

# An incretin analog

Inkterin analogues are medicinal substances used for the therapy of type 2 diabetes mellitus . They are synthetically prepared incretins . Substances similar to glucagon-like peptide 1 (GLP-1) or GLP-1 agonists are used in therapy.

## Effect

### Pancreatic effect

The effect of incretins on the pancreas is to increase the secretion of insulin and, conversely, to decrease the secretion of glucagon . Furthermore, de novo insulin synthesis, GLUT 2 expression and pancreatic beta cell protection occur , which slow down the progression of DM (as the only antidiabetic drug).

### Pancreatic effect summary

Thanks to **the incretin effect** , there is a decrease in postprandial glycemia.

### The principle of the incretin effect

First we give glucose **per os** (po). The intestinal wall responds by **producing incretins** , which act on the pancreas via incretin receptors. This results in the **pancreatic effect** , which is described above.

The administration of glucose **after** causes a higher production of insulin than if it were given intravenously.

### Extrapancreatic effect

Effects can also be observed outside the pancreas, namely in the GIT or cardiovascular system.

### Cardiovascular system

The effects on the cardiovascular system are still in the phase of studies, an **antiatherogenic effect** is assumed .

### GIT

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

### Adverse effects

Adverse effects are mainly manifested in the GIT, namely dyspepsia type such as abdominal pain, nausea and others. They occur at the beginning of treatment and disappear over a period of days to weeks.

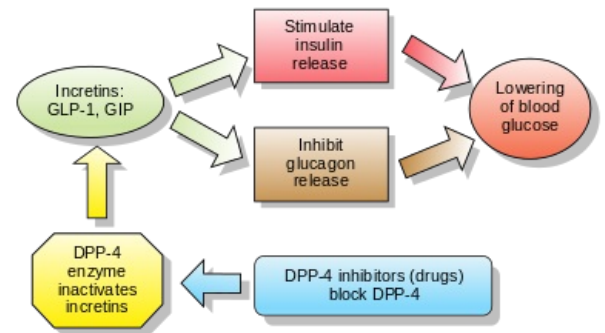
## History of incretin analogs

In **1964-1967** , several research groups independently described the incretin effect. Then, in **1971** , gastric inhibitory peptide ( GIP ) was described, which has inhibitory effects on the secretion of HCl in the stomach. It is referred to by an alternative name as glucose-dependent insulintropic peptide precisely because of its insulintropic effects. The year **1985** brought the description of the cleavage product of glucagon GLP-1 (glucone-like peptide).

Before GIP and GLP-1 or their analogues could be used in practice, the problem of their early enzymatic degradation by **dipeptidyl peptidase IV** (DPP-IV) had to be solved. An ideal analog of incretins that would not be subject to early enzymatic degradation was sought, and DPP-IV inhibitors, or **gliptins** , were also developed in parallel . **Sitagliptin** was the first to be approved for therapy in 2006 .

In **1992** , **exendin 4** was isolated from poison ivy saliva , which binds to human GLP-1 receptors in a manner similar to GLP-1, but is resistant to DPP-IV. The discovery of exendin 4 was a breakthrough for later incretin analog therapy.

## Present



**Pancreatic effect of incretins and the role of DPP-IV** enzyme (see history of analogues)



**Exendin 4** , an incretin, was isolated from **poison ivy** saliva , which marked a breakthrough for analog therapy

Currently, three incretin analogs have been developed, namely **EXENATID** (2005), **LIRAGLUTID** (2009) and **LIXISENATID** (2013). All must be administered subcutaneously ( sc ). GIT proteases would break them down **after administration**.

### Exenatide

*Exenatide* was the 1st therapeutically used incretin analog. It was released under the name **Byetta** . It 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** .

### Exenatide LAR

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

### Liraglutide

*Liraglutide* 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** .

### Lixisenatide

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

## Indication

In 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-line preparations, most often in combination with metformin or sulfonylurea derivatives. Clinically, a combination of an incretin analogue and basal insulin is popular. Any other indications are so-called **off-label** in the Czech Republic (e.g. obesity therapy using incretin analogues).

## Comparison of incretin analogs

Studies have been conducted that compare the effects of exenatide, liraglutide, and lixisenatide.

### Exenatide vs. liraglutide

The study was conducted on patients using *metformin* or *glimepiride* in combination with one of these two incretin analogues.

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

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

Liraglutide had a more significant decrease *in glycated Hb* as well as a more significant **decrease** in fasting blood glucose. The use of liraglutide was accompanied by **a lower frequency of side effects** compared to exenatide.

### Exenatide vs. lixisenatide

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

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

## Future

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

### Development of new GLP-1 agonists

In **2010** , the development of the drug **taspoglutide** was suspended 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 made available under the name **Xultophy** , which is the **first ever fixed combination** on the market. It consists of a **basal insulin** called *degludec* and a GLP-1 liraglutide called *IDegLira* .

## Use of incretin analogues for indications other than DM2

Incretin analogs can be used to **treat obesity** or **type 1 diabetes mellitus** . In the first case, the ability of incretin analogs to **reduce weight** by slowing gastric emptying is used. 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 the beta cells of the pancreas** is used, when protection against the progression of the disease is mainly achieved. In DM1, a proportion of beta cells is still preserved (20–30%).

## Links

### Související články

- Type 2 diabetes mellitus (endocrinology)
- Oral antidiabetics
- Incretins

### Zdroj

1. Postgraduate medicine. *Incretin analogues in the therapy of diabetes mellitus*. Available from: <https://zdravi.euro.cz/clanek/postgradualni-medicina/inkretinova-analoga-v-terapii-diabetes-melitus-481153>
2. Remedia magazine online. *Liraglutide* . Available from:: <http://www.remédia.cz/Clanky/Aktuality/Liraglutid/6-E-B3.magarticle.aspx>
3. Diabetes.co.uk. *Byetta (exenatide)* . Available from: <https://www.diabetes.co.uk/diabetes-medication/diabetes-and-byetta.html>