

Fundamentals of Metabolic Pathway Regulation

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.

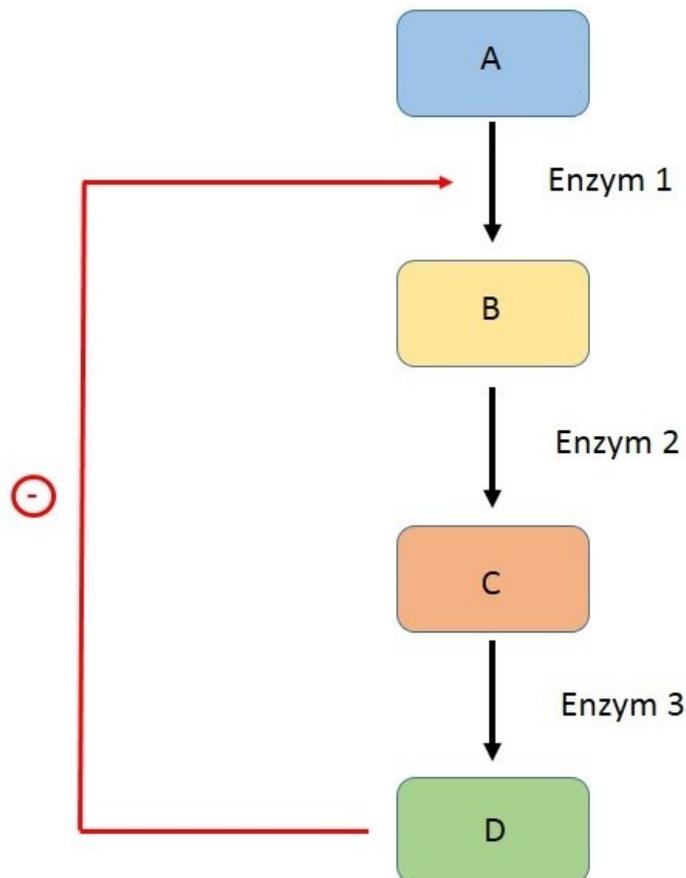
The feedback principle *is applied in the regulation of metabolic pathways. It is a feedback effect on the course of the reaction from the created intermediates or the final product. We distinguish between two types of feedback:*

- 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, ...).