

A Review on Glucagon like Peptide-1 Approach in Diabetes Mellitus

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Abstract- Epidemiology of diabetes has gained great significance both in estimating the burden of the disease and also in finding out the risk factors with an ultimate goal of prevention of the disease. Type 2 diabetes is a progressive chronic disease resulting from a dynamic interaction between defects in insulin secretion and insulin action. New molecules have recently been launched and many others are under clinical investigation. Besides classical sulfonylureas and glinides, new insulin secretagogues are now available, which target the incretin gut hormone glucagon-like peptide-1 (GLP-1). Indeed, oral incretin enhancers acting as antagonists of the enzyme DPP-4 (dipeptidylpeptidase-4), which inactivates natural GLP-1, and injectable incretin mimetics (exenatide) or analogues (liraglutide), which reproduce the actions of GLP-1 while resisting to DPP-4, represent new opportunities to stimulate insulin secretion, without increasing the risk of hypoglycaemia and weight gain. Therapies based on the incretin hormone glucagon-like peptide 1 (GLP-1) are novel treatment options for type 2 diabetes. Incretin hormones cause an increase in the amount of insulin released from beta cells in the pancreas following ingestion of food. Glucagon-like peptide-1 (GLP-1) is the most well-characterized incretin hormone, which is considered to be the most important incretin released by the gut into the bloodstream in response to meal. In addition to its effects on insulin secretion after eating, primary function of GLP-1 is to enhance insulin secretion. GLP-1 also has additional effects that can help in the management of diabetes.

Index Terms—Diabetes mellitus, Glucagon like peptide-1, incretins.

I. INTRODUCTION

Diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Harris (1997). All forms of diabetes are treatable since insulin became medically available in 1921, but there was no cure. The injections by a syringe, insulin pump, or insulin pen deliver insulin, which is a basic treatment of type 1 diabetes. Type 2 is managed with a combination of dietary treatment, exercise, M.M Engelgau (1994) medications and insulin supplementation. Diabetes and its treatments can cause many complications. Acute complications (hypoglycemia, ketoacidosis, or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. The primary focus of treatment for diabetes is medical management of the complications of disease. The good news is that there are multiple opportunities to intervene and either prevent or control the disease.

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II. GLUCAGON LIKE PEPTIDE-1

D.J Drucker (1986) Glucagon-like peptide 1 (GLP-1) is an incretin hormone which is released from gut.

It stimulates insulin secretion, suppresses glucagon secretion and the combined effects on insulin and glucagon secretion result in inhibition of hepatic glucose production, which importantly contributes to the glucose lowering effect of the hormone. It seems GLP-1 can be used in treatment of diabetic patient but because of its rapid elimination by DPP-4, is not suitable for clinical use. Therefore two strategies have been used to exploit the beneficial actions of the hormone (i) development of more stable activators of the GLP-1 receptor so-called GLP-1 mimetics like exenatide, Liraglutide and (ii) inhibitors of DPP-4 like sitagliptin, vildagliptin and saxagliptin. These components can be used in monotherapy or in combination with metformin, insulin, sulphonylurea. GLP-1 exerts multiple effects that contribute to the maintenance of glucose homeostasis as shown in table-1. GLP-1 enhances glucose-dependent insulin secretion; suppresses inappropriate glucagon secretion; reduces appetite, leading to reduction of food intake; regulates the rate of gastric emptying, so that nutrients are not absorbed as quickly into the bloodstream. GLP-1 and Type 2 Diabetes People with type 2 diabetes often have inappropriately elevated levels of glucagon. The elevated glucagon, which is produced in pancreatic alpha cells, causes the liver to release an excessive amount of glucose into the bloodstream, which then contributes to high blood glucose seen in type 2 diabetes. Many people with diabetes may also have an accelerated rate of gastric emptying, which leads to increased nutrient delivery to the intestine resulting in an abnormally rapid rise in glucose following a meal. The levels and actions of GLP-1 appear to be deficient in many people with type 2 diabetes, thus creating an opportunity for antidiabetes medications that act directly on the GLP-1 receptor or inhibit the breakdown of GLP-1 in the bloodstream.

M.Zander (2004) Metabolic actions of GLP-1; which shows the importance of GLP-1 in diabetes management. Administration of GLP-1 by continuous subcutaneous infusion (CSI) for 6 weeks in patients with T2DM caused a significant decrease in hemoglobin A1C (A1C) and reduced hyperglycemia significantly over the course of 8 hours, during which the patients ate breakfast and lunch. The effect of GLP-1 was noted at 1 week of treatment and was maintained over 6 weeks. GLP-1 concentrations in the picomolar range induce insulin secretion from pancreatic b-cells in vitro and in vivo when elevated glucose concentrations (> 5 mmol/l) are present. In patients with non-insulin-dependent diabetes mellitus.

(NIDDM) parenteral (i.v. and s.c.) administration of GLP-1 led to reconstitution of the early phase insulin secretion and reduction of postprandial glucose excursions. Even in insulin-deficient type-1 diabetic patients GLP-1 reduced the insulin requirements, suggesting additional peripheral activities.

Organ	GLP-1 Actions
Gastrointestinal tract	Inhibits gastric emptying (+) Inhibits gastric acid secretion (+)
Central nervous system	Inhibits food and water intake (+) Promotes satiety and weight loss (+) Enhances memory and neuronal survival (+) Activates aversive pathways leading to nausea/vomiting (+)
Cardiovascular system	Improves cardiovascular function after ischemia (+) Reduces the extent of cardiomyocyte death after experimental injury
Adipose tissue	Insulin-like lipogenic actions (-) Lipid storage

Fig 1.1: Singhal(2010) Summary of GLP-1 actions relevant to glucose control and Treatment of Type 2 Diabetes Mellitus.

III. GLP-1 DEGRADATION

Knudsen(1996) and Gribble (2007) The catalytic enzyme dipeptidyl peptidase IV is a 766 amino acid, membrane associated ecto-peptidase that is widely distributed in numerous tissue. This enzyme also exist as soluble circulating form in plasma and significant DPP-IV-like activity is detectable in plasma from human and rodents. DPP-IV action is rapid and local. In experiments using isolated perfused porcine ileum. It was observed that less than 25% of newly secreted GLP-1leaves the gut in an intact active form. In liver it suffers similar degradation. Hence only about 10-15% of newly secreted GLP-1 enters the systemic circulation in an intact form.GLP-1 metabolites are also cleared rapidly, mainly by the kidneys.

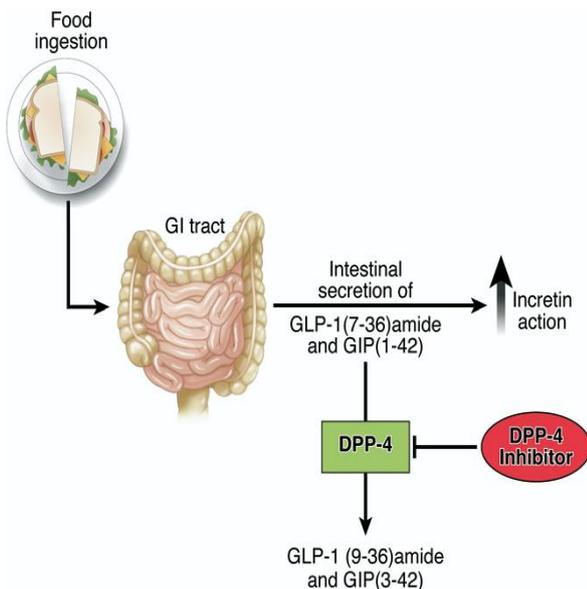


Fig1.2: Laurie (2007)Bioactive GLP-1(7-36)amide and GIP (1-42) are released from the small intestine after meal ingestion and enhance glucose stimulated insulin secretion (incretin action). DPP-4 rapidly converts GLP-1 and GIP to their inactive metabolites GLP-1 (9-36) and GIP (3-42) in vivo. Inhibition of DPP-4 activity prevents GLP-1 and GIP degradation, thereby enhancing incretin action

IV. STIMULATION FOR GLP-1 SECRETIONS

Gribble (2008)The secretion of Glp-1 is meal related. Although there is a basal rate of secretion, fasting GLP-1 plasma concentration remains very low, meal intake stimulates rapid increase of GLP-1 secretion from L-cells Orskov(1996) which is evident after about 10min. Instead the presence of nutrients in the gut, probably there interaction with L-cells stimulates GLP-1.

V. GLP-1 DIABETES TREATMENTS

B Richter (2008) Native human GLP-1 is rapidly inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme, resulting in an extremely short half-life-approximately two minutes—in the blood. The short half-life presents a challenge for its use as a therapeutic agent given the constraint around duration of action. However, two treatment approaches have been developed to increase the amount of circulating GLP-1: GLP-1 receptor agonists and DPP-4 inhibitors.

VI. BIOLOGICAL ACTIONS OF GLP-1

Pancreas: S. Mojsov and GC (1987) and B.Kreymann(1987) GLP-1R agonists produce several biological actions in the pancreas including stimulation of glucose-dependent insulin secretion. (JJ Holst and C Orskov(1987).The binding of GLP-1 to its specific receptor on pancreatic beta-cells leads to activation of adenylate cyclase activity and production of Camp. GLP-1R agonists maintain beta-cell insulin stores and secretory capacity by increasing glucose-induced insulin biosynthesis at the translational level.

C Alarcon(2006)GLP-1 also inhibits glucagon and stimulates somatostatin secretion. The stimulatory effect of GLP-1 on somatostatin secretion likely is caused by direct interaction with GLP-1Rs on somatostatin-secreting pancreatic beta-cells. The mechanism(s) whereby GLP-1 inhibits glucagon secretion from pancreatic beta-cells is less clear. HC Fehmann and JF Habener (1991).

Central and peripheral nervous systems: K Merran and D O’shea (1999) GLP-1Rs are located on the no dose ganglion of abdominal vagal afferent nerve fibers whose central branches terminate in the nucleus of the solitary tract of the brainstem. Rodent studies demonstrate that central or peripheral administration of GLP-1R agonists reduces short-term food and water intake and decreases body weight. Similarly, MSzayna(2000)peripheral administration of GLP-1R agonists promotes satiety, decreases energy intake, and leads to weight loss in healthy, diabetic, and obese humans.

Gastrointestinal system: JJ Meier and B Gallwitz (2003) GLP-1R agonists exhibit potent inhibitory effects on pentagastrin- and meal-stimulated gastric acid secretion and gastric emptying .

Deceleration of gastric emptying attenuates increases in meal-associated blood glucose levels by slowing the transit of nutrients from the stomach to the small intestine and contributes to the normalization of blood glucose levels in type 2 diabetic patients after exogenous GLP-1 administration

Cardiovascular system: JM Barragan(1999) GLP-1Rs are expressed in both the rodent and human heart, although the identity of the specific cell type(s) within the heart that express the GLP-1R is not known. GLP-1Rs also are present in the nucleus of the solitary tract and area postrema, regions of the CNS that regulate cardiovascular function. Intravenous administration of GLP-1R agonists increases systolic, diastolic, and mean arterial blood pressures and heart rate in rodents and increases heart rate in conscious calves

Muscle, adipose tissue and liver: C Ruiz Grande (1992) GLP-1 also inhibits hepatic glucose production and stimulates glucose uptake in fat and muscle. GLP-1 and exendin-4 increase glycogen synthase activity and glucose metabolism in rat soleus muscle and human skeletal muscle

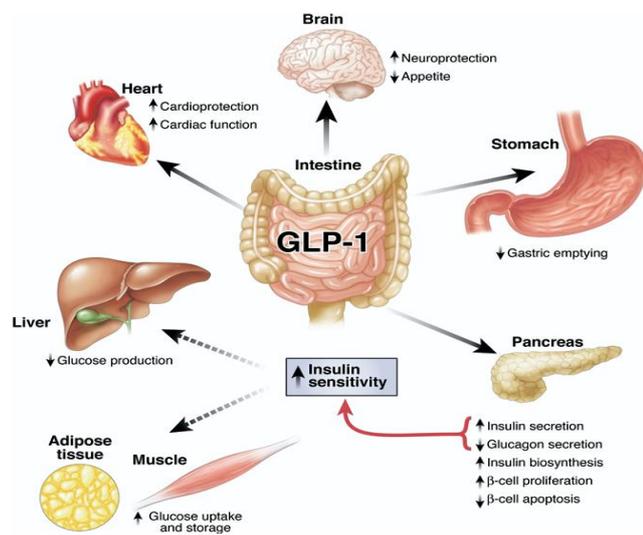


Fig1.3- DJ Ducker(2007)GLP-1 actions in peripheral tissues.

VII. CONCLUSION

The current review suggests that personalized programs need to be implemented. Interventions that decrease insulin resistance, and preserve or improve beta-cell function are effective in slowing progression to T2DM. The intervention in lifestyle changes, such as increasing activity or exercise, and reducing weight, is the most important prevention therapy. First, it is too early to conclude that advancing type 2 diabetes is characterised by a progressive loss of the potential to secrete GLP-1 as part of the process of disease progression. To draw such a conclusion, we need studies that longitudinally assess GLP-1 secretion in cohorts of prediabetic participants followed until diagnosis of type 2. Second, small differences in glp-1 concentrations within physiological limits are not sufficient to affect insulin secretion. Incretin mimetics provide a pharmacological stimulus to insulin secretion and elicit other GLP-1-receptor mediated activity as drugs, but are typically introduced at much higher concentrations compared with physiological levels of glp-1. Incretins are also promising drugs in patients with igt, due to the reduction in postprandial glucose excursions demonstrated in studies.

Finally, and as a consequence of the above, dpp-4 inhibitors can exert their clinical effects even in advanced stages of type 2 diabetes. This condition is not in itself characterised by reduced meal-induced glp-1 concentrations that are too low to be effective, as supported by recent studies.

In conclusion, while reduced glp-1 levels have been described individually in some participants as well as in groups with type 2 diabetes mellitus, this does not seem to be a universal characteristic that is representative of all patients. Apart from the pharmacological treatment, approaches to delay the t2dm onset and identify high-risk patients include performing pre-diabetes testing, by blood 14 measuring fasting glucose values or, more appropriately, an oral glucose tolerance test to define impaired glucose tolerance. Lifestyle changes require an implementing disciplinary programme supervised by the physicians on a daily based training of patients. Ultimately, bariatric surgery is recommended for obese patients to improve glycemic control.

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