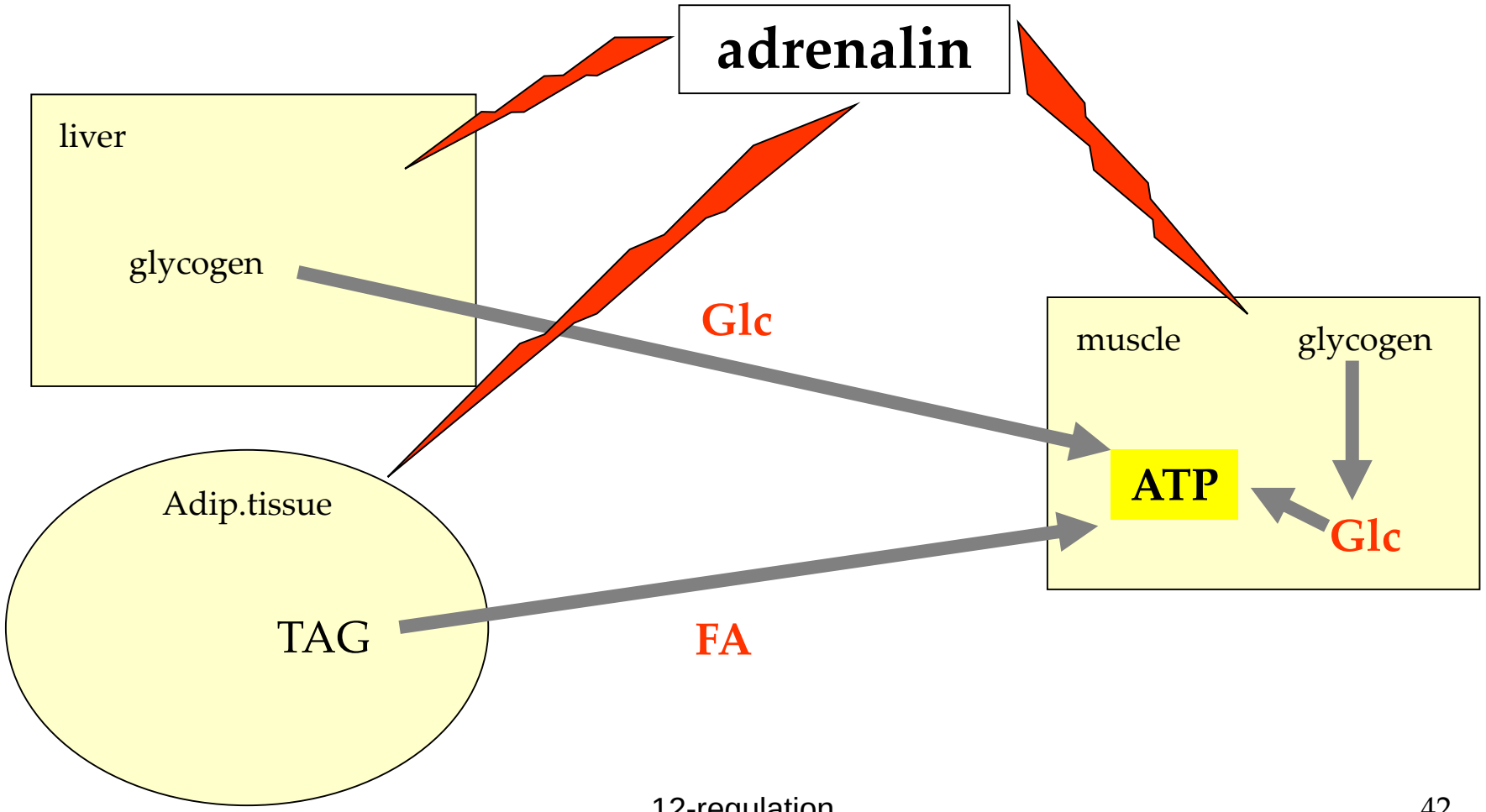
- Saving of glucose (utilization of ketone bodies in the brain)

  Saving of proteins (ketones limit of gluconeogenesis AA)

Metabolism during stress - catecholamines

- Noradrenaline, adrenaline - released from the adrenal medulla
- It operates via adrenergic receptors
- β-receptors - cAMP - muscles, fat. tissue
- α1-receptors - IP3 DAG + (Ca2 +) - liver
- Effect of very quick - seconds
- Primarily stimulate:
- Glycogenolysis in the liver (increase in blood Glc)
- Glycogenolysis and glycolysis in muscle
- Lipolysis in adipose tissue
- The power supply for the muscles that must react quickly to the situation (fight, flight)

Organism in a state of emergency (fight or flight)



Glucocorticoids are released in chronic stress

- Cortisol - potentiates the effect of adrenaline
- Prepares the body for the effect of adrenaline
- Affects the expression of genes - the effect of slow – hour to days
- stimulates the HSL synthesis in fat. tissue – instress, there is enough available enzyme cleavage of stored fats
- supports muscle proteolysis - substrates for gluconeogenesis
- Induces the synthesis of PEPCK (gluconeogenesis) and glycogen synthase