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A Review on Incretins

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ABSTRACT

Now a days Diabetes is a dreadful disease which alter the metabolism of carbohydrates, proteins and fatty acids. Most commonly occurring type is non-insulin dependent diabetes mellitus which may affect 90-95% of the people. Incretins are becoming popular these days. Incretins are gut hormones secreted in response to food. They mainly increase the secretion of insulin. Now a days Incretin mimetics, DPP- IV inhibitors are used in the treatment of type-2 diabetes. However, many oral hypoglycemics are available, but still there is a need to overcome the problems associated with oral hypoglycemics.

Keywords: Diabetes, Incretins.

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INTRODUCTION

Diabetes

Diabetes mellitus, commonly known as diabetes, is a group of metabolic disorders in which high blood sugar levels over a prolonged period[1].

There are three types of diabetes mellitus

1. Type 1 diabetes mellitus
2. Type 2 diabetes mellitus
3. Gestational diabetes

- **Type 1 diabetes mellitus** also called as insulin dependent diabetes mellitus or juvenile diabetes. This results from the pancreas failure, not producing sufficient insulin.
- **Type 2 diabetes mellitus** also called as non insulin diabetes mellitus. In this body cells develop resistance towards insulin.
- **Gestational diabetes** is commonly occurred in pregnant women, may develop diabetes during pregnancy.

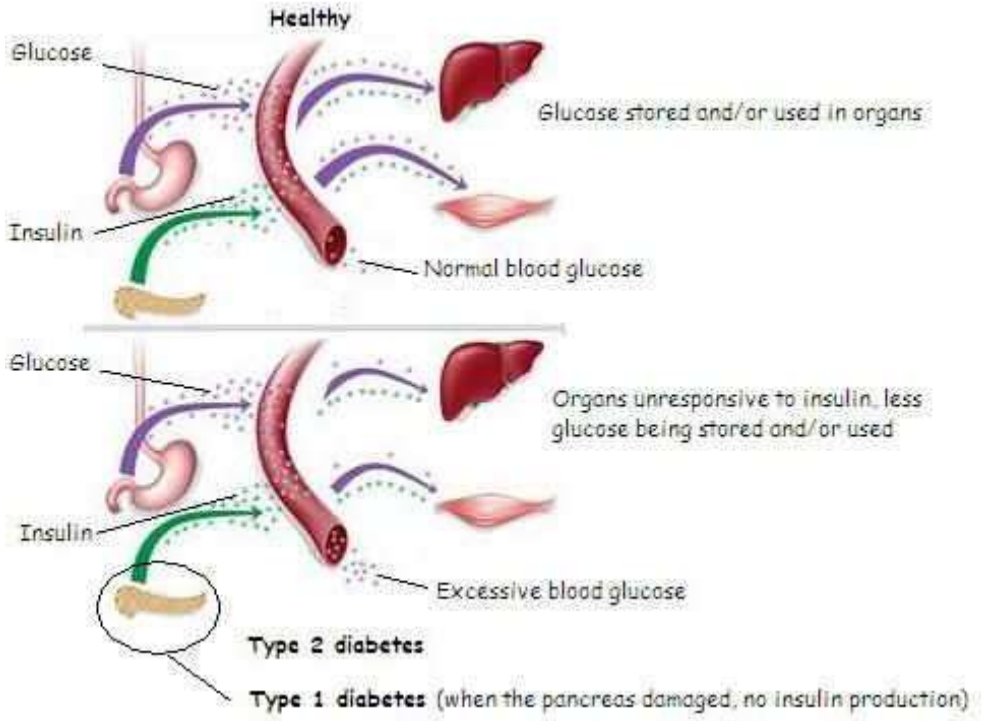

Figure1: Types of diabetes

Incretins

Incretins are peptide hormones secreted from gut. These are the hormones will influence the release of insulin from pancreas. Incretins were released in response to food containing glucose.

so the release of incretins is glucose dependent manner[2]. whenever the food is ingested, incretins were released and stimulate the release of insulin by interacting with receptors present in beta cells of islets of langerhans. Majorly two incretins were identified. Glucagon-like peptide-**1** (GLP-1), glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is secreted by the L cells in the ileum and colon, while GIP is secreted by the K cells in the duodenum. They exert their action through G- protein coupled receptors which were abundantly located in islet cells[3]. Incretins receptors are also present in cells other than islet cells. So they exert pancreatic and extra pancreatic actions. Their predominant role is regulation of energy homeostasis. They delay gastric emptying time and suppress appetite. These effects make a significant role in glucose homeostasis, particularly the control of postprandial glucose[4,5]. The two hormones were almost similar actions but very slight differences.

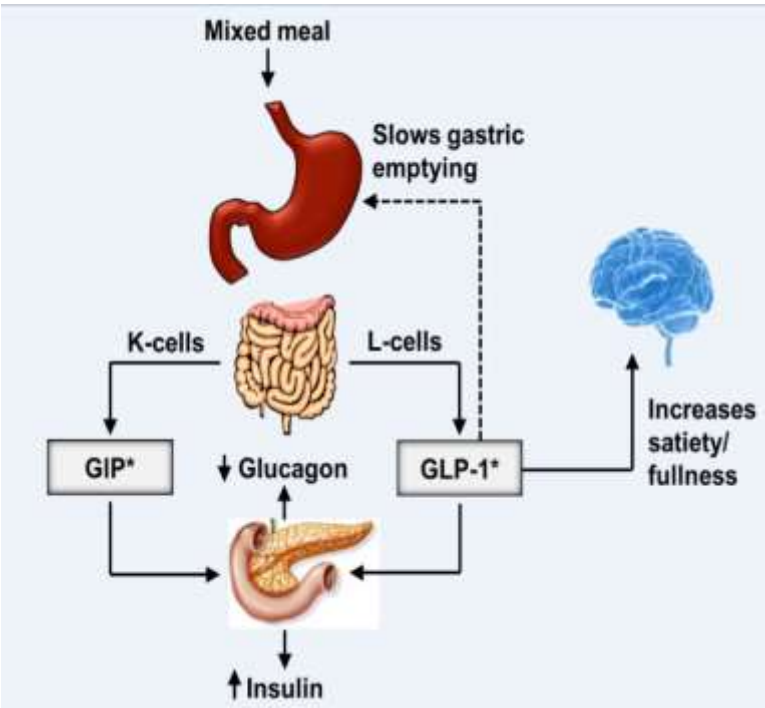

Figure 2: Actions of incretins on various organs

Types of Incretins

Glucagon-like peptide-1(GLP-1)

Glucagon-like peptide-1(GLP-1) is a 30 amino-acid peptide (3355.67 Da) derived from a gene that is secreted by L-cells of the ileum and colon is dependant on the presence of nutrients in the lumen of the small intestine. The GLP-1 receptor is expressed in β-cells and non β- cells like gut, brain, kidneys heart cells etc., but it is more predominant in β cells and less predominant in non β-cells. The agents which cause secretion of GLP-1 include carbohydrate, protein, lipids. Generally sulfonylureas are widely used to treat type 2 diabetes, these compounds can promote

insulin secretion independent of blood glucose and can therefore cause hypoglycemia. Because of the reason Glucagon-like peptide-1 and their analogues are currently used clinically[6].

Actions of GLP-1

Pancreatic actions (Direct actions) [7]

- Stimulates insulin synthesis, secretion.

This action is very particular because, when the plasma glucose concentrations in normal fasting range, GLP-1 no longer stimulates insulin to cause hypoglycemia. GLP-1 appears to restore the glucose sensitivity of β- cells, by possibly increasing the expression of GLU-2 and glucokinase (causing breakdown of glucose) [8, 9.]

- decreases glucagon secretion and suppresses its release
- stimulating neogenesis
- increasing proliferation of β cells
- increases pancreas mass
- inhibits cell apoptosis

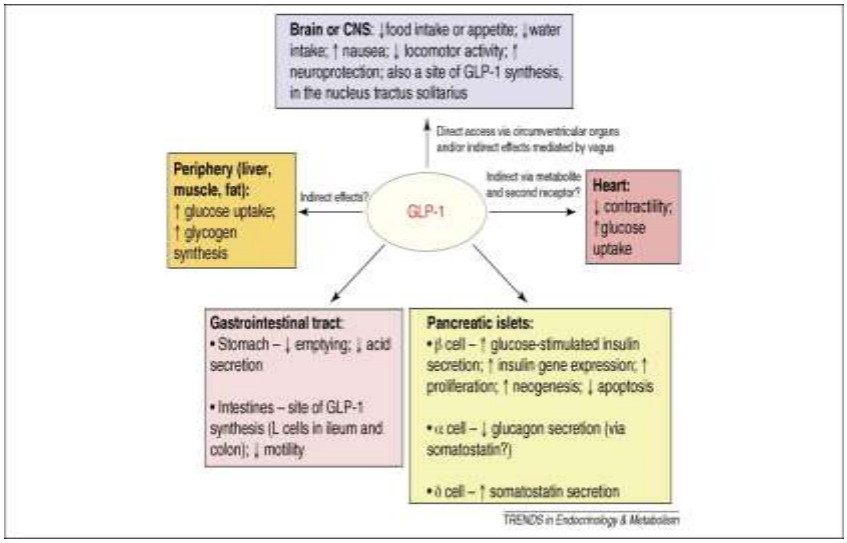

Figure 3: Actions of GLP-1

Extra pancreatic actions

Gastrointestinal tract (GI): reducing the rate of gastric emptying, decreases bowel motility, decreases acid secretion[10].

Brain: As a neurotransmitter in the hypothalamus, GLP-1 increases satiety[11].

On liver, fat, muscle (indirect actions) [12]:

- ✓ Increases glucose uptake
- ✓ Increases glycogen synthesis

✓ Increases lipogenesis

GLP-1 analogues: They also called as incretin mimetics, are agonists of GLP-1 receptor.

E.g. of GLP-1 agonists: Exetanide, liraglutide, lixisenatide, albiglutide, dulaglutide.

Mechanism of action of GLP-1 analogues

All actions related to GLP-1 are applicable to GLP-1 agonists. They include

- Increases insulin secretion, suppresses glucagon release, slows down gastric emptying, increasing satiety via hypothalamic receptors[12].

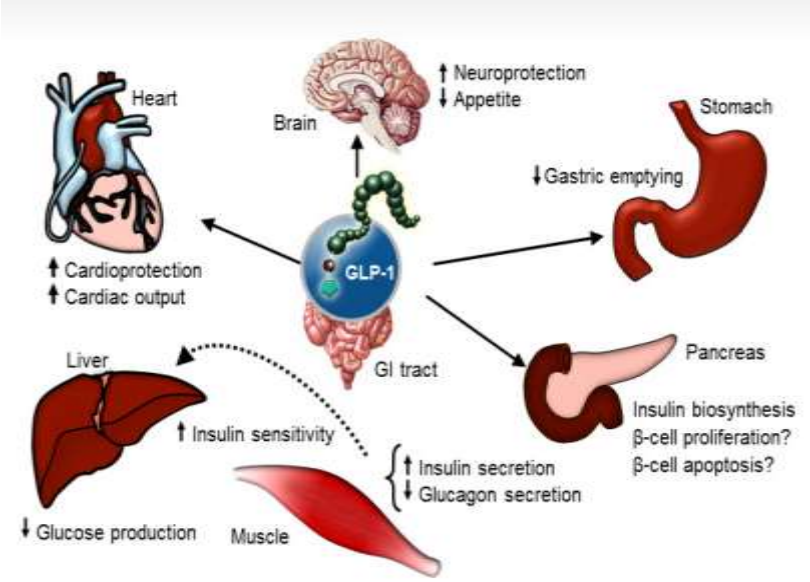

Figure 4: Schematic diagram of actions of GLP-1 analogues

Mainly the action of GLP-1 is increasing the insulin release from the pancreas. But the action of GLP-1 was very limited. Because GLP-1 has very short half life (less than 2 min) and immediately degraded by the enzyme Dipeptidyl peptidase-IV (DPP - IV) [14].

Glucose Dependent Insulinotropic Polypeptide (GIP)[15]

- It is a single 42 amino acid peptide. It is synthesized in and released in response to nutrients from enteroendocrine cells (called K cells) primarily in the proximal small intestine. This is also stimulated by food containing glucose or fat. Unlike GLP-1, it is induced by fat alone, but less extent.
- It achieves its insulinotropic effects by binding to its specific receptor, increases intracellular CAMP and Ca^{2+} levels in β- cells.
- It also interacts with fat metabolism in adipocytes. It increases synthesis of fatty acids into triglycerides and stimulates lipoprotein lipase activity (fatty acid synthesis), promotes β- cell proliferation. It is also very quickly degraded by DPP-IV.

Dipeptidyl peptidase-IV[16]

It is a membrane associated peptidase of 766 amino acids that is widely distributed in numerous tissues. It is normally expressed by the cells of the intestinal brush boarder and is essential for the complete break down of proline containing dietary proteins such as gluten and casein. It is also called as Adenosine deaminase complexing protein-2 or CD26. It plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1[17]. Examples: Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Analgliptin, Teneligliptin, Alogliptin, Gemigliptin.

CONCLUSION

Incretins and Incretin mimetics have many advantages over existing therapies for the treatment of T2DM, including a superior ability to increase glucose-dependent insulin secretion and glucose-dependent glucagon suppression with consequent low risk of hypoglycemia. As oral delivery of proteins and peptides is still a great challenge. Oral delivery of GLP-1 and its analogs is a promising new scheme therapy.

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