THE ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS AND DIABETES TREATMENT

Graduation project prepared by

Mariam

Hiba Laith Wafaa

Supervised by

Dr.Qutaiba Abdulkareem Qasim

Background and Introduction

Incretins are hormones that are released from the gut into the blood stream in response to ingestion of food, and they modulate the insulin secretory response to the nutrients in the food. The insulin secretory response of incretins, called the incretin effect,accounts for at least 50% of the total insulin secreted after oral glucose.

Background and Introduction

There are two incretins, known as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), that share many common actions in the pancreas but have distinct actions outside of the pancreas. Both incretins are rapidly deactivated by an enzyme called dipeptidyl peptidase 4 (DPP_4).

Glucose-Dependent Insulinotropic Peptide (GIP)

The first incretin hormone described, GIP, is a single 42-amino acid peptide derived from the post-translational processing of a 153-amino acid precursor encoded by the GIP gene.

Glucose-Dependent Insulinotropic Peptide (GIP)

It is synthesized and released in response to nutrients from entero-endocrine cells (called K cells) primarily in the proximal small intestine (duodenum and jejunum). In the fasted state circulating levels of GIP are low relative to levels attained after eating, and GIP release into the bloodstream is then stimulated by food ingestion containing glucose or fat

Glucose-Dependent Insulinotropic Peptide (GIP)

GIP achieves its insulinotropic effects by binding to its specific receptor (GIPR), which is positively coupled to increases in intracellular cAMP and Ca_ levels in cells. In addition to being insulinotropic, GIP is involved in fat metabolism in adipocytes: it enhances insulin-stimulated incorporation of fatty acids into triglycerides, stimulates lipoprotein lipase activity, modulates fatty acid synthesis, and promotes cell proliferation and cell survival

Glucagon-Like Peptide-1(GLP-1)

is a posttranslational cleavage product of the proglucagon gene by the prohormone convertase and is a second peptide with incretin activity that potently stimulates glucose dependent insulin secretion

Glucagon-Like Peptide-1(GLP-1)

It is mainly produced in entero-endocrine L cells that are scattered among the enterocytes throughout the small bowel and ascending colon, where they are secreted into the bloodstream in response to nutrient ingestion

Incretin secretion in type 2 diabetes mellitus (T2DM)

T2DM is characterized by a severely impaired or absent GIP insulinotropic effect that most likely results in worsening insulin secretion. However, T2DM seems unlikely to result from deficient incretin secretion.

Incretin secretion in type 2 diabetes mellitus (T2DM)

Based on results obtained in the course of oral glucose tolerance testing and during meal testing, GIP secretion and fasting levels seem to be actually increased, in both the impaired and diabetic state whereas the insulinotropic effect is almost totally lost in T2DM.

Incretin secretion in type 2 diabetes mellitus (T2DM)

most studies seem to agree that the secretion of GIP is normal or even higher in patients with T2DM compared with healthy control subjects.

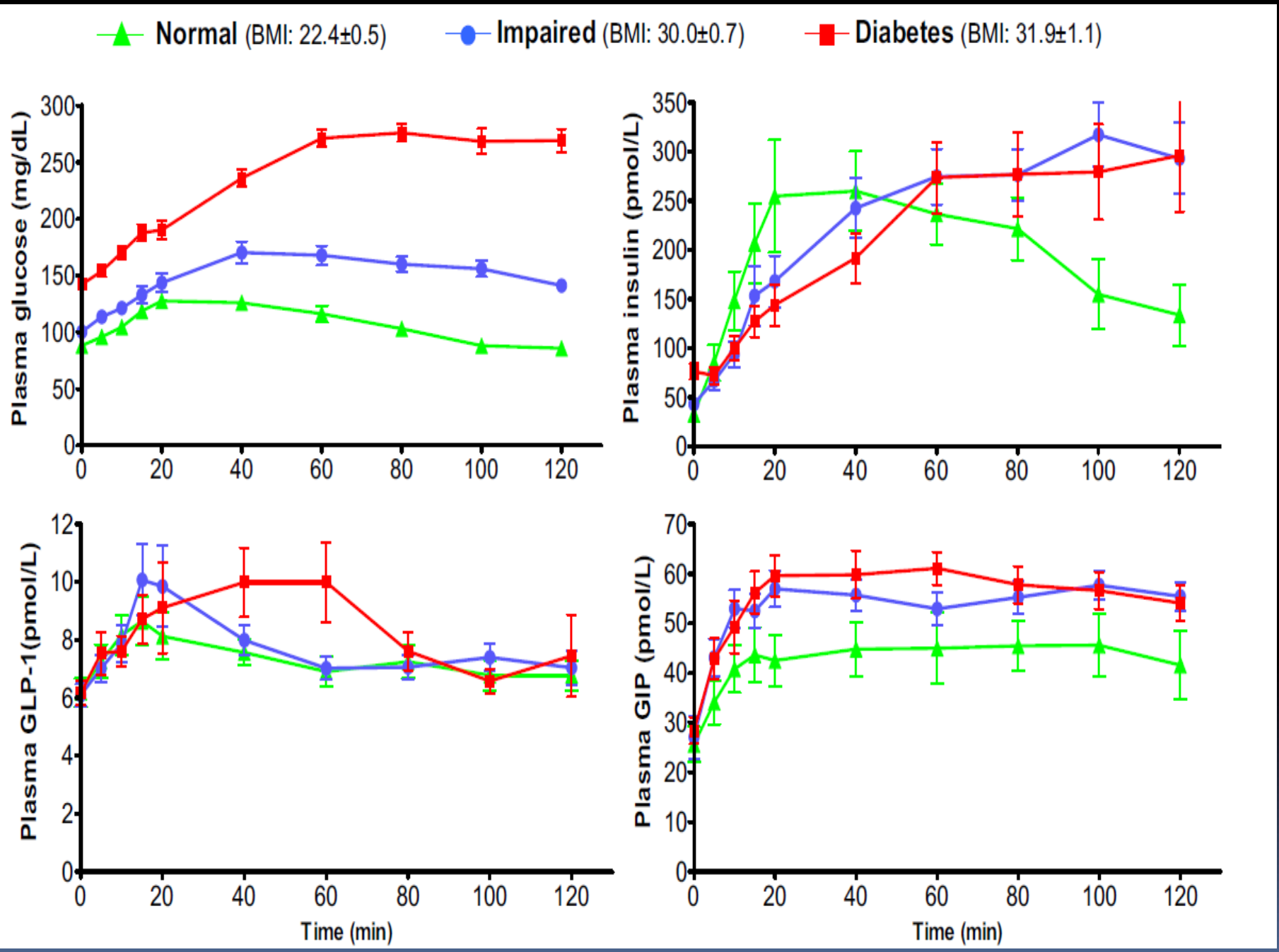
For GLP-1 secretion in T2DM, the data has been confusing, especially those from earlier studies, although a consensus is finally emerging thanks to studies performed in newly diagnosed subjects and subjects with impaired glucose tolerance before receiving any treatment for glucose control

Incretin secretion in type 2 diabetes mellitus (T2DM)

In general, GLP-1 levels reach maximum secretion 17 to 20 min after oral glucose administration, followed by a slow decline toward fasting levels; unfortunately, many older studies began sampling 30 min after oral glucose, thereby missing peak secretion. In contrast, peak secretion occurs 60 to 90 min after a mixed meal.

Incretin secretion in type 2 diabetes mellitus (T2DM)

Data from the Baltimore Longitudinal Study of Aging shows that GLP-1 secretion is not deficient in either the fasting state or after oral glucose in glucose-impaired or diabetic subjects not taking any drugs affecting glucose homeostasis.


Normal (BMI: 22.4±0.5)
Impaired (BMI: 30.0±0.7)
Diabetes (BMI: 31.9±1.1)
Plasma glucose (mg/dL)
Plasma insulin (pmol/L)
Plasma GLP-1(pmol/L)
Plasma GIP (pmol/L)
Time (min)
Time (min)

Incretin secretion in type 2 diabetes mellitus (T2DM)

Therefore, it was evident that T2DM develops in the setting of normal incretin secretion and reduced secretion cannot be evoked as causing the disease. Older studies, using patients with worse metabolic control, on multiple drugs and suffering from diabetes for longer times, have found impairments in GLP-1 secretion and so chronic hyperglycemia and its metabolic consequences may be the cause of the slightly impaired GLP-1 secretion seen in those earlier studies.

Incretin secretion in type 2 diabetes mellitus (T2DM)

Continuous i.v. infusion of GLP-1 also lowers postprandial plasma glucose (PPG) levels in subjects with type 1 diabetes by delaying gastric emptying . These effects of GLP-1 have been consistently shown in a number of human studies

Efficacy of incretin therapy in type 2 diabetes mellitus

-Therapeutic approaches for enhancing incretin action include incretin mimetics, and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity .

-Clinical trials with the incretin mimetic (exenatide and liraglutide) show reductions in fasting and postprandial glucose concentrations, and haemoglobin A1c (HbA1c) (1–2%), associated with weight loss (2–5 kg)..

Efficacy of incretin therapy in type 2 diabetes mellitus

-Orally administered DPP-4 inhibitors (sitagliptin and vildagliptin,) reduce HbA1c by 0·5–1·0%, with few adverse events and no weight gain.

-These new classes of antidiabetic agents also expand β-cell mass in preclinical studies

Concluding remarks

1-T2DM is characterized by a severely impaired or absent GIP insulinotropic effect that most likely results in worsening insulin secretion.

2- It is evident that T2DM develops in the setting of normal incretin secretion and reduced secretion cannot be evoked as causing the disease.

Conclusions

3- Abnormalities of incretin secretion are unlikely to be a primary pathogenic factor in the development of T2DM and are instead a consequence of the diabetic state

4-long-term clinical studies are needed to determine the benefits of targeting the incretin axis for the treatment of type 2 diabetes.

Thanks for listening