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Incretin hormone agonists as promising antiobesity drugs - review of literature

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Purpose

The aim of this study is to present the current state of knowledge on incretin hormone agonists used in obesity treatment.

Review methods

The PubMed and Google Scholar databases were used for the literature review. The following phrases were searched for in English: “obesity”, “antiobesity drugs”, “glucagon-like peptide-1”, “glucose-dependent insulinotropic polypeptide”.

Abstract

The aim of this work is to draw attention to the recently growing problem of obesity and complications related to it. Dietary recommendations and recommendations regarding physical activity turned out not to show satisfactory effects in patients with obesity in terms of weight loss, but also in maintaining the effects of the actions taken. The basic basis of the problem turned out to be much more complicated. It is not only related to the occurrence of a positive energy balance, but also to the dysfunction of the entire organism. The discovery of incretin hormones and their complex mechanism of action gave a new direction to the treatment of metabolic diseases. The drugs presented below act on the incretin receptor, stimulating it and causing an effect that leads to weight loss.

Key words

obesity, antiobesity drugs, glucagon like peptide-1, glucose-dependent insulinotropic polypeptide, incretin hormone agonists

Introduction

Obesity is a chronic disease that has been present for years in the international classification of diseases. It is currently widespread throughout the world and is becoming a problem for more and more people every year (currently over 800 million worldwide). Its scope also concerns healthcare workers who try to effectively treat it and limit and eliminate complications that occur because of it.[1, 2] To simplify the definition of obesity, it is an increase in body weight caused by an excess of energy intake, in relation to its expenditure.[3] However, we know that the whole process is not that simple. Many factors related to the functioning of the body play a role in the pathogenesis, such as: hormonal dysregulation - including the gut-brain axis [4] and chronic inflammation of the body, for which adipose tissue and insulin resistance are responsible.[5] Due to the systemic impact, many complications of this disease have been identified - including type 2 diabetes, cardiovascular diseases, liver diseases, musculoskeletal diseases and many others.[6] It is considered a risk factor for certain types of neoplastic diseases, including cancers.[2] It is also associated with the occurrence of chronic pain, the intensity of which increases linearly with the increasing value of the Body Mass Index [BMI] [7], causing a decrease in the quality of life of patients with obesity.[8] In order to identify sick patients, screening BMI and waist circumference indicators are used.[9] The basis of treatment is lifestyle modification, which consists of developing dietary strategies and regular physical activity, which allows for a negative energy balance in the patient. Thanks to the enormous development of medicine, numerous studies have been conducted in recent years on drugs that show the potential to reduce body weight in various groups of patients. It is emphasized that the aim of pharmacological treatment is not only to reduce the patient's body weight, with the possible limited side effects of therapy, but also to maintain the reduced body weight.[10]

A major breakthrough came in the 1960s, when incretin hormones were discovered. These include glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP].[11] GLP-1 is an endogenous peptide hormone consisting of 30 or 31 amino acids. It is secreted by intestinal epithelial endocrine L-cells [12], pancreatic alpha cells, and cells in the central nervous system. It stimulates its receptor located in various tissues.[8, 13,14] Its secretion is stimulated by food intake, and the enzyme dipeptidyl peptidase IV [DPP-IV] is responsible for its degradation.[12] Its action affects glucose homeostasis, causing: insulin secretion dependent on ATP-sensitive or voltage-gated potassium and calcium channels, delays gastric emptying through vagal pathways, affects the immune system by increasing the number of transforming growth factor-β1–secreting lymphocytes and decreased IFN-γ–secreting

lymphocytes,[15] additionally promotes the proliferation of pancreatic beta cells. [16] In turn, GIP is also a peptide hormone consisting of 42-amino acid polypeptide, produced by enteroendocrine K cells of the upper small intestinal epithelium. Its secretion is stimulated by food intake. [17, 18] It causes glucose-dependent insulin secretion and promotes the proliferation of pancreatic beta cells. [19] GIP receptors have been located in hypothalamic feeding centers [20], which regulates food intake.[21] The incretin hormone analogues and their combinations used in obesity therapy that are available in clinical practice and are currently being studied are presented below. [1]

Single receptor agonists

Liraglutide is an amino acid with 97% homology to endogenous GLP-1. It acts on this receptor, causing its activation and leading to an increase in endogenous insulin concentration. The drug is administered in daily subcutaneous injections at a dose increasing from 0.6 mg to 3.0 mg or the maximum tolerated by the patient in the presented ranges. It causes anorexigenic effects, reducing appetite, which has been used in the therapy of patients with obesity. There are numerous studies that describe its effectiveness in reducing body weight, which is about 5.7% of the initial weight vs. placebo during 32 weeks of observation, in combination with recommendations for lifestyle modification. [22, 23] It is a drug used in the treatment of type 2 diabetes, without causing episodes of hypoglycemia during treatment. [24] It has been used in patients before bariatric surgery, as an adjuvant drug for preoperative weight loss. [22, 25] Currently, it is the only GLP-1 agonist approved for the treatment of obesity in adolescents over 12 years old [26]. This provides a new direction for research on the therapy of children, not only with obesity, but also in order to reduce hyperphagia, which occurs in the course of diseases, e.g. in children with Prader-Willi syndrome.[27] The most common adverse events reported by study participants are gastrointestinal symptoms [28], including nausea, vomiting, dyspepsia, constipation and diarrhea [24], most likely caused by delayed gastric emptying.[29] Patients at risk of acute pancreatitis should be identified before starting the drug, because an elevation in pancreatic enzyme levels and pancreatic inflammation is possible during therapy. [24]

Semaglutide has 94% structural homology with human GLP-1. The drug is available in oral form (taken daily) and subcutaneous form (administered once a week), however, currently only the subcutaneous form is registered for the treatment of obesity at a maximum dose of 2.4 mg.[30] In its action, it has a beneficial effect not only on body weight reduction and glycemia, but also reduces the occurrence of serious cardiovascular events [31], causes improvements in

cardiometabolic risk factors, including high blood pressure and atherogenic lipids.[32] In a 68-week observation in obese people after recommendations for lifestyle modification and receiving semaglutide once a week at a dose of 2.4 mg, a body weight reduction of about 15% was shown vs placebo.[33, 34] Its effectiveness is not influenced by factors such as gender, age, etc.[35] Adverse effects are mainly digestive disorders and an increased risk of biliary disease.[36, 34] Benefits on physical function and improved quality of life were noted.[32] Oral semaglutide 50 mg is being studied in overweight and obese patients.[37]

In studies comparing the above two drugs, which were followed for 68 weeks in overweight or obese patients without type 2 diabetes, semaglutide 2.4 mg vs liraglutide 3.0 mg showed greater effectiveness in reducing body weight in favor of semaglutide.[38] The study showed 5.4% weight reduction on liraglutide 3.0 mg compared to 12.4% weight loss on semaglutide 2.4 mg.[39] The incidence of total adverse events occurred in both patient groups, but with a higher rate in the semaglutide group.[40]

Dual receptor agonists

Tirzepatide is a dual agonist for the GLP-1 and GIP receptors.[41] It is administered by subcutaneous injection, once a week, the initial dose is 2.5 mg, then, depending on the patient's tolerance of the drug, it remains on a maintenance dose or the therapy is escalated to a maximum dose of 15 mg every week.[41] The treatment is used in combination with diet and adequate physical activity.[42] Dual agonist action has been shown to have satisfactory clinical effects in reducing body weight.[43] Studies show that tirzepatide in doses of 10 and 15 mg administered once a week shows greater weight loss than semaglutide in a dose of 2.4 mg administered once a week [44] with a comparable frequency of gastrointestinal side effects. [45] They usually appear during dose escalation [46] and are similar to the side effects caused by single GLP-1 agonists.[47] Studies indicate that discontinuation of therapy leads to renewed weight gain.[48] The use of tirzepatide at the maximum dose allowed for a reduction of HbA1c level by more than 2% in 40 weeks of observation [41] and this reduction was greater than in patients using semaglutide at a dose of 1 mg weekly [49], without increasing the risk of hypoglycemia.[50] Currently, the costs of tirzepatide treatment are higher than semaglutide. [51]

Mazdutide is a dual agonist of the glucagon-like peptide 1 and glucagon receptor, which is currently under investigation. It is observed in subcutaneous injections once a week at a maximum dose of 6 mg and shows an effect on reducing HbA1c and body weight reductions.[52,53] Studies show that during 20 weeks of observation, the reduction in body

weight was about 7% vs. placebo.[53] Adverse events occurred mainly in the gastrointestinal tract.[54]

Triple receptor agonist

Retatrutide is a triple agonist of GLP-1, GIP and glucagon, currently under investigation. In a 36-week observation, it shows a reduction in body weight of 16.94% versus placebo 3.00% at a dose of 12 mg, while without incidents of hypoglycemia. [55] Correlations have been shown between the dose of this drug and the percentage reduction in body weight, which is 22.8% and 24.2% with retatrutide 8 and 12 mg, respectively. [56] It has been shown to improve metabolic parameters in patients with obesity or overweight, both in those with and without type 2 diabetes. [57]

Summary

In recent years, the problem of increasing obesity and complications associated with it has been increasingly studied, which has led to the search for new solutions. Previous nutritional advice and recommendations regarding the time and type of physical activity necessary for weight loss have not shown satisfactory results in most cases.[54] With the growing interest in this topic, many studies have been conducted that have shown that the problem itself is not only related to excessive caloric intake in relation to its expenditure, but also disturbances in the body's regulation, such as the gut-brain axis, also have an impact. [58]

The above-mentioned drugs: liraglutide, semaglutide, tirzepatide are used in clinical practice and others currently under investigation, show an effect on reducing body weight by stimulating the incretin receptor. This affects, among others, the digestive system, gastric emptying, the secretory function of pancreatic cells, the hormonal, nervous, and immune systems, etc. [15,16,19,20] This broad spectrum of action means that these drugs affect the entire body, not just a single organ. The discussed drugs contribute to reducing caloric intake, reducing it by about 16-39%. It is important not to cause malnutrition in patients using incretin hormone analogues, by developing appropriate nutritional recommendations during therapy with these drugs. [59]

Reducing body weight in obese patients provides many health benefits, reducing the number of complications, improving the quality of life, reducing pain [60, 7], but also provides economic benefits and shows that treating people suffering from obesity is also in the public interest. [61]

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