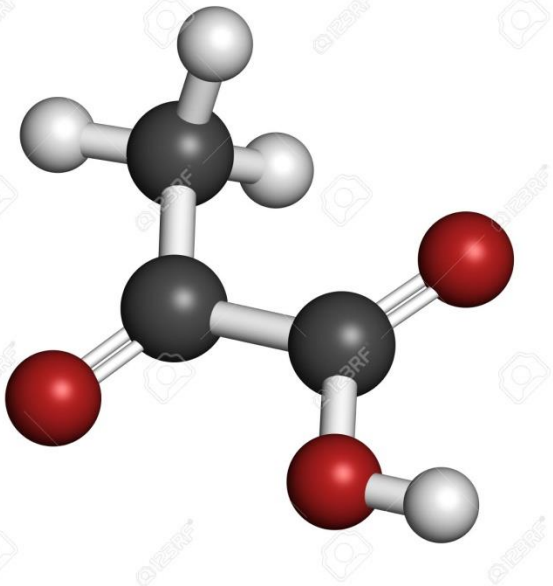
METABOLISM OF GLYCOGEN

REGULATION OF CARBOHYDRATE METABOLISM

Lecture III

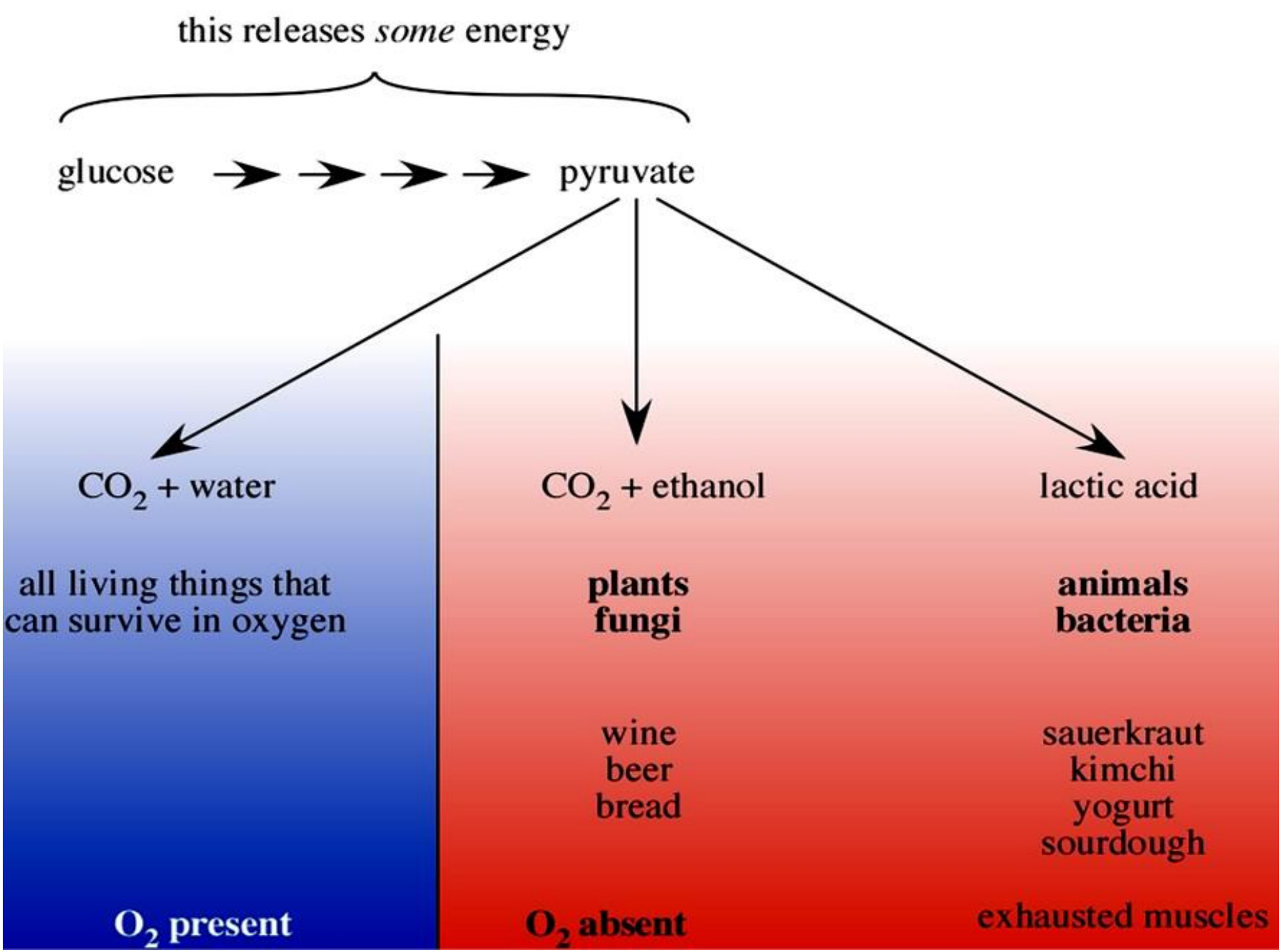


Pyruvate metabolism

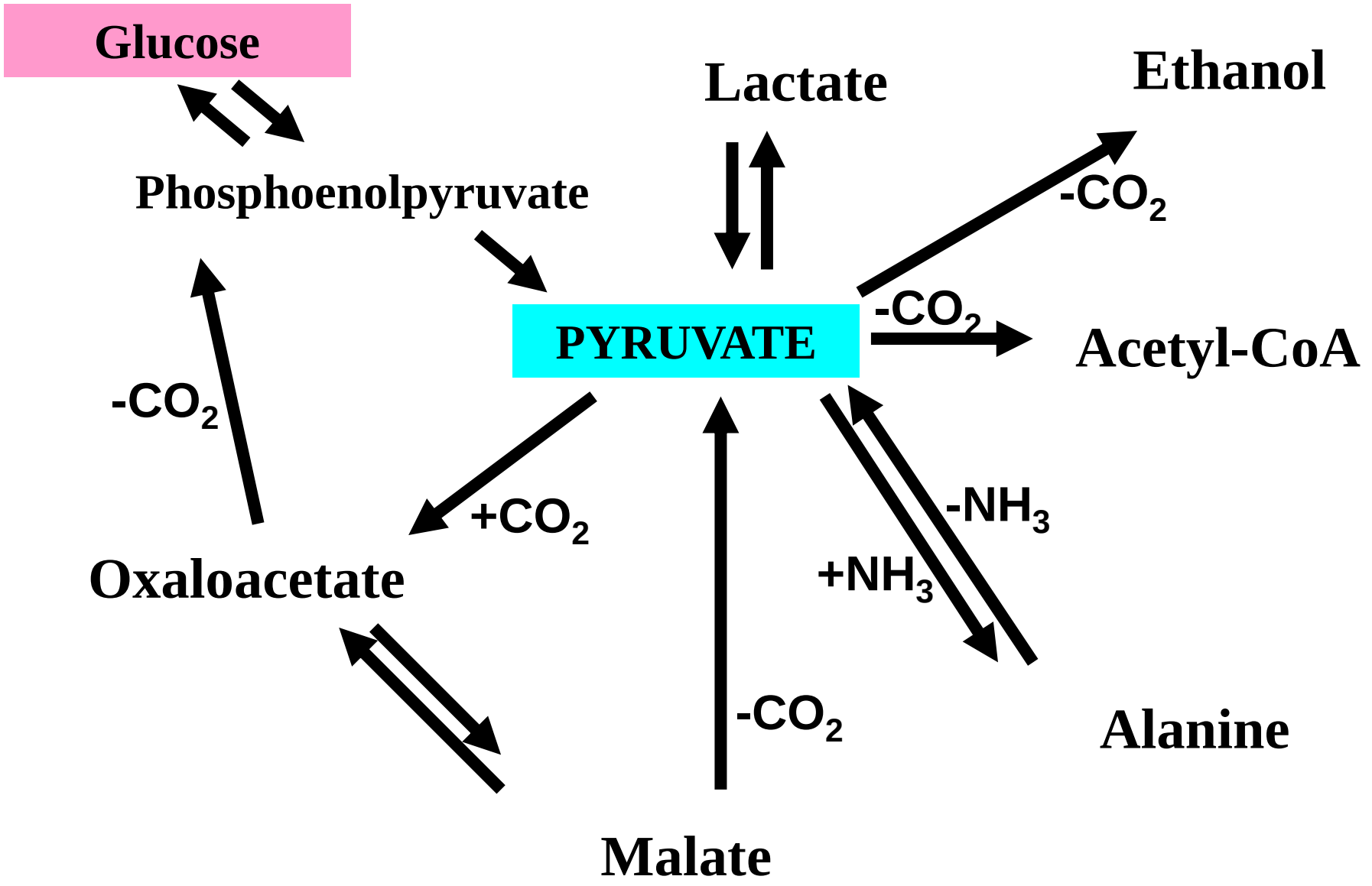
Glucose convert to pyruvate in same way

but the fate of pyruvate varies depending on conditions

and species


this releases *some* energy
glucose
pyruvate
CO_2 + water
CO_2 + ethanol
lactic acid
all living things that can survive in oxygen
plants
fungi
animals
bacteria
wine
beer
bread
sauerkraut
kimchi
yogurt
sourdough
exhausted muscles
O_2 present
O_2 absent

Scheme of pyruvate metabolism



Formation of Pyruvic Acid in the Body

- From oxidation of glucose (Glycolysis)
- From lactic acid by oxidation
- Deamination of Alanine
- Decarboxylation of oxaloacetic acid
- From malic acid by *malic enzyme*

Fate of Pyruvic Acid

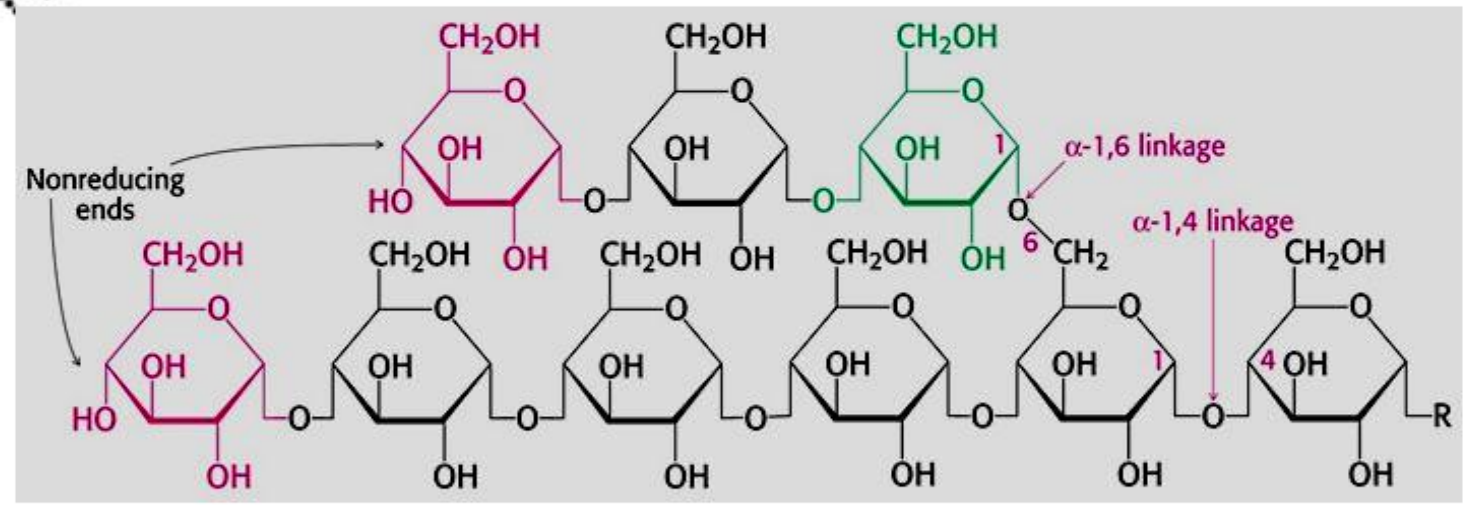
- **Forms acetyl-CoA by oxidative decarboxylation (in presence of O_2)**
- **Forms lactic acid by reduction (in absence of O_2)**
- **Forms alanine by amination**
- **Forms glucose (gluconeogenesis)**
- **Forms oxaloacetic acid by CO_2-fixation reaction**

Fate of pyruvic acid depends on the redox state of the tissues

Metabolism of Glycogen

Glycogen structure

- Large molecule
- Branch points are frequent (about every fourth residue) – allows glucose residues to be easily added or removed quicker than a linear molecule.

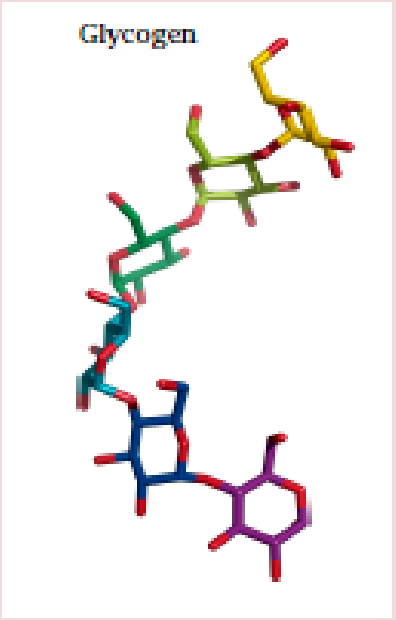


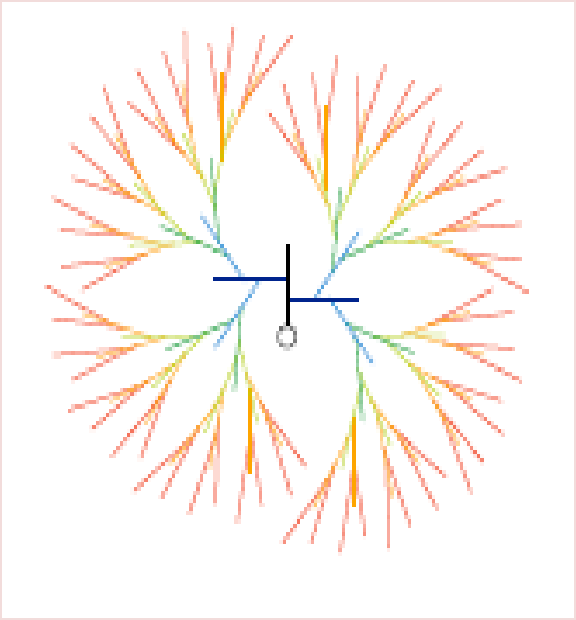
Glucose residues linked by α (1-4) glycosidic bonds into chains & chains branch via α (1-6) linkage

Metabolism of Glycogen

Glycogen is the major storage carbohydrate in animals.

It is a branched polymer of α-D-glucose.





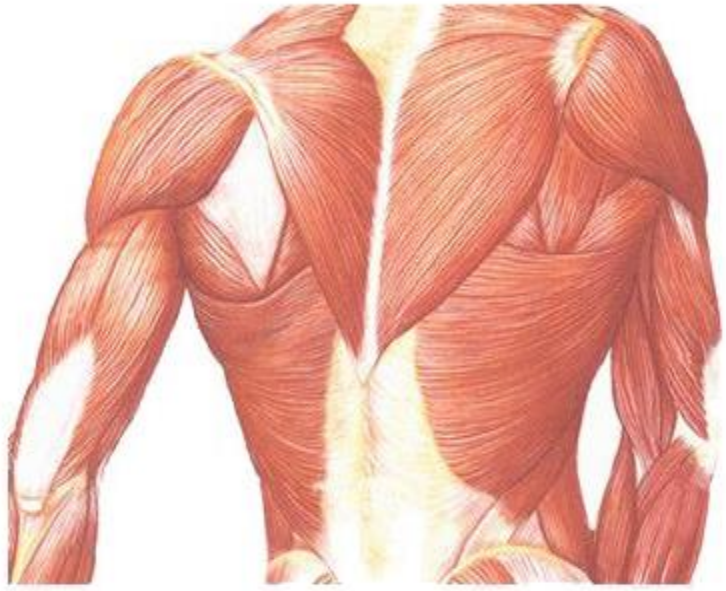
It occurs mainly in liver and muscle.

Muscle glycogen provides a readily available sours of glucose for glycolysis whithin the muscle itself.

!!!

Muscle glycogen cannot directly contribute to blood glucose level.

Muscle glycogen



Provides available source of glucose while exercising in order to support anaerobic & aerobic conversion within muscle cells.

Muscle cells do not contain enzyme glucose 6-phosphatase, which allow the release of glucose into the blood.

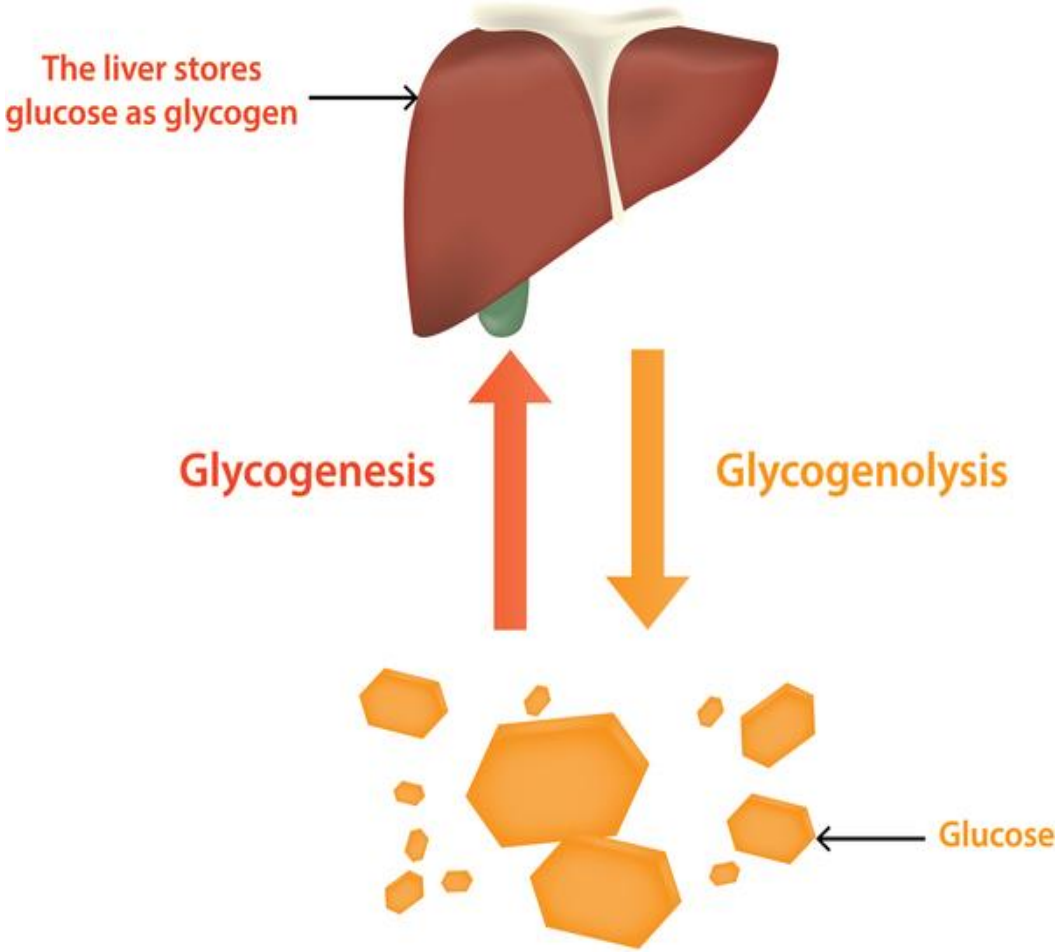
Liver glycogen functions:

to store and export glucose

to maintain blood glucose between meals.

Short term energy source for an organism, which provides a means to store and release glucose in response to blood glucose levels.

The liver does not use this glucose for it's own energy.



Glycogen biosynthesis (or glycogenesis)

- Occurs in muscle and liver

- Involves a special nucleotide of glucose

- uridine diphosphate glucose (UDPGlc)

Glycogenesis

Glucose

↓

Glc 6-Ph

↓

Glc 1-Ph

↓

UDPGlc

↓

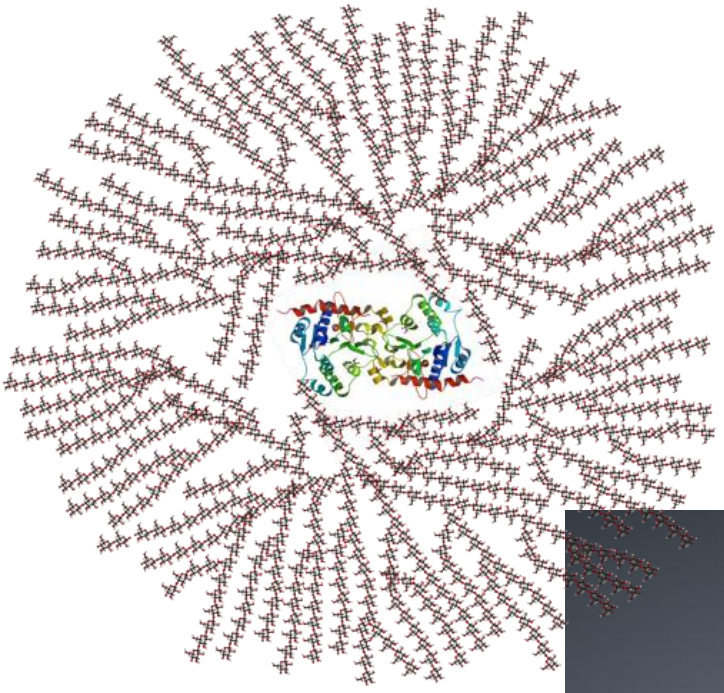
$(1\rightarrow 4\ \text{Glycosyl units})_x$

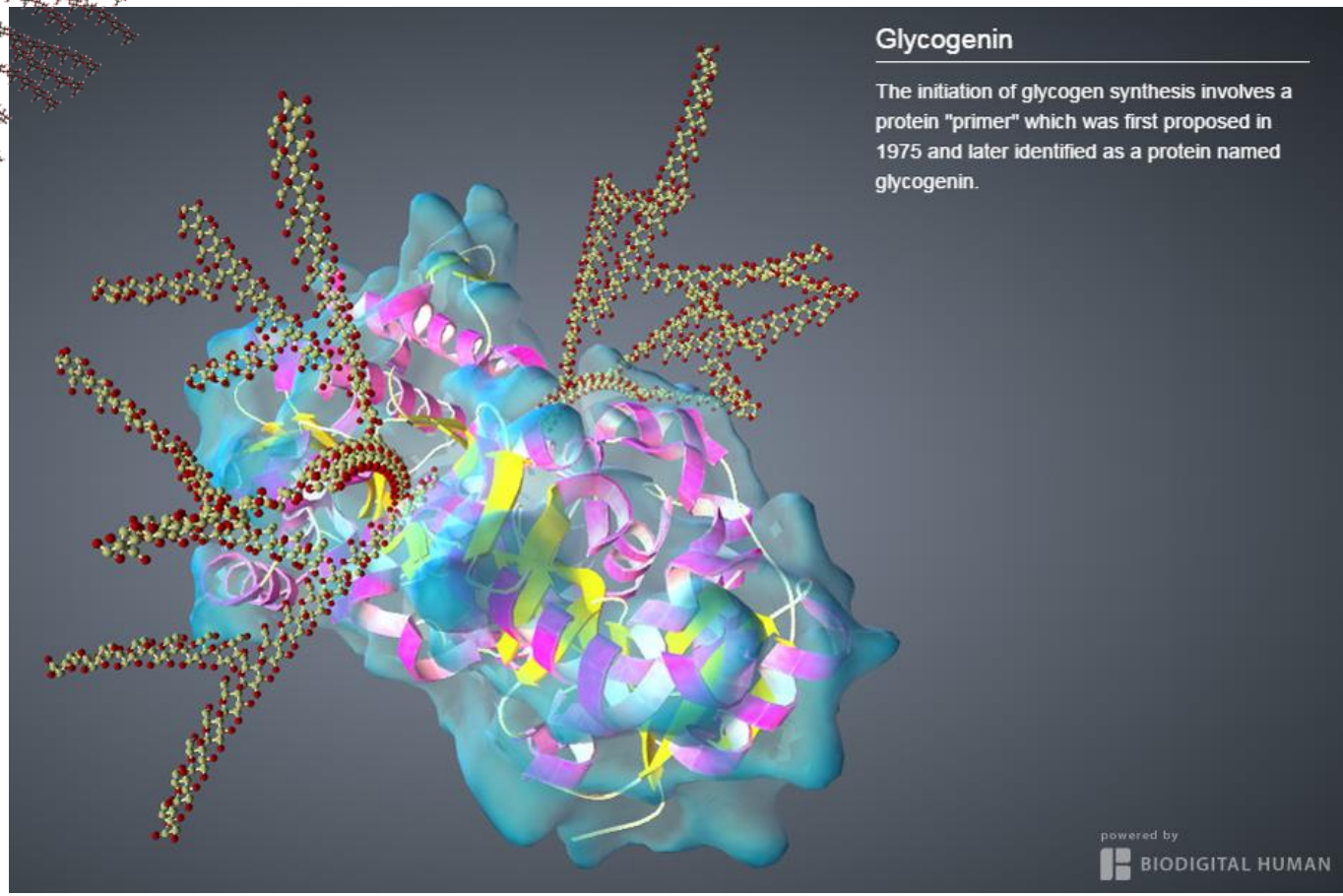
↓

Glycogen $(1\rightarrow 4$ and $1\rightarrow 6$ glycosyl units$)_x$

By the action of the enzyme glycogen synthase,
C-1 of the activated glucose (UDP-Glc) forms a glycosidic bond with the C-4 of a terminal glucose residue of pre-existing glycogen molecule, or "primer". Primer must be present to initiate this reaction.

The glycogen "primer" is formed on a protein primer known as glycogenin.




Glycogenin
The initiation of glycogen synthesis involves a protein "primer" which was first proposed in 1975 and later identified as a protein named glycogenin.
powered by
BIODIGITAL HUMAN

Mechanism of branching:

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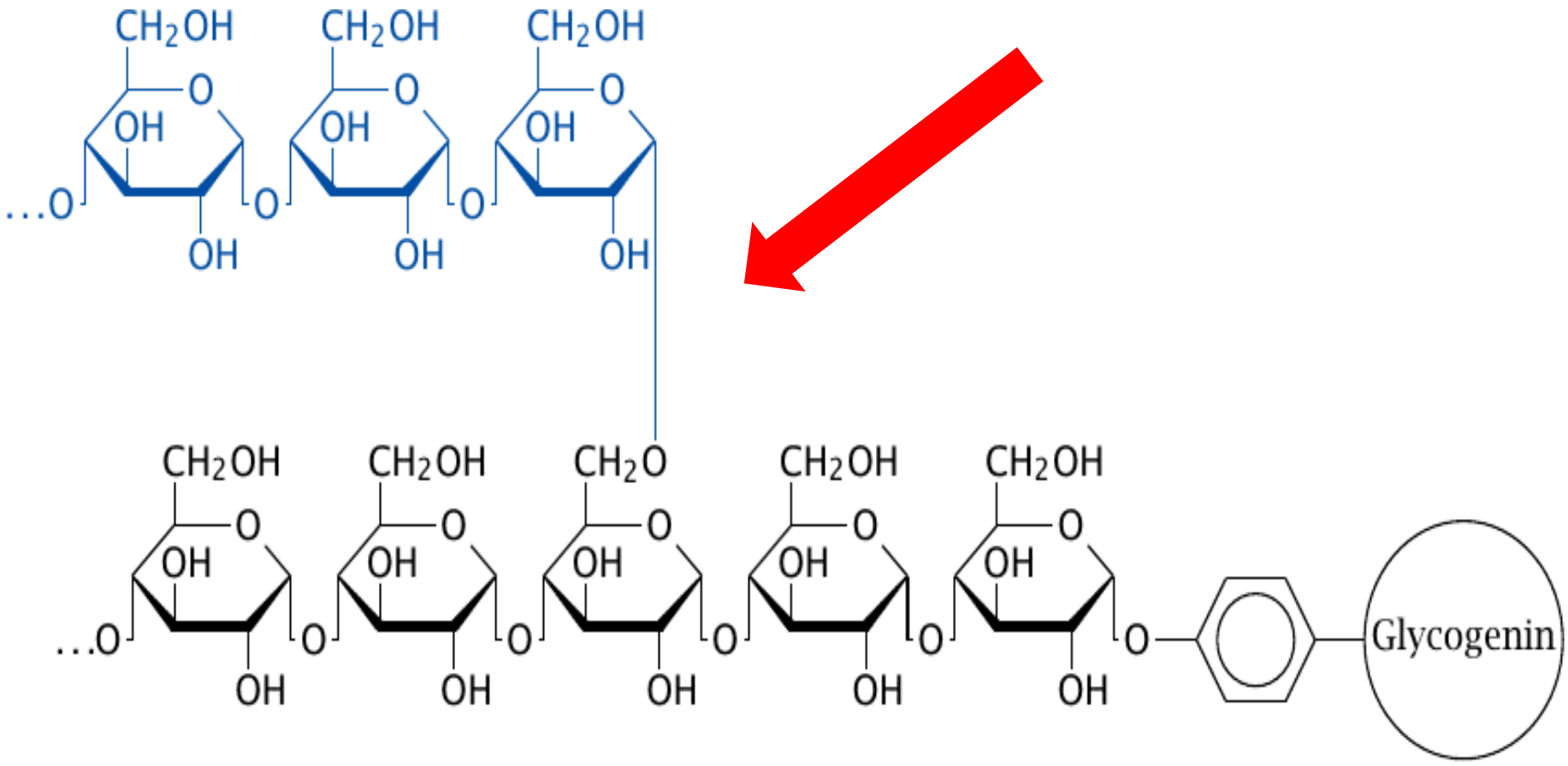
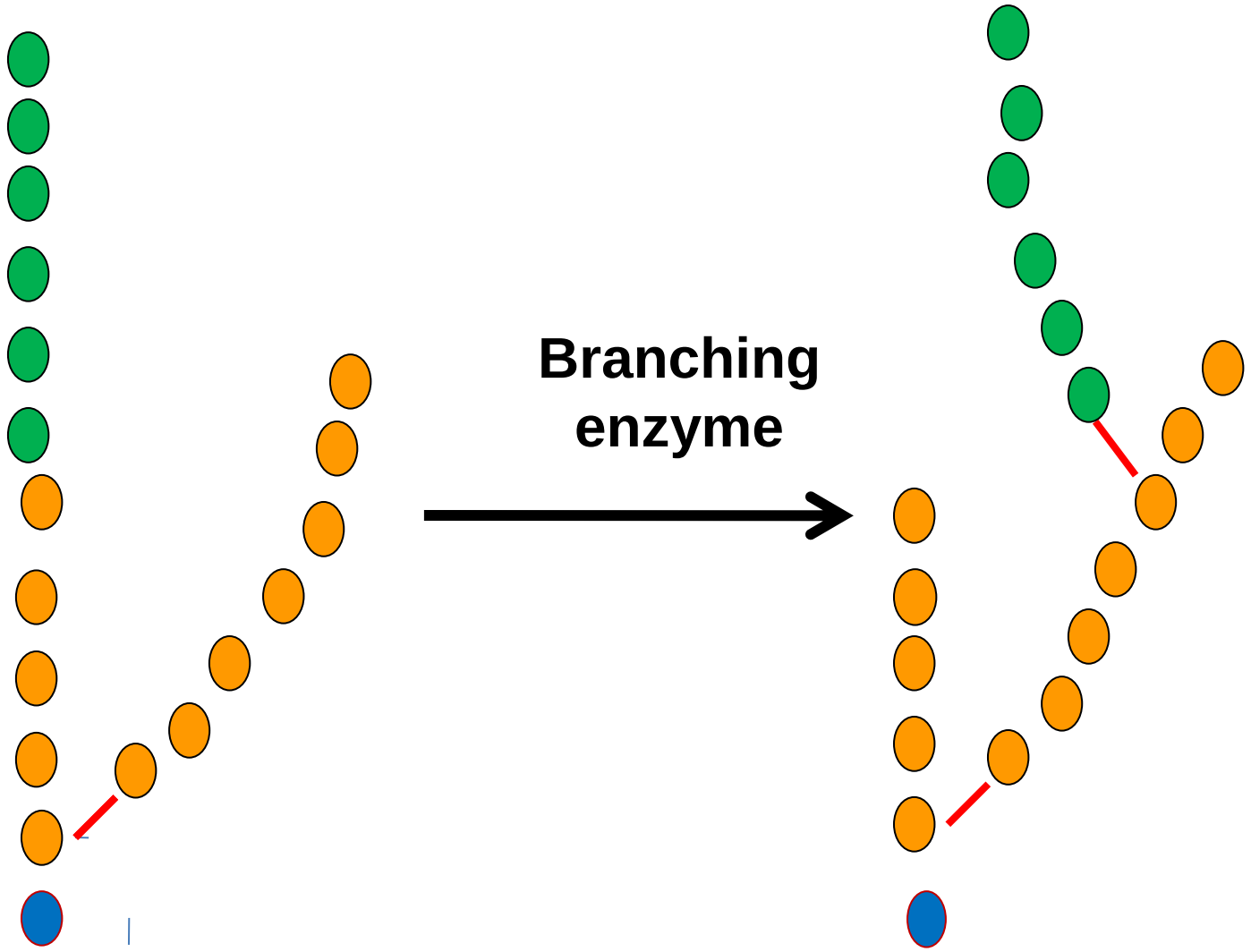

CH2OH
O
OH
…O
O
OH
CH2O
Glycogenin

Mechanism of branching

When the chain has been lengthened to minimum of 11 glucose residues, a branching enzyme (amylo-1, 4 → α1, 6-transglucosidase) transfers a part of 1→4 chain, minimum length 6 glucose residues, to a neighbouring chain to form α1→6 linkage.

The branches grow by further additions of 1 →4 glucosyl units and further branching.

Mechanism of branching



GLYCOGENOLYSIS
(mobilisation of glycogen)

Breakdown of glycogen to glucose

It is initiated by the action of a specific enzyme *phosphorylase*,

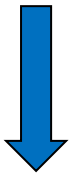
***which breaks α 1→ 4 linkage to yield glucose-1-phosphate*.**

Phosphorylase step is the first step which is the *rate-limiting and key enzyme in glycogenolysis*

Glycogen

Glc 1-Ph

Glc 6-Ph



Glucose

Mechanism of debranching

- **Debranching enzyme**
  - **glucan transferase (transglycosylase activity)**
  - **1,6-glucosidase activity**

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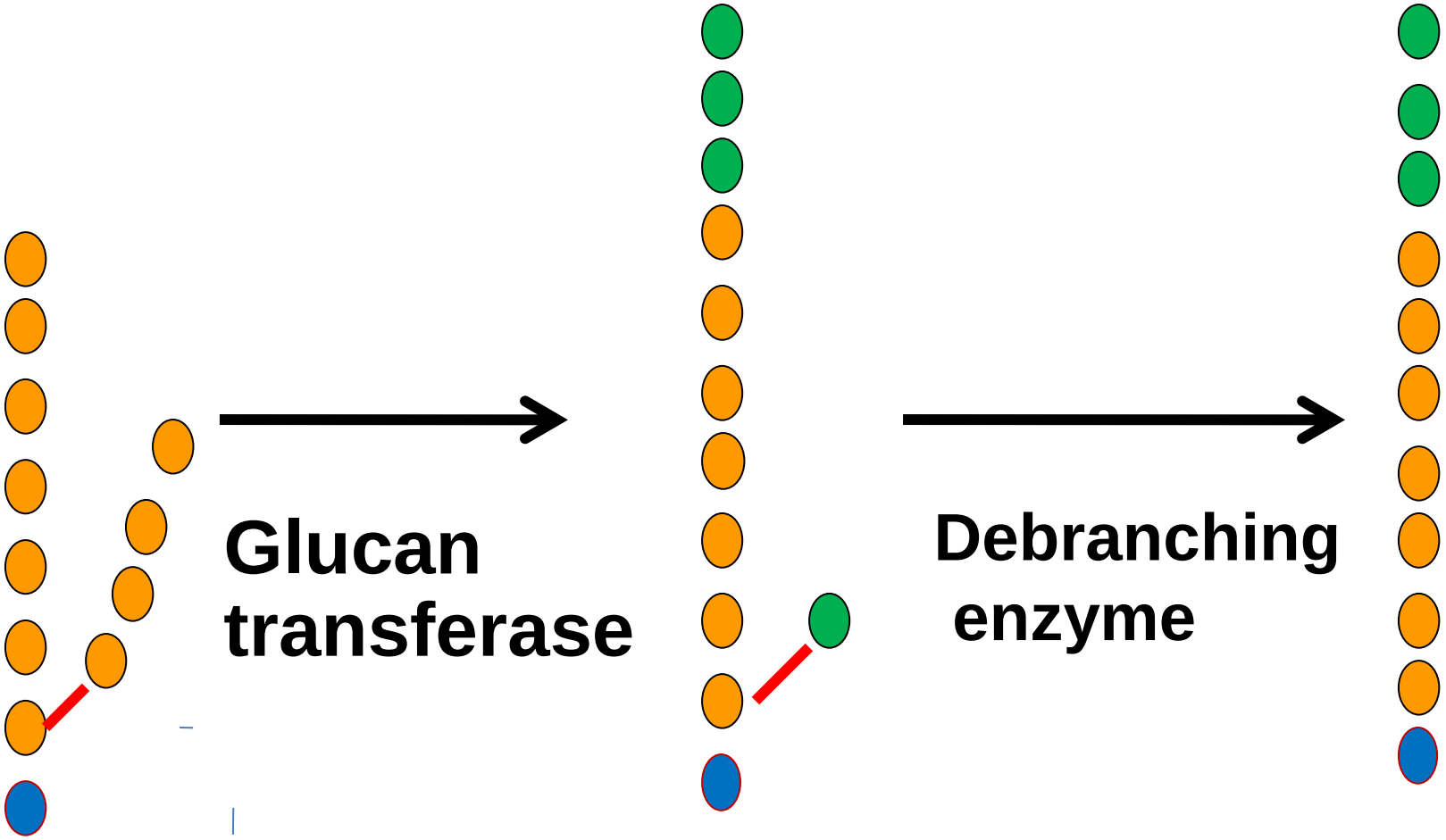
Mechanism of debranching

When four glucose residues are left from the branch point, α-1, 4 → α-1, 4 glucan transferase *transfers a trisaccharide unit from one* side to the other thus exposing α 1 → 6 branch point.

The splitting of α-1 → 6 glucosidic linkage requires the action of *amylo-1 → 6-glucosidase.*

In this reaction one molecule of free glucose is produced.

Mechanism of debranching



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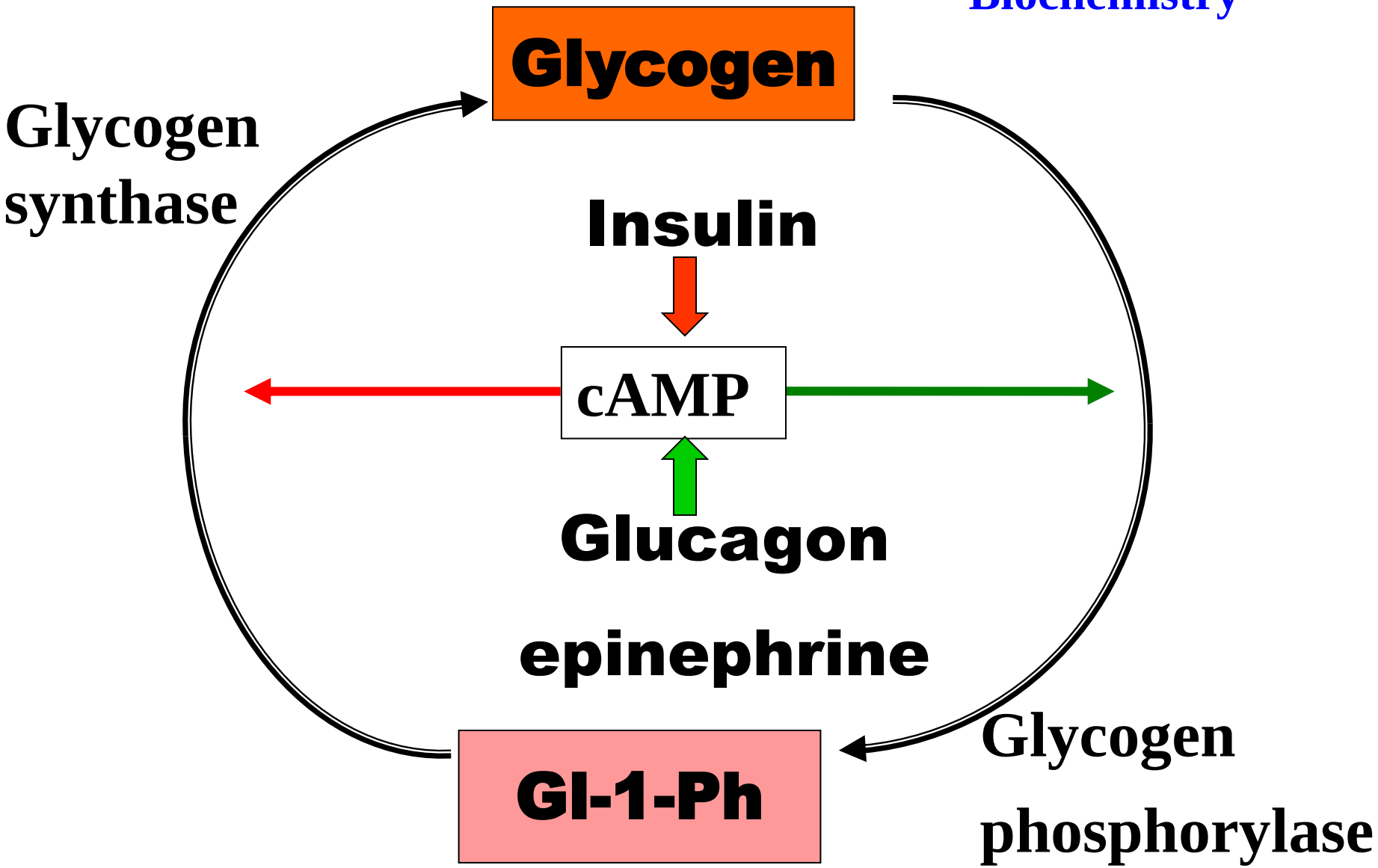
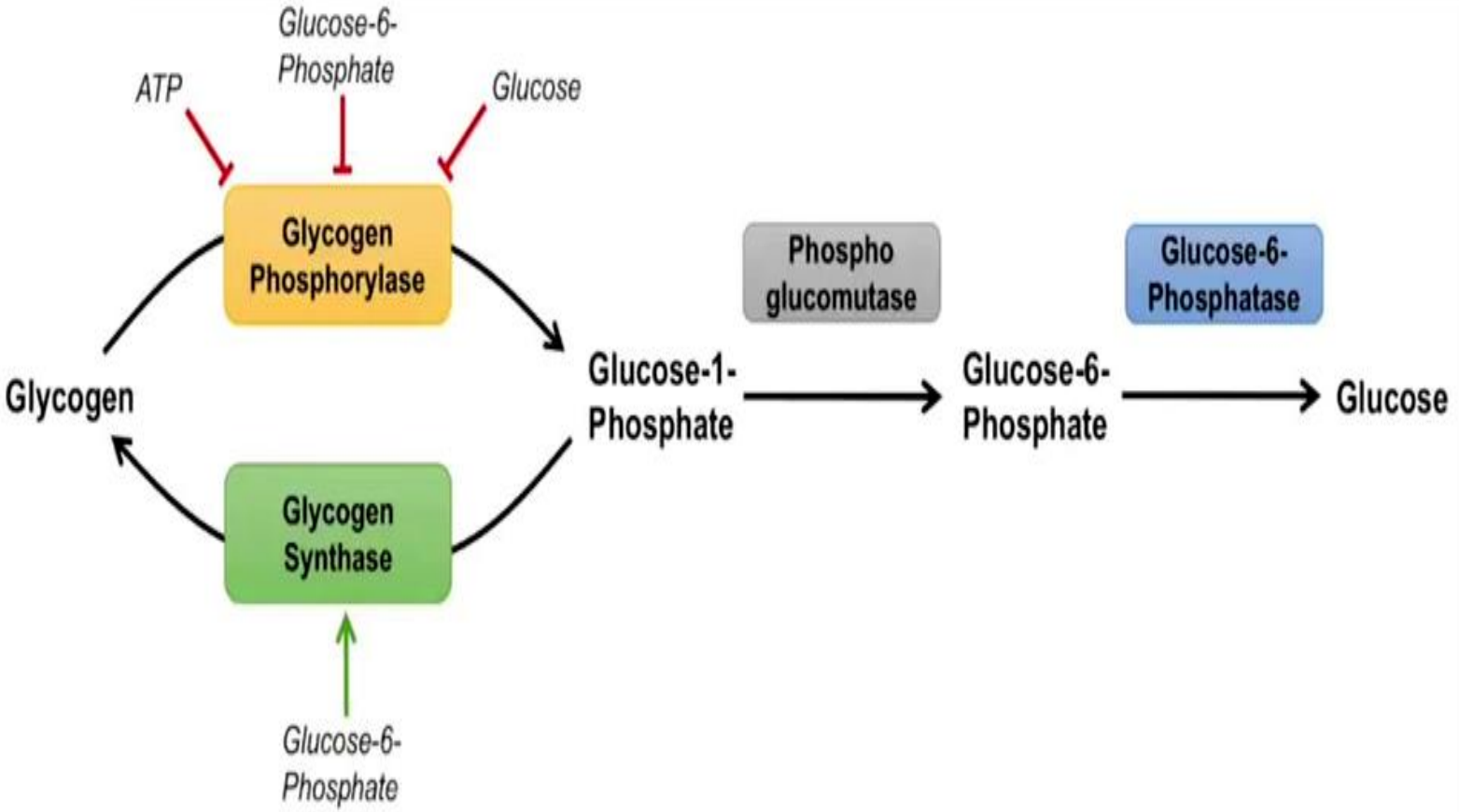
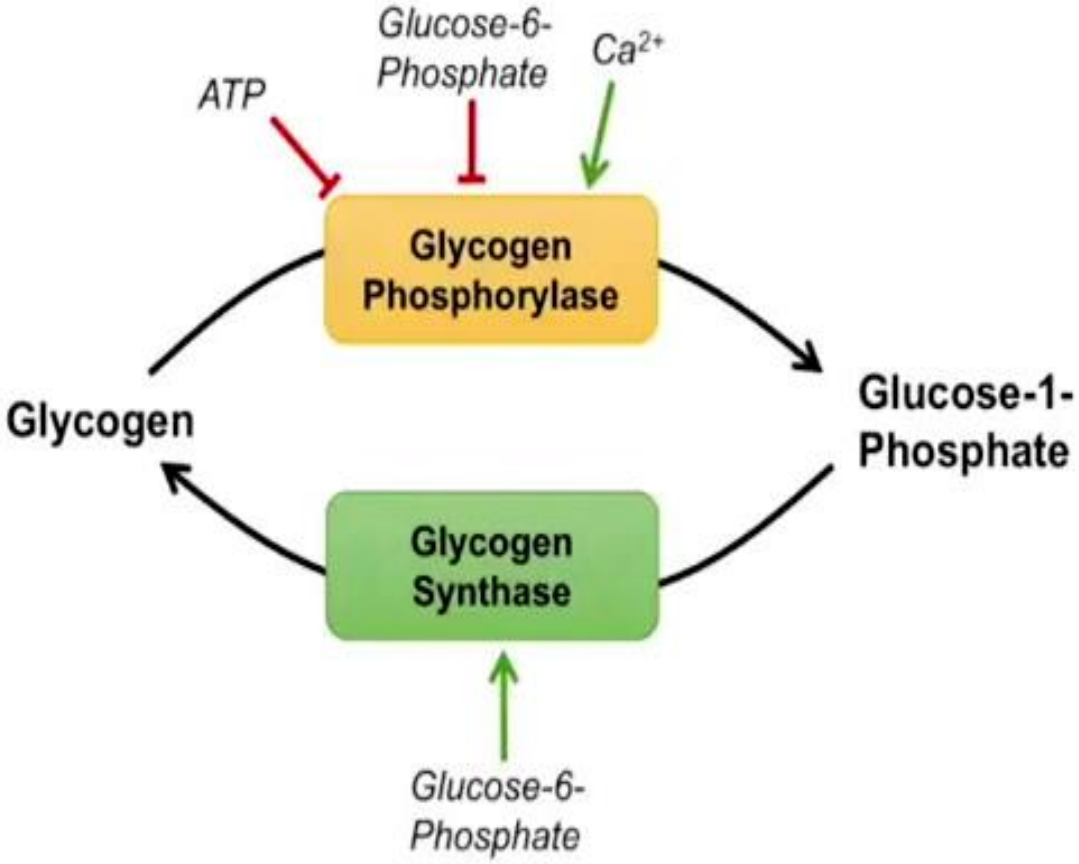


Liver


Glucose-6-Phosphate
ATP
Glucose
Glycogen Phosphorylase
Phospho glucomutase
Glucose-6-Phosphatase
Glycogen
Glucose-1-Phosphate
Glucose-6-Phosphate
Glucose
Glycogen Synthase
Glucose-6-Phosphate

Skeletal Muscle



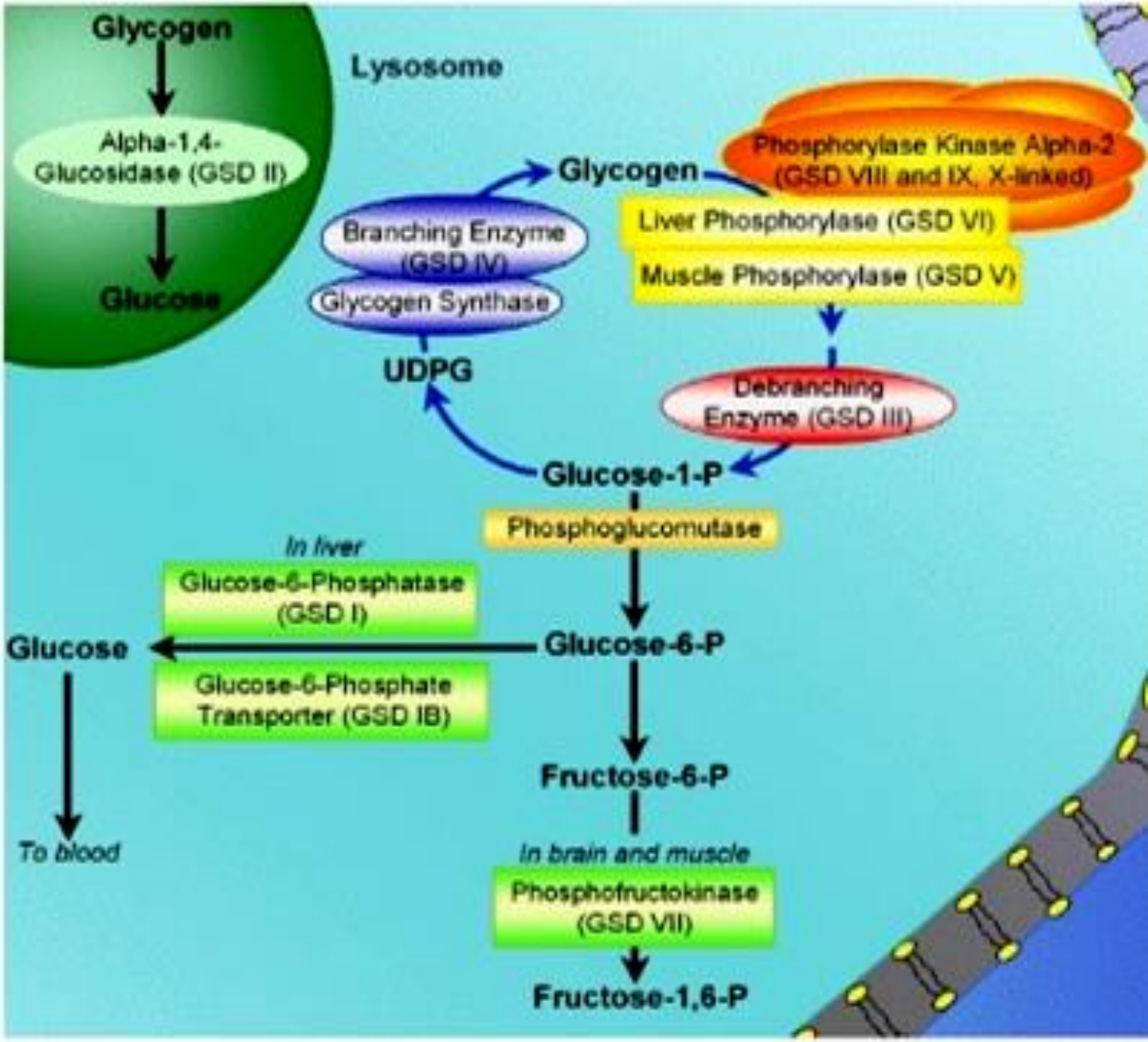
Glycogen srorage deseases

Group of inherited disorders characterized by deficient mobilisation of glycogen or deposition of abnormal forms of glycogen, leading to muscle weakness

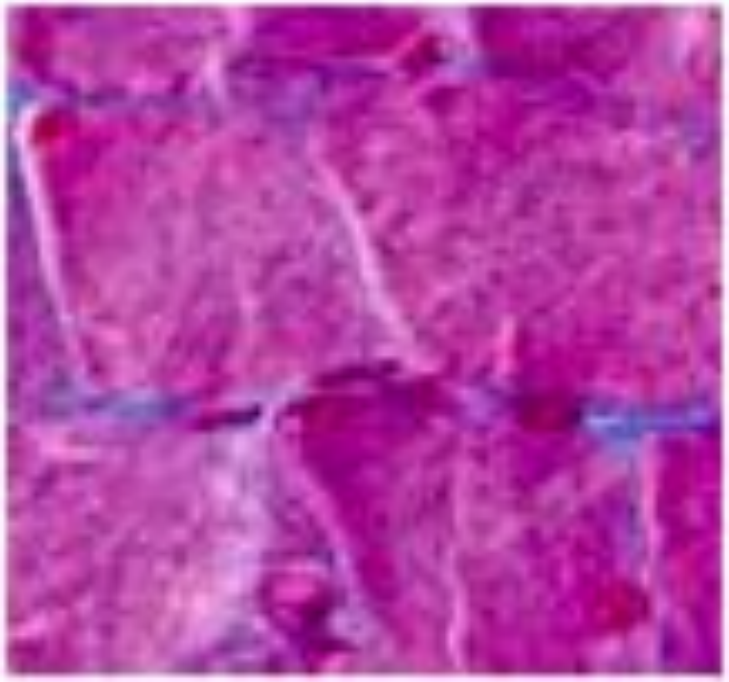
some glycogen storage diseases result in early death

Glycogen srorage deseases

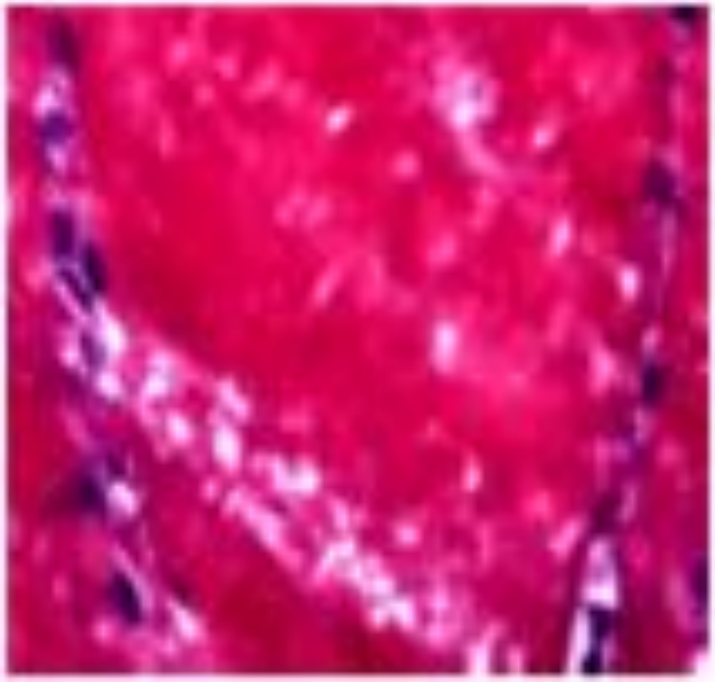
- **Von Gierke desease – deficiency of Glucose-6-phosphatase**
- **Pompe disease – deficiency of α 1 → 4 and α 1 → 6 glucosidase (acid maltase)**
- **Forbe (or Cori) desease – deficiency of debranching enzyme**
- **Andersen desease – deficiency of branching enzyme**
- **Hers desease – deficiency of liver phosphorylase**



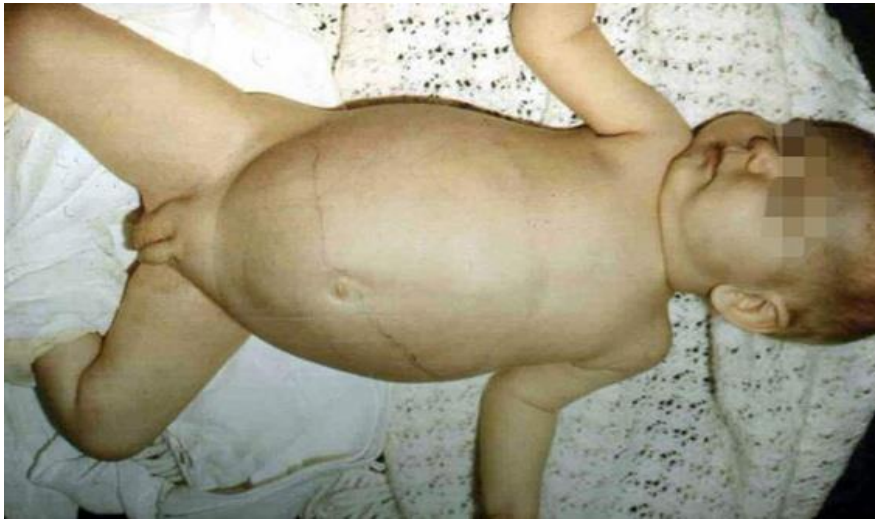
Duke Children's



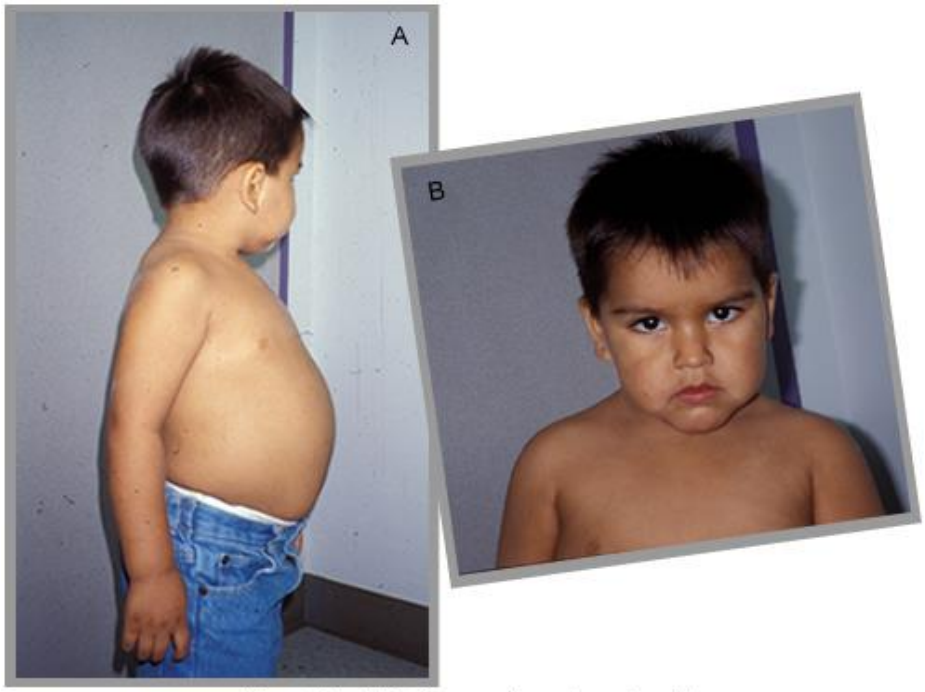
Normal skeletal muscle



Glycogen aggregates in Pompe disease



Gierke desease



Pictures 7A and 7B - Glycogen storage disease type III

Forbe (or Cori) desease

GSD Type 0

- An inherited genetic disease
- Enzyme affected: glycogen synthase
- The body is unable to store glycogen
- LIVER: Chromosome 12

-hypoglycemia when fasting

-hyperglycemia right after meals

- MUSCLE: Chromosome 19

-frequent fatigue and muscle cramps

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Uronic acid pathway

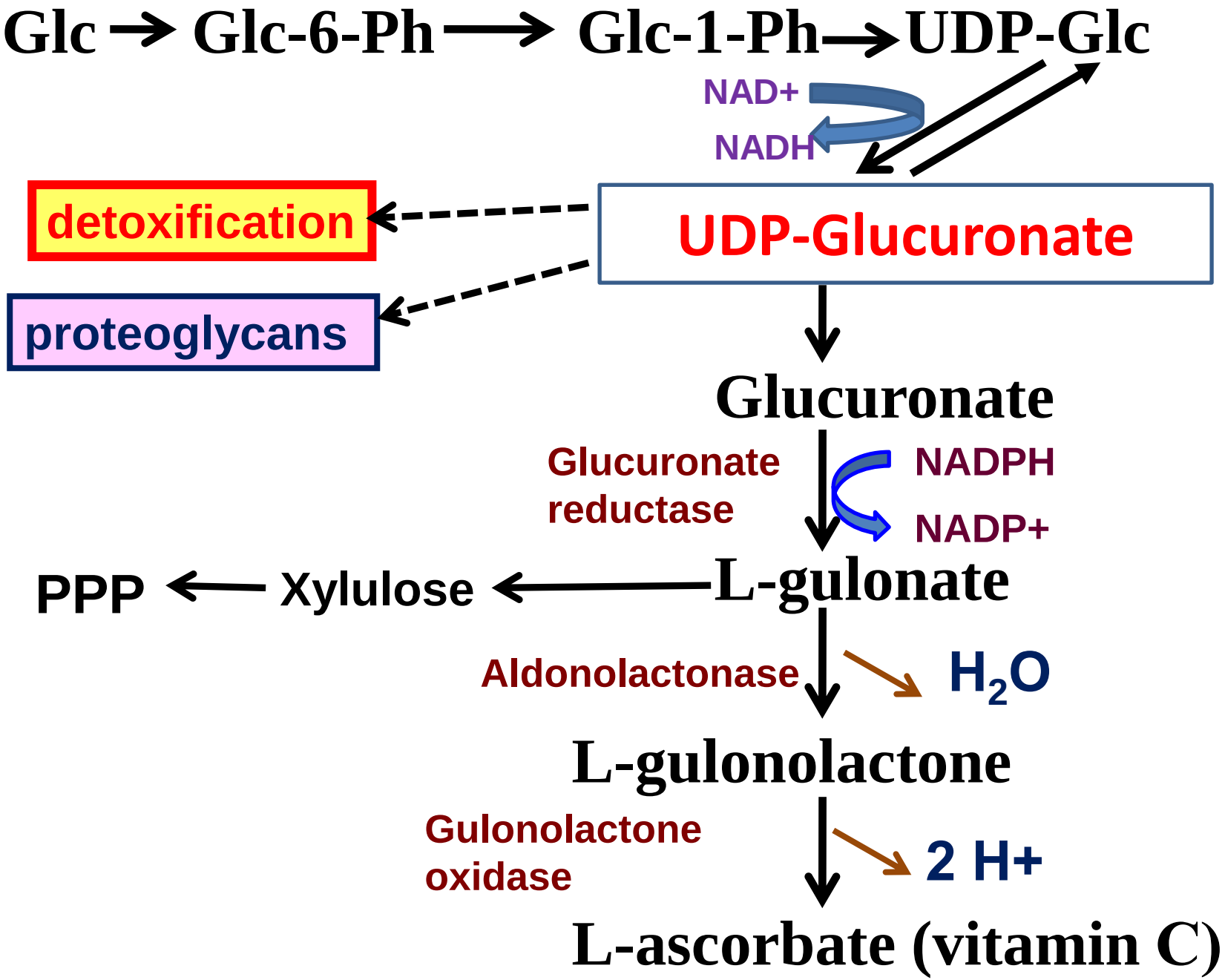
It is an alternate pathway for oxidation of glucose

Convertion of glucose to glucuronic acid

UDP-glucoronate is the source of glucuronate

- **for proteoglycans synthesis**

- **for reactions with substrates such as steroid hormones, bilirubin and a number of foreign compounds (xenobiotics) that are excreted in urine or bile as a glucuronide conjugates**


Glc
Glc-6-Ph
Glc-1-Ph
UDP-Glc
NAD+
NADH
detoxification
proteoglycans
UDP-Glucuronate
Glucuronate
Glucuronate reductase
NADPH
NADP+
PPP
Xylulose
L-gulonate
Aldonolactonase
H2O
L-gulonolactone
Gulonolactone oxidase
2 H+
L-ascorbate (vitamin C)

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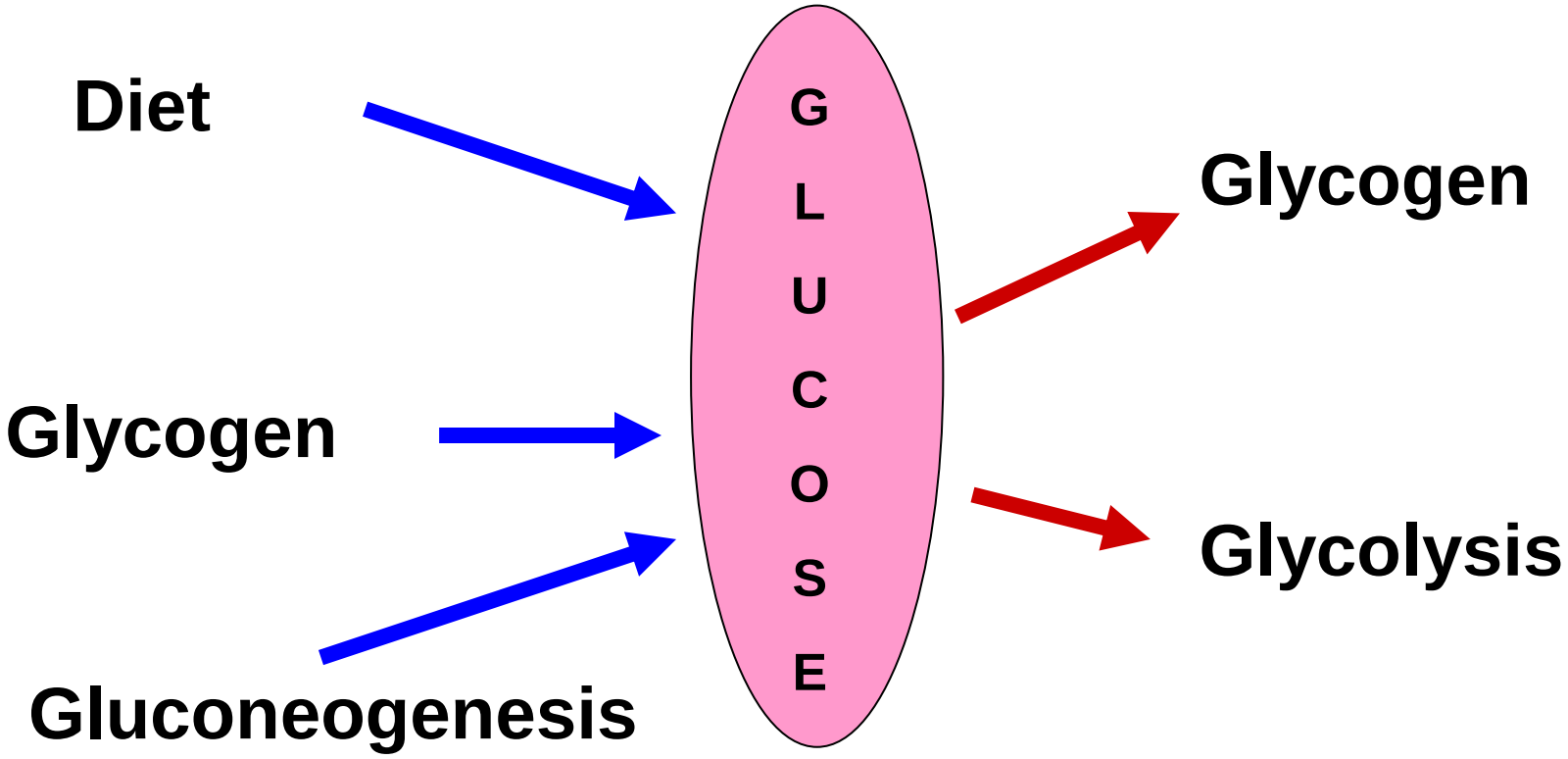
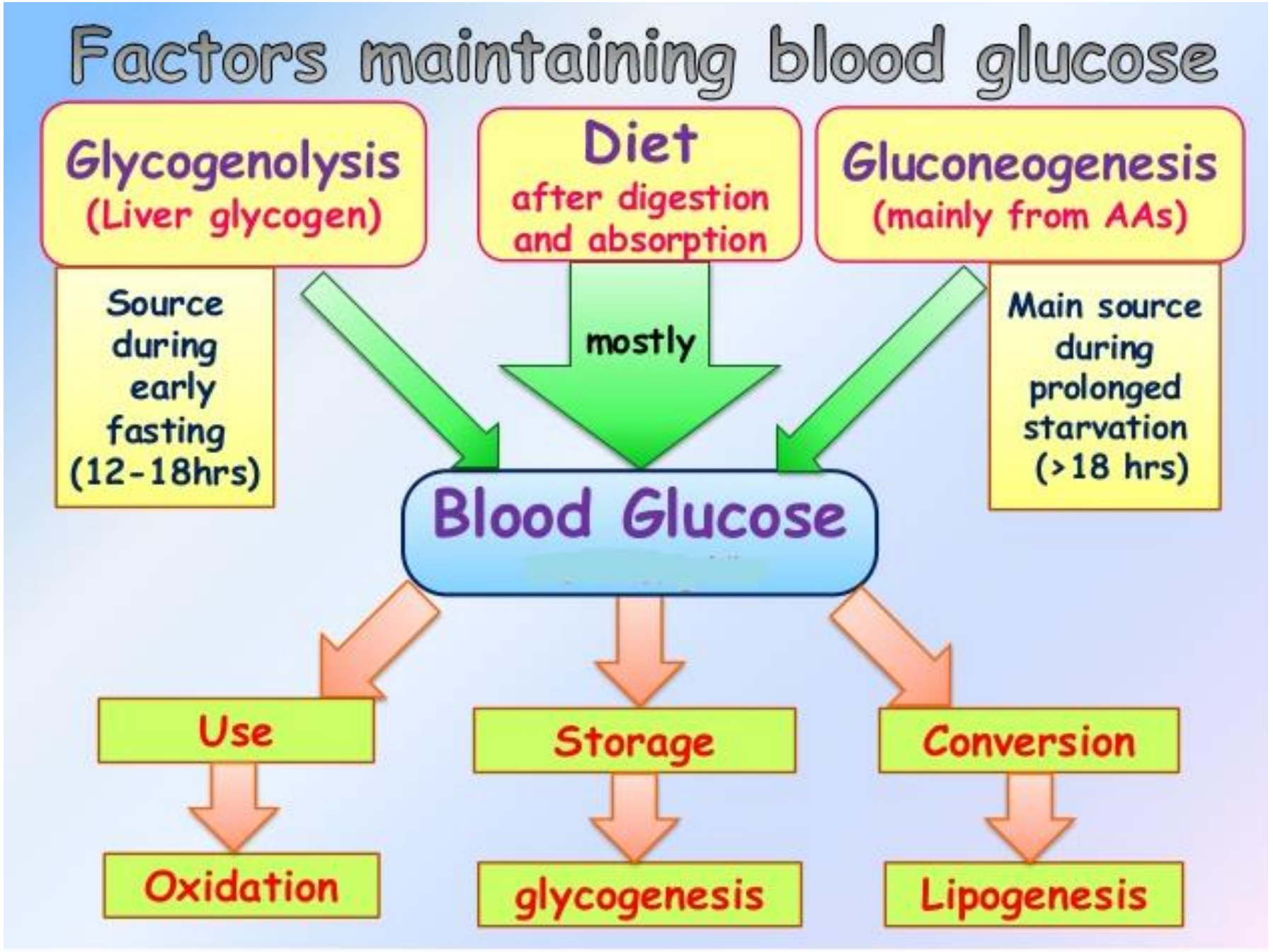
Regulation of Glucose Concentration in the Blood




Factors maintaining blood glucose
Glycogenolysis
(Liver glycogen)
Diet
after digestion
and absorption
Gluconeogenesis
(mainly from AAs)
Source during early fasting (12-18hrs)
mostly
Main source during prolonged starvation (>18 hrs)
Blood Glucose
Use
Storage
Conversion
Oxidation
glycogenesis
Lipogenesis

Signs & Symptoms

Here's what may happen when your blood sugar is high:

Very thirsty

Needing to pass urine more often than usual

Dry skin

Very hungry

Sleepy

Blurry vision

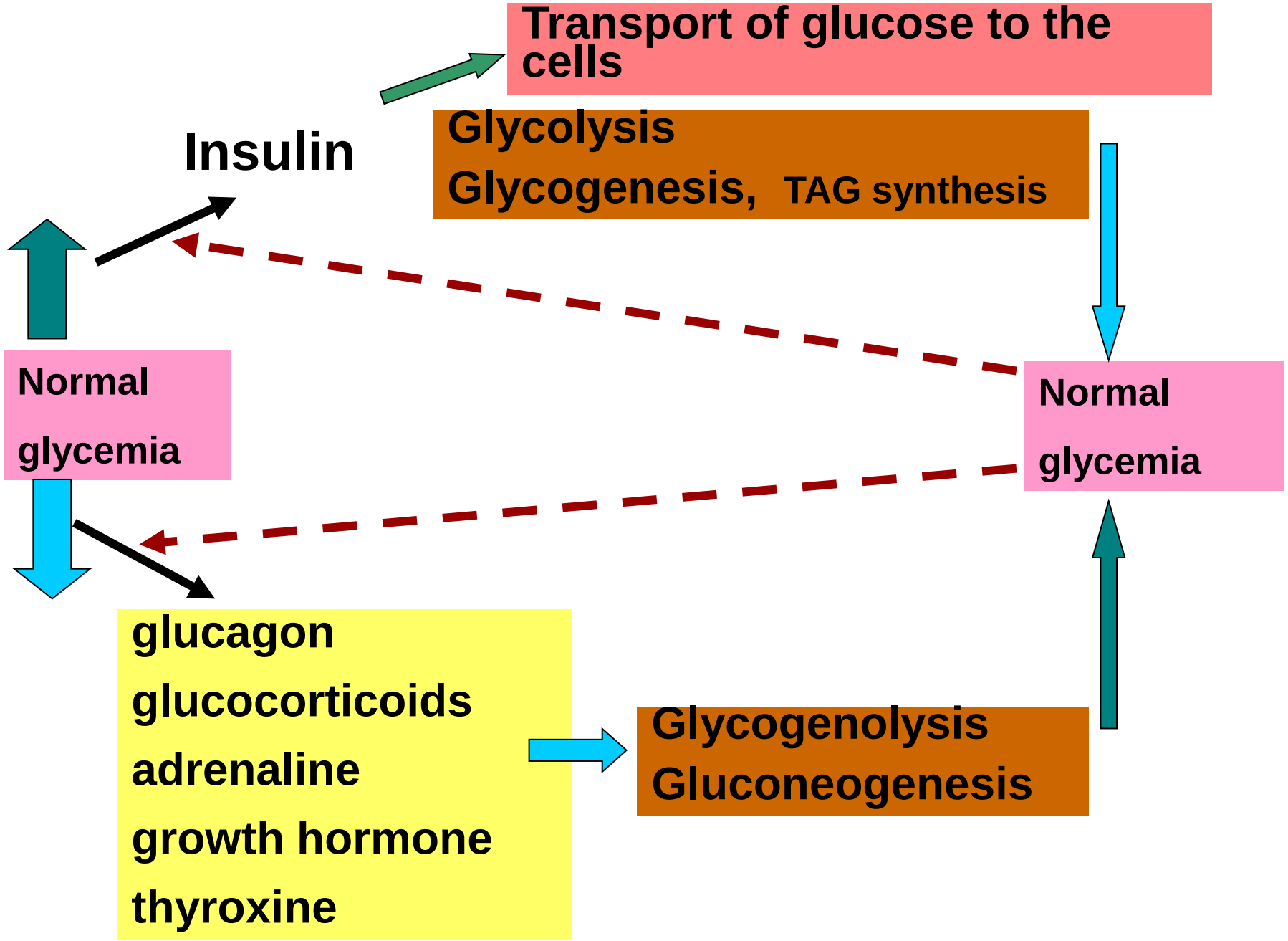
Infections or in
heal more slo
than usua

What goes wrong when the concentration decreases?

Hypoglycaemia

The symptoms associated with low blood sugar are:

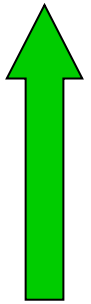
tiredness, confusion, dizziness, headaches, mood swings, muscle weakness, tremors, *irreversible CNS damage, coma, death*


Transport of glucose to the cells
Insulin
Glycolysis
Glycogenesis, TAG synthesis
Normal glycemia
Normal glycemia
glucagon
glucocorticoids
adrenaline
growth hormone
thyroxine
Glycogenolysis
Gluconeogenesis

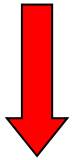
Regulation of Glucose Concentration in the Blood

Insulin:

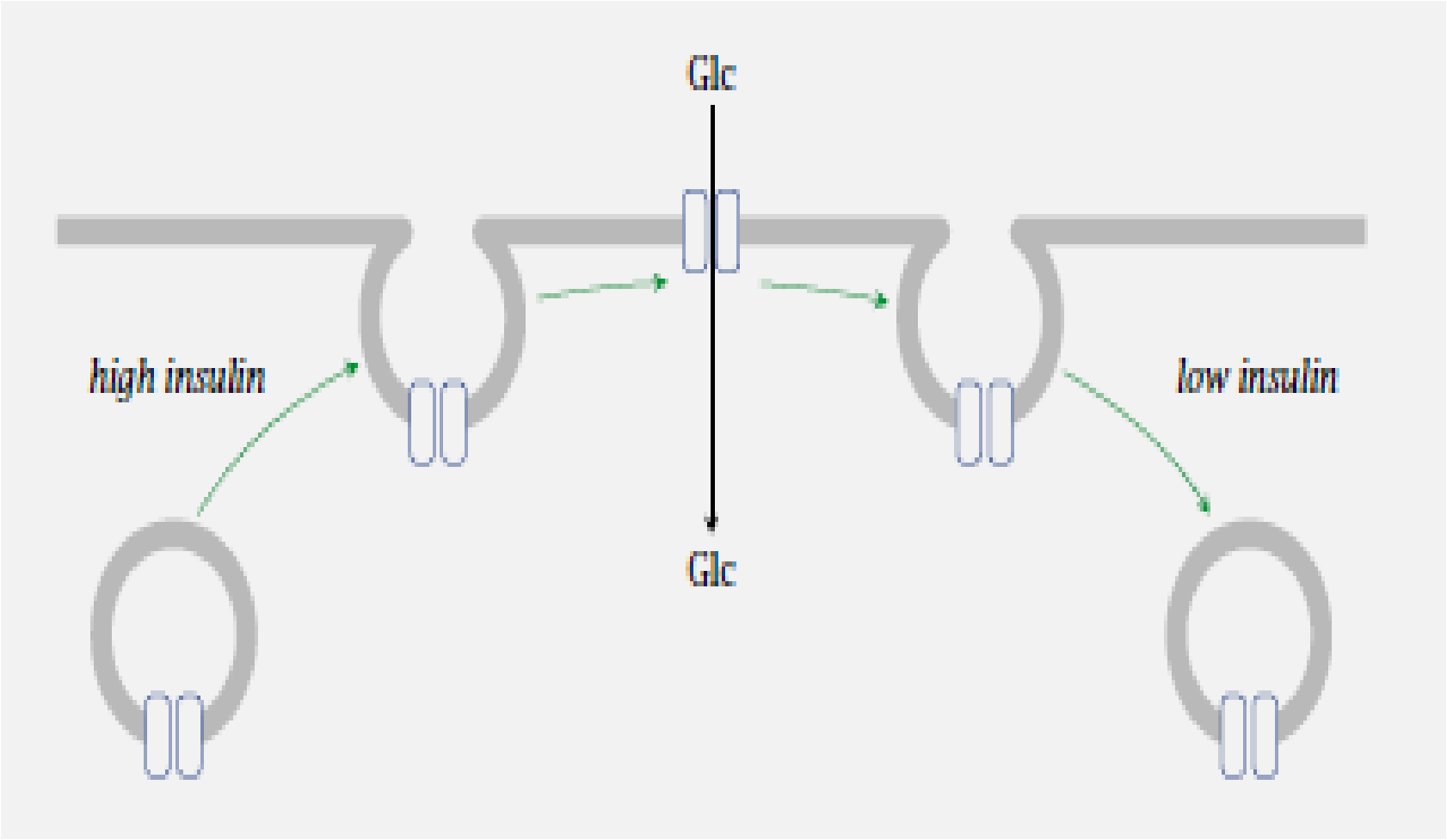
- **transport of glucose to the cell**
- **glycogen synthesis**
- **glycolysis**



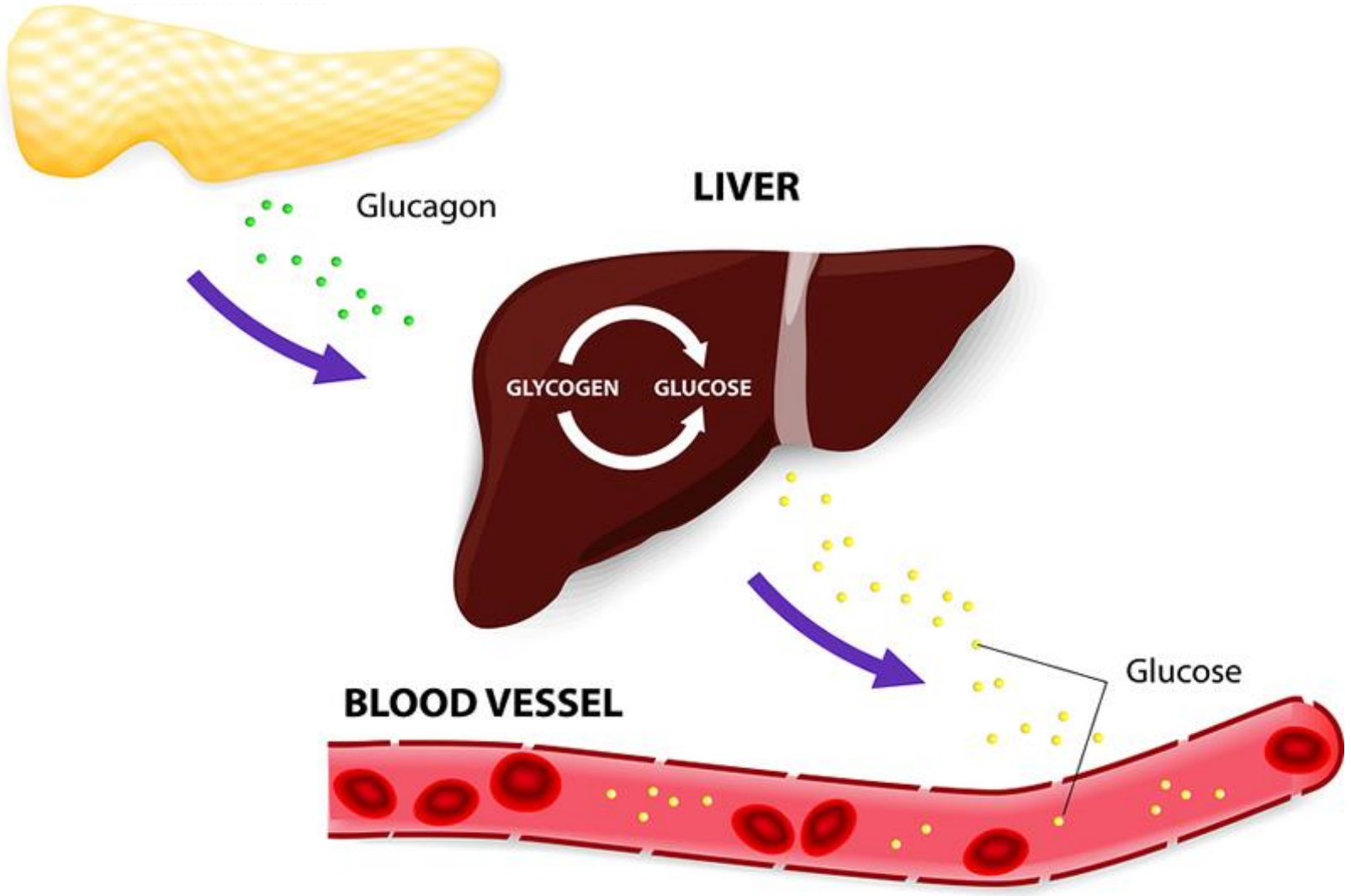
- **glyconeogenesis**



Insulin promotes glucose uptake by increasing the surface exposure of GLUT 4 transporters



Glucagon ↑ **- glycogenolysis**
- glyconeogenesis



Epinephrine ↑ - glycogenolysis

Thyroid hormone ↑ - glycogenolysis
- glyconeogenesis

Growth hormone ↓ - glucose uptake

Glucocorticoids ↑ - glyconeogenesis
↓ - glucose uptake

Diabetes mellitus

A chronic disease due primarily to a disorder of carbohydrate metabolism, cause of which is

deficiency or diminished effectiveness of insulin,

resulting in hyperglycaemia and glycosuria.

Secondary changes may occur in the metabolism of proteins, fats, water and electrolytes and in tissues/organs sometimes with grave consequences.

Two clinical types:

- **Type-I — Insulin dependent—IDDM** —typically observed in the young**.** It arises from an immunological cross-reaction that destroys the insulin-producing *β-cells of the pancreatic islets* which causes a lack of insulin.
- **Type-II— Non-Insulin Dependent — NIDDM** typically observed in the elderly. Type 2 diabetics may secrete normal insulin. The hormone also binds to its receptors on the cells in the body, which however fail to respond adequately to this stimulus (lacking functional response).

Types of diabetes

Type 1 – No Insulin

Type 2- Less insulin+ Insulin resistance

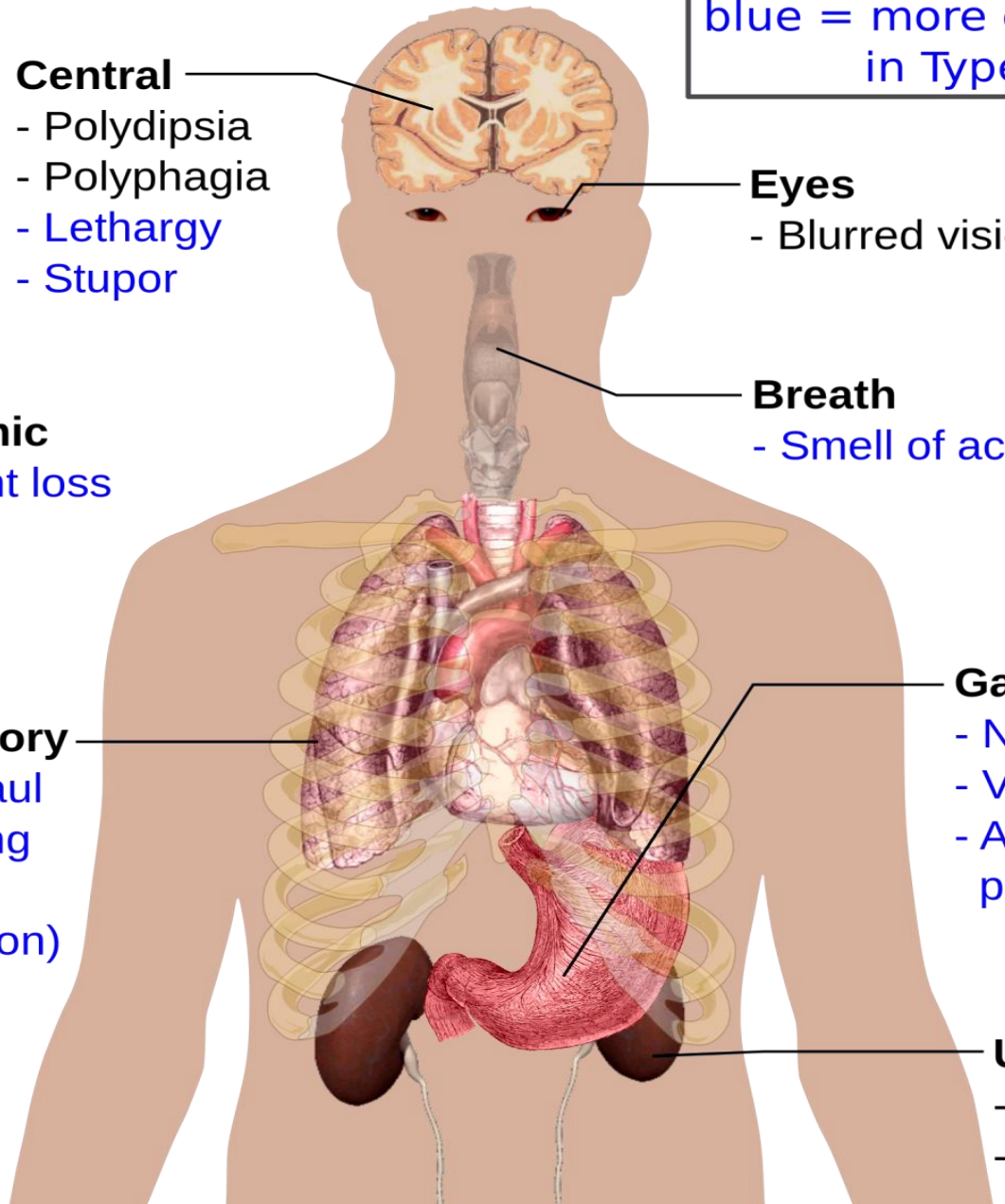
Gestational Diabetes

SANOFI 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

CLINICAL FEATURES

- **Large amounts of glucose may be excreted in urine (glucoseuria)**
- **Loss of solute produces osmotic diuresis thus large volume of urine (polyuria).**
- **Loss of fluid leads to thirst and polydypsia.**
- **Polyphagia: eats more frequently.**
- Tissues cannot use glucose due to absolute or relative deficiency of insulin/ or transport defect to cells. This causes **weakness** and **tiredness.**

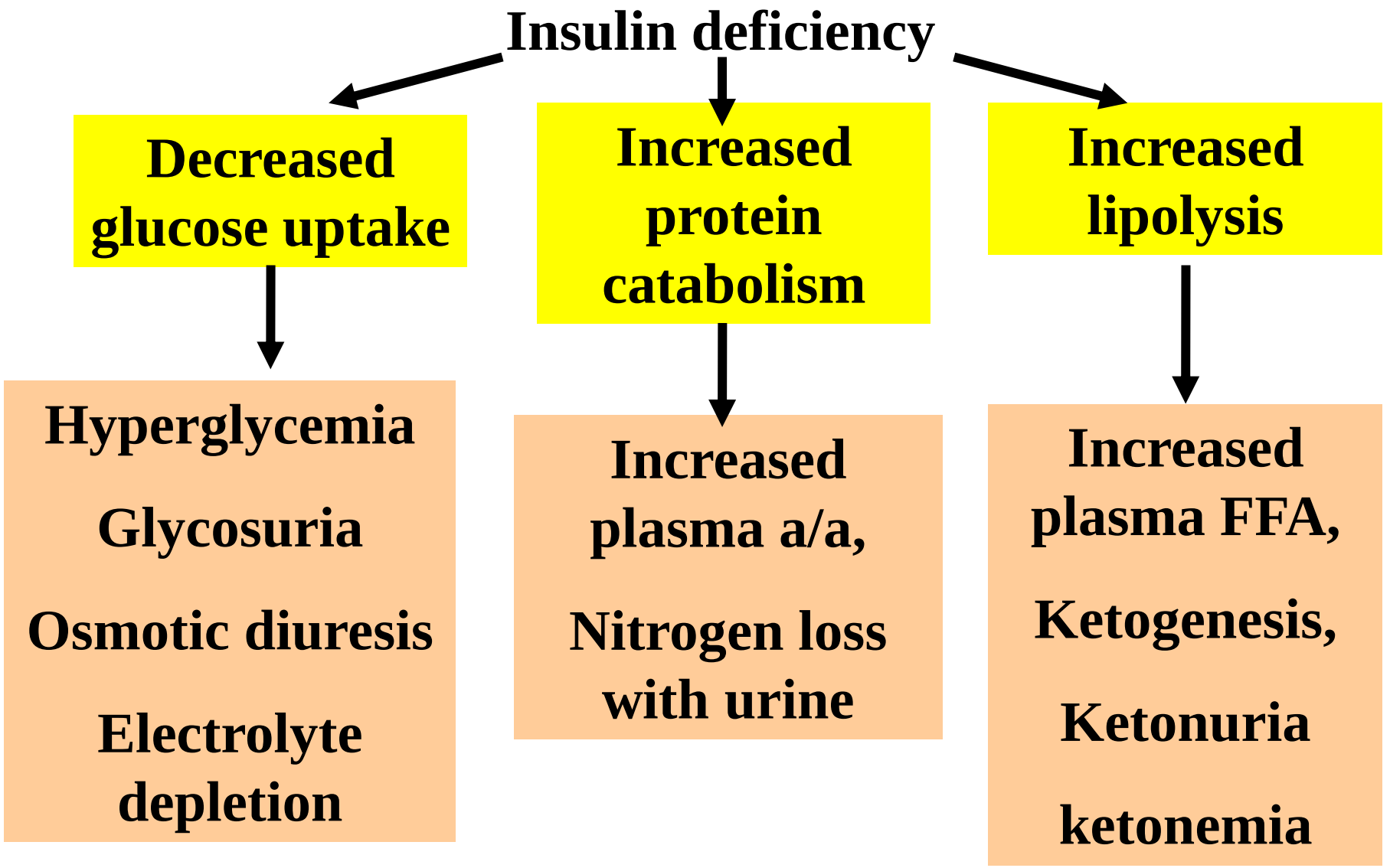
CLINICAL FEATURES

- As glucose cannot be used for fuel, fat is mobilized leading to **increase FFA in blood**.
- Increased acetyl-CoA is diverted for cholesterol synthesis - **hypercholesterolaemia and atherosclerosis**. Xanthomas may develop.
- **Increased ketone bodies leads to acidosis**.If ketosis is severe, acetone will be breathed out, giving characteristic “fruity” smell in breath (due to acetone).

CLINICAL FEATURES

- Excessive breakdown of tissue proteins. Deaminated amino acids are catabolised to provide energy, which accounts for **loss of weight**.
- Continued loss of water and electrolytes increases **dehydration**.
- Ketoacidosis produces increasing drowsiness, leading to diabetic coma in untreated cases.

Diabetes mellitus



Long-term complications of diabetes

Biochemical deviation	Clinical manifestation
accumulation of sorbitol in the lens of the eye	cataract
increased conversion of glucose to lipids	increased blood fats, atherosclerosis
glucosylation of proteins sorbitol accumulation	damage to nerve fibres, kidneys, other organs

Factors Causing