Glycogen

- synthesis and degradation

Glycogen supplies

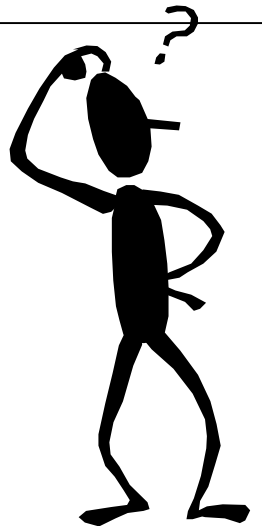
• The synthesis and degradation of glycogen occurs in most cells, the greatest extent is in the liver and muscles.

• Glycogen is a supply of glucose in the cells, which is very readily available

• In muscles - weight of glycogen is about 1(-2)% of muscle mass, degradation occurs during hard work or stress

•In the liver: about 5 (-10)% weight of the liver after a meal, degradation occurs when glucose level in blood is decreased about 0.1% weight of the liver after 24 hours of fasting

The formation of glycogen allows the preservation of a large number of glucose molecules in the cell, without creating a hyperosmotic environment

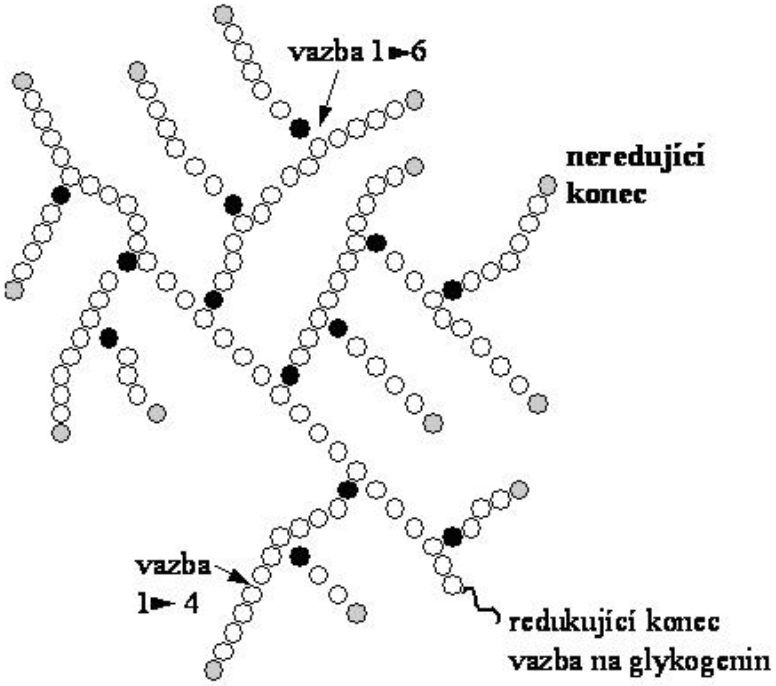


Localization of glycogenolysis and synthesis of glycogen

Glycogen is stored in cytoplasmic granules of cells.

Enzymes involved in synthesis and degradation bind to the surface of the granules.

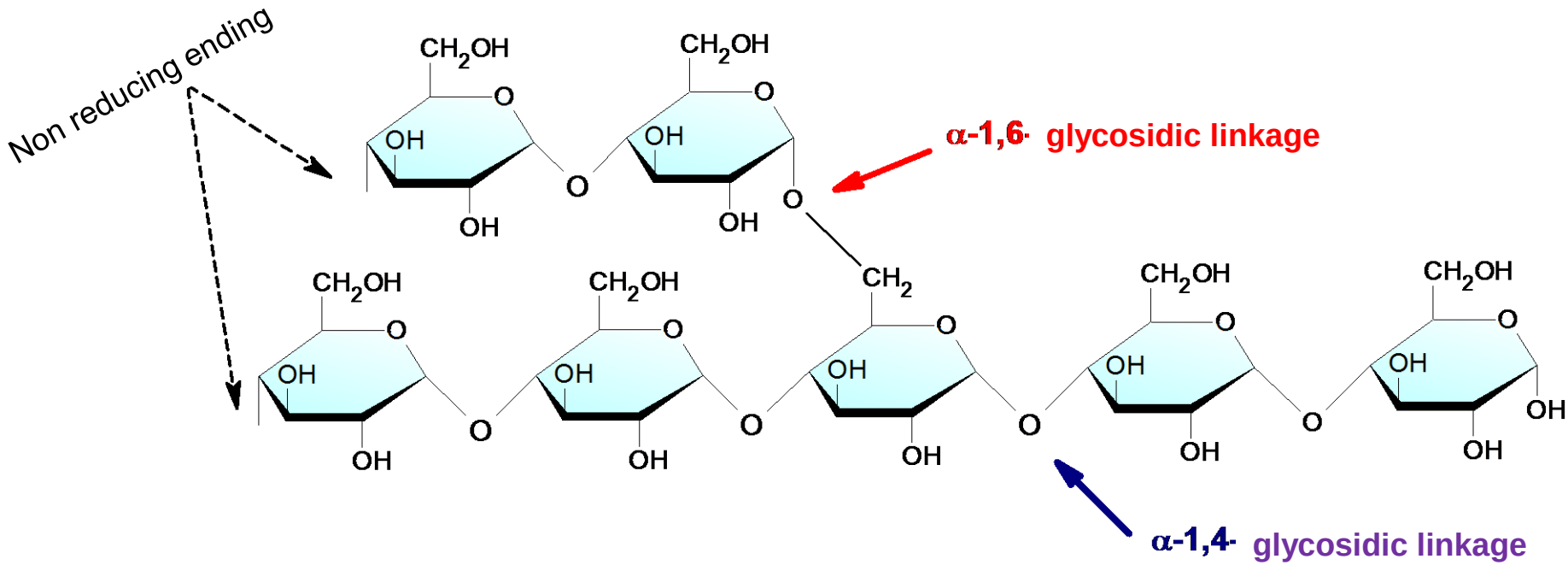
Glycogenolysis is not the opposite of synthesis.



Glycogen molecules have mass M_r ~10^8

Články a informace z různých oblastí lékařství: Tvorba glykogenu. [online]. 20.6.2006 [cit. 2014-07-18]. Dostupné z: http://www.biology.estranky.cz/clanky/biochemie/tvorba-glykogenu.html

Types of linkages in glycogen



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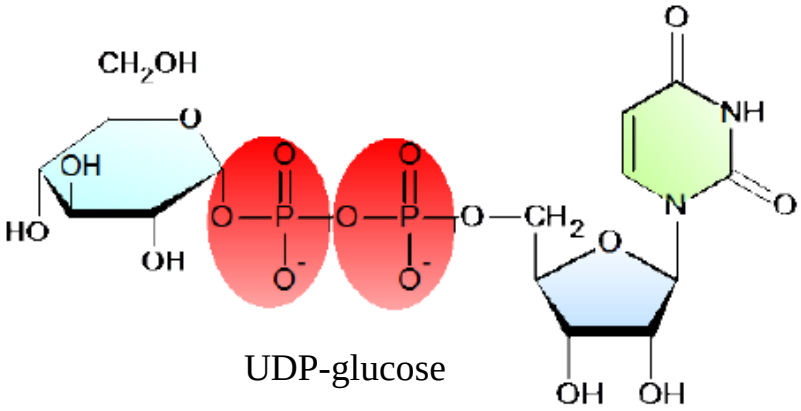
Glycogen synthesis (glycogenesis)

Takes place after a meal, insulin activation

1. activation of glucose to UDP-glucose
2. transfer of activated molecules to 4-end of existing primer or glycogen chain
3. creation α -1,4 glycosidic bond
4. branching

1. UDP-glucose synthesis



UDP-glucose

- Glucose-6-P ⇌ Glucose -1-P

phosphoglucomutase

- Glucose-1-P + UTP ⟶ UDP-glucose + PP_i

$PP_i + H_2O \longrightarrow 2P_i$

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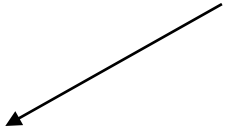
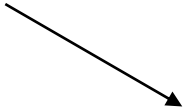
2. Primer is needed for glycogen synthesis





glycogen fragment

specific protein, if glycogen is completely depleted (glycogenin)

Auto glycosylation at serine residue

3. Formation of α -1,4 glycosidic bonds

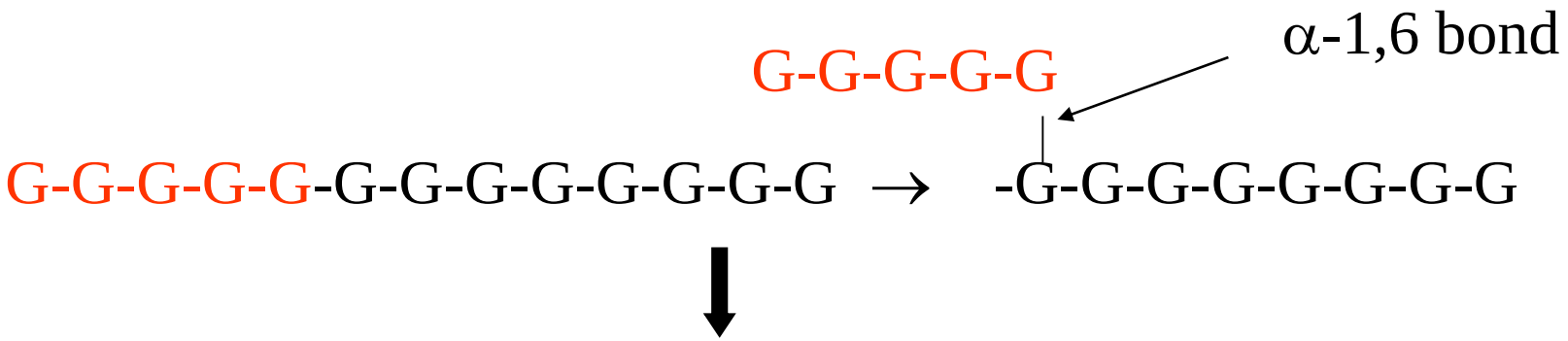
- Initiation - binding of glucose to primer by α -1,4 glycosidic bond (glycogensynthase)

- Elongation - formation of linear chains with α-1,4 bond (glycogensynthase)
- UDP-glucose + $[glucose]_n \rightarrow [glucose]_{n+1}$ + UDP

4. Branching

(branching enzyme)

5-8 terminal glucose residues at the non-reducing end is transferred and bound by1,6 bond



Further elongation by **glykogensynthase** on non-reducing ends

Further branching by **branching enzyme**

The significance of branching:

- increase the solubility of glycogen
- increasing the number of non-reducing ends
  $\Rightarrow$acceleration of synthesis (and degradation)

Degradation of glycogen (phosphorolyse)

Proceeds during starvation (liver), muscle work (muscle) or stress (liver and muscle).

1. Phosphorolytic digestion α-1,4 glykosidic bonds (phosphorylase)
2. Deletion of α-1,6 branching (debranching enzyme)

Compare:

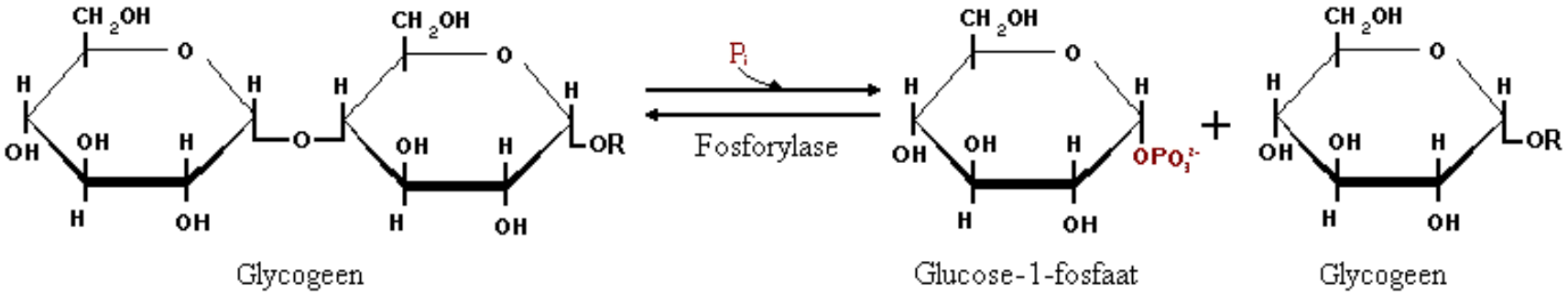
Hydrolysis x phosphorylolysis

1. Phosphorylase

Phosphorolytic digestion α-1,4 glykosidových glykosidic bonds from non-reducing ends

$Glycogen_n + P_i \longrightarrow$ **glucose-1-P** **+ glycogen$_{n-1}$**

digestion proceeds until phase of "limit dextrin" (typically 4 glucose units before α-1,6 bond)



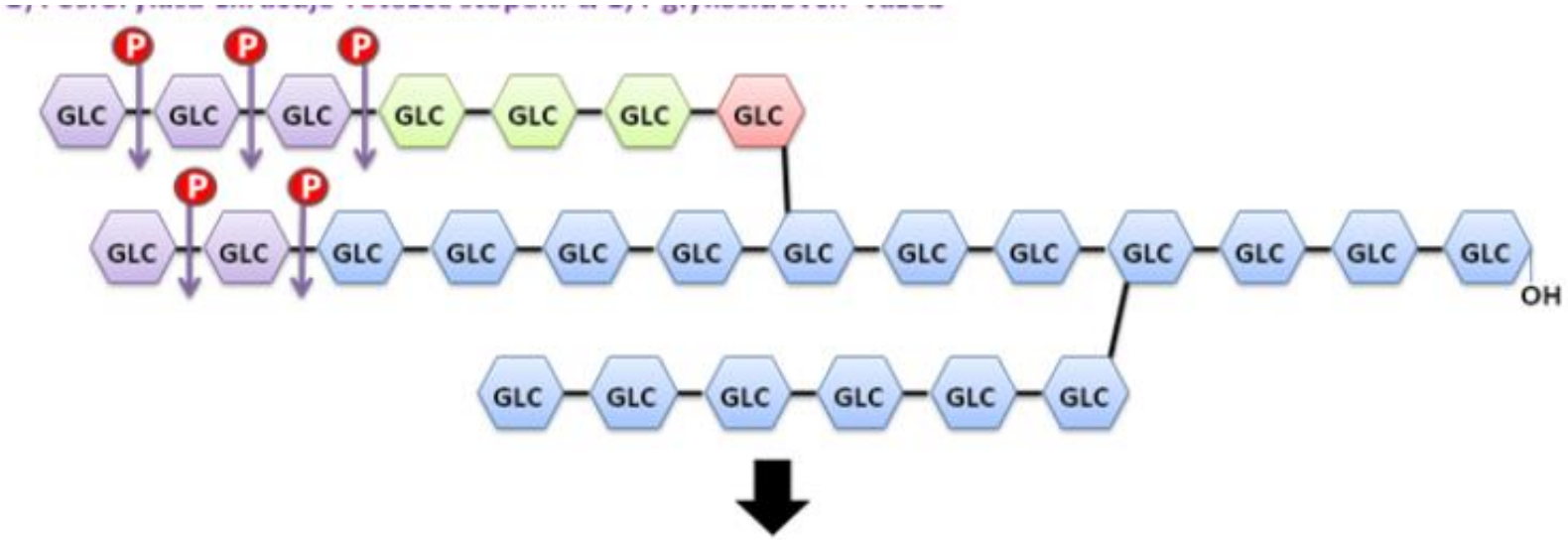
n residues

n – 1residues

Rob's web: Glycogeen metabolisme [online]. [cit. 2014-07-18]. Dostupné z: http://www.robkalmeijer.nl/voedingsleer/metabolisme/glycogeenmetabolisme/

Degradation of glycogen

Phosphorylase effect leads to the formation of **limit dextrins**:



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2. Debranching enzyme

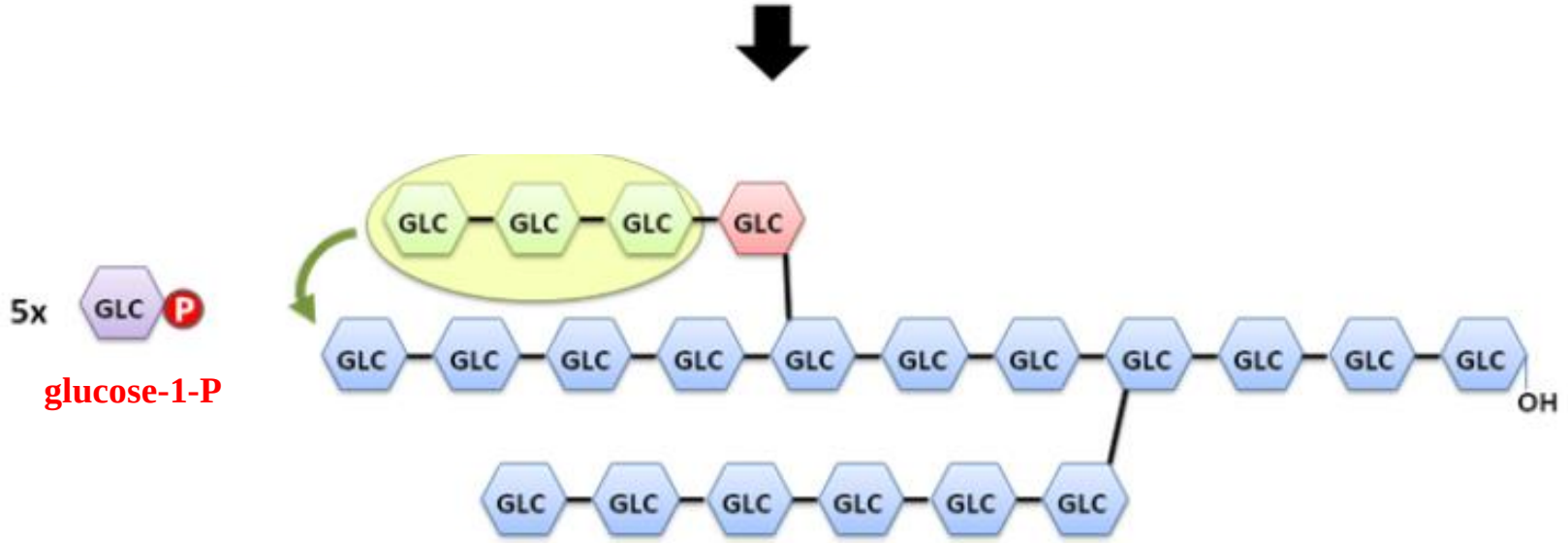
transferase activity: enzyme transferes 3 of the remaining 4 glucose bound on chain by α-1,6 bond to the non-reducing end of another chain
glucosidase activity: cleavage of glucose bound by α-1,6 bond

(Free glucose is released! No Glc-1-P)

Effect of debranching enzyme

Following the effect of phosphorylase

Enzyme TRANSGLYCOSYLASE transferes 3 of the remaining 4 glucose bound on chain by α-1,6 bond to the non-reducing end of another chain



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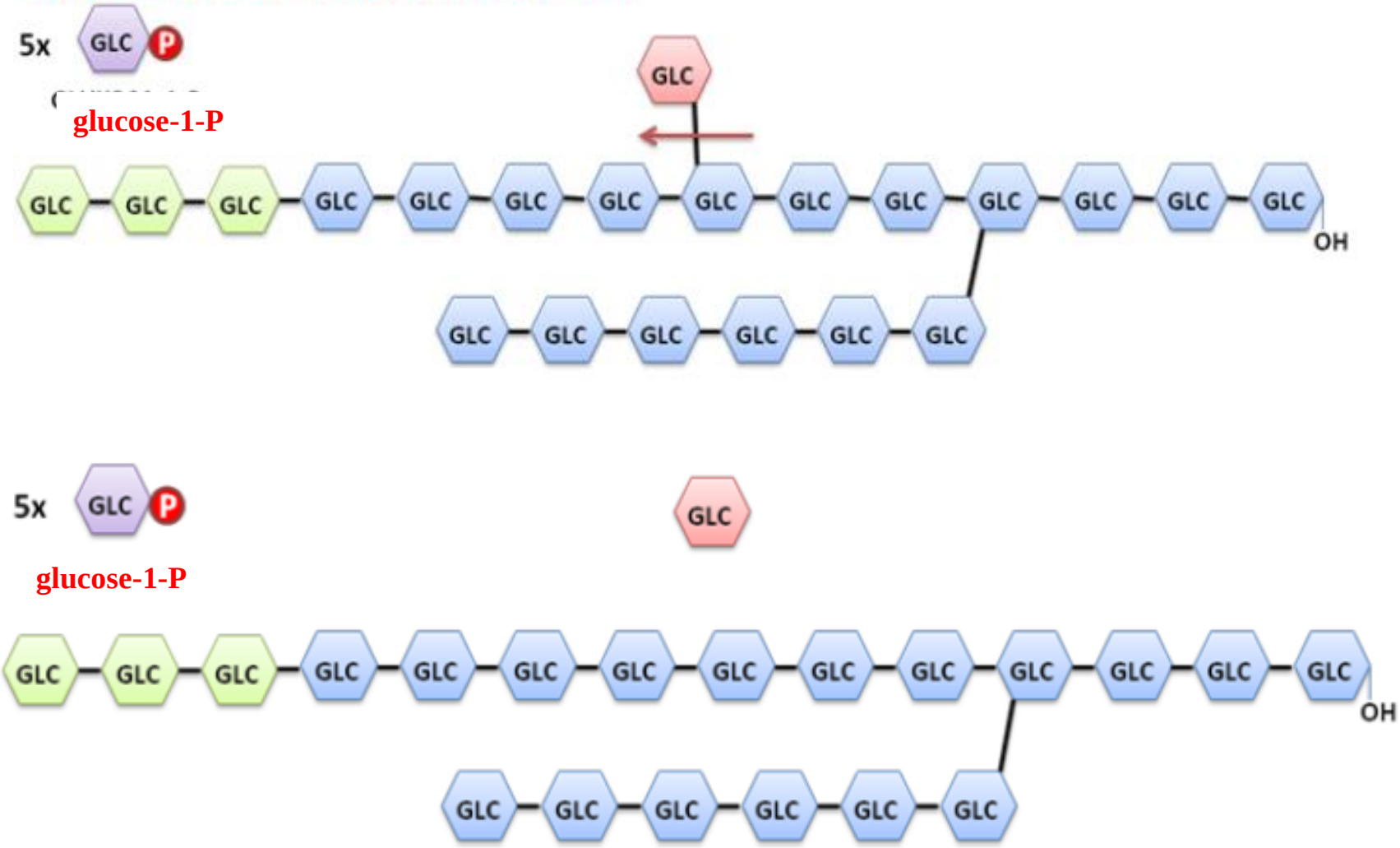
DEBRANCHING ENZYME glucosidase activity: cleavage of glucose bound by α-1,6 bond

(Free glucose is released! No Glc-1-P)



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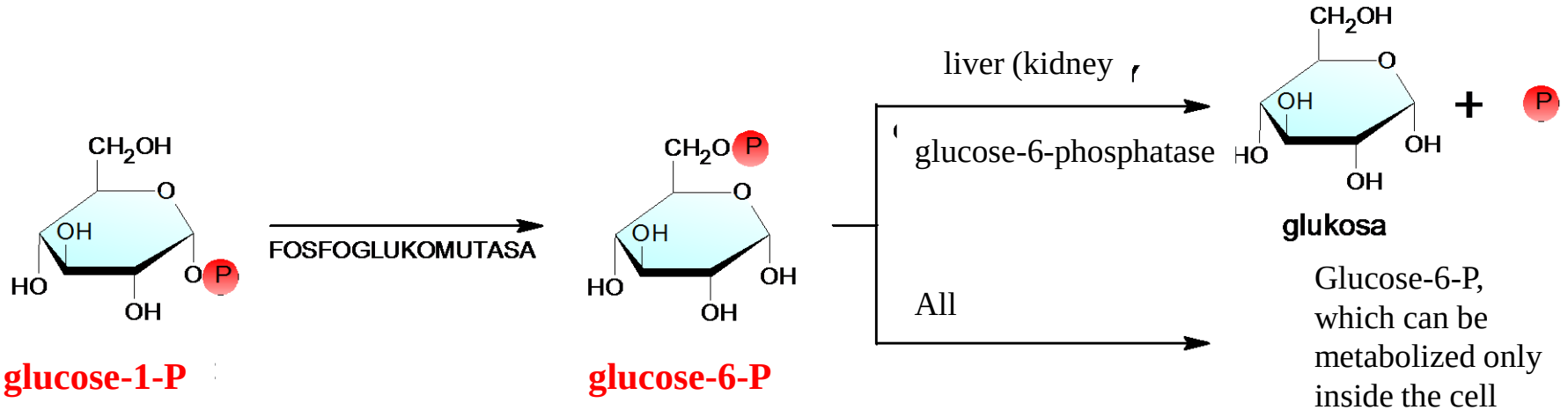
The fate of glucose-1-phosphate generated from glycogen

release into the blood



Glucose-6-P, which can be metabolized only inside the cell (glycolysis) can be obtained by cleavage of glycogen in muscle and other cells

Glucose-6-P can not pass across the cytoplasmic membrane, transfer is possible only for glucose

The enzyme glucose-6-phosphatase is only in the liver (kidney) - not in muscle.

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utilization of glucose-6-P

Glucose-6-P can not pass across the cytoplasmic membrane, transfer is possible only for glucose

The enzyme glucose-6-phosphatase is only in the liver (kidney) - not in muscle.

The blood glucose level can be supplied only by cleavage of liver glycogen

Glucose-6-P, which can be metabolized only inside the cell (glycolysis) can be obtained by cleavage of glycogen in muscle and other cells

Lysosomal degradation of glycogen

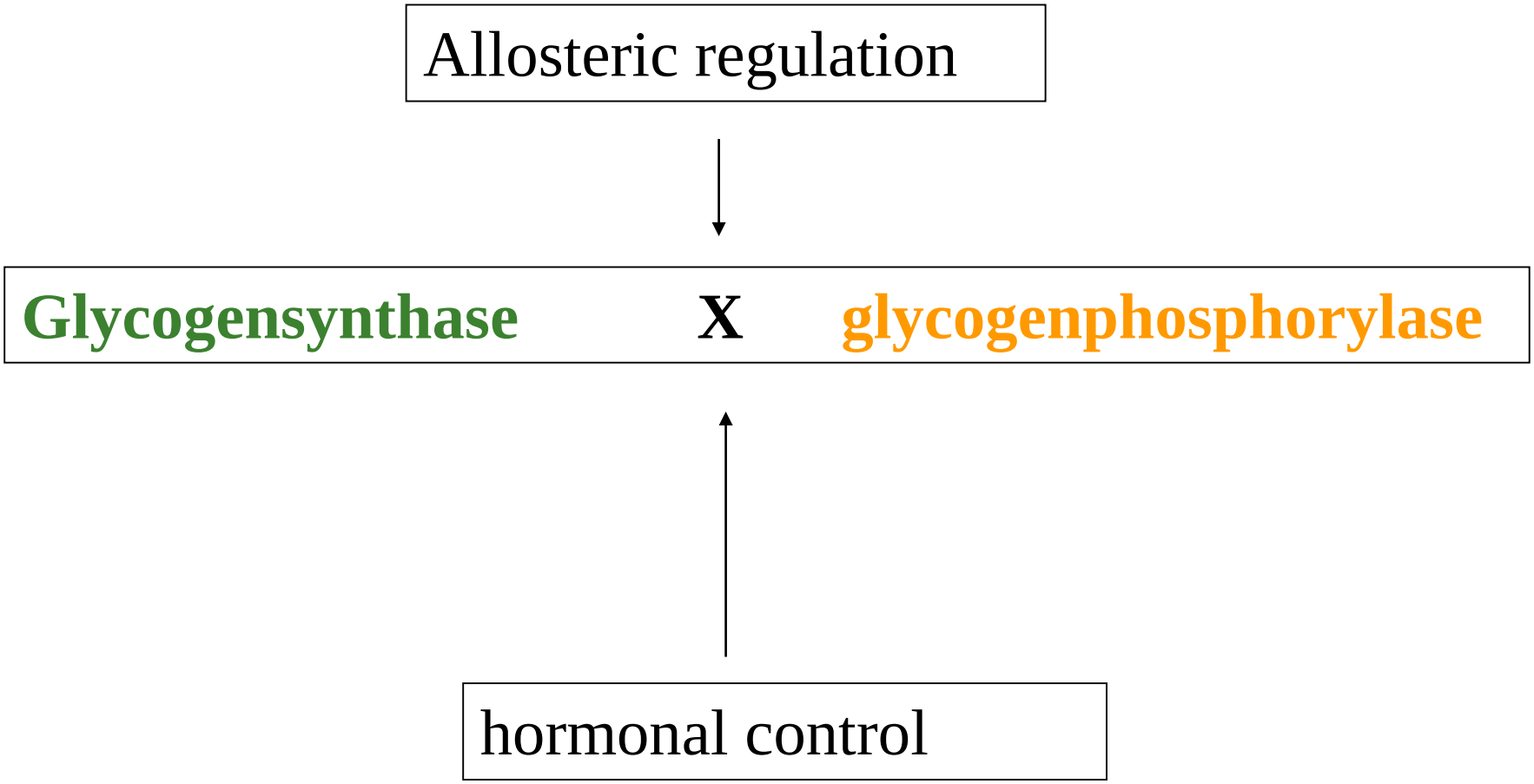
lysosomal acidic glucosidase (pH optimum 4)

- degrades α1,4 bonds from non-reducing ends

- glucose is released

degradation 1-3 % of cellular glycogen

Regulation of metabolism of glycogen



Hormones affecting the synthesis and degradation of glycogen

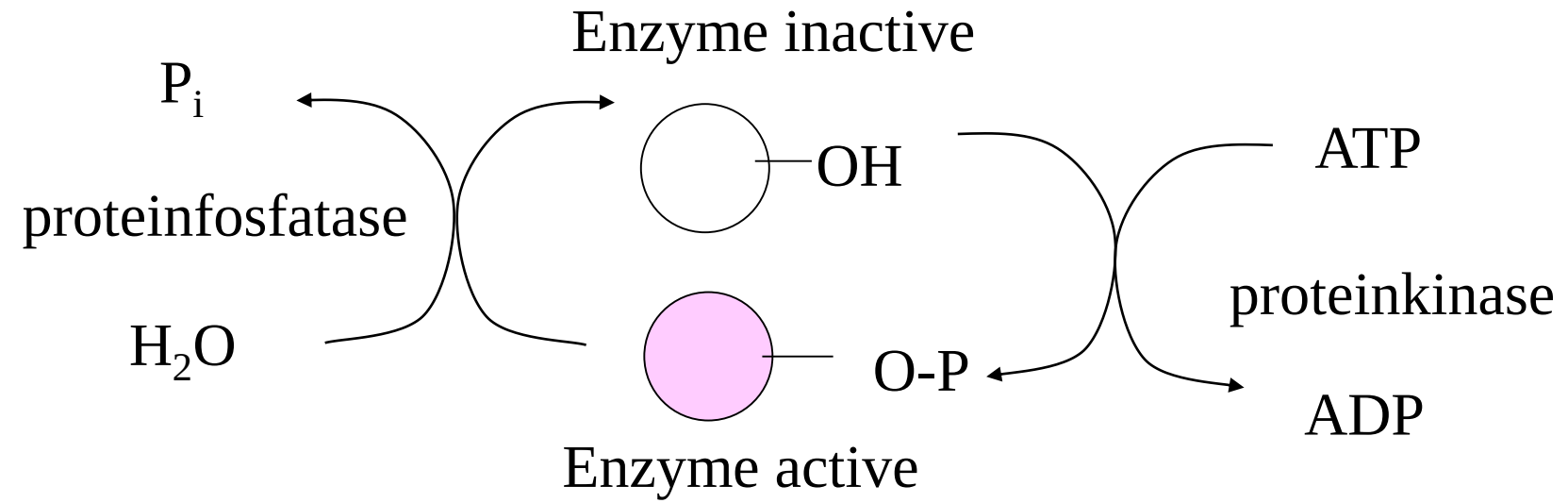
Hormone	synthesis	degradation
Insulin	↑	↓
Glucagon	↓	↑
Adrenalin	↓	↑

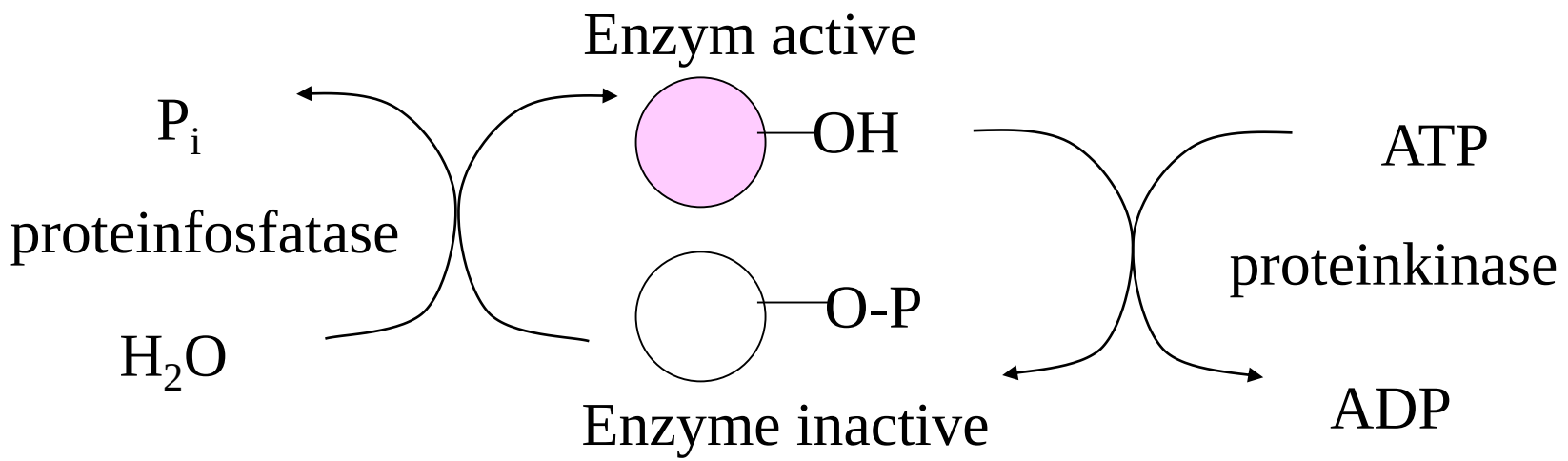
Hormones operates through its "second messengers"

Phosphorylation and dephosphorylation of proteins plays an important role in the regulation of glycogen metabolism

- phosphorylation by kinases and ATP
- dephosphorylation through phosphatases

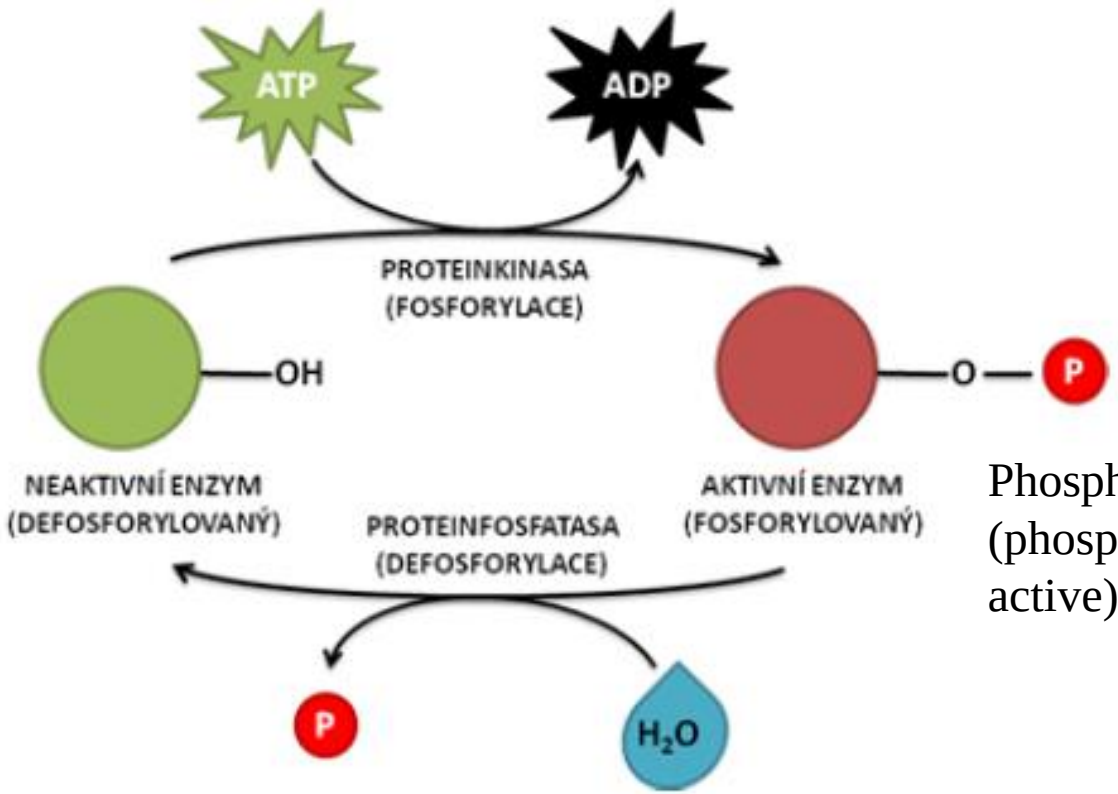
Common examples of activity changes induced by phosphorylation and dephosphorylation





Activation and inactivation of glycogenphosphorylase

phosphorylase b (phosphorylated form - not very active)



Obrázek 3 - Aktivace fosforylací

Phosphorylase a (phosphorylated form - active)

Phosphorylase in the liver and muscles varies

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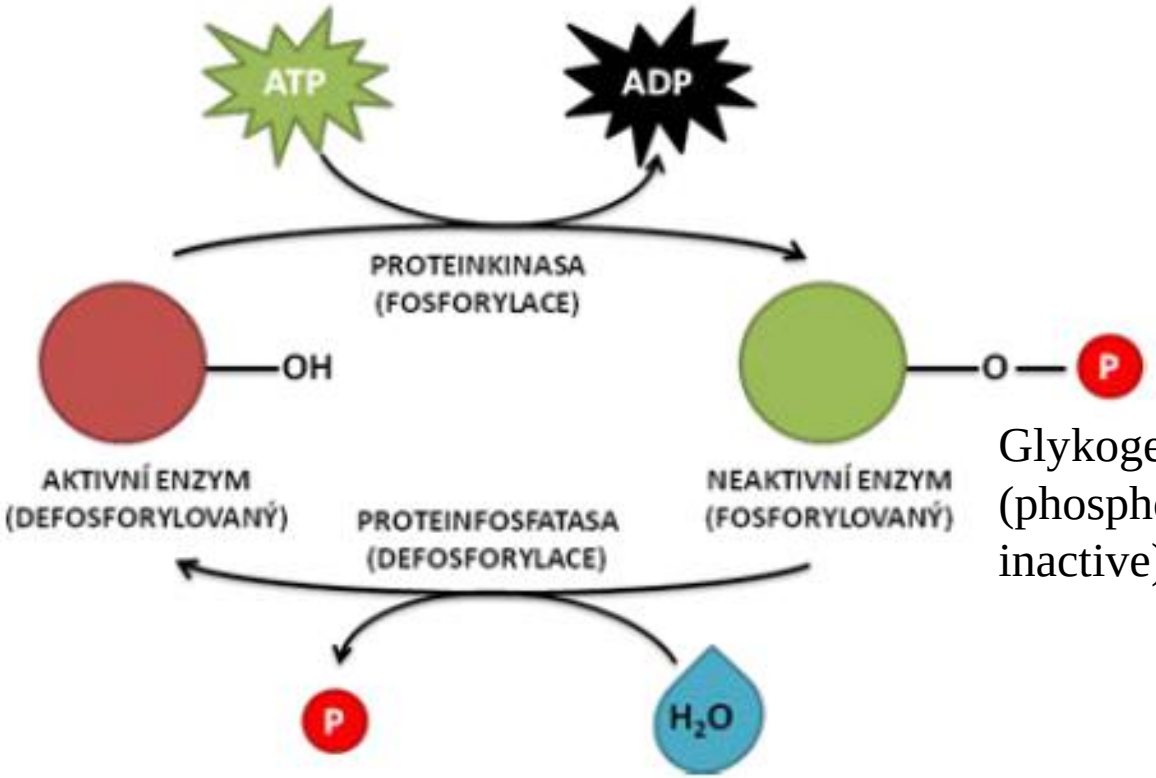
Activation and inactivation of glykogensynthase

Glykogensynthase a (phosphorylated - active)



Obrázek 4 - Deaktivace fosforylací

Glykogensynthase b (phosphorylated - inactive)

NOVÁK, Jan. *Biochemie I.* Brno: Muni, 2009, s. 105.

Degradation of glycogene

the effect of **hormones:** **allosteric regulation**

Liver:

glucagon (cAMP),

adrenaline (cAMP, Ca^{2+} kalmoduline)

Muscle:

adrenaline (cAMP) under stress

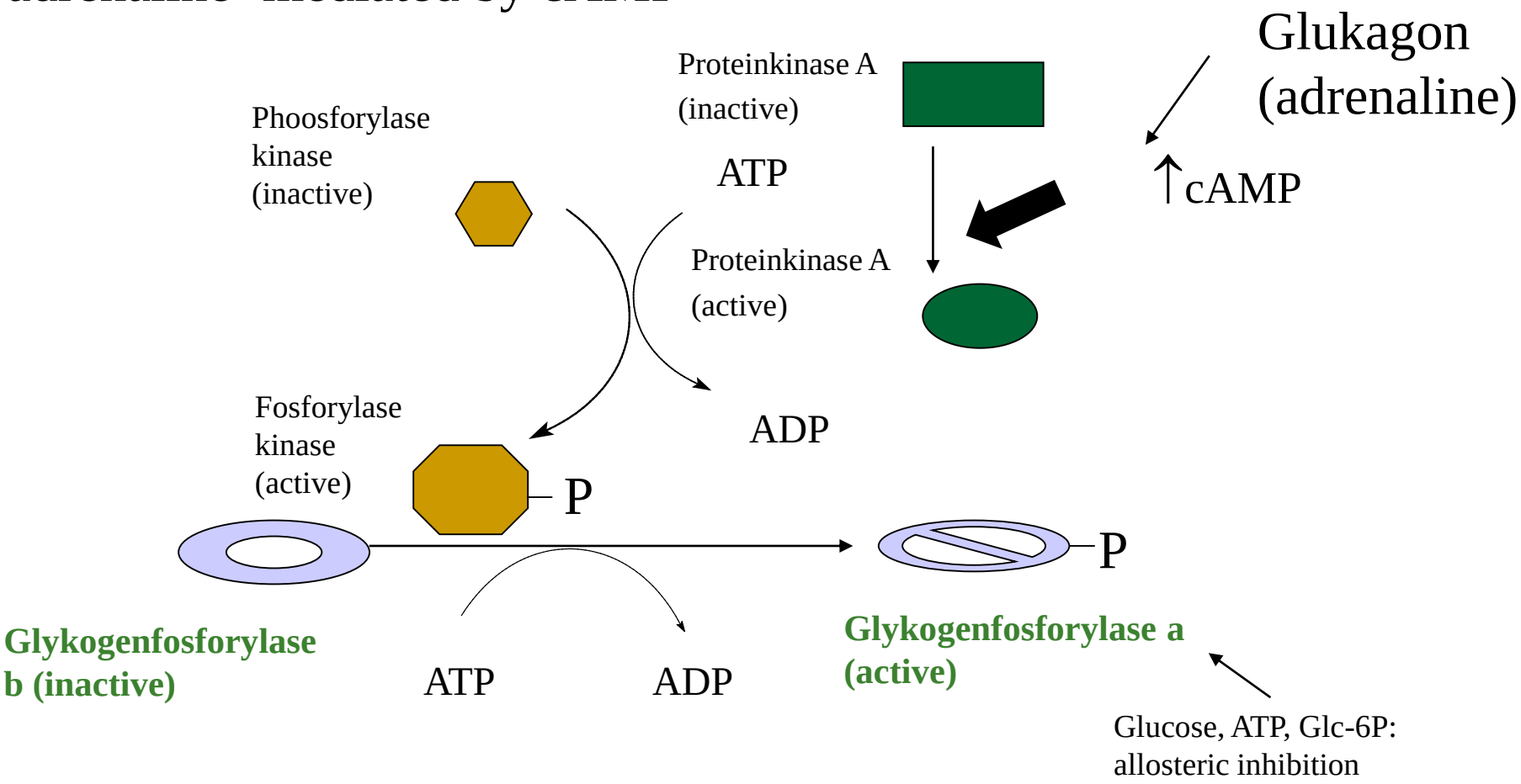
↑ Ca^{2+} during muscle contraction

No effect of glucagon!

AMP

Activation of phosphorylase takes place in stages

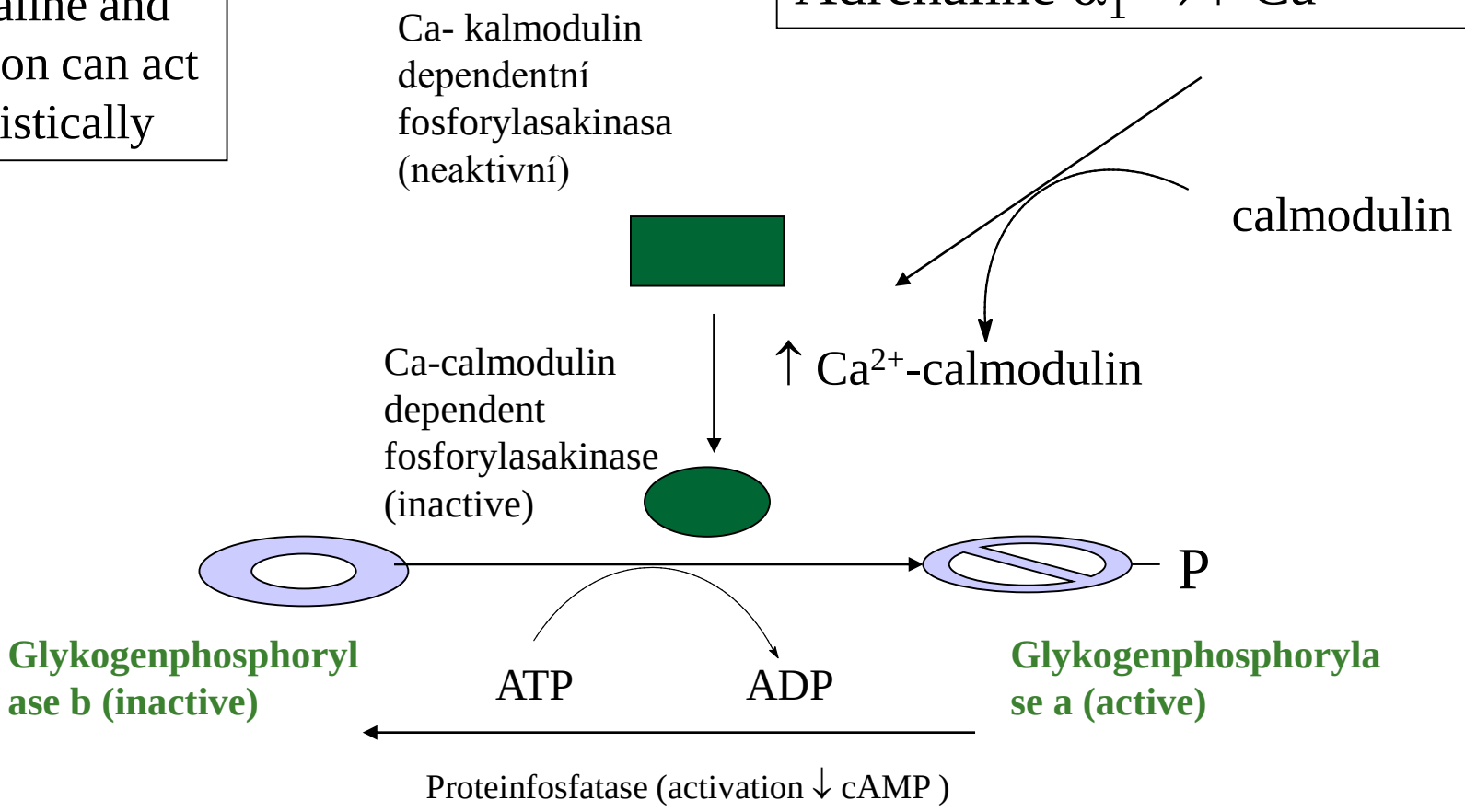
Liver - activation of glycogenphosphorylase by glucagon and adrenaline -mediated by cAMP



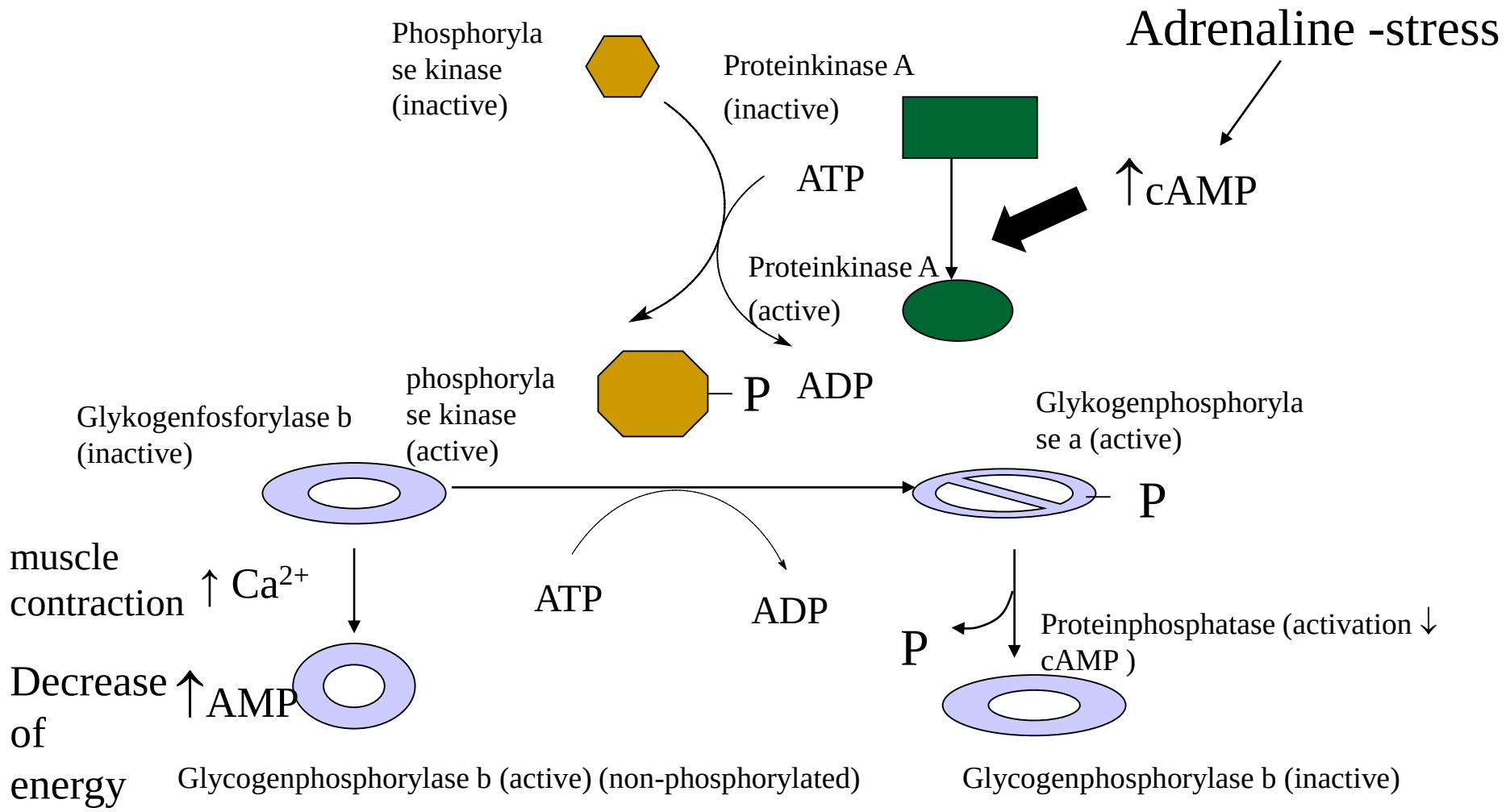
Liver - activation of glycogen phosphorylase by adrenaline, mediated by increase of intracellular Ca^{2+}

Adrenaline and glucagon can act synergistically

Adrenaline $\alpha_1 \Rightarrow \uparrow Ca^{2+}$



Muscle - activation of glycogenphosphorylase by adrenaline, Ca^{2+} and AMP

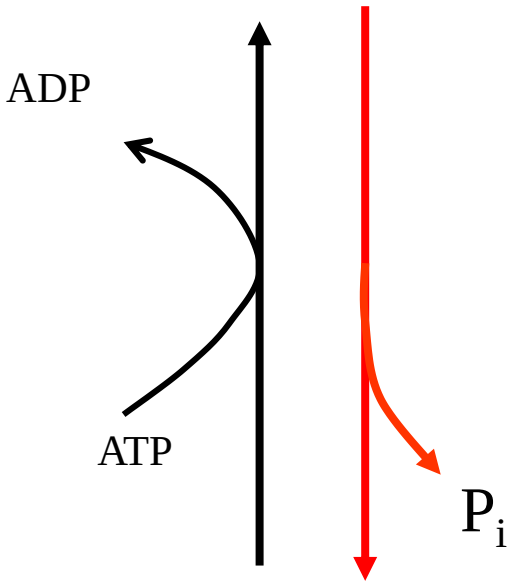


Activation and inactivation of glycogensynthase in liver

Glykogensynthase b (phosphorylated, inactive)

inactivation

activation



Proteinkinase (activation by glucagon /cAMP/ or adrenaline /Ca-calmoduline/

Proteinfosfatase 1

(activation by insuline, allosterically glucose-6-P

inactivation ↑ cAMP)

Glykogensynthase a

(dephosphorylated, active)

Check of glycogensynthase in muscle is more complex and is also regulated by glycogen content.

Glycogen functions as a reverse inhibitor of synthesis

Glycogenoses

- Enzymes that play a role in glycogen metabolism, are often damaged in any way - it is usually a **inherited deficiency of enzymes**. These deficiencies manifest themselves in different ways - it depends on which particular enzyme it is and also on specific isoform (disorders may therefore be tissue specific - e.g. isoform in muscle is damaged and metabolism of glycogen in muscle will be disturbed, on the other hand isoform in liver will be fine, so glycogen metabolism in them will proceed normally).

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Glycogenoses – enzymes disorders

Inherited deficiency of enzymes. Since different isoenzymes can occur in various tissues, thus the disorders can be tissue specific. (F - fatal)

Type	Enzyme defect	Organ	Characteristic
0	Glykogensythase	liver	Hypoglycemia **F**
I	Glc-6-phosphatase	liver, kidneys	Enlarged liver, kidneys. Hypoglycemia. Cells are overcrowded by glycogen
II	Lysosome. α-glukosidase	muscles, heart	The accumulation of glycogen in lysosomes **F**
III	Branching enzyme	liver, muscle, heart	Accumulation of charact. branching polysach.
IV	Branching enzyme	liver	Accumlation of non-branched polysacharide **F**
V	Muscle phosphorylase	muscle	High glycogen content in muscle decreased ability body exertion
VI	Liver phosphorylase	liver	High glycogen content in the liver, a tendency to hypoglycaemia
VII	phosphofruktokinase	muscles	Same as type V

Examples of glycogenoses

Von Gierkes disease (glykogenose type I)

The most common of glycogenoses

Deficiency of glucose-6-phosphatase or transporter for glucose-6-P

Consequences:

hypoglycaemia during a short starvation

lactacidemia

(hyperlipidemia, hyperurikemia)

Pompes disease (glykogenose type II)

Absence of α-1,4-glucosidase in lysosomes

Glycogen accumulation in lysosomes

Loss of function of lysosomes

Damage to muscle, glycogen accumulates in the cytoplasm of muscle → muscle weakness

Mainly affects the muscles of the respiratory system and heart

Type I a - in infants (fatal)

Type II b - in older children and adults, shortens life

McArdles disease (type V)

Absence of of muscle phosphorylase

Glycogen stores are not available for energy production

The muscle is unable to perform permanent work

The muscle is easily damaged (myoglobin in the blood)