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Review Article

Role of Glucagon like peptide -1 (glp1) in health, disease and weight loss

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دور البيبتيد شبيه الجلوكاغون (GLP1) في الصحة والمرض وفقدان الوزن

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الملخص

يبدو نظام البيبتيد شبيه الجلوكاغون 1 (GLP1) معقدا للغاية. هذا النطام له تأثير إيجابي على توازن الطاقة الذي يؤدي إلى فقدان الوزن وتحسين التحكم الأيضي. المعرفة بهذا النظام يمكن استغلالها علاجيا لكل من البدناء والاشخاص المصابين بالداء السكري من النوع 2 .العقاقير المستعملة في علاج الداء السكري (ما عدا الميتفورمين ومثبطات4-DPP) ، ترتبط عادة مع زيادة الوزن.

منبهات مستقبلات البيبتيد شبيه الجلوكاغون 1 تساعد في تحسين السيطرة على نسبة السكر في الدم وترتبط مع فقدان الوزن .تدل الكثير من الأدلة والخبرة السريرية على ان منبهات مستقبلات لببتيد شبيه الجلوكاجون 1 (GLP1) يمكن أن تؤدي إلى تحسينات كبيرة في مستوى الهيموجلوبين السكري (HbA1c) فضلا عن الآثار المفيدة المستمرة على وزن الجسم.

القدرة على تحقيق فقدان الوزن في سياق تحسين السيطرة على مرض السكري هو سمة مهمة ومرغوب فيها من أي تدخل علاجي .هذا الاستعراض يساعد في إظهار آثار البيبتيد شبيه الجلوكاغون 1 (GLP1) وقابليته على فقدان الوزن المحتملة في ضوء الدراسات المختلفة.

ABSTRACT

Objective:
The endogenous GLP-1 system appears to be highly complex. It has a positive impact on energy homeostasis that leads to weight loss and improved metabolic control. This knowledge can be exploited therapeutically for both obese people and subjects with type 2 diabetes. Diabetes therapies, apart from metformin and DPP-4 inhibitors, are associated with weight gain. The GLP-1R agonists improve glycemic control and are associated with weight loss. Accumulating evidence and clinical experience for glucagon like peptide 1 (GLP1) receptor agonists shows that they can effect considerable improvements in glycated hemoglobin (HbA1c) levels as well as sustained beneficial effects on body weight.

The potential to achieve weight loss in the context of improved diabetes control is an important and desirable characteristic of any therapeutic intervention.

This review help in showing the effects of GLP 1 and its weight loss potential in the light of different studies.

Keywords: *Glp1, Exendin 4,Type2 Diabetes*

INTRODUCTION

Researchers theorized that the gastrointestinal tract might release a hormone in response to glucose that could stimulate insulin secretion above and beyond that stimulated by glucose alone. This then-undiscovered hormone was called "incretin." The incretin GLP-1(glucagon like peptide) was found to have a profound effect on stimulating the release of insulin from the pancreas. (1)

The glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of injected drugs for the treatment of type 2 diabetes. They have additional effects in reducing glucagon, slowing gastric emptying and inducing satiety. In clinical practice they are associated with significant reductions in glycosylated haemoglobin (HbA 1c), weight loss and a low risk of hypoglycaemia. Beneficial effects have also been observed on blood pressure and lipids.

A solution to the issue of GLP-1's short action time came from an unusual source. Scientists working on toxins in the saliva of the lizard Heloderma suspectum, otherwise known as the Gila monster, found a protein that activated GLP-1 receptors. This protein, named exendin-4, originates in the salivary glands but has endocrine effects. (1)

Exendin-4 is a protein composed of 39 amino acids that mimics many of the actions of GLP-1 but that, unlike GLP-1, has a prolonged half-life in the bloodstream (meaning it remains in the blood for longer). Exendin-4 has several properties that mimic those of GLP-1. These include the stimulation of insulin secretion, the suppression of glucagon (a hormone that signals the liver to release glucose when blood glucose levels drop) secretion, and the slowing of stomach emptying.

PHYSIOLOGICAL ACTIONS OF GLP-1

Glp-1 Has Multiple Physiological Effects

1. It increases insulin secretion while inhibiting glucagon release.
2. Lower plasma glucose while reducing the likelihood of hypoglycemia.
3. It delays gastric emptying and food intake is decreased after GLP-1 administration .
4. It also Promotion of β-cell proliferation and reduced β-cell apoptosis .All patients were subjected to the following:

With respect to β-cell function, GLP-1 rapidly and potently stimulates insulin secretion. However, GLP-1 also stimulates insulin gene transcription, islet cell growth, and neogenesis, additional potentially important functions that may be clinically relevant for the treatment of diabetes. GLP-1 appears to improve insulin sensitivity and glucose uptake of both human and rat adipose tissue and skeletal muscle. (2) Several studies suggest that GLP-1 may directly enhance glucose disposal in an insulin-independent fashion, although this may also result from the overall inhibition of glucagon secretion. (2) Administration of GLP-1 agonists also leads to decreased hunger and increased satiety. (3)

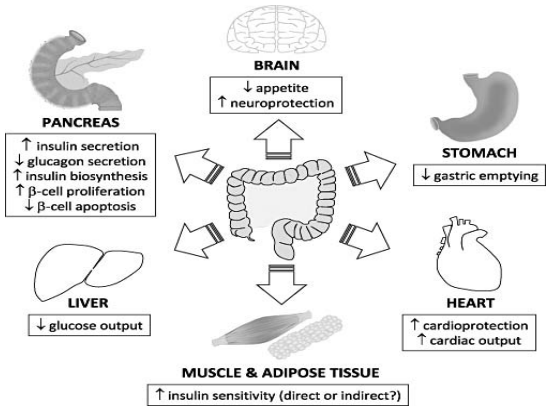

Figure source Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits

EFFECT OF GLP1 IN TYPE 2 DIABETES.

It is well known that type 2 diabetes is characterized by defects in both insulin secretion and peripheral insulin sensitivity. Current treatments for the β-cell defect include the sulfonylurea (SU) drugs, which were the first therapy targeted against insufficient insulin secretion. However, these compounds promote insulin secretion independent of blood glucose and can, therefore, cause hypoglycemia.(4)

The properties of GLP-1, including glucose-dependent stimulation of insulin secretion and the expansion of β-cell mass, coupled with the inhibition of glucagon secretion and food intake, suggest that it would greatly complement current β-cell therapies. Trials with GLP-1 in diabetic patients have shown it to stimulate insulin secretion, inhibit gastric emptying, lower circulating glucagon, and improve overall glycemic control through both intravenous and subcutaneous injection.(5)

EFFEECT OF GLP 1 ON CVS

Although the major physiological function of GLP-1 appears to be in relation to glycaemia control, there is growing evidence to suggest that it may also play an important role in the cardiovascular system. GLP-1 receptors (GLP-1Rs) are expressed in the heart and vasculature of both rodents and humans. Recent studies have demonstrated that GLP-1R agonists have wide-ranging cardiovascular actions, such as modulation of heart rate, blood pressure, vascular tone and myocardial contractility. Importantly, it appears that these agents may also have beneficial effects in the setting of cardiovascular disease.(6)

EFFECT ON KIDNEY

GLP-1 can induce protective actions on the glomerular (renal) endothelial cells by inhibiting the signaling pathway of Ang II and its pro-inflammatory effect; and demonstrated a dual signaling mechanism by which hyperglycemia, via PKC β (protein kinase c) activation, can increase Ang II action and inhibit GLP-1's protective effects by reducing the expression of GLP-1 receptors in the glomerular endothelial cells.(7)

GLP 1 AND ITS MECHANISM OF WEIGHT LOSS

The principal action of GLP-1 agonists is mediated via their inhibition of eating. In searching for the underlying mechanism of GLP-1 receptor agonist induced anorexic effect, scientists have discovered pathways in the central nervous system, as well as in the periphery.(8)

The potent dose-dependent inhibition of gastric emptying observed following GLP-1 infusion in human subjects with Type 2 diabetes produce significant lowering of meal-related glycemic excursion, even without any increase in levels of circulating insulin.(9)

The inhibitory effects of GLP-1 on GI motility are also detected in human studies in the inter-digestive state. (10)

Administration of GLP-1 agonists also leads to decreased hunger and increased satiety in both the fed and fasted state; it appears that retarded gastric emptying is not the sole explanation of GLP-1–induced anorexia

Some studies suggest that GLP-1 has effects in appetite control centers in the human brain. Pannacciulli et al studied 42 healthy, normal volunteers using positron emission tomography imaging of the brain and demonstrated that peak postprandial increases in plasma GLP-1 concentrations were correlated with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex and the hypothalamus, areas previously shown to be related to food intake.

Effect on Hb A1C levels

Data from published clinical trials using long-acting GLP-1 receptor agonists (liraglutide, exenatide, albiglutide, taspoglutide, reveal that reductions in A1C from baseline range from −0.87 to −1.9%.

Results with exenatide demonstrated that these improvements in A1C could be maintained after 2 years (mean A1C decrease at 2 years: −1.8%) (11).

Greater reductions in A1C were seen with liraglutide compared with the DPP-4 inhibitor sitagliptin (mean A1C decrease: −1.50 and −1.24% with 1.8 and 1.2 mg liraglutide, respectively, vs. −0.90% with sitagliptin) (12).

Summary

Endogenous GLP-1 released from entero endocrine cells is a prandial satiety hormone

1- In the periphery, satiety including effects of GLP-1 are likely to be mediated via vagal apparent originating in the intestine

2- In the central nervous system, ascending GLP-1 containing pathway arising in the dorsal vagal complex is a mediator of satiety

3- Both central and peripheral GLP-1 receptors are valid targets for weight management therapies

GLP-1 MIMETICS AND WEIGHT LOSS IN CLINICAL TRIALS

Most clinical trials of GLP-1mimetics have demonstrated modest weight loss.
With exenatide, the phase III studies indicate that weight loss occurs particularly when exenatide is given as mono therapy or combined with metformin therapy.(13)

GLP-1 is secreted into circulation after food intake. In the pancreas, GLP-1 stimulates glucose-induced insulin secretion (an incretin hormone) and inhibits glucagon secretion, thereby substantially contributing to maintaining the glucose homeostasis (14).
Activation of both peripheral GLP-1 receptors and GLP-1 receptors in the central nervous system reduces appetite and food intake thereby ensuring that body weight is kept down. There are 2 principal mechanisms by which GLP-1 can have weight-related effects. GLP-1 has been shown to have important effects on the GI system as well as the central nervous system.(14) The infusion of GLP-1 has been shown to decrease the rate of gastric emptying and to reduce acid secretion.
This, in turn, is expected to lead to an increase in satiety and, thus, decreased food intake (15)
Clinically, the degree of weight loss appears to be positively correlated with the dose of GLP-1 analog. A recent two-year prospective study (including non-diabetic patients with baseline BMI ≥30) randomized to treatment with the GLP-1 analog liraglutide (2.4 to 3.0 mg once-daily) reported a weight loss of 7.8 kg (compared to a 2 kg weight loss in the placebo group) (16).

At present, six different GLP-1 analogs have been subject to trials: exenatide (Eli Lilly), liraglutide (Novo Nordisk), albiglutide (GlaxoSmithKline), taspoglutide (Ipsen and Roche), lixisenatide (Sanofi-Aventis) and LY2189265 (Eli Lilly). Only exenatide and liraglutide have been approved by the U.S. Food and the Drug Administration and European Medicines Agency.

GLP-1 analogues have the indication type 2 diabetes in combination with metformin and/or sulphonylurea, when treatment with these drugs is insufficient. Much academic and commercial effort is being put into investigating the possibility of extending the indication to obesity.

EXANATIDE

Both exenatide and liraglutide are administered subcutaneously; exenatide was shown to reduce weight by approximately 1.5-3.0 kg over a 30-week period. Exenatide exists in two formulations: twice daily (Byetta®) and once weekly (Bydureon®).

LIRAGUTIDE

Liraglutide, a glucagon-like peptide (GLP-1) analogue, is a member of new classes of anti-diabetic agents and is characterized by induction of insulin secretion only during hyperglycaemia as an incretin effect. Liraglutide (Victoza®, Novo Nordisk A/S, Bagsvaerd, Denmark) is administered once daily. The Liraglutide Effect and Action in Diabetes (LEAD) studies have demonstrated a significant weight reduction by liraglutide (17). The LEAD (Liraglutide Effect and Action in Diabetes) program represents a large series of studies undertaken in approximately 4200 patients with type 2 diabetes to characterize the effect of liraglutide over the spectrum of type 2 diabetes care.

In a pilot study, it was recently reported that short-term liraglutide treatment reduced BMI, waist circumference, and visceral fat area, and reduced the scale for eating behaviour (18). However, this short-term study was performed only during hospitalization and thus it remains uncertain whether these effects of liraglutide are maintained after discharge. (19)

Potential clinical implications of GLP-1 analog treatment

First, encouraging and growing evidence supports that a sizable and enduring weight loss can be obtained by GLP-1 analog treatment in both diabetic and non-diabetic overweight or obese patients.

The results of the seven incretin-based clinical trials have generally demonstrated the same benefits observed in comparative trials with other glucose-lowering agents. More specifically, depending on background glucose-lowering therapy, a weight loss of 1–4 kg is observed in patients treated with a GLP-1 receptor agonist (20)

The major side effects of exenatide and liraglutide are mild to moderate nausea and vomiting. These side effects are dose-dependent and decline over time, and they do not explain the observed weight loss

Study design	Study results of weight loss	Lipid levels
Exenatide Versus Liraglutide (LEAD-6) Buse et al[22]	In the 26-week trial , weight losses of 2.9 and 3.2 kg were observed with exenatide and liraglutide, respectively. In the 14-week extension phase, those switched from exenatide to liraglutide experienced an additional weight loss of 0.9 kg compared to 0.4 kg for those who remained on liraglutide	Compared to exenatide, triglycerides were reduced significantly more with liraglutide, 1.8 mg daily
Liraglutide Versus Sitagliptin Pratley et al[23]	In the comparison of liraglutide with sitagliptin a weight loss of 2.9 kg was observed in the group taking liraglutide, 1.2 mg; a loss of 3.4 kg in the group taking liraglutide, 1.8 mg	
Exenatide Versus Sitagliptin[24]	In the crossover comparison of exenatide with sitagliptin, patients treated with exenatide for 2 weeks before the crossover lost 0.8 kg, and those treated with sitagliptin lost 0.3 kg	Compared to sitagliptin, exenatide resulted in a significantly greater reduction in triglycerides, whereas liraglutide resulted in a similar reduction after 26 weeks
The SCALE study (Satiety and Clinical Adiposity – Liraglutide Evidence in Non-Diabetic and Diabetic Subjects [25]	This study Investigated liraglutide's efficacy for weight loss in a particularly obese population. Baseline BMI of the SCALE patients averaged 38 kg/m2, while approximately one third of SCALE patients had a BMI of over 40 kg/m2.The result of a 5% weight loss was achieved	

associated with GLP-1 analog treatment (21).

The following table shows the results of some studies carried out to see the effect of Exanatide and Liraglutide on weight reduction.

A random meta-analysis including 3395 participants randomly assigned to GLP-1R agonists and 3016 assigned to the control groups, from 21 trials showed that the weighted mean change in body weight was larger for patients in the GLP-1R agonist group than for those in the control group.(26)

In summary, treatment with GLP-1 mimetic is associated with decreases in appetite and body weight. On average, the weight loss is modest, but in some individuals it can be significant. The effect appears to be dose dependent, with higher doses of GLP-1 mimetics associated with more weight loss.(27)

CONCLUSION

The endogenous GLP-1 system appears to be highly complex. GLP-1 has a positive impact on energy homeostasis that leads to weight loss and improved metabolic control. This knowledge can be exploited therapeutically for both obese people and subjects with type 2 diabetes.

Diabetes therapies, apart from metformin and DPP-4 inhibitors, are generally associated with weight gain. The GLP-1R agonists improve glycemic control and are associated with weight loss.

Accumulating evidence and clinical experience for glucagon like peptide 1 (GLP1) receptor agonists shows that they can effect considerable improvements in glycated hemoglobin (HbA1c) levels as well as sustained beneficial effects on body weight.

The potential to achieve weight loss in the context of improved diabetes control is an important and desirable characteristic of any therapeutic intervention. Further studies examining the impact of longer-acting preparations on long-term body weight will be of great interest.

In summary, treatment with GLP-1 mimetic is associated with decreases in appetite and body weight. On average, the weight loss is modest, but in some individuals it can be significant. The effect appears to be dose dependent, with higher doses of GLP-1 mimetics associated with more weight loss.(28)

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