Chemical reactions in metabolism

Subchapter content

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2. Fundamentals of regulation of metabolic pathways

The most important chemical reactions in metabolism

The metabolic pathways of the human organism form an *extensive network* of interconnected reactions that often share *common intermediates*. Chemical transformations of individual substances are usually classified according to a general mechanism common to all substances undergoing a given reaction. For example, *decarboxylation **is the** splitting of CO_2 from the carboxyl group**, where the substrate may be different** carboxylic acids.*

Alcohols, carbonyl compounds and carboxylic acids

Alcohols, carbonyl compounds and carboxylic acids are important substrates for many reactions of metabolic pathways of organisms.

Alcohols contain the functional group **−OH**. Depending on the number of OH groups in the molecule, alcohols can be *one-*, *two-* or *polybasic*. Furthermore, depending on which carbon atom the OH group binds to, we distinguish between *primary*, *secondary* and *tertiary* alcohols.

Primárni	R -CH -OH
Sekundárni	R_1 R_2 > CH-OH
Terciárni	R_1 R_2 R_3 — C-OH

*Aldehydes **with** ketones **form a group of** carbonyl* compounds. The functional group of aldehydes is the group **−CHO**, in ketones **−C=O**. Of this group of substances, the most important substrates are probably the reactions of **carboxylic acids**, characterized by the presence of the functional group *−COOH**, and their** derivatives*.
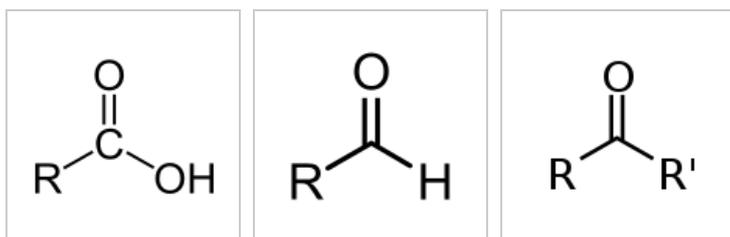
carboxyl group   Aldehyde group   ketone group

Significant reactions of alcohols, aldehydes and carboxylic acids

1. Formation of anions and acyls derived from carboxylic acids
2. Dehydrogenation and hydrogenation (oxidation and reduction)
3. Esterification

Formation of anions and acyls derived from carboxylic acids

The carboxyl group is capable of *dissociation**, with the degree of dissociation for individual acids given by dissociation constant. Carboxylic acids are* weak**, which means that their dissociation is only partial. The acid thus gives rise to the *anion* (group −COO⁻)**. After splitting off the whole −OH group from the carboxyl group, its **acyl** is formed.

Dehydrogenation and hydrogenation (oxidation and reduction)

During the chemical reaction, **dehydrogenation***, the* H is removed from the molecule**. The obtained hydrogen can then be used for the formation of a proton gradient in mitochondria and for** energy gain **(ATP).** The introduction of hydrogen **into a molecule is called** hydrogenation. In the body, dehydrogenation and hydrogenation occur, for example, in the following processes:

Acile

> **Oxidation of single bonds to double bonds**
>
> $$-CH_2-CH_2- \rightleftharpoons -CH=CH- + 2\,H^+ +_2\,e^-$$
>
> These reactions occur, for example, in **Krebs cycle**, at **β-oxidation of fatty acids** or **desaturation reactions**, which aim at the synthesis of unsaturated fatty acids.
>
> **Mutual conversion of alcohols, aldehydes / ketones and carboxylic acids**
> Alcohols, carbonyl compounds and carboxylic acids *form a series* differing from each other in the degree of oxidation / reduction.
> The general scheme of their mutual transformation is as follows (oxidation takes place towards the carbonyl compound and carboxylic acid, reduction in the opposite direction):
>
> > - **Primary alcohol ⇌ aldehyde ⇌ carboxylic acid**
> >
> > $$R-CH_2-OH \rightleftharpoons R-CHO \rightleftharpoons R-COOH$$
> >
> > - **Secondary alcohol ⇌ ketone**
> >
> > $$R_1-CH(OH)-R_2 \rightleftharpoons R^1-CO-R^2$$
> >
> > - **Tertiary alcohol**
> >
> >   "Slight" oxidation does not take place (it can be oxidized only with simultaneous splitting of the carbon chain).
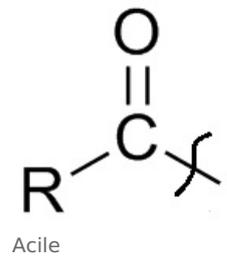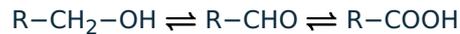
An example of oxidation is the formation of *dihydroxyacetone phosphate* (DHA-P) from **glycerol-3-phosphate** (cofactor is **FAD**), through which glycerol enters glycolysis or gluconeogenesis according to the current needs of the organism.

Esterification

Esterification is the reaction of a carboxylic acid with an alcohol, producing an **ester** *and* water:
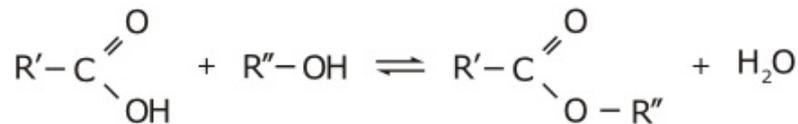
The most important carboxylic acids, their anions and acyls

Saturated monocarboxylic acids

C	Systematic name	Trivial name	Latin name	Acyl	Anion
1	methane	ant	*ac. formicum*	formyl	formate
2	Ethan	Vinegar	*ac. aceticum*	acetyl	acetate
3	Propane	propionic	*ac. propionicum*	propionyl	propionate
4	Butane	butter	*ac. Butyricum*	Butyryl	butyrate
5	pentane	Valérová	*ac. Valericum*	Valeryl	valerate
12	Dodecanese	Laurova	*ac. Lauricum*	Lauryl	laurate
16	hexadecane	Palmito	*ac. palmiticum*	Palmitoyl	palmitate
18	Octadecane	Stearova	*ac. stearicum*	stearoyl	Stearate

Saturated dicarboxylic acids

C	Systematic name	Trivial name	Latin name	Acyl	Anion
2	Etandi	Štavelová	*ac. oxalicum*	oxalyl	oxalate
3	Propandiová	Malonova	*ac. malonicum*	Malonyl	malonate
4	Butandi	amber	*ac. succinicum*	succinyl	succinate
5	Pentondia	glutaric	*ac. glutaricum*	Glutaryl	glutarate
6	hexandium	adip	*ac. adipicum*	Adipoyl	adipate

Unsaturated monocarboxylic acids

C	Systematic name	Trivial name	Latin name	Acyl	Anion
18:1	*cis*-octadec-9-eno	oil	*ac. oleicum*	oleoyl	oleate
18:2 (ω−6)	*cis*,cis-*octadeka-9,12-dienova*	linoleic	*ac. linoleicum*	Linoloyl	linolate
18:3 (ω−3)	*cis*,cis,*cis*-octadeka-9,12,15-trienová	Linolenic	*ac. linolenicum*	Linolenoyl	Linolenate
20:4 (ω−6)	*cis*,*cis*,*cis*,*cis*-eikosa-5,8,11,14-tetraenová	arachidonová	*ac. arachidonicum*	arachidonyl	arachidonát

Unsaturated dicarboxylic acids

C	Systematic name	Trivial name	Latin name	Acyl	Anion
4	*cis*-butendi	Malein	*ac. maleicum*	Maleinyl	maleate
4	*trans*-butendi	Fumarova	*ac. fumaricum*	Fumaroyl	fumarate

Carboxylic acid derivatives

C	Systematic name	Trivial name	Latin name	Acyl	Anion
3	2-oxopropane	pyrogrape	*ac. pyruvicum*	Pyruvyl	pyruvate
3	2-hydroxypropane	milk	*ac. lacticum*	lactoyl	lactate
4	3-oxobutaneous	acetoacetic		acetoacetyl	acetoacetate
4	3-hydroxybutane	β-hydroxybutyric			β-hydroxybutyrate
4	2-hydroxybutanedia	apple	*ac. malicum*	Maloyl	Malate
4	2-oxobutandium	oxaloacetic			oxaloacetate
5	2-oxopentandia	α-ketoglutar		α-ketoglutaryl	α-ketoglutarate
6	2-hydroxypropane-1,2,3-tricarboxylic	lemon	*ac. citricum*		citrate

Hydroxy acids and keto acids

Hydroxy acids in addition to the −COOH group also contain the −OH group replacing one −H. **Keto acids** or **oxo acids** contain in the molecule in addition to the group −COOH also the group =O replacing one −H. Their mutual conversion is relatively common in metabolic pathways.

An example is the relatively common *keto-enol tautomery* in metabolism. It converts two forms of organic compounds:

- *ketoform* (or *oxoform*) contains double-bonded oxygen as a group **=O**,
- *enolform*, which contains a double bond between carbons and one of them binds −OH group (i.e. contains the structure $R^1−CH=C(OH)−R^2$).
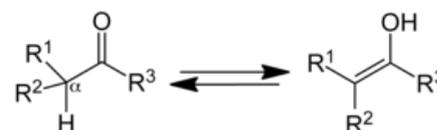
The mutual transformation of the two forms represents the **migration of the hydrogen atom** or the proton, accompanied by the **swapping of the single bond** and the adjacent **double bond**.

Amino acids and oxo acids

Amino acids and oxo acids are substitution derivatives of carboxylic acids. Amino acids contain in the molecule in addition to the −COOH group also the group −NH 2, oxo acids group =O. Their mutual transformations are frequent in the organism, for example, there is a **NH$_2$ group for group =O** and vice versa.

These transformations occur mainly in two processes:

Transamination

In this reaction, the amino acid is a donor $-NH_2$ of the oxo acid group. From the corresponding oxo acid, an amino acid is formed, and the original amino acid becomes an oxo acid:

AK1 + OxoK2 $\rightleftharpoons$ OxoK1 + AK2

TRANSAMINACE
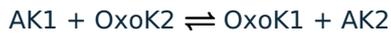
Oxidative deamination
It is the formation of oxo acid from the amino acid **by removing $-NH_2$ group***, which is released as* ammonia *(NH_3). **Oxidative deamination is one of the important reactions through which amino acids initiate the process of their** degradation*. In the human body, they take place mainly in the liver, and the released ammonia is broken down in **urea synthesis**.
This reaction is mainly catalyzed by glutamate dehydrogenase.
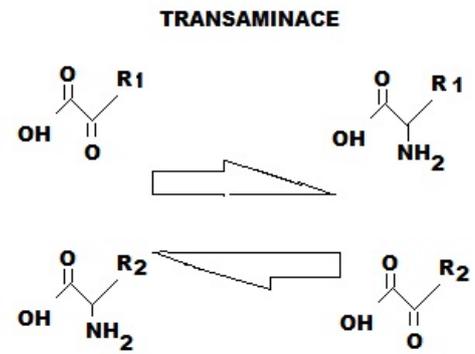
Decarboxylation and carboxylation

Decarboxylation removes the carboxyl group, which is released as a CO_2 molecule and replaced by a proton. They are significant, for example, for

- conversion of amino acids to *biogenic amines* (e.g. in the synthesis of many neurotransmitters),
- dehydrogenation of 2-keto acids – pyruvate dehydrogenase reaction and two reactions of the Krebs cycle.

Carboxylation **is the opposite reaction, involving the introduction of a** *COOH* group into the molecule. It occurs, for example, in

- fatty acid synthesis,
- gluconeogenesis.

Fundamentals of regulation of metabolic pathways

The regulatory reaction of a specific metabolic pathway is usually localized at its beginning – typically it is the **first irreversible step***. **The reason for this is to** limit the waste* of resources and the unnecessary production of intermediates that would occur if the track stopped in the middle instead of at its beginning.

The regulatory enzyme is usually present in a low concentration that limits it. It is an "allosteric enzyme" working on the principle of "all or nothing". For regulation, it is advantageous if there is a sort of *concentration limit* above which the reaction starts and quickly reaches maximum speed, and vice versa, below which the reaction hardly takes place.

The feedback principle *is applied in the regulation of metabolic pathways. It is a feedback effect on the course of the reaction from the created intermediates or the final product. We distinguish between two types of feedback:*

- negative feedback,
- positive feedback.

Negative Feedback

It leads to a sequence of reactions in which the system returns to its original value. This is the source of stability of the system, which constantly returns to the value of the set point, the set value. Negative feedback is therefore part of most pathways.

> *For example, the enzyme ALA-synthase I (the regulatory enzyme of heme synthesis located in the liver), which is retroactively inhibited by the product of the entire pathway – heme via negative feedback.*
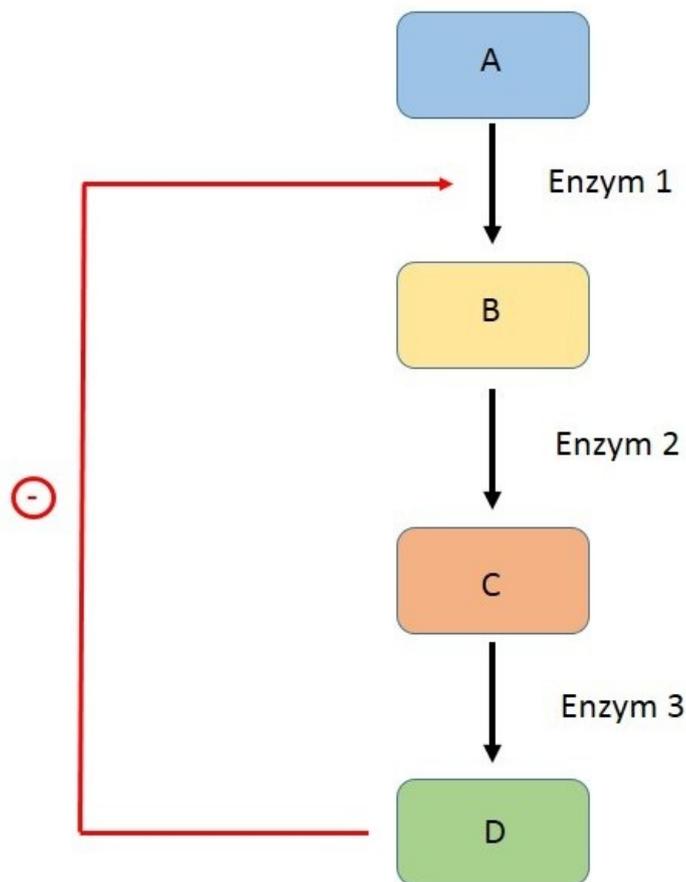
Positive Feedback

It leads to a series of reactions that '*deepen* it even more. There is, however, a risk of a "vicious circle" (circulus vitiosus). Each further increase in deviation accelerates its increase until finally the instability of the system causes its collapse.

> *For example oxytocin. It is a hormone produced in the nuclei of the hypothalamus, which (among other things) induces contractions of the smooth muscle of the uterus and thus enables childbirth. Each contraction through the activation of the mechanoreceptors of the uterine wall acts as a stimulus for further oxytocin secretion. Its effect thus continuously increases until the time when the child and subsequently the placenta are delivered and the pressure on the uterine wall drops again.*

Regulatory step affects

Change in Absolute Enzyme Concentration (Amount of Enzyme)

The process of transcription and translation is affected, namely the induction (activation) or repression (inhibition) of the expression of the gene encoding the given enzyme. An example is **substrate induction**, where the presence of a substrate induces enzyme synthesis.

Modulation of the activity of an already existing enzyme (enzyme activity)

- the presence of activators / inhibitors,
- covalent modification of the enzyme molecule (phosphorylation / dephosphorylation, formation of active enzymes from proenzymes, ...).

Source

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