Incretin analogs

Inkterin analogues are drugs used to treat type 2 diabetes mellitus. They are synthetically prepared inkretins. Glucagon-like peptide 1 (GLP-1) or GLP-1 agonists are used in therapy.

Effect

náhled|400x400px|**Pankreatický** efekt inkretinů a role enzymu **DPPIV** (viz. historie analog)

Pancreatic effect

The effect of incretins on the pancreas is an increase in insulin secretion and a decrease in glukagonsecretion. There is also de novo insulin synthesis, GLUT 2 expression and protection of pancreatic beta cells, which slow the progression of DM (as the only antidiabetic agent).

Summary of the pancreatic effect

Due to the **incretin effect** postprandial glycaemia decreases.

Principle of incretin effect

We first administer glucose **per os** (p. o.). The intestinal wall responds by **producing incretins**which act on the pancreas via incretin receptors. This results in the **pancreatic effect** described above.

Administration of glucose **p. o.** causes higher insulin production than if administered intravenously.

Extrapancreatic effect

The effects can also be observed outside the pancreas, in the area of the GIT or the cardiovascular system.

Cardiovascular system

The effects on the cardiovascular system are still in the study phase, an **antiatherogenic effect**is expected.

GIT

The effect on the GIT is manifested in **slowing down gastric emptying**. This effect can be both **negativ** (see side effects below) and has its **advantages**. The benefit is **the reduction of patient's weight**.

Side effects

Side effects occur mainly in the GIT, such as dyspepsia such as abdominal pain, nauzea and others. They occur at the beginning of treatment and disappear within days to weeks.

History of incretin analogues

náhled|219x219px|Ze slin **korovce jedovatého** se izoloval **exendin 4**, inkretin, který znamenal přelom pro léčbu analogy In **1964–1967** several research groups independently described the incretin effect. Then, in **1971** a gastric inhibitory peptide (GIP), was described which has inhibitory effects on HCl secretion in the stomach. It is referred to by the alternative name as a glucose-dependent insulinotropic peptide due to its insulinotropic effects. **1985** saw the description of the cleavage product of glucagon GLP-1 (glucon-like peptide).

Before GIP and GLP-1 or their analogs could be used in practice, the problem of their early enzymatic degradation by the enzyme **dipeptidyl peptidase IV** (DPPIV)had to be solved. An ideal analogue of incretins was sought, which will not undergo early enzymatic degradation, and DPPIV inhibitors or **gliptins**. or gliptins were also developed in parallel. The first to be approved for therapy was **sitagliptin** in 2006.

In **1992**, exendin 4 was isolated from the saliva of the poison ivy, which binds to human GLP-1 receptors in a manner similar to GLP-1 but is resistant to DPPIV. The discovery of exendin 4 was a turning point for the later treatment of incretin analogues.

Present

Currently, three incretin analogues have been developed **EXENATID** (2005), **LIRAGLUTID** (2009) and **LIXISENATID** (2013). All should be administered subcutaneously (**s.c.**). When **p.o.** administration would break down them by GIT proteases.

Exenatid

Exenatid was the 1st therapeutically used incretin analogue. It came out under the name **Byetta**. t has been available in the Czech Republic since **2009**. It is a synthetically prepared **exendin 4**, which is **resistant** to **DPPIV**. It is applied **twice a day**.

Exenatid LAR

Exenatid LAR (long acting release) has been available since 2012 under the name **Bydureon**. It can be found in the Czech Republic since **2014**. It is **retarded form of exenatide**, which is applied **once a week**.

Liraglutid

Liraglutid is the 2nd therapeutically used incretin analogue that can be found under the name **Victoza**. It has been present in the Czech Republic since **2010**. It is applied **once a day**.

Lixisenatid

Another species is **Lixisenatide** available under the name **Lyxumia** (in the Czech Republic since **2014**). Structurally, it is derived from **exendin 4**, but unlike exendin 4, it **lacks proline** and six lysines are attached to the **C-terminus of the peptide**. It is applied **once a day**.

Indication

n the Czech Republic, incretin analogues (GLP-1 agonists) are indicated only for the treatment of **type 2 diabetes mellitus**. They are used as second or third choice preparations, most often in combination with metformin or sulfonylureas. The combination of an incretin analogue and basal insulin is clinically popular. Any other indications in the Czech Republic are so-called **off-label** (eg therapy of obesity using analog incretins).

Comparison of incretin analogues

Studies comparing the effects of exenatide, liraglutide and lixisenatide have been performed.

Exenatid vs. liraglutid

The study was performed in patients using *metformin* or *glymepiride* in combination with one of the two incretin analogues.

The results showed that a more significant **decrease in postprandial glycaemia** was observed with the use of *exenatide*, but a higher **frequency of side effects**.

Both exenatide and liraglutide caused **comparable weight loss**.

Liraglutide had a more significant **decrease in glycated Hb** and also a more significant **decrease in fasting glucose**. The use of liraglutide was accompanied by a **lower frequency of adverse reactions** compared to exenatide.

Exenatid vs. lixisenatid

During this study, *metformin* was used in combination with one of these two types of analogue.

Exenatide caused a greater **decrease in glycated Hb**, a greater **weight loss** and had **more side effects** than *lixisenatide*.

Future

The future of incretin analogs is associated with the development of new GLP-1 agonists, the development of fixed combinations with basal insulin, or the use of incretin analogs for indications other than DM2.

Development of new GLP-1 agonists

In **2010**, the development of **taspoglutide** was stopped due to numerous allergic reactions and side effects. In **2014**, **albiglutide** was released for the first time under the name **Eperzan**, which is not yet available in the Czech Republic. It is applied once a week.

Development of fixed combinations with basal insulin

In 2015, **IDegLira** was released under the name **Xultophy**, which is the **first fixed combination** on the market. It consists of a basal insulin called *degludek* and a GLP-1 liraglutide called *IDegLira*.

Use of incretin analogues for indications other than DM2

Incretin analogues can be used to **treat obesity** or **type 1 diabetes mellitus**. In the first case, the ability of incretin analogues to **reduce weight** by slowing gastric emptying is invoked. In **2015**, liraglutide was made available for this purpose under the name **Saxenda**, which is not yet available in the Czech Republic. It is applied **once a day.**.

In the second case, **the protective function of pancreatic beta cells** is applied, which mainly protects against disease progression. In DM1, a proportion of beta cells are still preserved (20-30%).

Links

Related articles

- Diabetes mellitus 2. typu (endokrinologie)
- Perorální antidiabetika
- Inkretiny

Source

1. Postgraduální medicína. *Inkretinová analoga v terapii diabetes melitus.* Dostupné z: https://zdravi.euro.cz/clanek/postgradualni-medicina/inkretinova-analoga-v-terapii-diabetes-melitus-481153

2. Časopis Remedia online. *Liraglutid*. Dostupné z: http://www.remedia.cz/Clanky/Aktuality/Liraglutid/6-E-B3.magarticle.aspx

3. Diabetes.co.uk. *Byetta (exenatide)*. Dostupné z: https://www.diabetes.co.uk/diabetes-medication/diabetes-and-byetta.html

Kategorie:Vnitřní lékařství Kategorie:Endokrinologie Kategorie:Farmakologie