Glucagon

Glucagon is a pancreatic hormone. It is produced in specialized cells – the so-called. *α-cells* of pancreatic islets. It is a polypeptide, it regulates energy metabolism. Its level rises especially a few hours after a meal, which is why it is also called the hormone of starvation and deficiency. *α-cells* are located mainly on the periphery, blood comes to them from the center of the islet of Langerhans, already enriched with insulin. Thre are considerably less *α-cells* than β-cells (about one-third the amount). Glucagon generally acts as an insulin antagonist.

pancreas

Glucagon is a simple peptide 29 amino acids long. Does not contain disulfide bridges. In terms of secondary structure, it forms an α-helix, that is stabilized mainly by hydrophobic interactions.[1]

G-protein coupled glucagon receptors

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Structure, synthesis, secretion

The structure is that of a simple polypeptide, there are no disulfide bridges in it.. **Synthesis** takes place in the usual manner – first the **preprohormone** is produced and then, after adjustments, definitively glucagon. **Secretion** is closely related to ion channels.

- In case of low glucose (glucose transporter SLC2A1 - active at low glucose level, normal glucose level is 3.6-5.5 mmol/l) **T-type Ca^{2+}** (channels are active (There are several subtypes of Ca^{2+} channels: L , T, N), the membrane potential of α-cells is around −60mV.
- At the same time ATP-dependant K^+ channels are inactive (they are open).
- The potential gradually increases **N-type Na^+ and Ca^{2+} channels** open – an action potential is created and glucagon is subsequently secreted.

In the event of an increase in the level of glucose, the amount of ATP in the cell rises and K^+ channels close. Depolarization causes the channels that participated in the action potential to become inactive.

- In addition to glucose, FFA (free fatty acids) and AMK. also affect the secretion of glucagon . The short-term action of FFA causes the release of glucagon (indirectly, it acts on **L-type Ca^{2+} channel**, thus increasing the entry of Ca^{2+} do buňky). into the cell). Long-term exposure to FFA causes glucagon release but inhibits cell proliferation.
- Different AMKs can stimulate (Arg, Glu, Ala, Leu) or inhibit (Ile, Leu) glucagon secretion.

Regulation of secretion at the level of the islet of Langerhans

In addition to all the mentioned processes, secretion is also affected at the level of the islet itself, i.e. autocrine or paracrine. Glucagon itself acts on α-cells in an autocrine manner. Receptors coupled to G proteins increase the level of cAMP, subsequently the level of protein kinase A (PKA) increases and the level of Ca^{2+} in the plasma rises. Calcium causes glucagon-containing granules to fuse with the cytoplasmic membrane (phosphorylation of the cytoskeleton, similar to β-cells). The remaining islet hormones – insulin and somatostatin act paracrinely (due to the arrangement of cells in the islet). On the one hand, insulin greatly stimulates ATP-dependent K^+ channels, **hyperpolarization** of the membrane occurs – this has an inhibitory effect on the release of glucagon. Insulin also inhibits Ca^{2+} kanály. channels. Together with insulin, **amylin** is released from α-cells which inhibits amino acid-induced glucagon secretion. **Somatostatin** is significantly less than insulin and glucagon, it has an inhibitory effect on the release of both hormones. There are several subtypes of the somatostatin receptor (SSTR1, SSTR5 – β-cells, SSTR2 – α-cells). In α-cells, similar to insulin, somatostatin activates the K^+ channel and causes hyperpolarization.

Mechanism of action

It is related to a G-protein-coupled receptor. The receptor is a simple transmembrane protein, by binding glucagon it transmits a signal mainly in two ways: on the one hand **adenylate cyclase gets activated**, the level of cAMP rises and PKA is activated. On the other hand **phospholipase C can be activated**, it cleaves phosphoinositol-bisphosphate, inositol-3-phosphate is formed and the result will be an increased level of Ca^{2+} (calcium spills out of the reserves of the endoplasmic reticulum).

PKA affects DNA (via *peroxisome proliferator-activated receptor γ-coactivator-1* (PPARGC1A) and *cAMP response element-binding protein* (CREB), nduction of transcription of genes for phosphoenolpyruvate carboxykinase and glucose-6-phosphatase – enzymes necessary for **gluconeogenesis**). Together with calcium, it also acts by phosphorylating the enzymes of metabolic pathways.

Effects of glucagon

Glucagon generally works against insulin. It is possible to say that the insulin/glucagon level ratio determines which pathways the energy metabolism will take (it is most pronounced in the liver):

- The above-mentioned induction in the nucleus **increases the level of gluconeogenesis enzymes**.
- At the same time (thanks to PKA) glycogen phosphorylase activates and **glycogenolysis** commences.

Glucose is saved for the brain, the energy substrate for other tissues/organs are mainly FFAs.
- Glucagon also promotes the entry of AMK needed for gluconeogenesis into the liver (Ala, Gly, Pro).
- It activates HSL (hormone sensitive lipase) in adipocytes, releasing glycerol and FFAs into the plasma.
- In addition, glucagon acts on ion transport and glomerular filtration in the kidneys.

Fetal period

Although α-cells form earlier than β-cells, glucagon is detectable in fetal plasma from about 15 weeks.

Usage

It can be administered in a variety of ways (SC; IV; SM). The indications include:

- Hypoglyceamia therapy
- Inhibition of motility during examination of the gastrointestinal tract

Links

Related articles

- Glycemia
- Glycolysis
- Pancreatic Hormones
- Gastrointestinal hormones

Reference

1. *X-Ray Analysis Of Glucagon And Its Relationship To Receptor Binding Hormone* [database]. National Center for Biotechnology Information. National Library of Medicine, The last revision 2009-07-14, [cit. 2010-11-07]. <https://www.ncbi.nlm.nih.gov/Structure/pdb/1GCN>.

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