# The integration of intermediary metabolism of nutrients at the tissue and organ level

Biochemistry II
Lecture 3

2009 (J.S.)

# Nutrients – dietary fuels

**Saccharides** are the most **universal nutrients –**
the overdose is transformed in the fat stores,
carbon skeleton of non-essential amino acids may originate from saccharides.

**Triacylglycerols** exhibit the highest **energetic yield** –
but **fatty acids cannot convert into saccharides** or the skeleton of amino acids.

**Amino acids** in the form of **proteins** represent the unique, precious **source of nitrogen** for proteosynthesis. They can be used as a **fuel** rather when the body is lacking in other nutrients – during starving, a disease, or injury.
Glucogenic amino acids can convert into glucose.

An overdose of diet protein may be transformed into fat stores.

# Fuel reserves in a typical 70-kg man

**Nutrient mass and available energy**

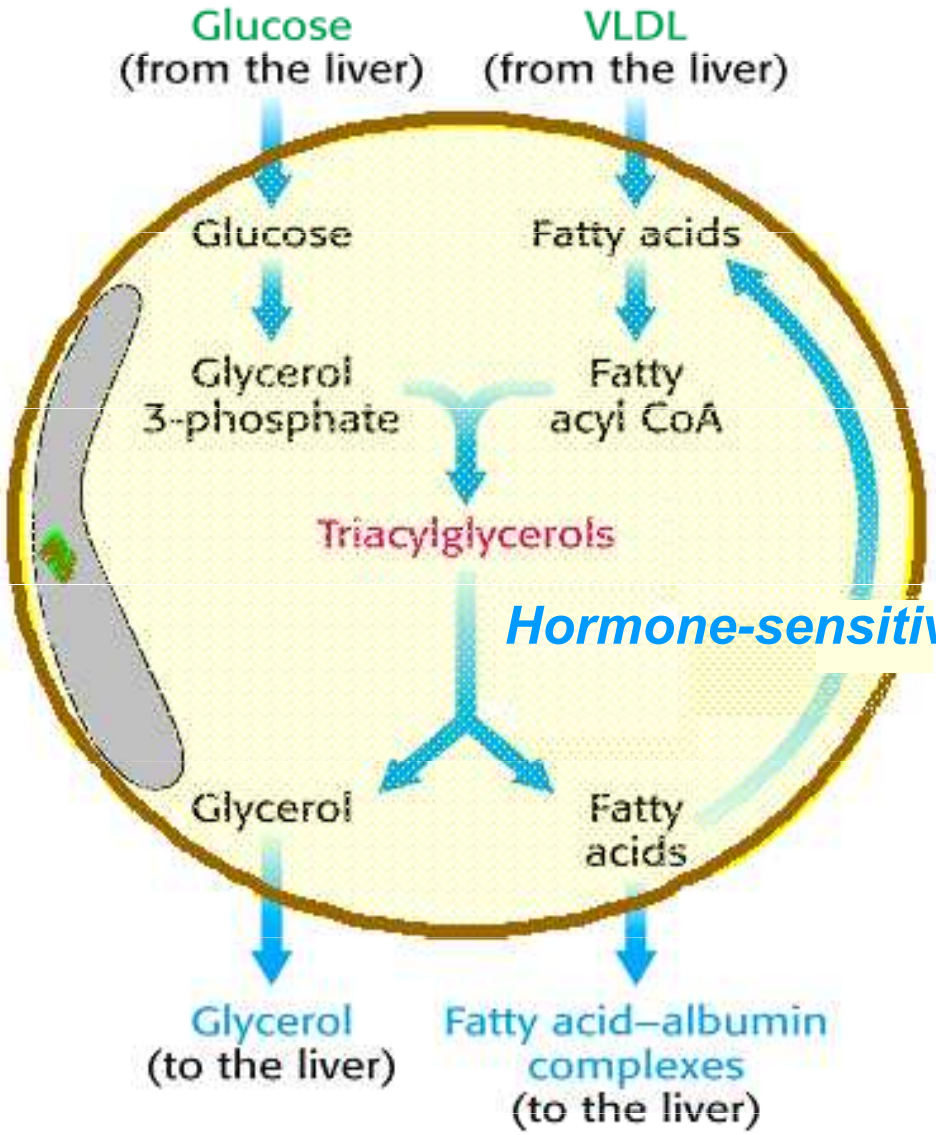
| Localization | Glycogen or glucose | | Triacylglycerols | | Mobilizable proteins | |
|---|---|---|---|---|---|---|
| | g | kJ | g | kJ | g | kJ |
| EC fluid | 14 | 240 | 5 | 190 | 0 | 0 |
| Liver | 70 | 1 200 | 50 | 1 900 | 90 | 1 500 |
| Brain | 2 | 34 | 0 | 0 | 0 | 0 |
| Muscle | 120 | **2 000** | 50 | 1 900 | 6000 / 3 | **34 000** (102 000 / 3) |
| Adipose tissue | 20 | 340 | 15 000 | **570 000** | 10 | 170 |

Total energy stores of the body equal about **700 MJ**, most of that as the **fat stores** (total body fat represents approximately 10 - 25 % body weight.

Glycogen in the liver is not very large, it is exhausted, without refilling, less than 24 h. Muscle glycogen can be utilized only within muscles, because there is no glucose-6-phosphatase activity to release free glucose.

Proteins have essential roles other than providing energy. Muscle protein may supply amino acids for gluconeogenesis, but only limited amounts (not more than approximately ⅓ of muscle protein) can be oxidized for energy to preserve the vital functions of the tissue.

# Synthesis and mobilization of TG stores in adipose tissue




***Hormone-sensitive lipase***

<u>stimulation</u> of the enzyme is mediated by **GLUCAGON** or **adrenaline** (in stress)

<u>inhibition</u>
mediated by **INSULIN**

# Basal metabolic rate (BMR)

Rough estimate: **100 kJ / d per l kg body weight**

Harris and Benedict equations (BMR in **kcal / kg**):

$BMR_{women} = 655 + (9.6 \times \mathbf{w}) + (1.8 \times \mathbf{h}) - (4.7 \times \mathbf{a})$

$BMR_{men} = 6.6 + (13.7 \times \mathbf{w}) + (5 \times \mathbf{h}) - (6.8 \times \mathbf{a})$

w – weight in kg
h – height in cm
a – age in years

1 kcal = 4.2 kJ

Basal metabolic rate depends on

- gender (women about 10 % lower than men),
- body temperature (increase by 12 % at 1 °C body temperature increment),
- environmental temperature (increased in cold climates),
- thyroid status (increased in hyperthyroidism),
- pregnancy and lactation (increased),
- long-term low-energy intake (low-calory diets, anorexia nervosa,
- age (increased in childhood).

Under basal conditions, muscle spends about 30 % BMR,
nervous system (namely central) 20 %,
myocard 11 %, and
the kidney up to 10 %.

## Energetic content of dietary components

corresponds to the **heat of combustion** of a nutrient:

| | |
|---|---|
| **Saccharides** | **17** kJ / g |
| **Fats** | **38** kJ / g |
| **Protein** *) | **17** kJ / g |

*) the biological value, final catabolites of proteins in human bodies are $CO_2$, $H_2O$ a urea $CO(NH_2)_2$.

Notice the energetic content of **alcohol**, which equals **30** kJ / g.

## Recommended ratio of nutrients in the human diet

for individuals performing light to moderate physical activity:

**Saccharides** **50 - 55 %** of energy intake (predominantly polysaccharides),
**fat** **25 - 30 %** (essential fatty acids should account for about 10 % of total intake, saturated less than 10 %),
**proteins** **10 - 15 %** (0.7 g / kg ideal body weight per day, containing satisfactory amounts of essential amino acids).

# Body mass index (BMI)

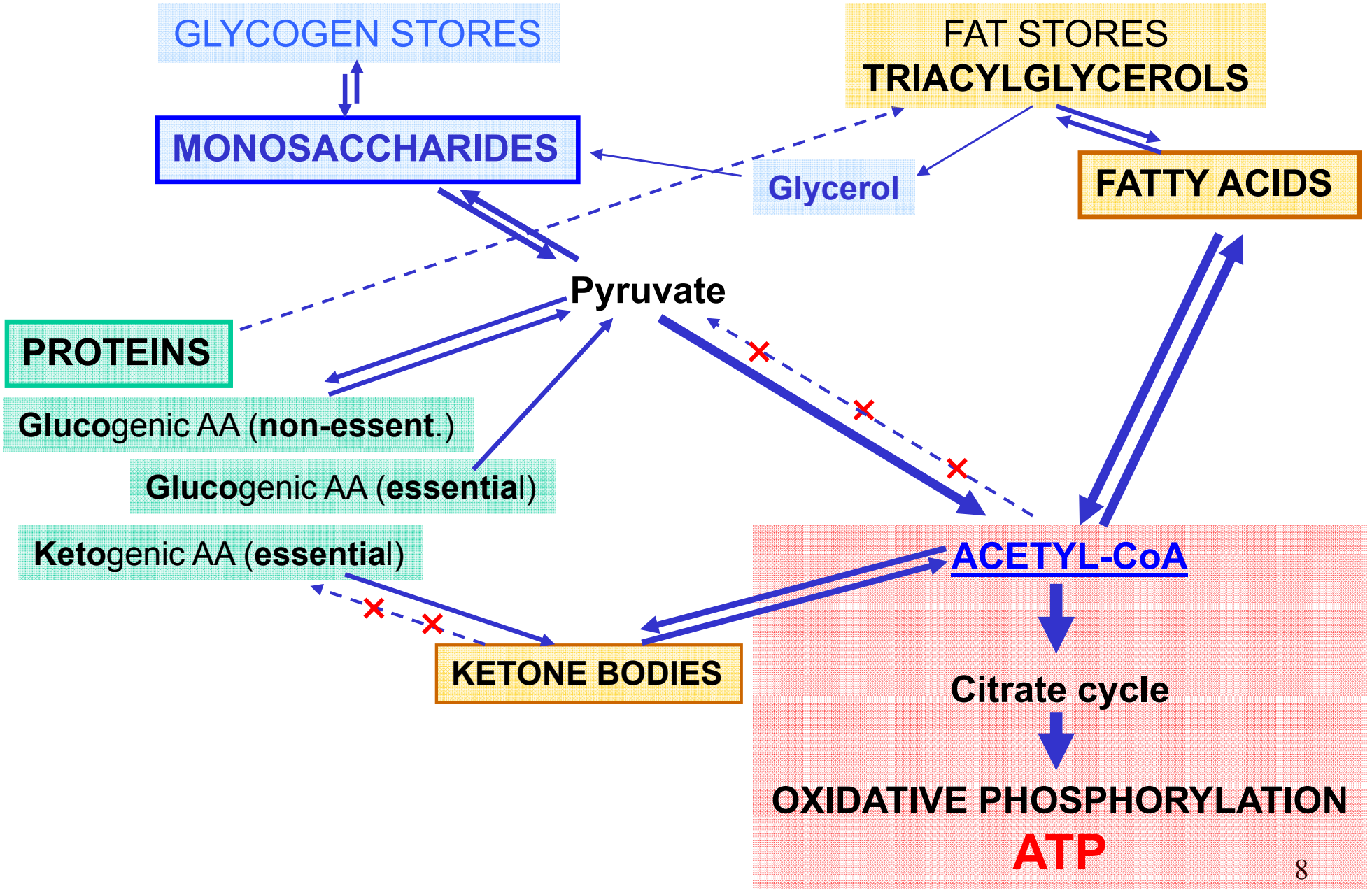
$$BMI = \frac{\text{weight}}{(\text{height})^2} \quad (kg/m^2)$$

| | |
|---|---|
| **BMI** < 16 | emaciation (extreme undernourishment) |
| 16-20 | underweight |
| **20-25** | **"ideal" body mass** |
| 25-30 | overweight |
| 30-40 | obesity |
| > 40 | extreme obesity |

## Daily energy expenditure (kJ / d)

| | |
|---|---|
| **$BMR_{women}$** | **6000 - 7000** |
| **$BMR_{men}$** | **7000 - 8000** |
| Very light activity | **8000 - 11000** |
| Light to moderate activity | **11000 - 14000** |
| Heavy work | **14000 - 18000** |

# Relationships among the major energy metabolism pathways



# Tissues differ in the ability to utilize nutrients
## due to their enzyme equipment:

| Pathway | Liver | Kidney | Muscle | CNS | RBC | Adipose tissue |
|---|---|---|---|---|---|---|
| **Glycolysis** | + | + | + | + | + | + |
| **FA β-oxidation** | + | + | + | 0 | 0 | 0 |
| **Utilization of ketone bodies** | 0 | + | + | (+) | 0 | + |
| **Ketogenesis** | + | 0 | 0 | 0 | 0 | 0 |
| **Gluconeogenesis** | + | + | 0 | 0 | 0 | 0 |
| **FA synthesis** | + | ± | ± | ± | 0 | + |

## The metabolism of nutrients is sophistically controlled

through different mechanisms in

the **fed state** (absorptive phase),

the **early fasting state** (post-absorptive phase), and in

the **metabolic adaptation in prolonged starvation**..

During **physical activity**, the nutrient sources for muscle contraction are determined by intensity and duration of activity. There are differences in the selection of fuels between anaerobic muscular work and prolonged aerobic work (e.g. sprinting and dostance running).

# The absorptive (fed, postprandial) state

After a typical high-saccharide meal, glucose leaves the intestine in high concentrations.

**Hyperglycaemia stimulates the pancreas to release insulin**, glucagon release is inhibited.

A part of nutrient is oxidized to meet the immediate energy needs, excessive nutrients are stored

– as glycogen in liver and muscle, and mainly
– as triacylglycerols in adipose tissue.

**Insulin secretion** from the B cells of Langerhans islets of the pancreas:
Basal secretion is very low, glucose levels below 4.5 – 5,5 mmol/l don't stimulate insulin release. During the **hyperglycaemia**, transporters GLUT 2 more effectively facilitates diffusion of glucose into the B cells. ATP produces by glycolysis closes the ATP-dependent $K^+$-channel; the resulting depolarization of the plasma membrane opens the voltage-operated $Ca^{2+}$-channels, and increase in intracellular $Ca^{2+}$ is followed by the exocytosis of secretion granules containing insulin.

## Insulin

is an anabolic hormone. It

– inhibits the secretion of glucagon from the pancreatic A cells (paracrine effect),

– supports the **entry of glucose into skeletal muscle and adipocytes** by translocation of GLUT4 transporters to the cell membrane,

– **promotes glycogen synthesis** and storage in the liver and muscle (at the same time inhibits glycogen breakdown through dephosphorylation of the key enzymes),

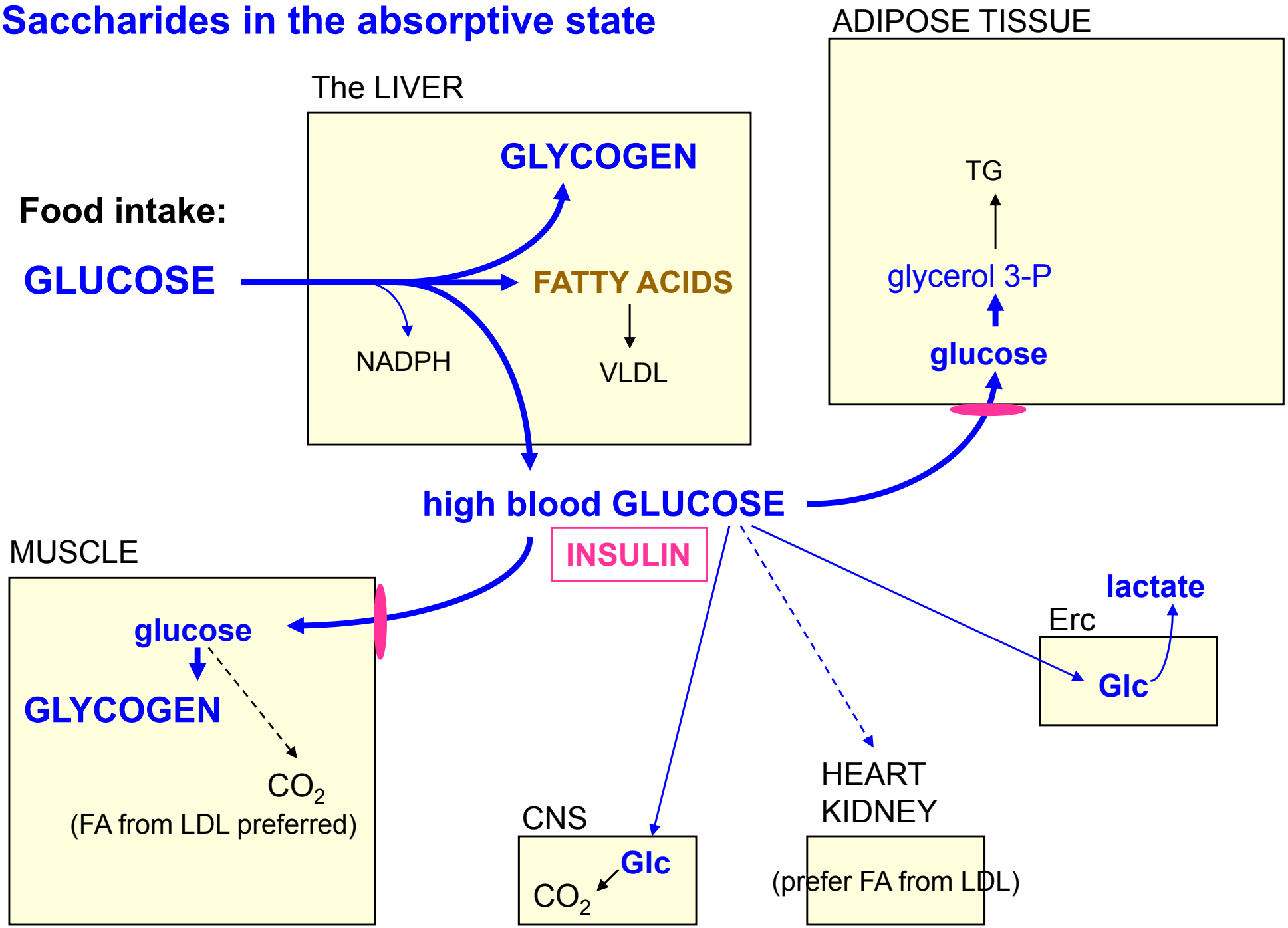
– **stimulates glycolysis** (at the same time inhibits gluconeogenesis) through its effects on glycolytic enzymes and induction of synthesis of those enzymes,

– **intensifies triacylglycerol synthesis** in the liver (secretion of VLDL) and in adipose tissue (induces the production of lipoprotein lipase in vascular beds and inhibits hormone-sensitive lipase),

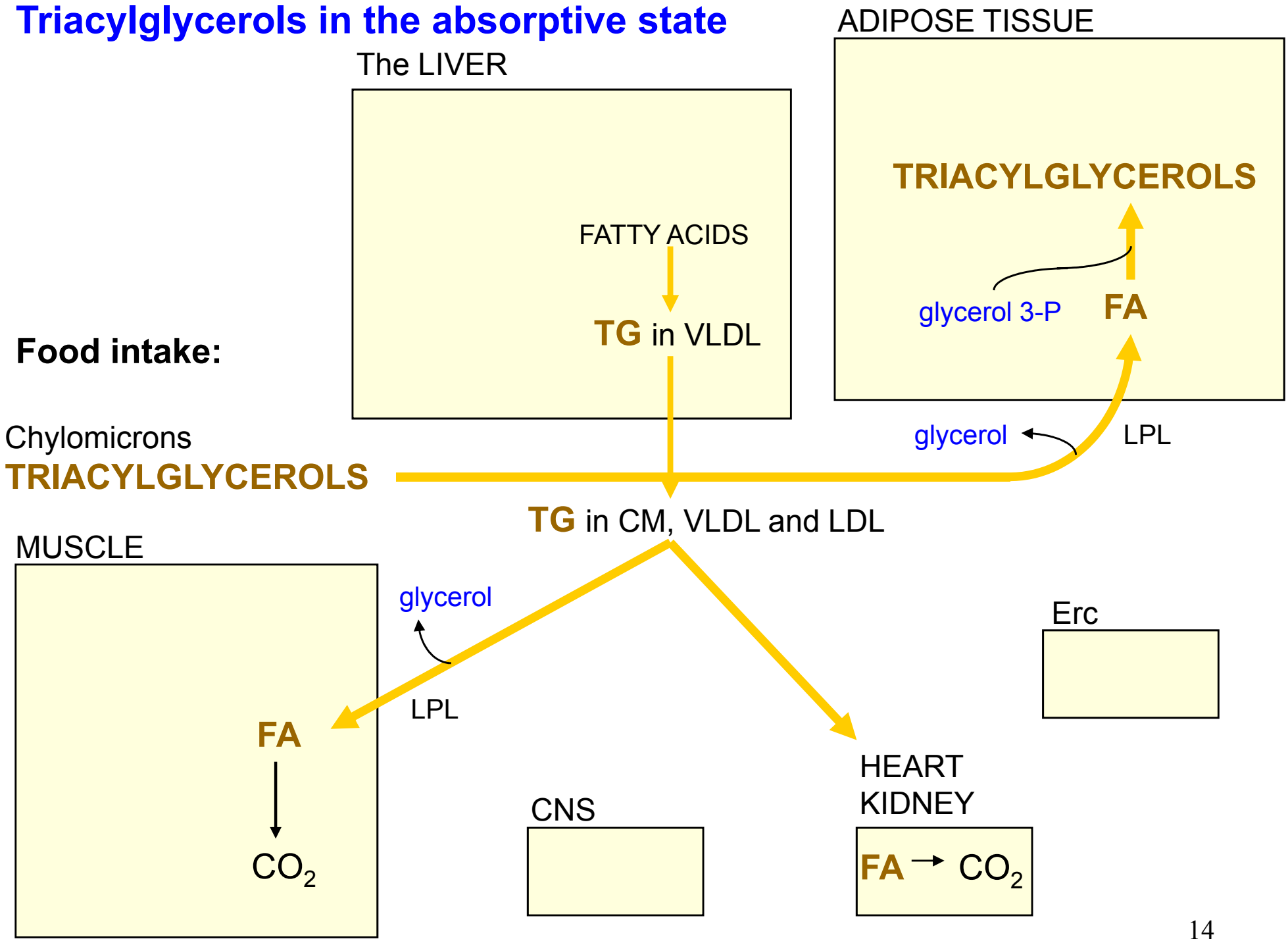
– **promotes synthesis of proteins** in muscle by increasing amino acid transport as well as by stimulating ribosomal proteosynthesis.

The mentioned effects result in the **hypoglycaemic effect.**

# Saccharides in the absorptive state



# Triacylglycerols in the absorptive state



# The postabsorptive phase – early fasting

is the time period from the first feeling of hunger (few hours after a meal), which doesn't last usually more than 10 -12 h (e.g. during the nightly starved-fed cycle, till the refed state is reached again after breakfast)

Within about one hour after a meal, blood glucose concentration begins to decline. As a consequence, **release of glucagon** from the A cells begins, the stimulation of insulin discontinues.

**Glucagon antagonizes the effect of insulin:**

– **stimulates the liver glycogenolysis** (inhibits glycogenesis),

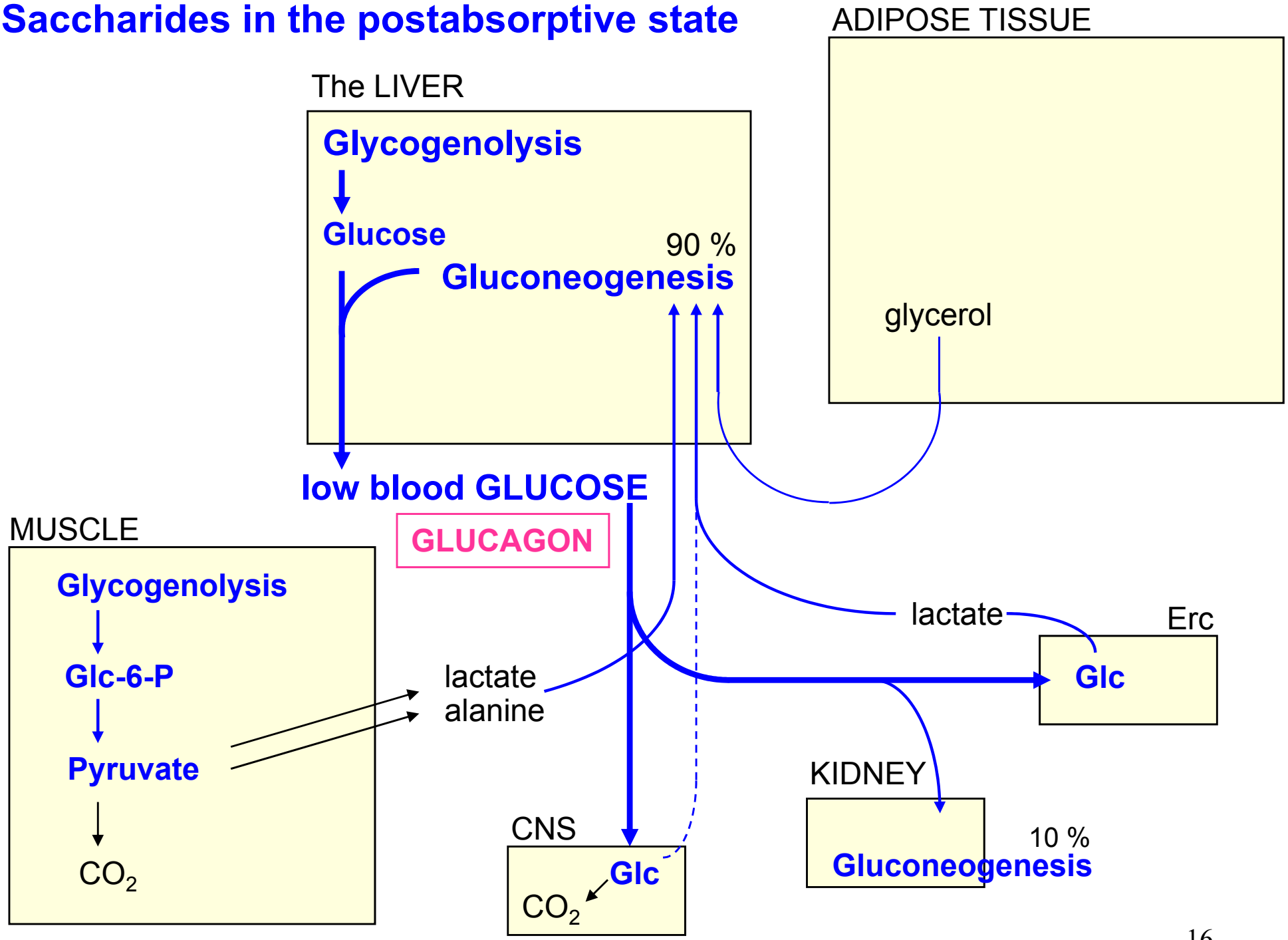
– **activates mobilization of fat stores** (fatty acid release from adipocytes),

– **supports gluconeogenesis** from lactate, glycerol, and amino acids in the liver and kidney, and induces the synthesis of key-enzymes of gluconeogenesis

All these effects result in **maintaining fuel availability in the absence of dietary glucose**.

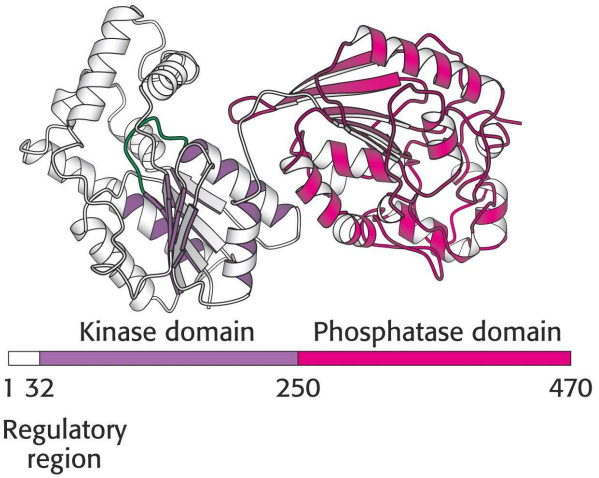
Glucagon has no influence on skeletal muscles metabolism.

# Saccharides in the postabsorptive state



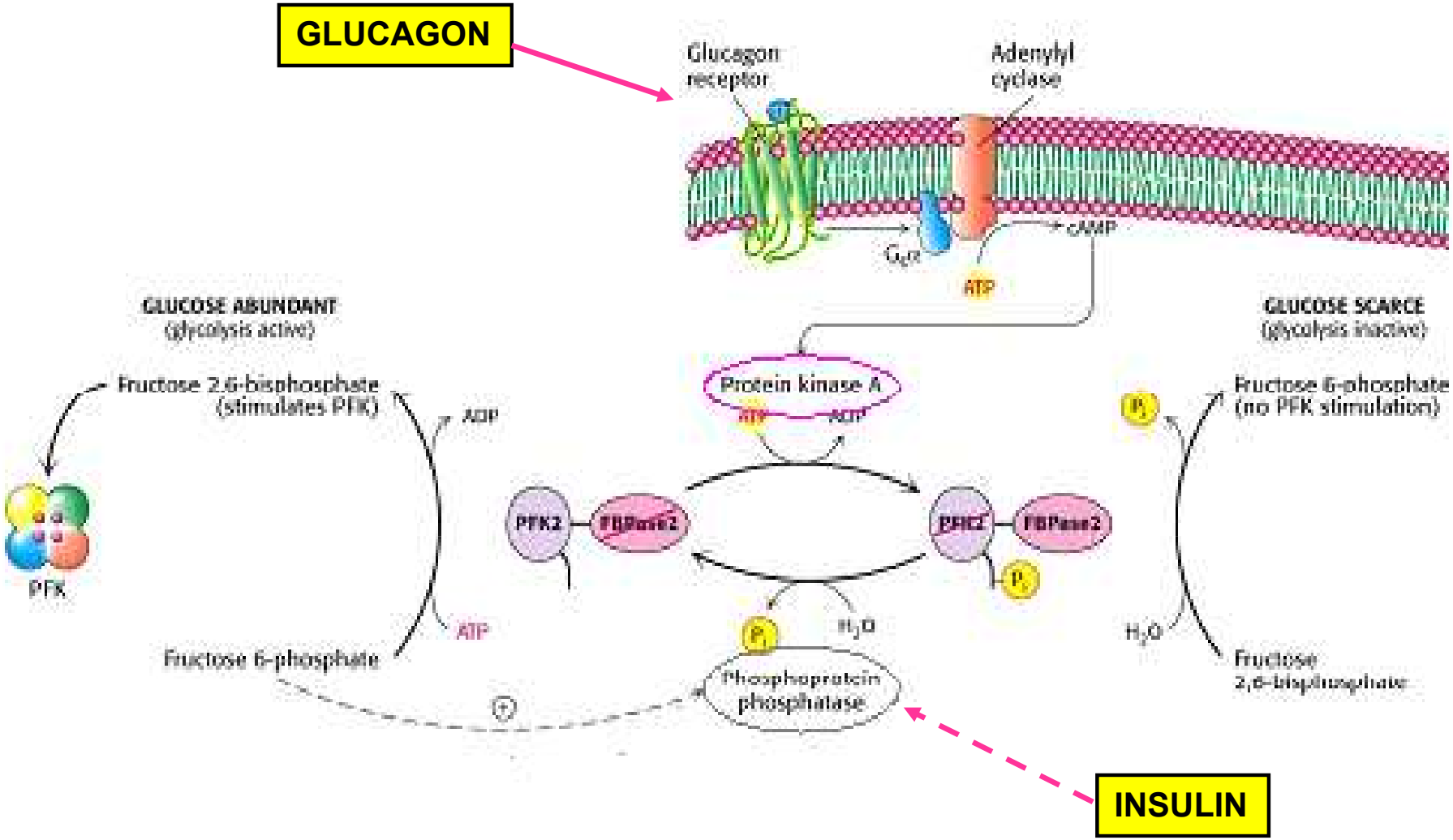
For example, **glucagon turns the glycolysis to gluconeogenesis through the decrease in the concentration of fructose 2,6-bisphosphate** (Fru-2,6-$P_2$), which acts as one of the allosteric activators of phosphofructo-1-kinase as well as an allosteric inhibitor of fructose 1-bisphosphatase.

The concentration of Fru-2,6-$P_2$ controlled by a **bifunctional enzyme**:
Its **phosphofructo-2-kinase** activity catalyzes the phosphorylation of Fru-6-P to Fru-2,6-$P_2$, the **fructose 2-bisphosphatase** activity of the same protein molecule, but another domain, catalyzes dephosphorylation of Fru-2,6-$P_2$ to Fru-6-P.

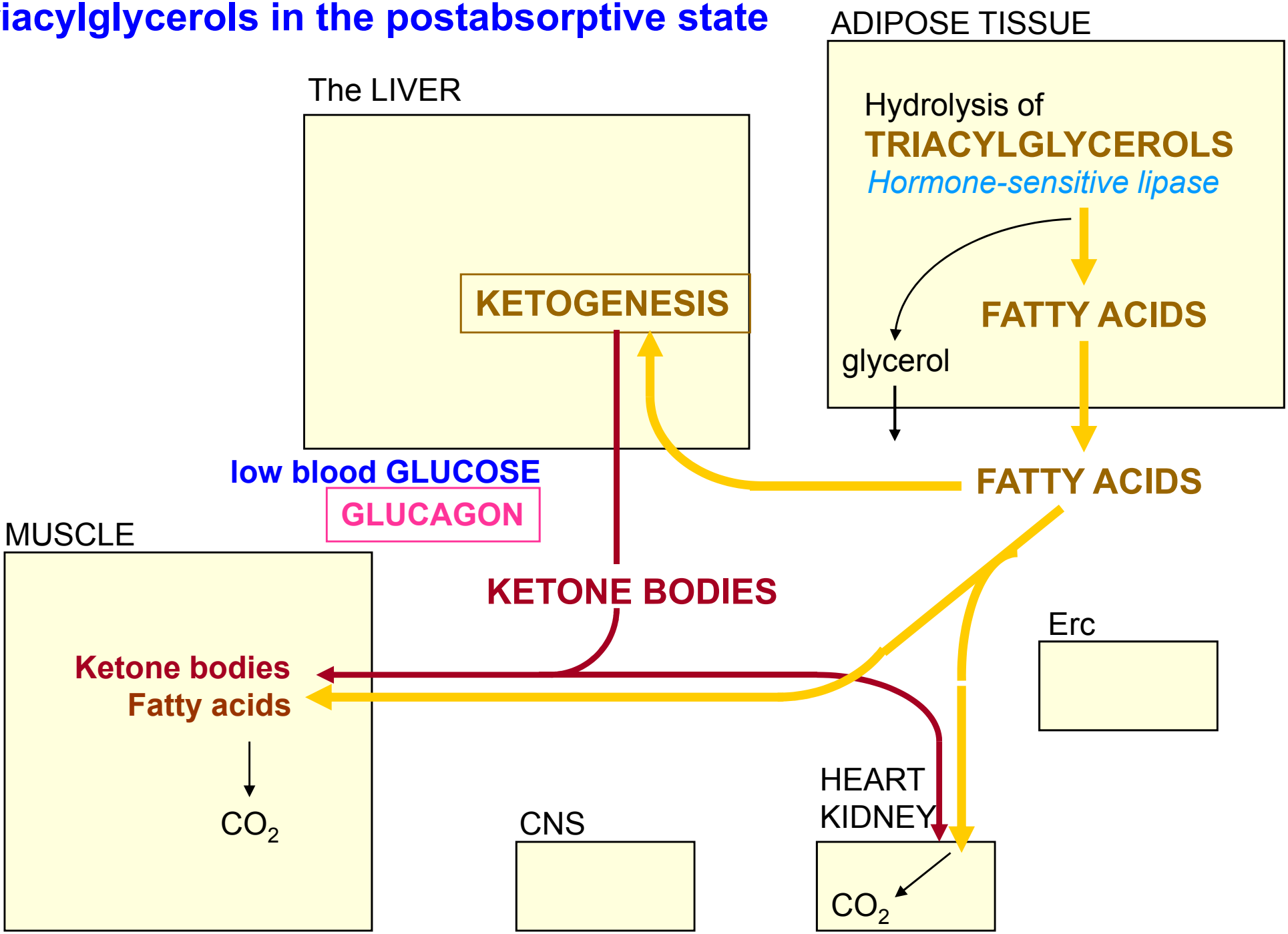



The phosphorylated form of the enzyme exhibits the **phosphatase** activity (it depends on glucagon, reversal of glycolysis to gluconeogenesis), the dephosphorylated form of the enzyme (controlled by insulin) catalyzes the formation of Fru-2,6-$P_2$.

## Control of the Fru-2,6-$P_2$ concentration by phosphorylation and dephosphorylation of the bifunctional enzyme:



# Triacylglycerols in the postabsorptive state



# Metabolism in the state of stress

## The state of simple acute stress

Sense of acute danger, exposure to cold, etc. initiates the alarm reaction ("fight or flight") provided by **adrenaline** and/or noradrenaline.

The effects of catecholamines on fuel metabolism are **similar to those of glucagon**. In addition, adrenaline stimulates glycogenolysis in skeletal muscles.

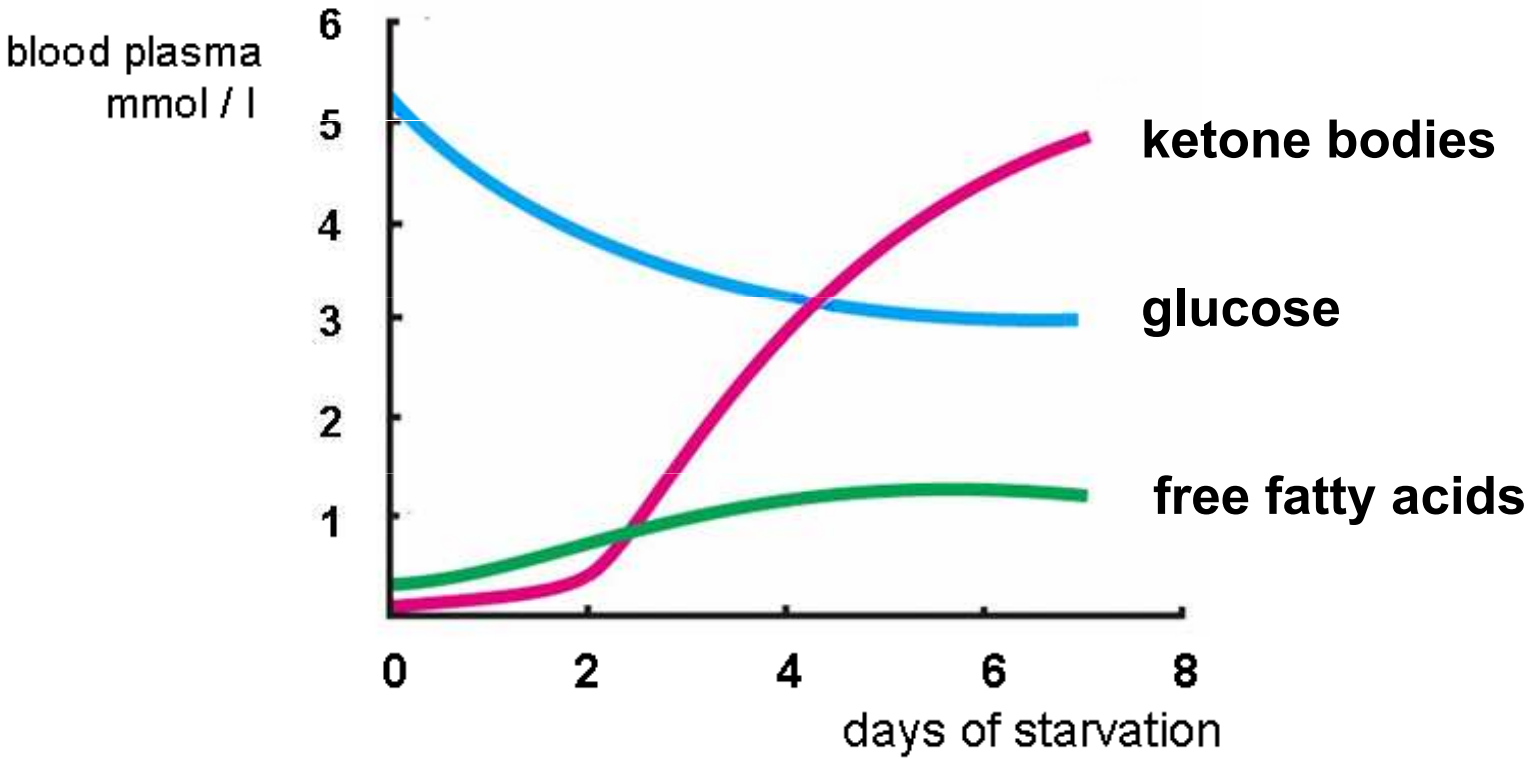
The adaptation syndrome follows, in which the fuel metabolism is maintained by the action of **cortisol**. Cortisol induces synthesis of hormone-sensitive lipase, and phosphoenolpyruvate carboxykinase stimulating so, among others, gluconeogenesis and glycogenesis.

## Metabolic stress

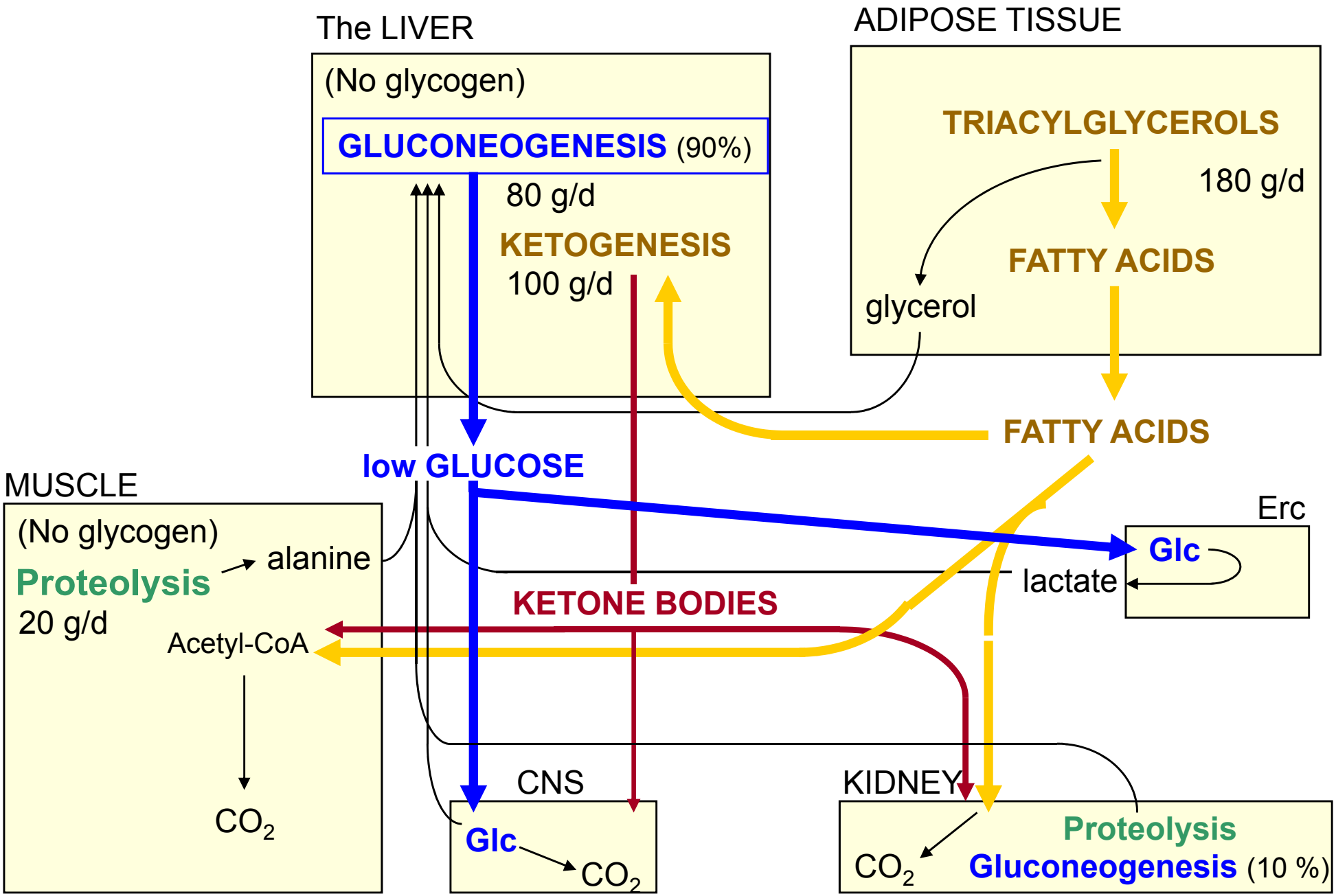
(trauma, severe diseases, sepsis) is influenced not only by stress hormones, but also by other signal molecules – predominantly by **cytokines** (namely interleukin-1 and TNFα - tumour necrosis factor α).

# Prolonged fasting - starvation

During prolonged fasting, changes in utilization of nutrients occur. A major goal is to **spare glucose**: tissues use less glucose than they use during a brief fast and use predominantly triacylglycerols and ketone bodies. After several days of starvation, the brain also begins to consume appreciable amounts of acetoacetate (30 – 60 %) in place of glucose.
The second priority is to **spare proteins.**



# Metabolism of nutrients in prolonged starvation (approx. 3 – 4 weeks)



| Nutrient consumption / production | Amount in grams per day | |
|---|---|---|
| | 3rd day | 40th day |
| Glucose needed for the brain | **100** | **40** |
| Ketone bodies needed for the brain | **50** | **100** |
| All other use of glucose | 50 | 40 |
| Glucose output of the liver | **150** | **80** |
| Ketone bodies output | 150 | 150 |
| Triacylglycerols mobilized | 180 | 180 |
| Muscle proteins degraded | **75** | **20** |

Amount of glucose consumpted in erythrocytes (about 30 g/d) remains the same, it can reach up to 50 % of glucose production in starvation.

Utilization of ketone bodies on muscles is stopped, ketone bodies are spared for the brain.

Proteolysis increases in the course of several days of starving temporarily, in the earliest weeks, after that it diminishes to spare proteins; 20 g degraded protein represent approx. 12 g glucose. Initial sources of proteins are proteins of intestinal epithelium, digestive enzymes, some of the liver enzymes, and in skeletal muscles, contractile proteins and enzymes of the glycolytic pathway.

# Fuels consumption in muscles

## Anaerobic phases of physical exercise or muscular work with maximal intensity

Initially, exercising muscle uses endogenous fuels, from its own stores). **ATP** (5 mmol/l), ATP regenerated from **phosphocreatine** (9 mmol/l), and muscle **glycogen**. The decrease in ATP concentration as well as appearance of AMP initiates breakdown of glycogen and stimulates glycolysis.

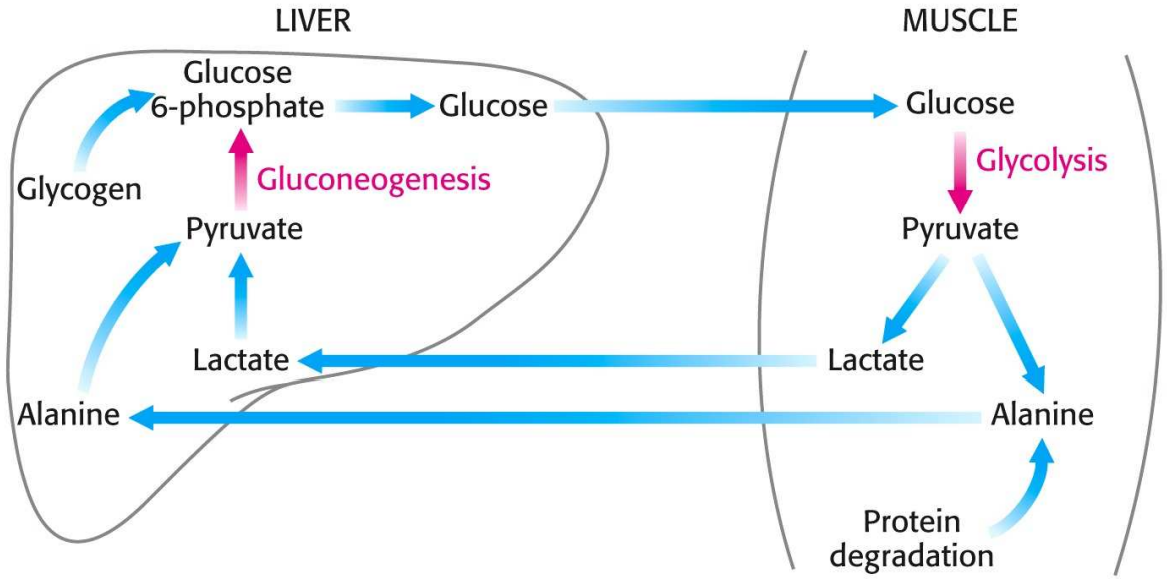
ATP and phosphocreatine can sustain exercise for only a few seconds. Glycogen stores in muscle are adequate to support an exercise with maximal output intensity for only a limited period of time, not longer than 1 - 2 minutes, because of **lactate accumulation**. The limited supply of $O_2$ disables aerobic glycolysis and fatty acid oxidation.

## Aerobic phase of physical exercise – prolonged exercise with sufficiently low energy expenditure

In initial 3 - 30 minutes, utilization of saccharides prevails (liver glycogen, gluconeogenesis from lactate and alanine – the Cori and the glucose-alanine cycles, later on also from glycerol – product of lipolysis).

After approximately 1 hour of exercise, fatty acid oxidation is the major source of ATP generation. Glucose is spared so that a sufficient amount of glucose is available to supply oxaloacetate for the citrate cycle.

### The Cori cycle and the glucose-alanine cycle



# Obesity

Is identified as a **risk factor** in a host of pathological conditions including diabetes, hypertension, and cardiovascular disease.

In the vast majority of cases, the cause of obesity is quite simple:

**more food is consumed than is needed**,

and the energy excess is stored as fat.

Two important signal molecules by which energy homeostasis and appetite control are usually maintained are **insulin and leptin**. They can be thought of as long-term regulators of energy homeostasis.

## Leptin

is a hormone **secreted by adipocytes** in a direct proportion to fat mass. Leptin acts through a membrane receptor (related in structure and mechanism of action to the growth hormone receptor) in the hypothalamus to **generate satiation signals**.

During the starved state when more energy is expended than ingested, adipose tissue loses mass. Under these conditions, both leptin and insulin declines, nutrient utilization is increased, and energy stores are used. The converse is true when food excess is consumed.

## Other signal molecules in energy homeostasis and appetite control:

### Resistin

Is secreted by the adipocytes, the amount is directly proportional to fat mass. There was a hypothesis that resistin **renders tissues insensitive to insulin** but the precise physiological role remains to be determined.

### Adiponectin

is a polypeptide hormone secreted by adipocytes. Its concentration in blood is much higher than that of insulin. Receptors for adiponectin occur in skeletal and heart muscles and in CNS. Adiponectin stimulates utilization of triacylglycerols and **supports the sensitivity of tissues to insulin**. In obesity, the blood concentration of adiponectin is markedly lower than in non-obese individuals.

### Visfatin

is a polypeptide produced in the visceral fat tissue. The biological effects resemble those of insulin: a decline tendency in glycaemia and induction of phosphorylation of signal molecules in the insulin receptor cascade. Visfatin can be thought of as a compound that **increases the sensitivity of tissues to insulin**.

### Ghrelin

Is a short-duration hormone – the appetite-stimulating gastric peptide secreted when the stomach is empty. The plasma concentration of ghrelin increases before meals and decreases rapidly after food intake.