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Research Progress in the Effect Evaluation of GLP1-1 Agonists

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Abstract: Glucagon-like peptide-1 (GLP-1) promotes insulin secretion, inhibits glucagon secretion, and repairs pancreatic islet cell function to enhance islet cell proliferation and regeneration. Furthermore, it includes a mechanism for weight loss and angiocarpy protection. This study covers the comparison of GLP-1 agonists with DPP-4 inhibitors and GLT-2 inhibitors, the mechanism of GLP-1 agonists, and its research possibilities based on a summary of current clinical tests of GLP-1 receptor agonists.

Keywords: Diabetes; GLP-1 receptor agonist; Effect evaluation; Adverse reaction

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1. Introduction

Type-2 diabetes is a group of common endocrine and metabolic diseases in clinics. The prevalence of diabetes in China has increased significantly from 0.9% in 1980 to 11.6% in 2010 [1]. By 2016, the total number of diabetes in China has reached 100 million and is still growing steadily [2]. As the country with the largest number of patients in the world, China is facing many problems and challenges. For example, diabetes patients pay insufficient attention to their own conditions, make poor blood glucose management, and are complicated with heart, brain, kidney, eye and nerve lesions. This not only seriously affects the quality of life of patients, but also leads to the high disability rate and mortality rate of diabetic patients [3]. Therefore, how to control blood glucose and delay the occurrence of diabetes related adverse events has become an urgent social problem.

The commonly used hypoglycemic drugs include biguanides, thiazolidinediones, sulfonylureas, insulin secretagogues, insulin and α-glycosidase inhibitors. Among them, insulin secreting agents are easily to lead to hypoglycemic events [4]. Some studies have shown that thiazolidinediones (rosiglitazone) can cause water-sodium retention and increase the incidence of worsening congestive heart failure; α- glucosidase inhibitors and biguanides are easy to cause gastrointestinal reactions such as anorexia, nausea, vomiting and abdominal distention, and biguanides can increase the risk of lactic acidosis [5]. Long term application can lead to vitamin B12 deficiency. For patients with long course of disease, multiple chronic complications and complications, the above drugs can only control blood glucose in an appropriate range, but fail to start from the fundamental purpose of controlling blood glucose, and show no advantages in protecting the function of target organs such as blood vessels, nerves and kidneys and reducing the occurrence of adverse events such as cardiovascular and cerebrovascular events. Considering the need to take medicine many times a day, poor patient compliance and other reasons, Chinese people's blood glucose control is still facing great challenges.

In recent years, new types of hypoglycemic drugs have been emerging in the field of diagnosis and treatment of type-2 diabetes, such as Dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT)-2 inhibitors, glucagon like peptide (GLP)-1 receptor agonists, and glucokinase activators (GKA) within clinical phase III. GLP-1 hypoglycemic drugs are newly developed target therapeutic drugs in recent years. This paper intends to compare GLP-1 drugs with DPP-4 inhibitors and SGLT-2 inhibitors to further explain the advantages of GLP-1 in hypoglycemic mechanism, indications, hypoglycemic effect and protection of heart and kidney, so as to provide doctors and pharmacists with a new reference for the treatment of type 2 diabetes.

2. Comparison of GLP-1 agonist with DPP-4 inhibitor and sglt-2 inhibitor

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that exists in human plasma and tissues and can decompose human protein. It can decompose glucagon like polypeptide-1 (GLP-1) protein, inhibit insulin secretion and promote glucocorticoid secretion [6]. DPP-4 inhibitor reduces the inactivation of glucagon like polypeptide (GLP-1) in vivo by inhibiting DPP-4 enzyme, prolongs its physiological function, increases Glucose dependent insulin secretion, inhibits glucagon release and liver glucose output, and inhibits intestinal glucose absorption, so as to achieve the purpose of reducing blood glucose [7]. GLP-1 analogues directly supplement exogenous GLP-1 and play a role in reducing blood glucose and its unique cardiovascular protection [8]. The two have similar effects on hypoglycemic mechanism, but there are significant differences between direct and indirect, that is, GLP-1 analogues can make the concentration of GLP-1 reach the pharmacological level, while DPP-4 inhibitors can only make the endogenous GLP-1 concentration reach the highest limit of physiological concentration [9].

Sodium glucose cotransporter (SGLT) is a family of glucose transporter genes found in renal proximal tubules (SGLT-2 and SGLT-1). SGLT-2 is a low affinity transport system, which plays an important role in specific expression in the kidney and plays a very important role in renal glucose reabsorption in the proximal convoluted tubules. SGLT-2 inhibitors selectively inhibit SGLT-2 activity, reduce the reabsorption of glucose by renal tubular epithelial cells, and increase the excretion of urinary sugar to achieve the goal of treating type-2 diabetes [10]. The European Society of Cardiology (ESC) and American Diabetes Association (ADA) suggest that patients with type 2 diabetes complicated with atherosclerotic heart disease (ACVDS) should be considered to be treated with Empagliflozin in order to prevent or delay the occurrence of heart failure and prolong life. However, in 2015, FDA issued several warnings stating that SGLT2 inhibitors may cause ketoacidosis [11]. Researchers found that the lack of quantity of heat caused by urinary glucose excretion requires lipolysis for energy supply, so that the level of free fatty acids and β-hydroxybutyrate increases, which leads to ketoacidosis [12]. In clinical trials, it was found that the use of SGLT2 inhibitors increased the concentration of urinary glucose, thus increasing the probability of urinary and reproductive system infection [13]. In contrast, there is no report on the use of GLP-1 agonists in the treatment of diabetes and the increase of genitourinary tract infections.

3. Mechanism of action of GLP-1 agonist

Compared with most oral hypoglycemic drugs, GLP-1 agonists can reduce glycosylated hemoglobin (HbA1c) by more than 1%, and the hypoglycemic effect is relatively strong. Secondly, Glp-1 agonists, in addition to lowering glucose, can also repair the function of pancreatic beta cells and promote the proliferation and regeneration of pancreatic β cells, inhibits their apoptosis, improves insulin secretion, and improves the sensitivity of peripheral tissues to insulin [14]. However, these are not the brightest points of GLP-1RAs in the clinic. In the treatment of diabetes, on the one hand, we should take care of the curative effect as well as safety. The risk of hypoglycemia and weight are of particular concern to endocrinologists. Many hypoglycemic drugs increase insulin secretion, which may lead to weight gain. But GLP-1 agonist

shows its outstanding additional benefits, which can inhibit appetite, delay gastric emptying and help diabetics lose weight. At the same time, because the GLP-1 agonist is Glucose dependent and plays a hypoglycemic role, the risk of hypoglycemia in clinic is very low, and the effective hypoglycemic effect is safe. Therefore, GLP-1 agonist is an ideal drug for the treatment of type 2 diabetes mellitus (T2DM).

4. Evaluation effects of GLP-1 agonist

A real-world research [15] included 1122 patients who used GLP-1 agonists for 2 years, and compared the changes of HbA1c before and after the use of GLP-1 analogues. The results showed that the early use of GLP-1 agonists was significantly correlated with the decline of HbA1c, and was more likely to reach the ideal level of HbA1c < 7%. Thus, the earlier GLP-1 agonist treatment is started, the more pancreatic β cell function is maintained, and the effect of drugs will be better, so as to realize the long-term and stable control of blood glucose as soon as possible. Another US retrospective real-world research showed that [1], after 3 months of dulaglutide use, HbA1c decreased by 1.41% compared with baseline in 872 T2DM patients. Two years later, 43% of patients reached HbA1c < 7%, and 74% reached HbA1c < 8%.

When 10 patients undergoing angioplasty after myocardial infarction were treated with GLP-1 agonist, it was found that continuous intravenous infusion of GLP-1 agonist for 72 hours after operation could improve left ventricular ejection fraction and local ventricular wall motion, significantly reduce the in-hospital mortality and hospital stay compared with the control group [16].

The research of patients with type 2 diabetes complicated with chronic heart disease with acceptable control of blood glucose treated with glutide confirmed that compared liraglutide combined with metformin treatment and placebo combined with metformin, the insulin sensitivity of the two groups was increased, but the B cell function of the liraglutide combined with metformin group was significantly improved compared with that of the control group. The research also found that liraglutide combined with metformin reduced postprandial insulin levels [17].

A post-mortem analysis of the AWARD CHN1 and CHN2 studies (studies on the marketing of dulaglutide in China) explored the relationship between the hypoglycemic effect of dulaglutide and the baseline saccharification level. In this research, in the stratification of HbA1c ≥ 8.5%, HbA1c in the dulaglutide 1.5mg dose group decreased by 2.2% from about 9.3% of baseline, and in the stratification of HbA1c < 8.5%, HbA1c decreased by 1.2% from about 7.5% of baseline. It can be seen that: in patients with higher baseline levels of glycosylated hemoglobin, moderate dulaglutide had a greater decrease in glycosylation levels. At the same time, compared with the control drug glimepiride and basal insulin secretion of research, in terms of saccharify blood glucose, the glycosylated hemoglobin of dulaglutide 1.5mg group was an additional 0.44% lower than that of glimepiride group. In terms of fasting blood glucose, the blood glucose of dulaglutide 1.5mg group decreased by 2.33mmol/l compared with baseline, while that of glimepiride group decreased by only 1.15mmol/l.

5. Expectation

GLP-1 agonist has a good hypoglycemic effect. While effectively reducing blood glucose and glycosylated hemoglobin, it has the additional benefit of reducing body weight, and the risk of hypoglycemia is low, which shows cardiovascular protective effects that most hypoglycemic drugs do not have. Therefore, it is recommended that patients with cardiovascular risk should be applied early. Through this review, we hope that such drugs can provide more comprehensive reference for both doctors and patients.

Disclosure statement

The author declares no conflict of interest.

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