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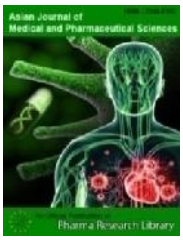

Review Article **Open Access**

A Review on Incretin Mimetics

D.S.S.N. Neelima, P. Hyma, D. Yashwanth Kumar*

Scientific and Applied Research Center, Hyderabad, Telangana, India

A B S T R A C T

Diabetes mellitus is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Acute complications include hypo-glycemia, diabetic ketoacidosis or nonketotic hyperosmolar coma. Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose become elevated. The incretin effect may have important implications in reducing mealtime hyperglycemia in individuals with T2DM. As many drugs are available as antihyperglycemic agents, new class of incretin mimetics are used in the treatment of diabetes type 2.

Keywords: Diabetes mellitus, hypoglycemia, T2DM

A R T I C L E I N F O

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***Corresponding Author**
D. Yashwanth Kumar
Scientific and Applied Research Center, Hyderabad, Telangana, India
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1. Introduction

Definition: Diabetes mellitus is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Diabetes mellitus, often simply referred to as diabetes is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). It is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes. Acute complications include hypoglycemia, diabetic ketoacidosis or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and retinal damage. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

2. Classification

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Type 2 diabetes

Diabetes mellitus type 2 is also known as non-insulin-dependent diabetes mellitus or adult-onset-diabetes. As insulin is not necessary for treatment of Type 2 diabetes, it is known as Non-insulin Dependent Diabetes Mellitus (NIIDM) or Adult Onset Diabetes. Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

This type of diabetes, also known as late-onset diabetes, is characterized by insulin resistance and relative insulin deficiency. The disease is strongly genetic in origin but lifestyle factors such as excess weight, inactivity, high blood pressure and poor diet are major risk factors for its development. People with type 2 diabetes are twice as likely to suffer cardiovascular disease. Type 2 diabetes may be treated by dietary changes, exercise and/or tablets. Insulin injections may later be required. Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.

The causes of type 2 diabetes are multi-factorial and include both genetic and environmental elements that affect beta-cell function and tissue insulin sensitivity. The onset is usually in middle age. Long-term complications from high blood sugar can include increased risk of heart attacks, strokes, and kidney failure. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, and features of autonomic dysfunction, including sexual dysfunction.

Pathophysiology of Type 2 Diabetes Mellitus

Pathophysiology is the study of functional changes in the body which occur in response to disease or injury. The pathophysiology of type 2 diabetes mellitus is characterized by peripheral insulin resistance and ß-cell dysfunction.

Insulin resistance (IR) is a physiological condition where the natural hormone, insulin, becomes less effective at lowering blood sugars. The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects. Certain cell types such as fat and muscle cells require insulin to absorb glucose. When these cells fail to respond adequately to circulating insulin, blood glucose levels rise. The liver helps regulate glucose levels by reducing its secretion of glucose in the presence of insulin. This normal reduction in the liver's glucose production may not occur in people with insulin resistance. Insulin resistance in muscle and fat cells reduces glucose uptake (and so local storage of glucose as glycogen and triglycerides, respectively), whereas insulin resistance in liver cells results in reduced glycogen synthesis and storage and a failure to suppress glucose production and release into the blood.

Insulin resistance normally refers to reduced glucose-lowering effects of insulin. However, other functions of insulin can also be affected. For example, insulin resistance in fat cells reduces the normal effects of insulin on lipids and results in reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Elevated blood fatty-acid concentrations (associated with insulin resistance and diabetes mellitus Type 2), reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose levels. High plasma levels of insulin and glucose due to insulin resistance are a major component of the metabolic syndrome. If insulin resistance exists, more insulin needs to be secreted by the pancreas. If this compensatory increase does not occur, blood glucose concentrations increase and type 2 diabetes occurs.

The most common type of insulin resistance is associated with overweight and obesity in a condition known as metabolic syndrome. Insulin resistance often progresses to full Type 2 diabetes mellitus (T2DM). This is often seen when hyperglycemia develops after a meal, when pancreatic β-cells are unable to produce sufficient insulin to maintain normal blood sugar levels (euglycemia) in the face of insulin resistance. Various disease states make body tissues more resistant to the actions of insulin. Examples include infection (mediated by the cytokine TNFα) and acidosis. As chronic hyperinsulinemia inhibits both insulin

secretion and action and hyperglycemia can impair both the insulin secretory response to glucose as well as cellular insulin sensitivity. Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease. A majority of individuals suffering from type 2 diabetes are obese, with central visceral adiposity. Severe complications can result from improperly managed type 2 diabetes, including renal failure, erectile dysfunction, blindness, slow healing wounds and arterial disease.

β-cell:

There is a progressive decline in β-cell function in Type 2 diabetes. It is coupled with increased insulin sensitivity in peripheral tissues and an eventual decline in β-cell-stimulated insulin production, reduced β-cell response is a primary contributor to the development of diabetes, and later the main determinant of disease progression. Glucagon also plays a contributing role to the hyperglycaemic condition characteristic of Type 2 diabetes. Plasma glucagon levels are elevated in Type 2 diabetes, and glucagon is not suppressed in the postprandial state; this results in increased hepatic glucose production in the fasting state and a failure to suppress this in the postprandial period. Loss of β-cell function and glucagon over-secretion are key components in Type 2 diabetes pathophysiology.

The secondary phenomenon, termed desensitization or ß-cell glucotoxicity, is the result of a paradoxical inhibitory effect of glucose upon insulin release and may be attributable to the accumulation of glycogen within the ß-cell as a result of sustained hyperglycemia. Other candidates that have been proposed are sorbital accumulation in the ß-cell or the neoenzymatic glycation of ß-cell proteins. In some early-onset patients with type 2 diabetes, there may be a deficiency in insulin secretion that may or may not be due to autoimmune destruction of the ß-cell and is not due to a deficiency in the glucokinase gene. In the great majority of patients with type 2 diabetes (±80%), the delay in immediate insulin response is accompanied by a secondary hypersecretory phase of insulin release as a result of either an inherited or acquired defect within the ß-cell or a compensatory response to peripheral insulin resistance.

Oral hypoglycemic agents:

Sulfonyl urea:

- Chlorpropamide
- Glibenclamide
- Tolbutamide

Biguanides:

- Metformin
- Phenformin

Meglitinides:

- Repaglinide
- Nateglinide

Thiazolidinediones:

- Rosiglitazone
- Piogllitazone

Alpha-glucosidase inhibitors:

Acarbose

Incretins

Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose become elevated. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. As expected, they also inhibit glucagon release from the alpha cells of the Islets of Langerhans. The effects of incretins on both insulin levels and glucagons levels are glucose dependent[20-24]. The effect of incretins on insulin stimulation and glucagon suppression can be suppressed in a hypoglycemic environment. This suppression, in turn, may reduce hypoglycemic incidents in patients with T2DM. The incretin effect may have important implications in reducing mealtime hyperglycemia in individuals with T2DM.

Two major incretins:

- GLP-1.
- GIP.

These incretins share a considerable amino acid identity. They both increase insulin secretion.

Mechanism of Action of Incretins

1. Enhancement of glucose-dependent insulin secretion.
2. Suppression of inappropriately elevated glucagons secretion.
3. Slowing of gastric emptying due to vasovagal reflexes which produces feeling of fullness.
4. Decreased food intake. They slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake.

Glucagon –Like Peptide 1

Endogenous GLP-1 is a gastrointestinal hormone secreted from the L cells of the distal aspect of the small intestine. It is derived from a large proglucagon (ie, glucagon precursor) that also encodes for glucagon. GLP-1 is reduced in the fasting state and increases rapidly after a meal. The increase in insulin secretion after a meal is only partially influenced by GLP-1 local activity. Most likely, influences that are hormonally and neurally mediated also exist. The release of GLP-1 is attenuated in patients with T2DM after ingestion of a mixed meal. The effect of GLP-1 action protects ß-cell function. The receptor distribution is located within several organs, including the brain, duodenum, kidneys, liver, lungs, pancreas, and stomach. GLP-1 stimulation produces direct effects on ß cells, resulting in proliferation of ß cells, increased cell regeneration, and reduced cell apoptosis.

The biological activities of GLP-1 include [1-3]

- Glucose-dependent insulin secretion to aid tissue uptake of plasma glucose.
- Suppression of postprandial glucagon to reduce hepatic glucose release.
- Slowing of gastric emptying to avoid overwhelming the circulation with glucose as food is absorbed from the gut.
- Suppression of food intake (appetite). The insulinotropic and glucagonostatic actions of GLP-1 were shown to be glucose dependent.

Gastric Inhibitory Polypeptide

It is also known as Glucose-dependent insulinotropic peptide. Endogenous GIP is a 42-chain amino acid peptide secreted by the lymphocyte K cells. GIP is located within the intestinal epithelium of the proximal duodenum and regulated predominantly with fat consumption. Glucose-dependent insulinotropic peptide is reduced during the fasting state and increased after food ingestion.

Mechanism of action:

- The primary action of GIP is to stimulate glucose-dependent insulin secretion. Thus, enhancement of GIP signaling may have beneficial effects in patients with T2DM.
- Both GIP and GLP-1 are ubiquitous hormones. Their receptor distribution is located within several organs, including the brain, duodenum, kidneys, liver, lungs, pancreas, and stomach.
- The receptors for these hormones are mediated through a G–protein-coupled adenylate cyclase, resulting in an increase of cyclic adenosine monophosphate and activation of protein kinase A.
- These actions lead to increased insulin secretion.

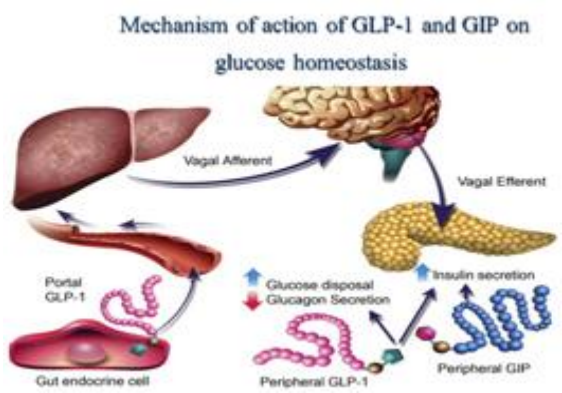

Figure 1: MOA of GLP-1 and GIP on glucose hemostasis

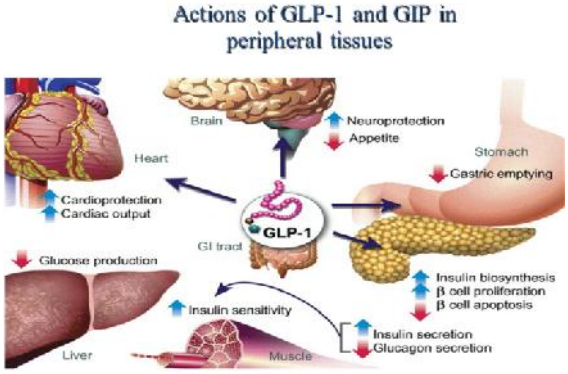

Figure 2: MOA of GLP-1 and GIP in Peripheral tissues

New Paradigms for the Treatment of Diabetes 2

1. Incretin mimetics.
2. DPP-IV inhibitors.

Incretin mimetics:

Incretin mimetics are a new class of pharmacological agents with multiple antihyperglycemic actions. Incretin mimetics mimic some effects of endogenous incretin hormones, including glucose-dependent enhancement of insulin secretion originate in the gastrointestinal tract. Although these agents may exhibit glucoregulatory effects similar to those of GLP-1, their actions might not be mediated solely through the pancreatic GLP-1 receptor. Therefore, the class name "incretin mimetic" is intended to emphasize the glucoregulatory and metabolic effects of these agents, rather than their specific mechanisms of action. Several incretin mimetic GLP-1 analogues have been developed that are resistant to degradation by DPP-IV.

3. GLP-1 analogues

Exenatide

Exenatide is a GLP-1 analogue. Exenatide (marketed as **Byetta**) is a medication approved for the treatment of diabetes mellitus type 2. Exenatide is the fires incretin mimetic approved for clinical use by the US Food and Drug Administration. It reduces HbA1c as well as reduces body weight. Exenatide is administered as a subcutaneous injection of the abdomen, thigh, or arm. Exendin-4, the naturally occurring form of exenatide, was originally isolated from the salivary secretions of the lizard *Heloderma suspectum* (Gila monster) [12].

Exendin-4 is resistant to degradation by mammalian DPP-IV and, thus, has a much longer plasma half-life than GLP-1. Pharmacological studies indicate that exenatide dosing is not recommended during the postprandial period[16] and exenatide administration is not suitable for patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease [17]. In addition, Exenatide has been shown to restore first-phase insulin secretion [13]and to promote ß-cell proliferation and islet neogenesis from precursor cells in both in vitro and in vivo models of diabetes [14-15].

Mechanism of action

1. Exenatide augments pancreas response (i.e. increases insulin secretion) in response to eating meals; the result is the release of a higher, more appropriate amount of insulin that helps lower the rise in blood sugar from eating.
2. Exenatide also suppresses pancreatic release of glucagon in response to eating, which helps stop the liver from overproducing sugar when it is unneeded, which prevents hyperglycemia.
3. Exenatide helps slow down gastric emptying and thus decreases the rate at which meal-derived glucose appears in the bloodstream.
4. Exenatide has a subtle yet prolonged effect to reduce appetite, promote safety via hypothalamic receptors.

Lilraglutide

Liraglutide is a GLP-1 analogue[4]. Liraglutide is administered by subcutaneous injection, once daily at any time, independent of meals. In early clinical trials, liraglutide displayed multiple glucoregulatory activities similar to the actions of endogenous GLP-1 [5-11]. It is a receptor agonist like exenatide; it is an analog of GLP-1 that is DPP-IV resistant. Liraglutide decreases the weight. The reduction in HbA_{1c} level by liraglutide was dose dependent,

with the lowest dosage failing to lead to a decrease in HbA_{1c} level.

Mechanism of action:

1. Liraglutide suppressed postprandial glucose excursions.
2. Reduced fasting plasma glucose concentrations.
3. Enhanced first-phase insulin response after meals.
4. Suppression of postprandial plasma glucagon concentrations.

4. DPP-IV Inhibitors

DPP-IV inhibitors suppress the degradation of a variety of bioactive peptides, including GLP-1, thereby extending their period of action [18]. Both GLP-1 and GIP are proteins that are rapidly degraded by dipeptidyl peptidase IV[25]. These peptidases are ubiquitous serine proteases that are widely distributed in numerous tissues. By cleaving N-terminal amino acids, they cause inactivation of both GLP-1 and GIP. The DPP-IV inactivation process results in greater than 50% inactivation of GLP-1 within 1 to 2 minutes, and greater than 50% inactivation of GIP within 7 minutes. By blocking this action, DPP-IV inhibitors can lead to an increase in endogenous GLP-1 concentration, benefiting patients with T2DM.

They include:

- Vildagliptin.
- Sitagliptin.

Vildagliptin

Vildagliptin (previously identified as LAF237, trade name **Galvus**) is an oral anti-hyperglycemic agent of the new dipeptidyl peptidase-4 inhibitor class of drugs. Vildagliptin was generally well tolerated with cough and nasopharyngitis, the most common adverse events.

Mechanism of action

1. It is a slow-binding inhibitor with a 2-step mechanism of action that is reversible and competitive.
2. Vildagliptin inhibits the inactivation of GLP-1 and GIP by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas.
3. Vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellitus.
4. Oral vildagliptin was associated with suppression of endogenous DPP-IV activity for 12 hours and suppression of postprandial and fasting plasma glucose concentrations[19].
5. Vildagliptin Reduces HbA1c.
6. Basal and postprandial glucagon levels were reduced, but no change in plasma insulin concentrations was observed.
7. There was no change in body weight during this short-term study.
8. Fasting and postprandial plasma glucose concentrations were reduced, but there was no change in plasma insulin.

Sitagliptin

Sitagliptin (Januvia) is an oral antihyperglycemic of the dipeptidyl peptidase-4 inhibitor. This enzyme-inhibiting drug is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for treatment of diabetes mellitus type 2. The benefit of this medicine is its lower side-effects in the control of blood glucose values.

Mechanism of action:

1. Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4).
2. The DPP-4 enzyme inactivates incretin hormones, which are involved in the physiologic regulation of glucose homeostasis.
3. By preventing GLP-1 and GIP inactivation, GLP-1 and GIP are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas.
4. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents.
5. Sitagliptin reduces HbA1c.
6. Sitagliptin slows the inactivation of incretin hormones and thus increases and prolongs their action. By inhibiting DPP-4, it increases and prolongs active incretin levels. This in turn increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

Table.1: Comparison of incretin mimetics and DPP-IV Inhibitors

Incretin mimetics	DPP-IV Inhibitors
Subcutaneous injection.	Oral
Increased sustained level of GLP-1.	GLP-1 increases only at mealtime
Weight loss.	Weight neutral.
Vomiting during 1to 2 months after initial treatment.	No nausea.

5. Conclusion

As many drugs are available as antihyperglycemic agents, new class of incretin mimetics are used in the treatment of diabetes type 2. Incretin mimetics are preferable because incretin mimetics produces less side effects like nausea, headache, and diarrhoea but oral hypoglycemic agents produce toxic effects like hepatic renal failure, diabetic ketoacidosis, hypoglycemia, myocardial infarction, water retention and weight gain. To avoid toxic effects of oral hypoglycemic agents, recent studies suggested that incretin mimetics can be used for the treatment of diabetes 2.

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