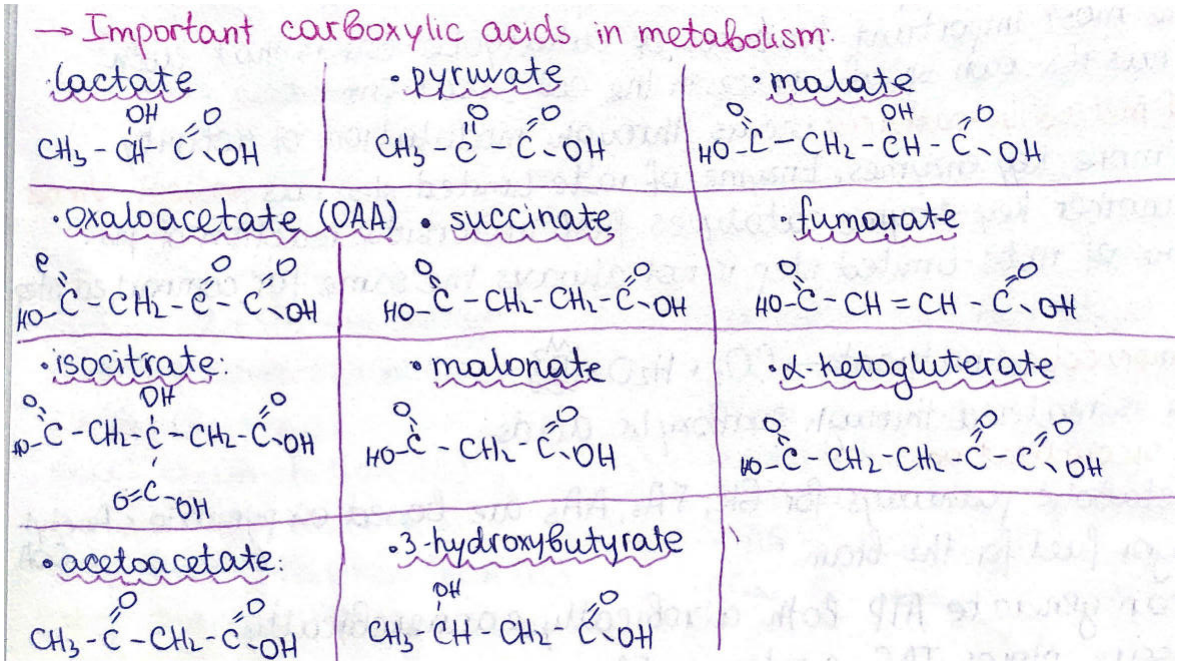
Course 2

Biochemistry



Definitions:

Matter – anything that occupies space and has a mass
In the body O, H, C, N, are making up 96% of the whole-body mass

Trace elements Trace elements are the elements in our body that make up 0,4% of the body mass; all of them are *crucial for the proper body functions*.

Compound – a substance that contains atoms of two or more elements

Free radical – an atom or group of atoms with the unpaired electrons which makes it *unstable and highly reactive*

Cation – **positively** charged ion

Anion – **negatively** charged ion

Electrolyte – ionic compound that **breaks down into positive and negative** ions in the solutions

Electronegativity – the power of an atom to attract electrons to it

Exergonic reactions – reactions that **release more energy** than they absorb

Endergonic reactions – reactions that **release less energy** than they absorb

Synthesis – combining something
Anabolism – to build up molecules (*synthesis*)
Catabolism – to break up molecules (*decomposition*)

Oxidation – **loss** of electrons
Reduction – **gain** of electrons

Inorganic compounds: usually lack carbon, structurally simple, hold together by ionic or covalent bonds

Organic compounds: always contain carbon, usually hydrogen, always has covalent bonds

A **colloid** is a solution, but it differs in the size of the particles. In the colloid, the **particles are large** enough to scatter light just like water droplets.

An **acid** is a compound which **donates protons**
A **base** is a compound which **accepts protons**

Salts are very important for **carrying of the electric current**. To create a salt, acid, and base have to react between each other.

Normal pH in the body is around 7.35-7.45
- lower than 7.35 is considered *acidosis*
- higher than 7.45 is considered *alkalosis*

In the body, we have **buffer systems** which **convert strong acids and bases into the weak** ones – *all for the protection of the organism*

Molecules which have the *same molecular formula, but different structures* are called **isomers**.

Enzymes

Enzymes are *catalysts of the biochemical reactions*; **catalyst** – ***lowers*** *the amount of energy* needed to start a chemical reaction **without being consumed** in the reaction itself (they **decrease activation energy**, but do not change the equilibrium constant of the reaction)

Isoenzymes are the enzymes which catalyze the same reactions but **differs in their physiochemical properties**. For example, glucose in our body can be converted into glucose-6-P by:
- *glucokinase* in *liver and pancreas*
- *hexokinase* in *the rest of the body*

Cofactors are the *helper molecules* that are required for proper function of the enzyme
Apoenzyme + cofactor = **holoenzyme**

Examples of *cofactors*:

- **metals** – required within 2/3 of all enzymes
  - **Zn, Mg, Cu, Fe**
- **Coenzymes** – **bound loosely** to the enzyme
  - **NAD+, ubiquinone, ATP, CoA**
- **Prosthetic group** – **bound tightly** to the enzyme
  - **Heme, FAD, lipoamide**

Allosteric enzymes are the enzymes which consist of **several subunits.**

An effector – small molecule which *either increases or decreases the activity* of the allosteric enzyme by **binding to its regulatory site**.

Classification of the enzymes

- **Oxidoreductases** – catalyze **redox reactions**. They need vitamin C as the cofactor, also NAD, FAD, heme and NADP (*dehydrogenases, oxidases, reductases, oxygenases, peroxidases, catalazes, hydrolases, desaturases*)
- **Transferases** – **transfer functional units**. (*aminotransferases, kinases*)
- **Hydrolases** – **protein degradation enzymes**. They do not need coenzymes (*esterases, glycosidases, peptidases, amidases, proteases, lipases, pepsin, phosphatase*)
- **Lyases** – **synthases**, they remove and ass small molecules to and from the substrates and form double bonds. (*decarboxylases, hydrotases, lyases*)
- **Isomerases** – *epimerases, mutases*
- **Ligases** – **synthetases** – catalyze reactions where two molecules are joined together – bond formation. For the reaction they use ATP. (*polymerases, carboxylases, ligases*)

Thermodynamics

1. Energy cannot be created or destroyed (law of conservation of energy)
2. Any spontaneous reactions increase the disorder of the universe

Entropy (s) is a measure of molecular randomness, aka disorder
Enthalpy (H) is the sum of internal energy, volume, and the pressure

Gibbs energy (delta G)
Delta G = H (enthalpy) – T (temperature) * S (entropy)

U – **internal energy**

Enzyme kinetics
It is the measure of the rates of chemical reactions, and it deals with the factors which can affect the rates.
Michaelis Menten Model tells us how the velocity of reaction of enzymes relates to the concentration of the substance.
Vmax – *describes the velocity of the reaction* – reached at the infinite concentration of the substrate

Michaelis constant (Km) – describes the affinity of the enzyme to the substrate
- High Km – *low affinity*
- Low Km – *high affinity*

Gibbs free energy tells us whether or not the chemical reaction will proceed

Km – the concentration of the substrate at which the rate of the reaction is equal to vmax/2

Inhibition of enzymes
There are two basic types of inhibitors – ***reversible and irreversible***.

Competitive inhibitors:
Are inhibitors which ***compete with the substrate for binding to the enzyme***
Competitive inhibitors usually **bind to the active site of the enzyme**. After the work of those enzymes
- *Km is increased* (the affinity of the enzyme to the substrate becomes lower)
- *Vmax remains unchanged*

Non-competitive inhibitors
Are inhibitors which ***do not compete with the substrate and bind the enzyme at the site, other than the active site*** which changes the enzyme conformation. → even if we have infinite amount of the substrate, the enzyme will still not be working as it should.
- *Vmax decreases*
- *Km remains unchanged*

Uncompetitive inhibitors
Are the enzymes that ***bind to the [enzyme-substrate] complex.*** → even if we keep on adding substrate, the [ES] complex will be inhibited by binding of the inhibitor to it.
- *Vmax decreases*
- *Km decreases*

Acetylcholine esterase – enzyme which *removes acetylcholine from the synaptic cleft.*
Inhibitors of this enzyme *keep acetylcholine in the cleft*, thus **making the signal last longer**.
- **Inhibitors**
  - **Alzheimer medications** – competitive inhibitors (Tacrine)
  - **Sarin** – irreversible inhibitor used for killing people through the muscle paralysis), now found in **organophosphates**.
- Myasthenia gravis (disease) – immune system disorder which destroys acetylcholine receptors in the synapse; therefore, muscles do not work properly. It is treated with the acetyl esterase inhibitors.
  - **Edrophonium** is used for the diagnosis – **inhibits the enzyme for a short period** which shows the improvement.

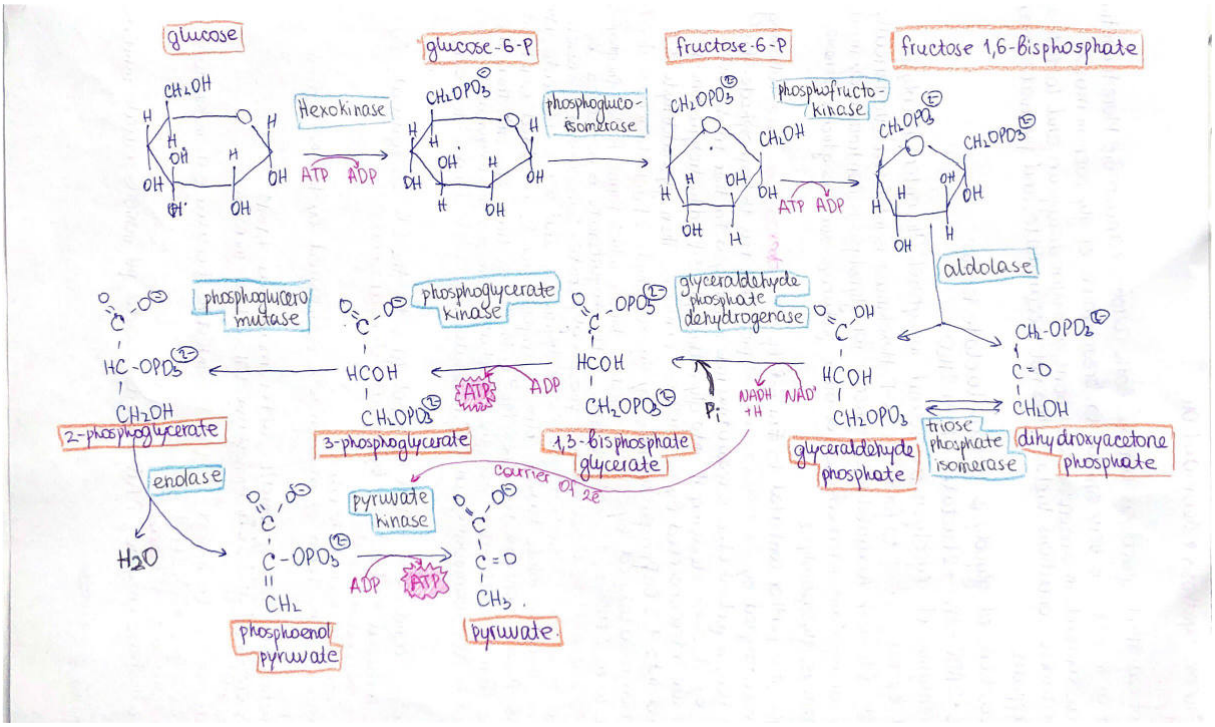
Carbohydrate metabolism

After digestion, **polysaccharides are hydrolyzed into monosaccharides**, such as glucose (80%), fructose and galactose. Fructose is converted into glucose and galactose is converted to glucose (by hepatocytes)

Glycolysis

Happens in the cytosol of the cells.

Glucose is converted into **two pyruvates**. This reaction produces **2 ATP** molecules (in case of **anaerobic metabolism, also 2 NADH+)**

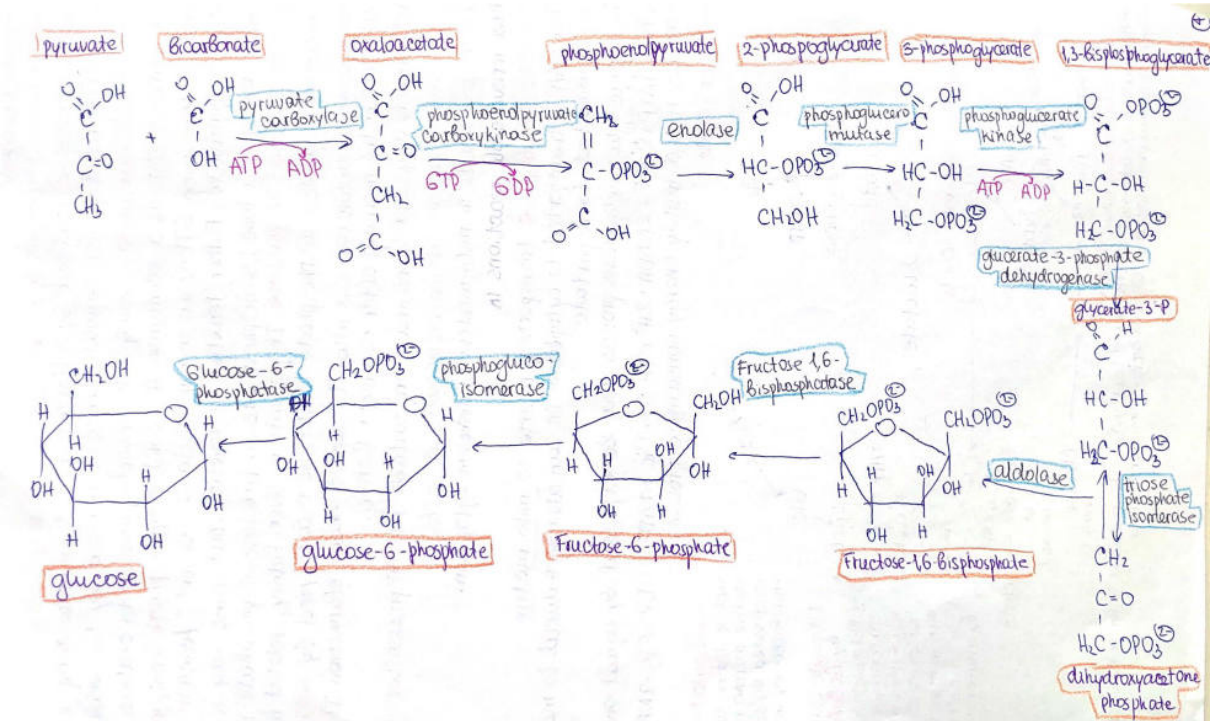


Regulation of glycolysis: (-) → inhibition, (+)→ activation

- **Hexokinase**
  - (-) high amounts of glucose-6-P
- **Glucokinase**
  - (-) high amount of fructose-6-P
  - (-) glucagon
  - (+) insulin
- **Phosphofructokinase**
  - (-) citrate
  - (-) glucagon
  - (+) high amount of AMP
  - (+) fructose-2,6-bisphosphate
- **Pyruvate kinase**
  - (-) glucagon

- (+) insulin
- (+) fructose -1,6-bisphopsphate (in liver)

Gluconeogenesis



- **Formation of glucose from other compounds** present in our body

This process does not usually occur in the large scale in our body unless a person is **starving or has an endocrine disorder**

Glycerol (a part of TAGs), lactic acid, pyruvate, certain amino acids can be used for synthesis of glucose in liver other than pyruvate. About 60% of amino acids can be used for gluconeogenesis.

Substrates for gluconeogenesis:

- **Glycerol** (degradation of TAGs)
  - Glycerol phosphate → *dihydroxyacetone phosphate*
- **Lactate** (glycolysis, Cori cycle)
- **Oxaloacetate/alpha-ketoglutarate** → *phosphoenolpyruvate*

If it starts from oxaloacetate, then gluconeogenesis begins in mitochondrion.

This process is located in **both cytosol and mitochondrial matrix**.

Regulation of gluconeogenesis

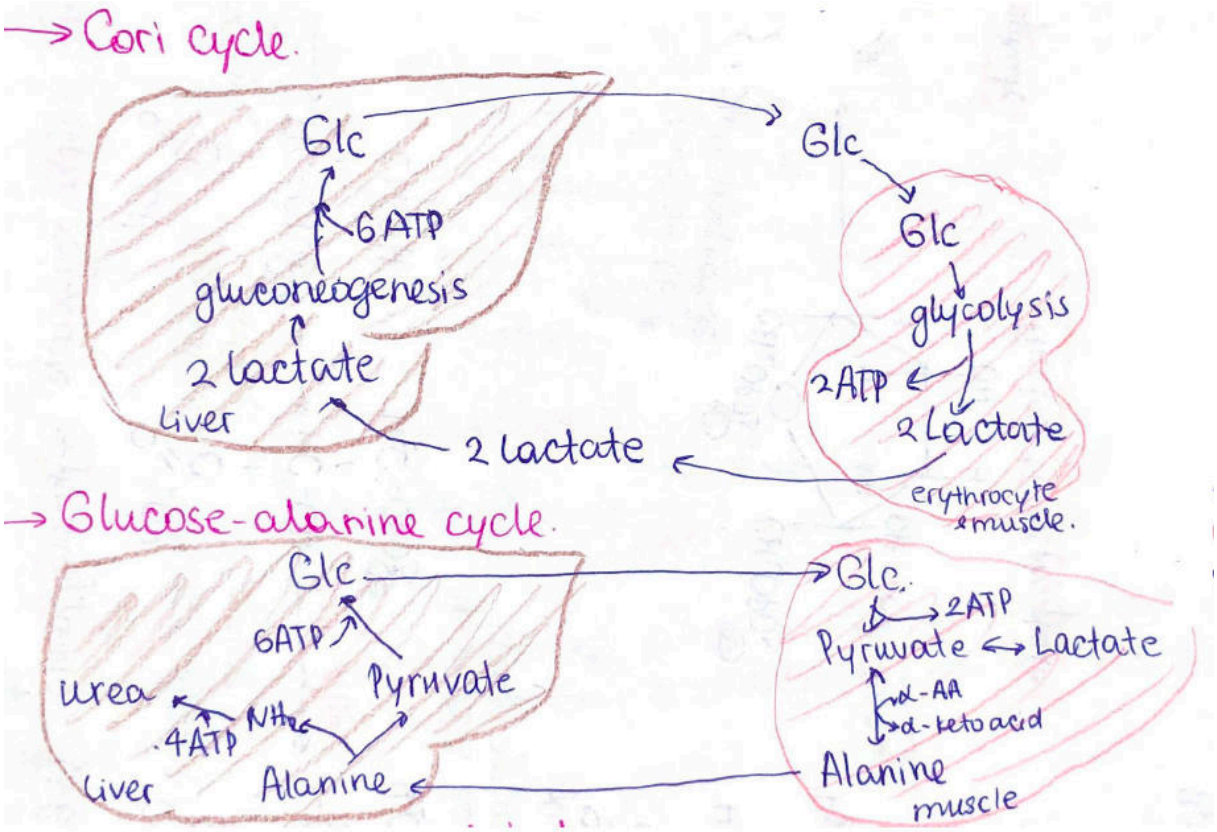
- **Fructose-1,6-bisphosphatase**
  - (-) fructose-2,6- bisphosphate
  - (-) high amounts of AMP
  - (+) glucagon
  - (+) high amounts of ATP
- **Phosphoenolpyruvate carboxylase**

  - (+) glucagon
- **Pyruvate carboxylase**
  - (+) high amounts of acetyl-CoA
- (+) stress hormones
- (+) citrate
- (-) insulin

Glycolysis together with gluconeogenesis form **Cori cycle**.

Gluconeogenesis in the liver and **glycolysis in the muscles**

1. **Muscles and red blood cells** take **glucose** and convert it into **lactate** (glycolysis)
2. **The liver** takes up the **lactate** and converts it back into **glucose** (gluconeogenesis)



Glycolysis and gluconeogenesis together with some extra steps also forms the **glucose-alanine** cycle.

It transports toxic **ammonia** *from the muscles into the liver* by pairing it with the **pyruvate** → forming **alanine**. Alanine then is transported into the liver, and there it is transaminated to **pyruvate** and *ammonia then goes* into the **urea cycle**.

1. *Muscles* take **glucose** and convert it to **pyruvate** (glycolysis)
2. Muscles convert **pyruvate** into **alanine** by adding **NH2** to it
3. *Liver* deaminates **alanine** and turns it into **pyruvate**
4. Liver converts **pyruvate** into **glucose** (gluconeogenesis)

Pyruvate + glutamate → **alanine + alpha-ketoglutarate** (*alanine aminotransferase*)

Formation of Acetyl-CoA

After glycolysis has taken its place, and **pyruvate is produced**, pyruvate is commonly converted to **Acetyl-CoA**, which is then used as a substrate for the **Krebs cycle**. The reaction of conversion of pyruvate into Acetyl-CoA is **irreversible under physiological conditions**.

Pyruvate dehydrogenase is a **complex of three enzymes** which are catalyzing reactions into *acetyl-CoA*

Formation of lactate

After glycolysis ended, and in **case of no presence of oxygen**, or **levels of NADH are very high, lactate will be produced** from pyruvate *instead of Acetyl-CoA*

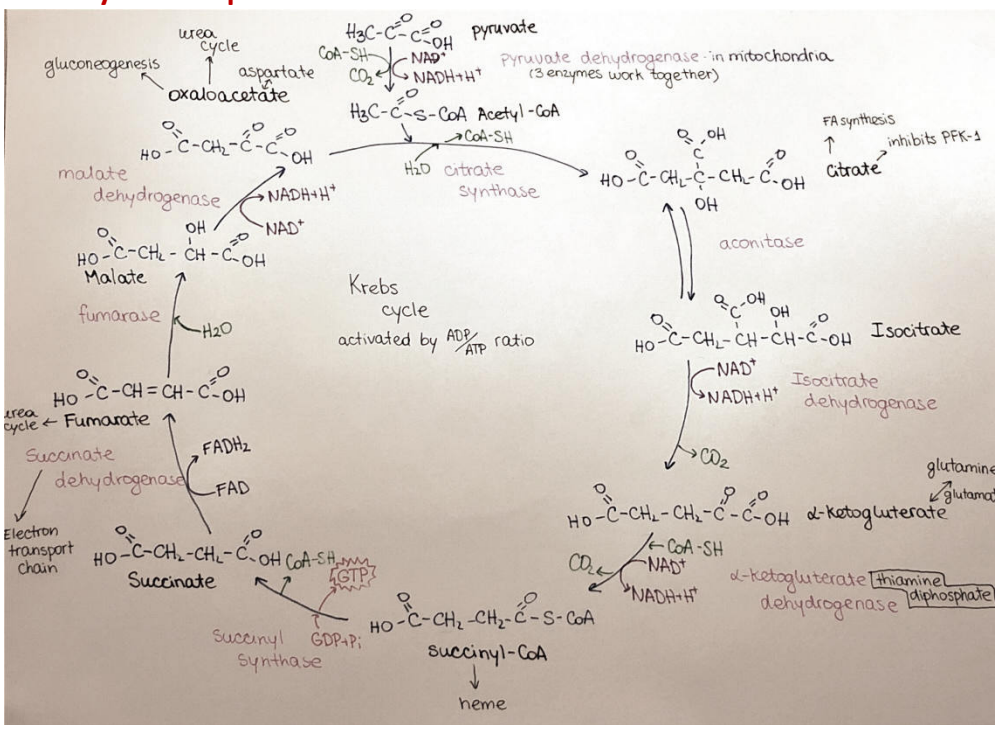
This reaction takes place *in erythrocytes* since **they do not have mitochondria**.

Pyruvate can also form **oxaloacetate**, which is another compound to initiate the **Krebs cycle**. This reaction requires **biotin** *as a cofactor.* The enzyme catalyzing it is called **pyruvate carboxylase**, and **ATP with bicarbonate** is needed.

Krebs cycle
Also known as **the citric acid cycle**. It takes place **in mitochondria**. **Acetyl-CoA** is **oxidized (aerobically)**. The cycle produces **2 CO2, 3 NADH+, 1 FADH2, and 1 GTP**

The cycle is activated when there are **low levels of ATP** in cells and **NADH+.**

Anaplerotic reactions are the reactions that form intermediates from other metabolic pathways.
Krebs cycle is **amphibolic** – both *anabolic* and *catabolic*.



Regulation of Krebs cycle:

- **Citrate synthase**
  - (+) high amounts of Ca2+
  - (+) high amounts is AMP and ADP
  - (-) high amounts of ATP
  - (-) Succinyl-CoA
- **Aconitase**
  - (-) fluroacetate
- **Isocitrate dehydrogenase**
  - (+) high AMP and ADP
  - (+) High Ca2+
  - (-) High ATP
  - (-) High NADH2
- **Alpha-ketoglutarate dehydrogenase**

  - (-) GTP, ATP, NADH2, succinyl-CoA
  - (+) high Ca2+
- **Succinate dehydrogenase**
  - (-) oxaloacetate

Electron transport chain

Electron transport chain transfers **electrons** through a series of **electron carriers** along with the **increasing redox potential**, and their goal is to *reduce O2 to H2O eventually*. In total, the electron transport chain generates **32-38 ATP** molecules from one molecule of glucose (glycolysis and Krebs)

Complex 1,3 and 4 are also functioning as **proton pumps** as they pump protons *from the mitochondrial matrix into the intermembrane space*. This process **creates a concentration gradient across the membrane**, therefore the **electric gradient**. This gradient then fuels a complex called **ATP synthase** and generates ATP as the protons are *returning to the matrix*. The synthesis of ATP happens as the *ATP synthase spins around*, which causes the turbulence inside of it and it *triggers ADP and inorganic phosphate to combine* creating the ATP.

UCPs – aka **uncoupling proteins**. They **decrease the membrane potential** across the membrane and produce heat. They are found in high concentrations in the *brown adipose tissue*.

Cyanide – deadly poison – an inhibitor of cytochrome C oxidase (complex 4). They bind to it, blocking the last reaction.

Coenzyme Q 10 – aka ubiquinone. In its structure, it contains the isoprenoid chain. It can be synthesized in our body, so it is not an essential component in our diet.

Ubiquinone ⍰ ubiquinol (reduction) CoQ10 can carry 2 electrons at a time, whereas Cytochrome C carries only 1 electron and passes them one by one to the complex 4.

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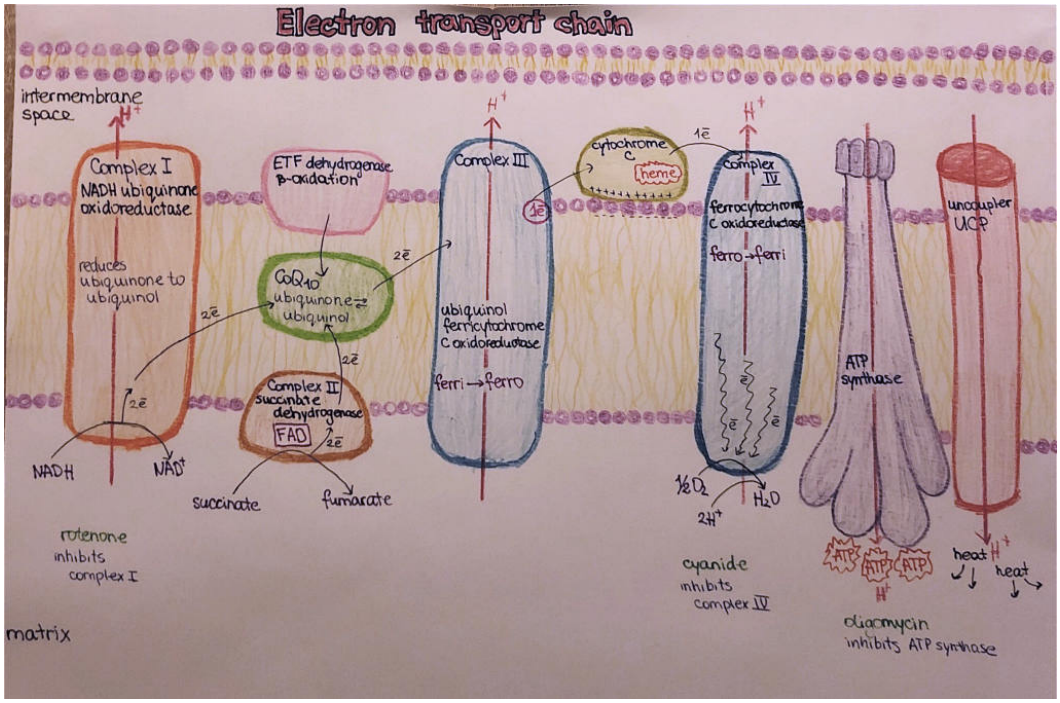
Ubiquinone → *ubiquinol* (reduction) **CoQ10 is able to carry 2** electrons at a time, whereas **Cytochrome C carries only 1 electron** and passes them one by one to the complex 4.

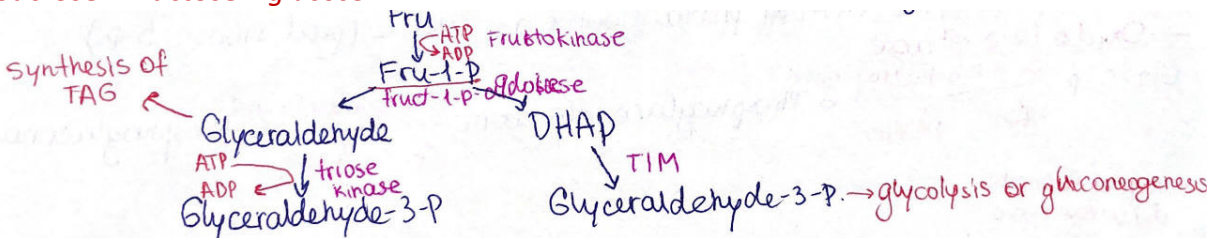
Complex 4 needs four electrons to reduce O2 to make H2O. This means that *Cytochrome C needs to bring electrons four times*. So, **complex 4 accumulates electrons** until there are 4 of them so they can then be passed to O2. Though there are many Cytochrome C molecules surrounding complex 4, and **complex 4 can accept electrons from different cytochrome Cs** at the same time to make the process of H2O formation the most productive.



Metabolism of other saccharides

Fructose metabolism

Sucrose = **fructose** + *glucose*



Fructose can be converted to **Fructose-6-P** by **hexokinase** in *all tissues in our body.*
Whereas, enzyme **fructokinase** in *kidneys, liver and small intestine* converts fructose into **Fructose-1-P**.
Then, *Fructose-1-P* can be split by **aldolase B** into *dihydroxyacetone phosphate* and **glyceraldehyde**.
Glyceraldehyde then is converted to **glyceraldehyde-3-P** by **glyceraldehyde kinase**.

Excess fructose is not good for our body, since **it skips the regulatory step of glycolysis** which can lead to **excess lipid synthesis**.

Fructose intolerance:

- Caused by the **deficiency of aldolase B**
- Leads to the **accumulation of Fructose-1-P**
    - Decrease amount of ATP and inorganic phosphate
        - **Decreased synthesis of clotting factors** and proteins. Causes *hypoglycemia and vomiting due to increased gluconeogenesis*. As well as *hyperuricemia* due to high amounts of adenine. Causes *hemorrhage, jaundice, hepatic failure and death* ☹
    - The only treatment is **removal of fructose from diet**

Fructosuria:

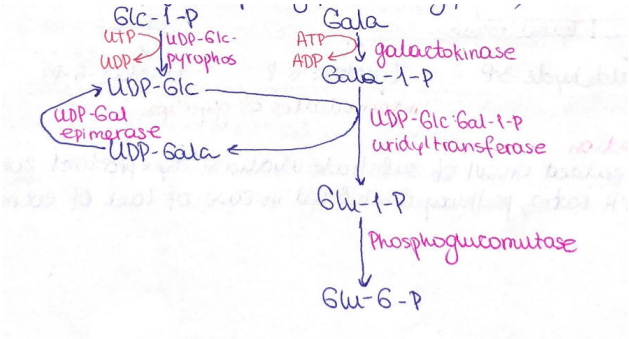
- Caused by **deficiency of fructokinase**
- It is *benign, asymptomatic accumulation of fructose in the urine*

Mannose metabolism

By enzyme **hexokinase** in *every cell in our body* mannose can be converted to **mannose-6-P**
Mannose-6-P is then converted to **fructose-6-P** by enzyme **phosphomannose isomerase**.

Galactose metabolism

Lactose (from milk) is broken down into **Galactose** and *Glucose*



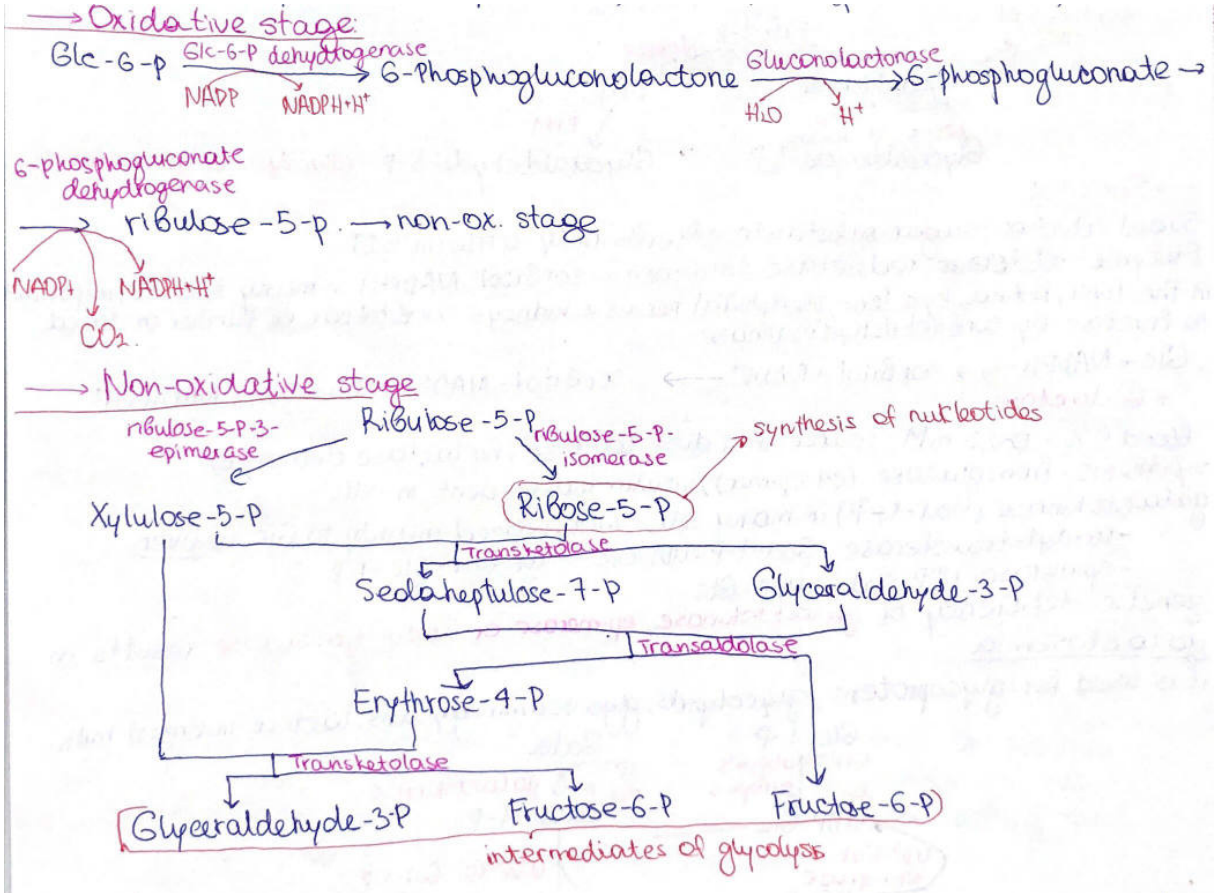
By enzyme **galactokinase**, *Galactose* is converted to **galactose-1-P**
Then, *Galactose-1-P* is combined with *UDP-Glucose* and by enzyme called **galactose-1-uridyltransferase** is converted into **UDP-Galactose** + *Glucose-1-P*
Then *UDP-Galactose* by enzyme **UDP-Galactose-4-epimerase** is converted into **UDP-Glucose**.

Galactosemia:

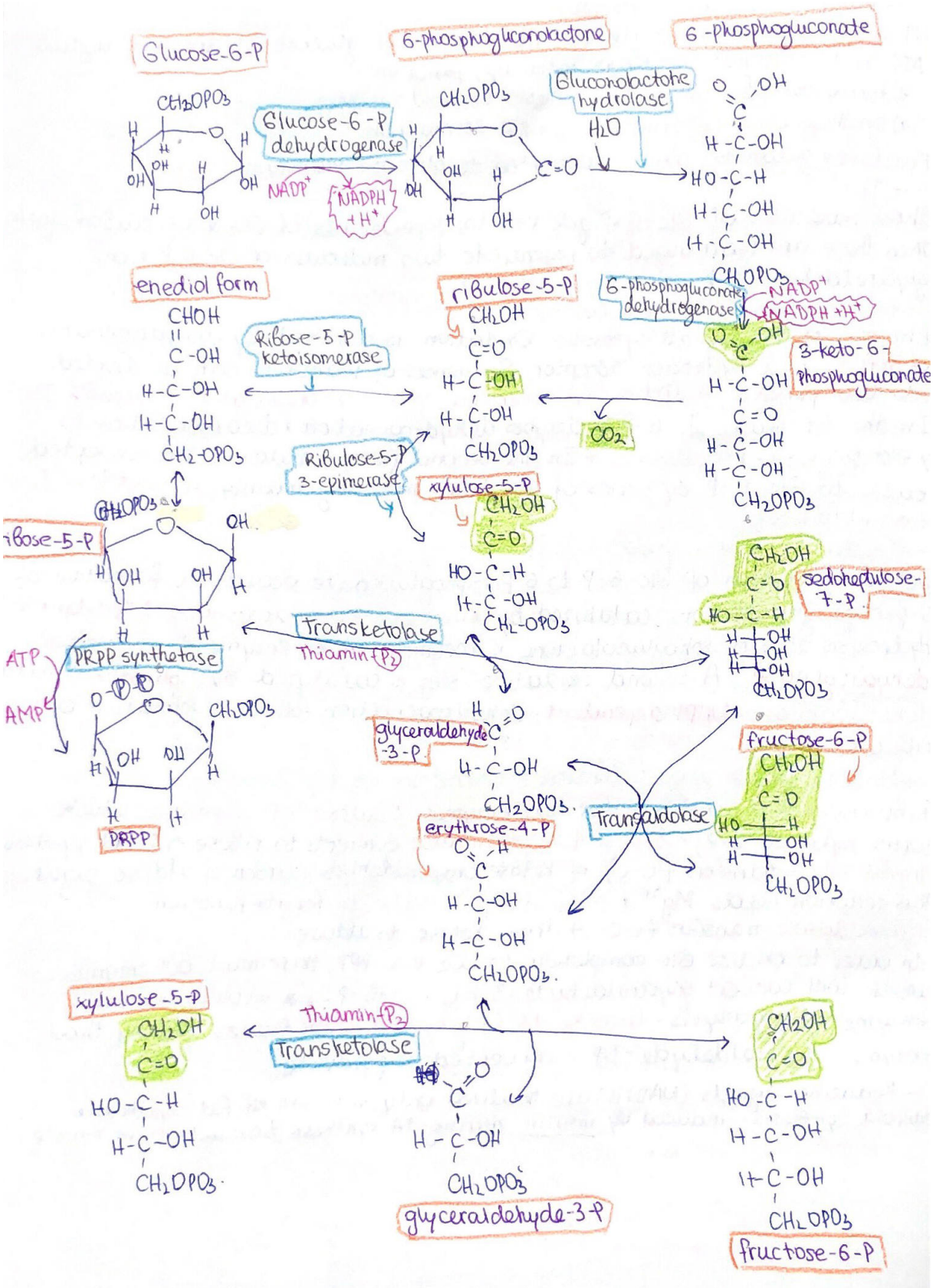
- Caused by **absence of enzyme Galactose-1-p-uridyltransferase**
- *Leads to mental retardation, liver damage, cramps, galactosurea, diarrhea, jaundice and cataracts* due to accumulation of galactose
- The only treatment is **removal of galactose from diet**.

Pentose phosphate pathway

This pathway *does not form ATP*, but **produces NADPH** for **synthesis of fatty acids, nucleic acids and elimination of reactive oxygen species**.



Its intermediate – **ribose-5-P** is used for **synthesis of nucleotides**.
This pathway is *located in the cytoplasm*
Glucose-6-dehydrogenase deficiency leads to **hemolytic anemia** due to the damage of *erythrocytes* by the **oxidative stress**.


Glucose-6-P
Glucose-6-P dehydrogenase
NADP+
NADPH + H+
6-phosphoglucono lactone
Gluconolactone hydrolase
H2O
6-phosphogluconate
6-phosphogluconate dehydrogenase
NADP+
NADPH + H+
3-keto-6-phosphogluconate
CO2
ribulose-5-P
Ribose-5-P ketoisomerase
Ribulose-5-P 3-epimerase
xylulose-5-P
enediol form
Ribose-5-P
ATP
AMP
PRPP synthetase
PRPP
Transketolase
Thiamin-P2
sedoheptulose-7-P
glyceraldehyde-3-P
Transaldolase
fructose-6-P
erythrose-4-P
xylulose-5-P
Thiamin-P2
Transketolase
glyceraldehyde-3-P
fructose-6-P

Synthesis of glycogen, aka glycogenesis.
If glucose is not immediately needed in the body, it can be turned to **glycogen** and stored, also easily broken down when needed. The **body stores up to 500g of glycogen**. 75% of that in *muscles* and 25% in the *liver.*

Glycogen has two ends: reducing and **non-reducing**. The **non-reducing end takes place in all of the reactions** (lengthening or shortening)
Synthesis of glycogen takes place **in the cytosol**. And catalyzed by **glycogen synthase** which is **activated by high amounts of Glucose-6-P**

Glycogenolysis, aka degradation of glycogen.
When glucose is needed in the body, glycogen is broken down to form molecules of glucose.

- Enzyme **glycogen phosphorylase** cleaves off **Glucose-1-P** from *glycogen*
- *Glucose-1-P* then is converted to **Glucose-6-P** in hepatocytes
- Enzyme **glucose-6-P-phosphatase** converts *glucose-6-P* into **glucose**

Since in the *liver glucose-6-P can be converted to glucose*, it **can cross the membrane and go into the blood stream** with the help of **GLUT transporters**.

On the other hand, *muscles do not have enzyme glucose-6-P-phosphatase*, therefore **all the glucose** from the glycogen **in the muscles stays phosphorylated**, and phosphorylated glucose **cannot use GLUT transporters**. Therefore, it *cannot be released into the bloodstream*. Instead, **it is catabolized and used in glycolysis and then in the Krebs cycle** for energy.

Glycolysis **takes place in cytosol. Intracellular Ca2+** in muscle tissue activates glycogen degradation.

Regulation:
- **Glycogen phosphorylase**
  - (-) high amount of Glucose-6-P
  - (-) high amount of glucose in the liver
  - (-) high amounts of ATP
  - (+) high amounts of AMP

Protein metabolism
Cells throughout the body can use glucose to form several types of *amino acids, which can be incorporated into proteins.*

Amino acids are never stored in the body. They are either **oxidized to directly produce ATP**, or used to **synthesize** new, needed **proteins for growth and repair**.

Excess proteins are converted into glucose and TAGs

Protein catabolism
Proteins can be broken down into different things in the body:
- Converted into different **amino acids**
- Converted to **fatty acids**
- Converted to **ketone bodies**
- Converted to **glucose**
- Oxidized to **Acetyl-CoA** to create ATP via the Krebs cycle and electron transport chain

It is **impossible to store amino acids** due to the fact that in order for them to be used in any way possible, **they have to be detoxified** (ammonia needs to be removed) and **it takes a lot of energy.**

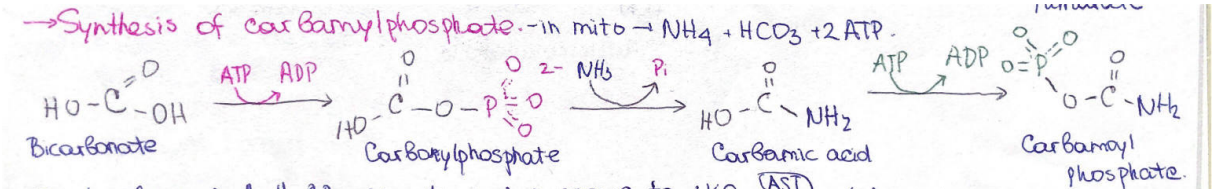
When the intake of proteins is **higher than required**, the ***excess needs to be degraded***, the process of *marking them for degradation* is carried out by protein **ubiquitin**, which binds to them and then *they are degraded by a big complex* called **proteasome**.

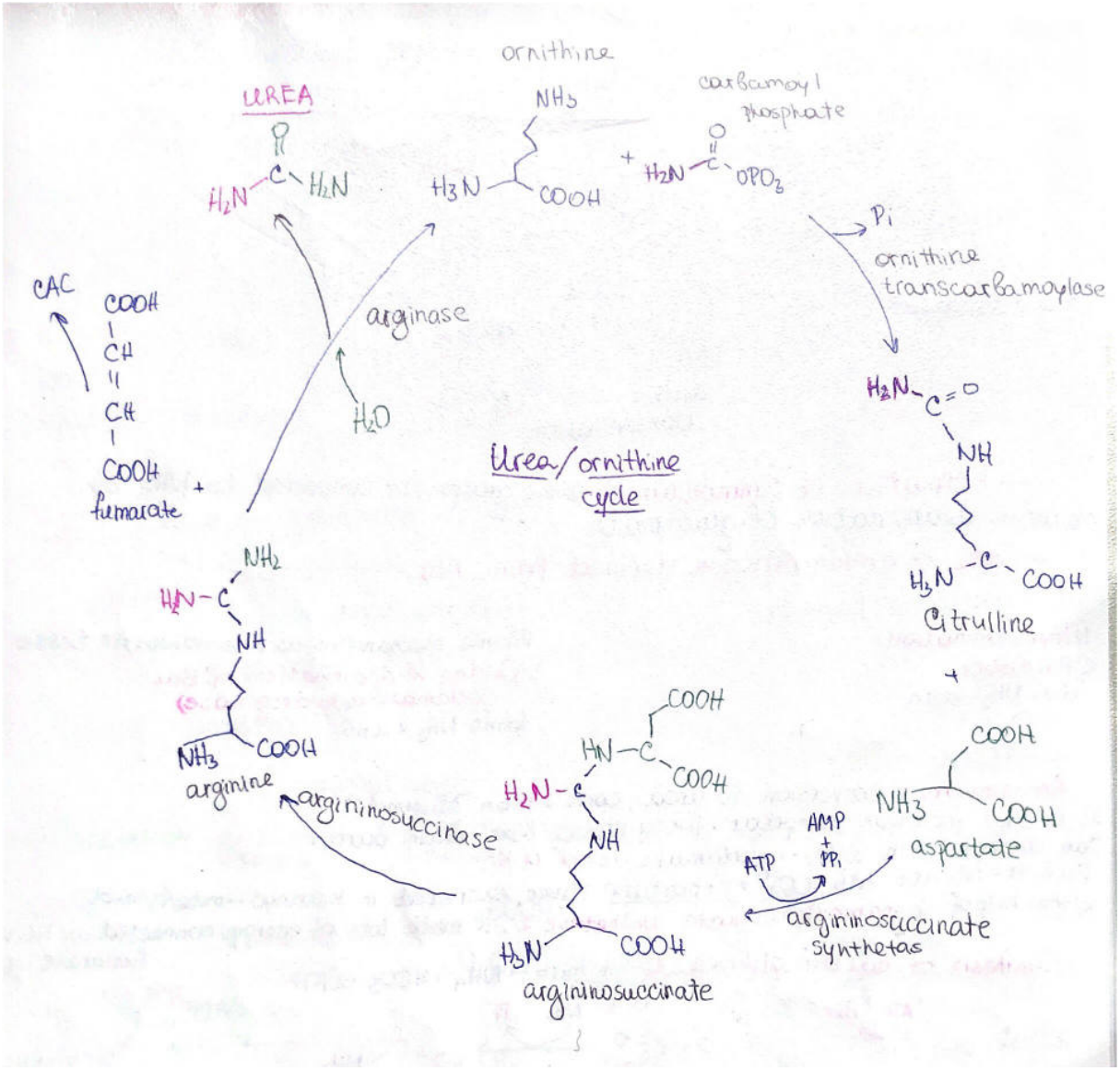
Protein anabolism
Is the formation of the **peptide bonds** between adjacent amino acids to make up a protein molecule.
This process is activated by **insulin growth factors, thyroid hormones (T3, T4), insulin, estrogen and testosterone**.

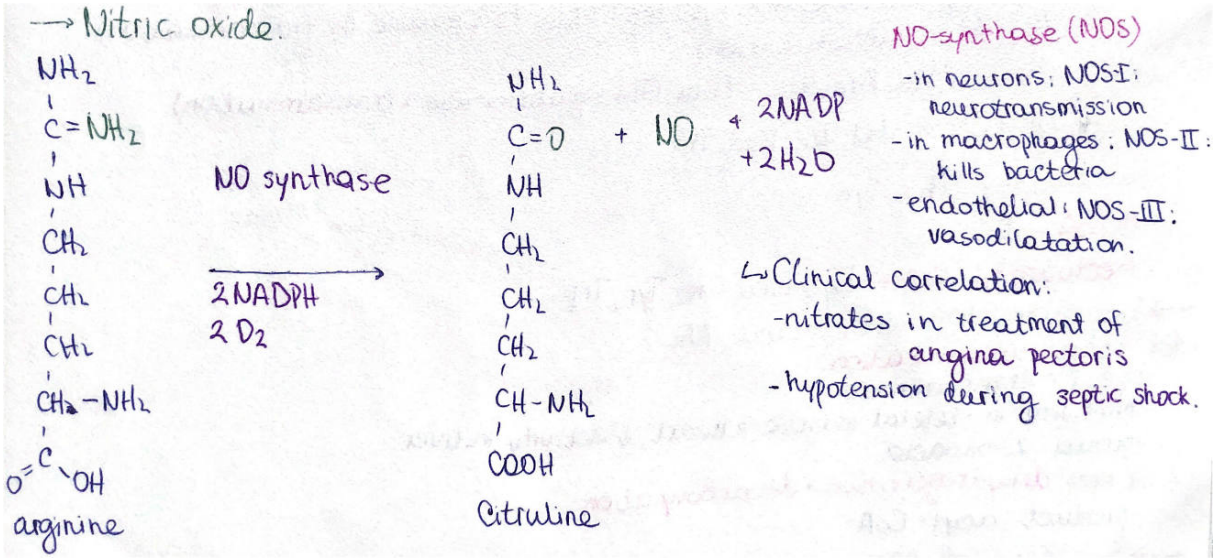
Amino acids are divided into **essential and non-essential**. **Essential amino acids** cannot be synthesized in the body, therefore, we have to get them **from our diet**. Whereas, **non-essential amino acids** can by synthesized by *transamination.*

Urea cycle
When there is too much of ammonia in our body, we need to get rid of it. In the urea cycle **ammonia** is transformed into the **urea** which can then be **excreted** with the **urine** from our body. ***Urea cycle is activated when the protein breakdown in the body increases.***

Urea cycle, aka **ornithine cycle** takes place primarily *in liver, but also in kidneys at some extend*. It takes place both in **cytoplasm and mitochondria** of the cells. Compounds needed for the cycle: **bicarbonate, ammonia, 3 ATP, and aspartate**.


→Synthesis of carbamylphosphate.-in mito → NH4 + HCO3 +2 ATP.
ATP ADP
NH3 Pi
ATP ADP
Bicarbonate
Carboxylphosphate
Carbamic acid
Carbamyl phosphate.





The removal of ammonia is super essential because it is **toxic for the brain**. Plasma concentration of ammonia should be ***below 35 umol/L***

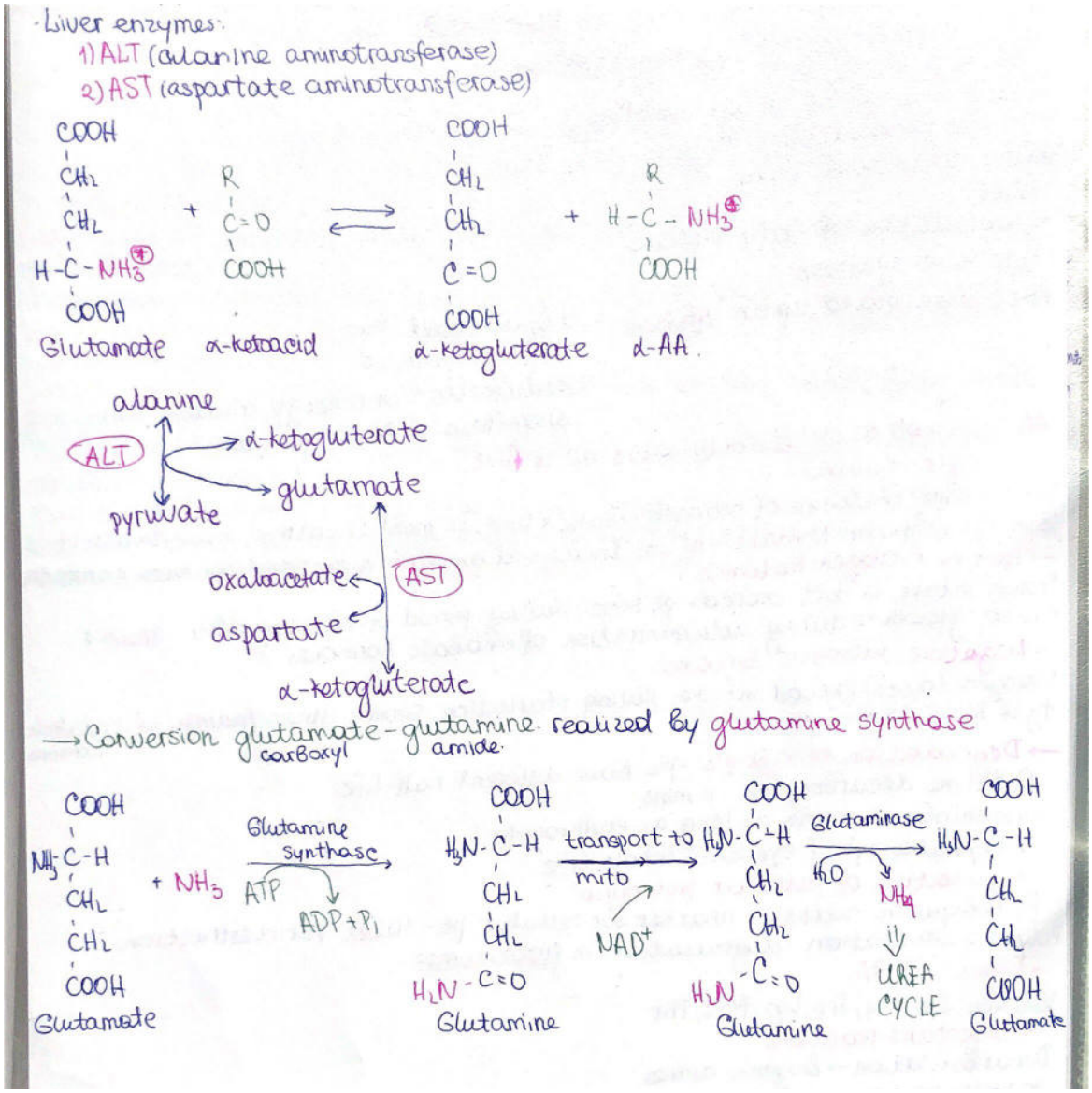
*Ammonia is transport*ed in the body as **glutamine**.

Amino acid metabolism

1. *Proteins are broken down* into amino acids in the body
2. Then *amino acids travel* to **the liver in the bloodstream**
3. In the liver then they can undergo:
    a. **Protein synthesis**
    b. **Synthesis of glucose**
        i. From glucogenic amino acids – *Ser, Thr, Cys, Met, Asp, Glu, Asn, Gln, Gly, Ala, Val, Pro, His and Arg*
    c. **Synthesis of fatty acids**
        i. From ketogenic amino acids – *Lys, Leu*
    d. Amino acids that are both ketogenic and glucogenic are – *Ile, Phe, Tyr, Trp*
    e. Or amino acids can be *sent to muscles* to be **transaminated into different ones** which are needed.

Transamination of amino acids

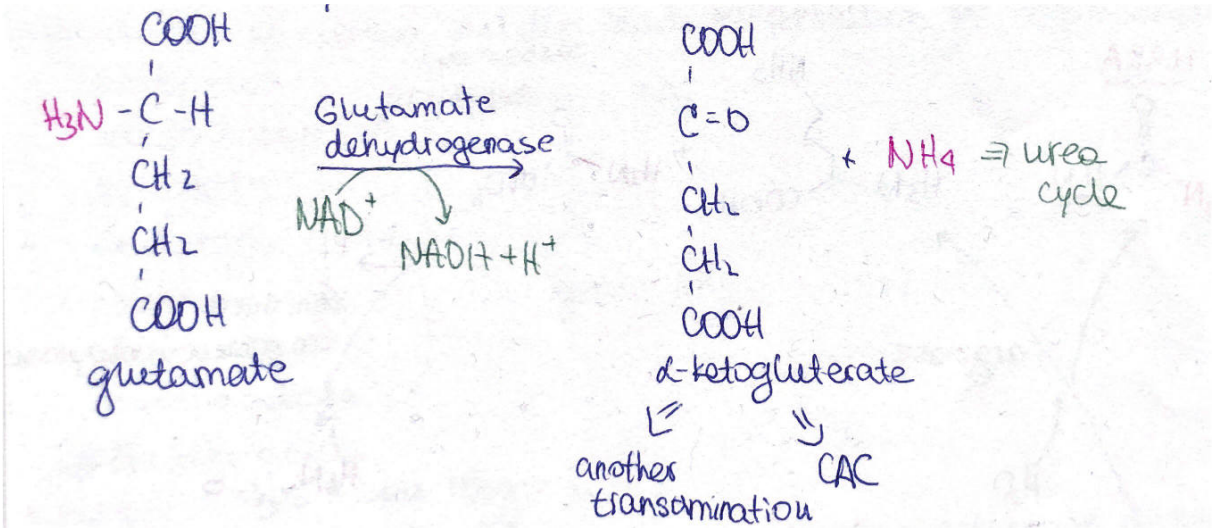
When amino acid is **transaminated, the ammonia is lost**. Then it becomes an *alpha-ketoacid.* The **ammonia(NH3)** is then **ammonium cation(NH4+)** [since it is in the aqueous solution] and *gets excreted undergoing the urea cycle*



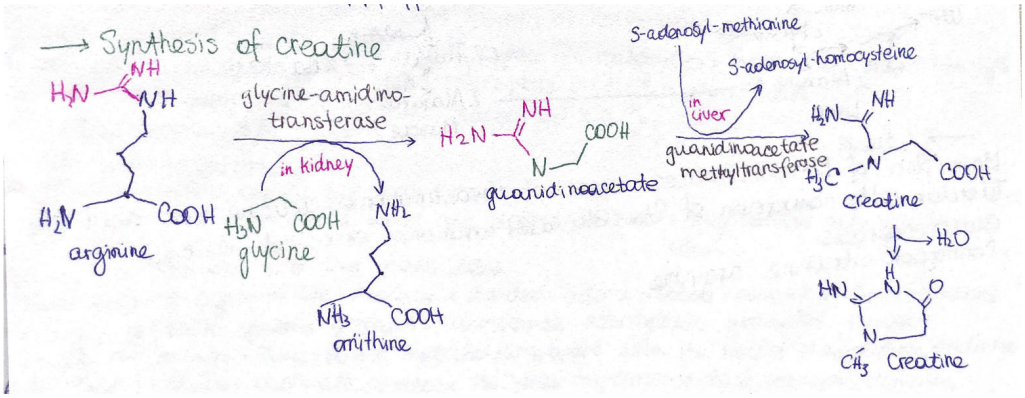
Alanine and glutamine are amino acids with the **highest concentration** *in the blood*

Glutamine/glutamate

Glutamine is a **primary source of energy for enterocytes**. It is *broken down in liver and kidneys*



Alpha-ketoglutarate is the most **frequent acceptor of amino groups** from amino acids. Then it is **converted into glutamate**.



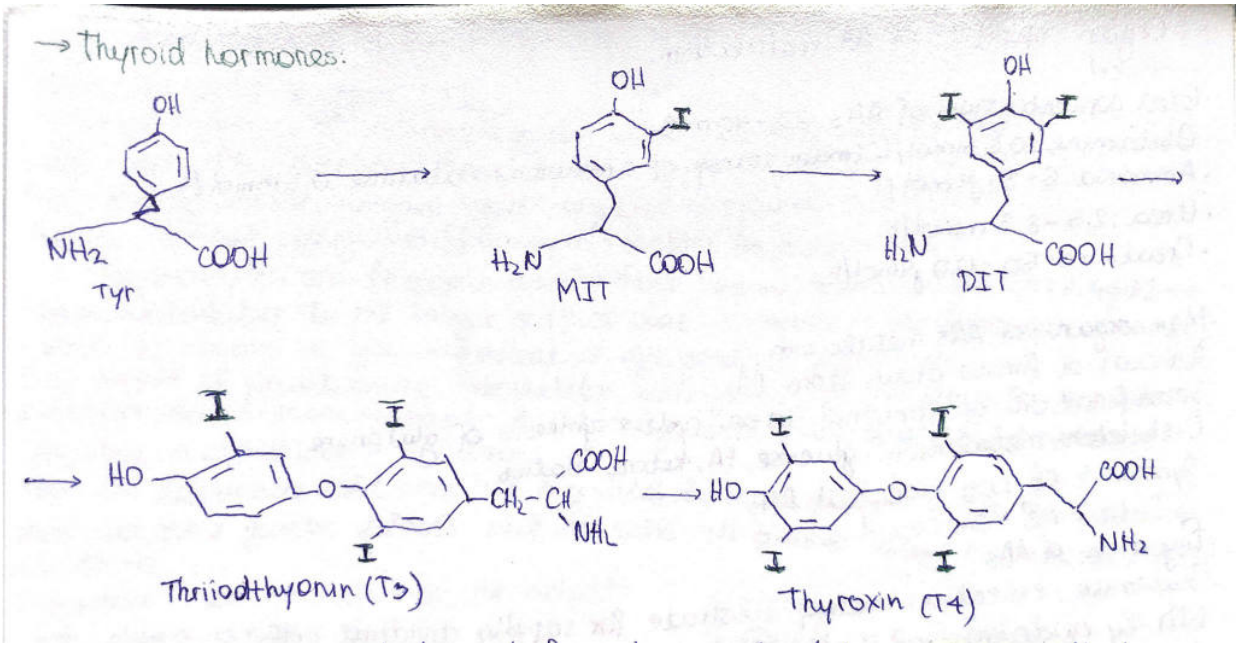
Decarboxylation of amino acids produces **biogenic amines** such as *serotonin and histamine*.

Important notes to remember:

- **Tyrosine** is synthesized from **phenylalanine** in cells by *phenylalanine hydroxylase*
- **Methionine** is turned into **homocysteine** and **cysteine** then is synthesized
- **Serine** is converted to **glycine**
- **Serotonin** is formed from **tryptophan**
- **Dopamine** is formed from **tyrosine**

Carboxylation of amino acids gives rise to **biogenic amines, aka monoamines**

- **Tyrosine → catecholamines**
- **Tryptophan → serotonin**
- **Histidine → histamine**
- **Serine → acetylcholine**
- **Cysteine/ aspartate → Aetyl-CoA**
- **Glutamate → GABA**


→ Thyroid hormones:
OH
NH2
COOH
Tyr
MIT
DIT
HO
CH2 – CH
NH2
Thriiodthyonin (T3)
Thyroxin (T4)

Lipid metabolism

Lipids may be oxidized to **produce ATP**, but if they are not in need at the moment, they can be **stored in the adipose tissue**. **TAGs** are stored in **adipocytes** and have the reserve as much as 98% of the body energy.

Lipolysis

Lipolysis is the process of **splitting TAGs** into **glycerol** and **fatty acids**. The reactions are catalyzes by ***lipases.***

In order for the body to use fatty acids as an energy source following steps have to occur:

1. TAGs need to **be mobilized** *and split into glycerol and fatty acids* which are transported in blood bound to **albumin**.
2. Fatty acids are activated ***in the cytosol*** and transported bound to **carnitine** inside the ***mitochondria***.
3. **Betta oxidation** occurs

Glycerol formed from lipolysis is converted to **glyceraldehyde-3-P** and in case of:

- **High ATP** – converted to glucose and glycogen
- **Low ATP** – enters catabolic pathway of pyruvate and then Krebs cycle.

Fatty acids formed from lipolysis are undergoing:

- **Betta oxidation** (acyl-CoA → acetyl-CoA)
    - Acetyl-CoA enters then **Krebs cycle**
    - Acetyl-CoA can form **Ketone bodies** (ketogenesis) (*acetoacetate, beta-hydroxybutyrate, and acetone*)

Activation – by **glucagon and epinephrine**
Inhibition – by **insulin**

Carnitine shuttle

Fatty acids are **activated in the cytosol**, but *they need to get inside of mitochondria to get oxidized*. Long chain fatty acids **can not freely diffuse** into the *mitochondrial matrix,* they need a **transport system.**

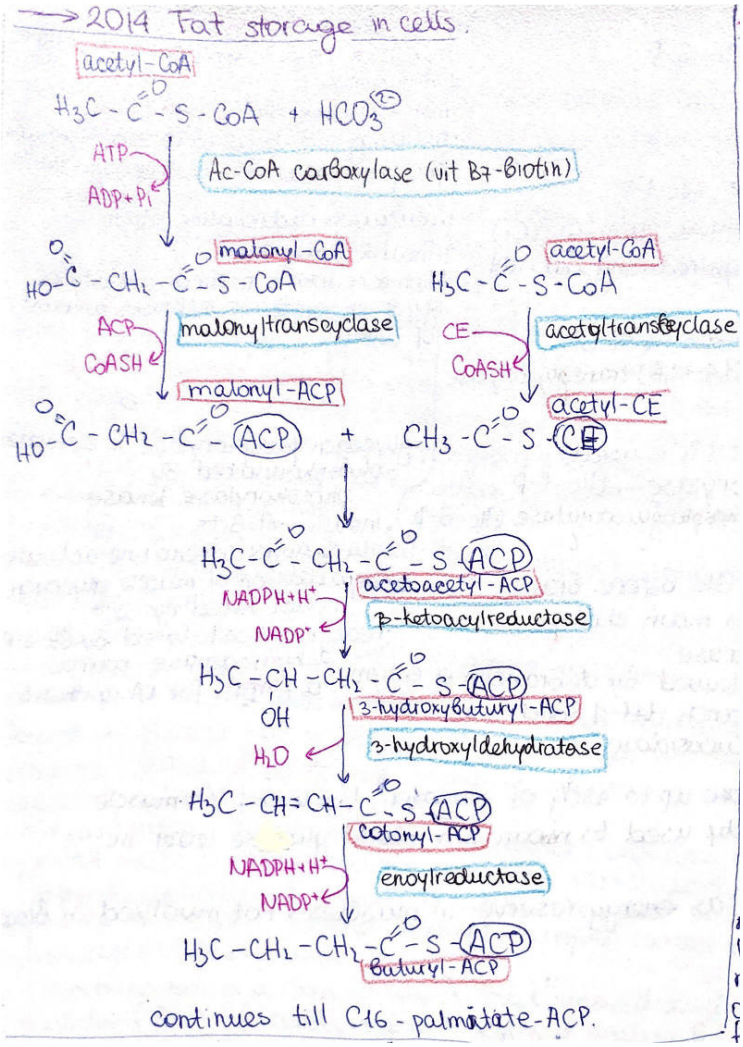
Carnitine acyltransferase 1 is located on the *outer mitochondrial membrane*, it takes ***acyl-CoA and a free carnitine*** and catalyzes it to form **acylcarnitine**. This complex can **translocate inside of the matrix**.
There, another enzyme called **carnitine acyltransferase 2** splits *acylcarnitine* into *free carnitine and fatty acid* and fatty acid can then **enter betta-oxidation.**
Carnitine, though, **moves freely back into the cytosol.**
Malonyl-CoA (the first step in fatty acid synthesis is the inhibitor for both acyltransferases).

Hormone-sensitive lipase is an enzyme which **releases fatty acids from adipocytes**. It is activated by glucagon.

Lipogenesis

Hepatocytes and adipocytes can convert **amino acids and glucose** into lipids. This process occurs *when a person eats more calories than the body requires.*

- **Glucose** → *glyceraldehyde-3-P* → ***glycerol***
- **Glucose** → *glyceraldehyde-3-P* → ***acetyl-CoA*** → **fatty acids**



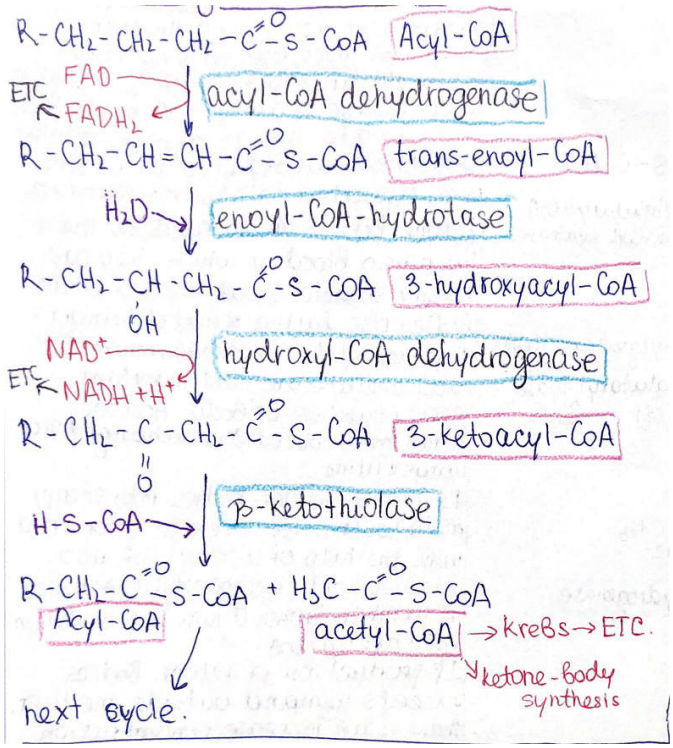
Both of those compounds (glycerol and fatty acids) can either be **converted into storage TAGs** or can **undergo series of reactions** to become **lipoproteins, phospholipids and cholesterol**

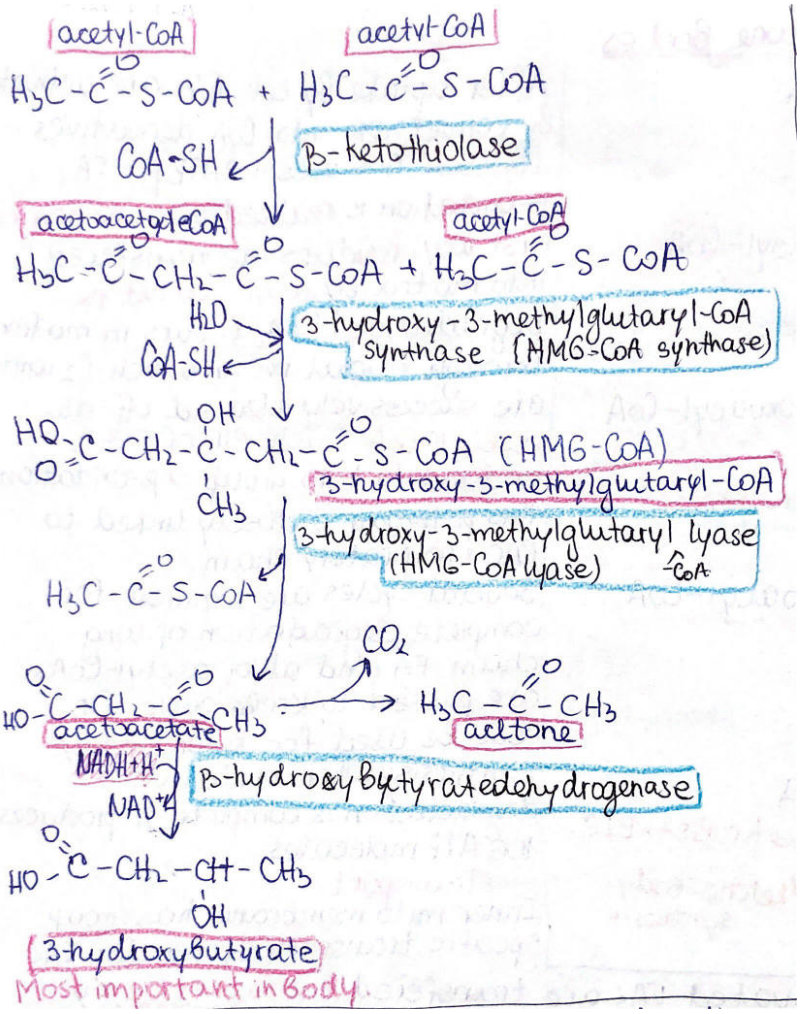
Enzymes required for the synthesis of fatty acids are *localized in the cytoplasm*, but *Acetyl-CoA* (the substrate) is *in mitochondria*. **Mitochondrial membrane in impermeable for Acetyl-CoA**, but in combination with *oxaloacetate* it makes up **citrate**, which is **permeable**. Therefore, *citrate* goes *out of mitochondria and enters cytosol*, there it splits back to *oxaloacetate* and ***Acetyl-CoA***. *Acetyl-CoA* then can enter Fatty Acid synthesis, whereas *oxaloacetate* is converted to **malate** which can *freely go back into the mitochondrial matrix*.

Betta- oxidation

Betta-oxidation is the breakdown of fatty acids into ***Acetyl-CoAs***. It produces **FADH2** and **NADH**

Betta -oxidation got its name due to the fact that the **oxidation proceeds on the third carbon.**





Ketogenesis

Ketogenesis, aka synthesis of ketone bodies (*acetone, acetoacetate and beta-hydroxybutyrate*) *takes place in mitochondria of hepatocytes*. It is used as the **energy source mostly during starvation** in most tissues in the body (**except liver**). *For the brain*, **Ketone bodies are not the most favorable source of energy**, but in starvation they still use it as an energy source. Under the normal conditions, **production of ketone bodies is very low**, and Acetyl-CoA is used to produce energy via **Krebs and electron transport chain**.

Lack of ***insulin*** *contributes to very high rate of catabolic processes* in the body, therefore production of ketone bodies is very high and it leads to **ketoacidosis**.

Ketogenesis is increased during increased during breakdown of fatty acids in liver.

Alcohol metabolism

Ethanol is converted to *acetaldehyde* and then to *acetate* (both of the reactions produce NADH)
Or it is converted to *formaldehyde*

Since *consumption of alcohol produce elevated levels of* **NADH**, it **activates alternative pathways** of our metabolism which includes:

- Increased *lactate* production
- Stimulation of *TAG synthesis* → **fatty liver**
- Decreased *glucose synthesis* → **hypoglycemia**

Fast-feed cycle

When we eat, our body is in the **absorptive state** – ingested *nutrients go to the bloodstream*. **Pancreatic betta cells** release *insulin* which increases the activity of ***anabolic enzymes.***

When the body is *done digesting*, it is in **post-absorptive state** [digestion of normal meal usually takes around 4 hours]. Therefore, **glucose blood levels start to drop**, which signals to **pancreatic alpha cells** to produce *glucagon*.

It is important to keep glucose levels stable because:

- Glucose is the **primary source for nerve cells**
- **Red blood cells** get all of the ATP from glycolysis since they don't have mitochondria

The body can get glucose from:

- Breakdown of liver glycogen
- Glycerol from lipolysis
- Gluconeogenesis using lactate or amino acids

The body though can get ATP from different sources:

- *Fatty acid* oxidation
- Oxidation of *lactate* in the heart
- Oxidation of *amino acids*
- Oxidation of *ketone bodies*
- Breakdown of muscle *glycogen* for use in muscles

Regulation of metabolism

Hormonal:

- **Insulin** (*decreases blood glucose levels*)
    - Has **anabolic effect** and contributes to the *glucose storage*
    - Activates glycolysis, gluconeogenesis and lipogenesis
    - Increases levels of **GLUT channels** for the glucose take up
    - Increases **tissue growth**
- **Glucagon** (*increases blood glucose levels*) [*epinephrine, GH, cortisol*]
    - Has **catabolic effect** and wants to produce glucose from other intermediates
    - Activated gluconeogenesis, lipolysis, proteolysis and ketogenesis
    - Works via **cAMP**

Hemostasis

Hemostasis is the **process of the bleeding stoppage** in the body. **Imbalance of it occurs in sepsis and tumors**.

Steps of hemostasis:

1. Reflex **vasoconstriction**
2. Platelet **activation and aggregation** → formation of **primary clot**
3. **Hemocoagulation** → *formation of fibrin clot*
4. **Thrombolysis** after the healing → *removal of the "bandage"*

Coagulation is the process of conversion of *soluble fibrinogen* into the **insoluble fibrin.**
Trombin *catalyzes a cascade of coagulation factors*.

Platelets

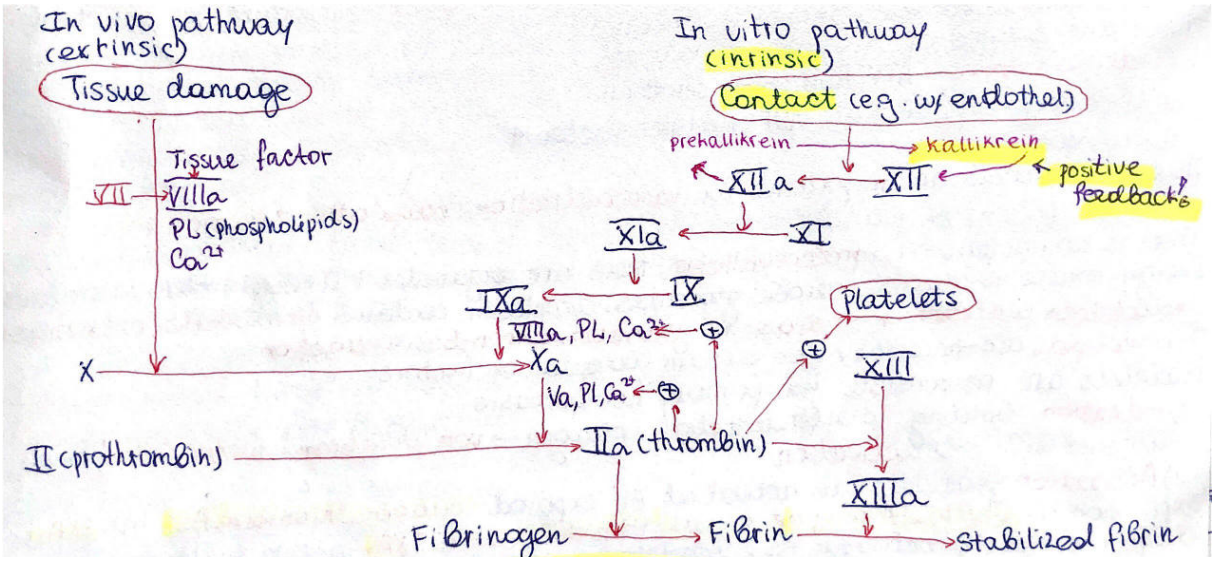
Platelets are the fragments of *megakaryocytes*. They have a **central zone with the granules**, aka **granulomere**; the granules contain:

- **Delta** – dense bodies – *ATP, ADP, Ca2+ and serotonin*
- **Alpha** – *fibrinogen, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) , von Willebrand factor (vWF) [aka factor VIII] and platelet factor 4*
- **Lambda** – *lysosomes*

And the **lighter peripheral area** – **hyalomere** – which has **canalicular system**, important for the secretion.

Since thrombocytes **do not have a nucleus,** there is **no proteolysis** in them. They gain energy from **aerobic glycolysis**. They contain *mitochondria and Golgi apparatus*. The cytoplasm contains **microtubules and actin with myosin** which help to extract the granules from the platelet. **Platelets produce phospholipids** which are crucial for the primary homeostasis.

1. **Adhesion**: **binding to subendothelial collagen** – *vWF* binds to collagen
2. **Activation**: *platelets are activated* by exposed **collagen, thrombin, ADP and TXA2 is expressed**, which activates the expression of **GP IIb/IIIa receptor**. It **triggers platelets to change its shape**.
3. **Aggregation**



Heme and iron metabolism

→ Iron & heme metabolism 2023

Fe^{3+} is hard for our body bc $Fe(OH)_3$ is poorly soluble. So we have to keep it either Fe^{2+}, which is a dangerous form of it or have to keep it connected w/ other elements to keep it soluble.

Fe^{3+} is bound in our body → as heme.

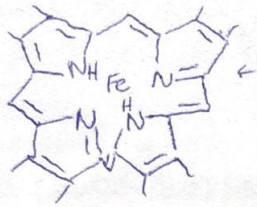
Molecule of heme is composed of 4 nitrogen-containing rings - pyrolles.

Heme belongs to tetrapyrroles. Tetrapyrolles can be either linear or cyclical

Heme is a cyclical tetrapyrrole - we have methyline (-CH_2-) groups that connects all togg

It is a conjugated system = lots of double bonds = more stable molecule = also colored

The whole structure of rings - porphyrin.



← porphyrin

there are some substituents on the rings and Fe in the middle

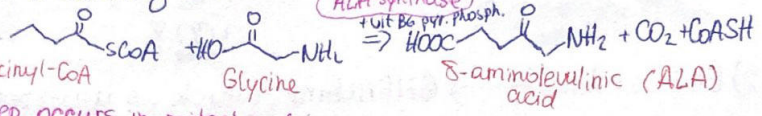
the substituents can be all different

→ Synthesis of heme - 3 Building Blocks

I - glycine

II - succinyl-CoA.

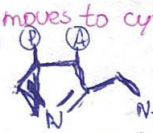
III - Fe

1) 

the step occurs in mitochondria.

↓

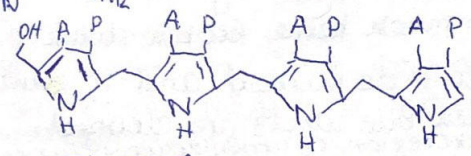
moves to cytosol.

2) 2 ALA ⟶ $2H_2O$ +  - porphobilinogen. (PBG)

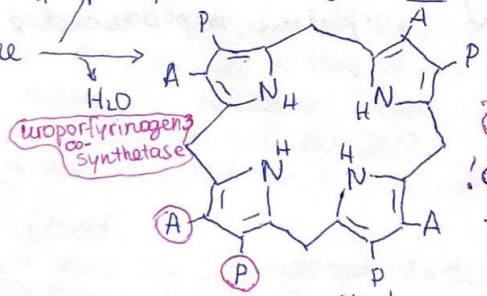
Ⓐ - acetyl

Ⓟ - propyl

ALA-dehydratase

3) 4 PBG ⟶ (PBG deaminase; ↓ $4NH_3$)  hydroxymethylbilane

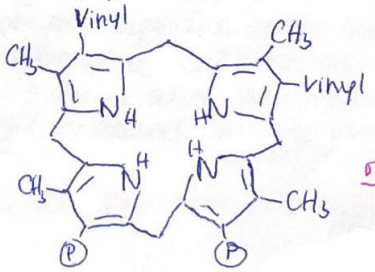
4) hydroxymethylbilane ⟶ (spontaneously; H_2O; uroporfyrinogen co-synthetase) uroporfyrinogen I but it's very toxic and not for heme



uroporfyrinogen III

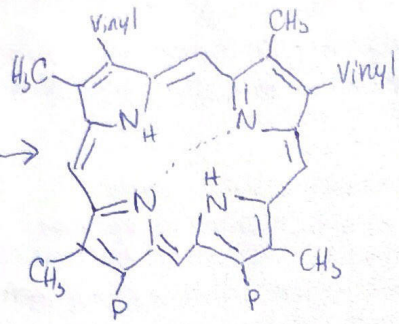
!colorless!

-gen - not colored

5) uroporfyrinogen III ⟶ (All the As + 2 Ps; ↓ $6CO_2$) 

protoporfyrinogen

mitochondria

6) 

Protoporfirin. mito

7) Protoporfirin + iron $\xrightarrow{\text{ferrochelatase}}$ heme. mito.

→ Degradation of heme.

1) heme + O_2 $\xrightarrow{\text{heme oxygenase}}$ linear tetrapyrrole (billiverdine)
+ Fe
+ CO !

2) billiverdine → billirubine which is transported to liver and then conjugated w/ glucuronic acid

and then excreted in bile.

When we have too much bile, → jaundice.

→ prehepatic – too much heme broken down

→ hepatic → liver is damaged and it cant excrete enough bil → viral hepatitis is the cause.

→ post-hepatic → excretion of urobilinogen w/ urine. (when bile ducts are clogged.

→ Diseases:

Porpherias - urine is red. – porphirine is produced & no heme in body.

Genetics

Enzymopathy – *heritable disorders of metabolism*

Hereditary metabolic disorders have **recessive character**, which means that *heterozygotes are phenotypically healthy.*
The diseases in **recessive homozygotes** though can manifest in different ways:

- **Accumulation** of molecules, proteins and enzymes which are *not excluded right away as they should*
- The **absence** of proteins which *are enzymes for the pathways*
- **Formation of toxic by-products** and derivatives of them.

The **combination** of one or another factor together can cause **slow or acute poisoning and sepsis.**