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Meenakshi
Medicinal and Process Chemistry Division CSIR-Central Drug Research Institute Lucknow, Uttar Pradesh, India.

Amar Kumar
Environmental Studies Sri Aurobindo College (Evening) University of Delhi, Delhi, India.

Correspondence:
Amar Kumar
Environmental Studies Sri Aurobindo College (Evening) University of Delhi, Delhi, India.

Therapeutic potential of GLP-1 for treatment of diabetes

Meenakshi, Amar Kumar

Abstract
Glucose homeostasis are primarily controlled by two indigenous peptides namely insulin and glucagon. In addition to insulin and glucagon several other endogenous substances are discovered that directly or indirectly control glucose metabolism. Diabetes is a metabolic disease which is caused by a deficiency of insulin or by improper functioning of insulin signaling. There are therapies which are used to cure diabetes but they are associated with limitations like they cause hypoglycemia and do not improve the health of beta cells. But with the discovery of incretin hormones like GIP and GLP-1 diabetes progression may be prevented as both of the peptides show insulinotropic activity and demonstrated that GLP-1 is primarily responsible for stimulation of insulin secretion GLP-1 stimulate insulin secretion dependent of glucose concentration and have potential long-term ability to improve the β-cell function, therefore the potential ability of the GLP-1 drug class may be helpful in delaying or perhaps even preventing diabetes progression.

Keywords: Diabetes, incretin hormones, GLP-1, Insulin

1. Introduction
Diabetes mellitus is a group of metabolic diseases characterized by abnormally high levels of plasma glucose in the fasting state [1, 2] or after administration of glucose during an oral glucose tolerance test. Diabetes is generally classified into Diabetes, type 1 and type 2. The Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM) is usually diagnosed in children and young adults, and is caused due to cellular-mediated autoimmune destruction of the β-cells of the pancreas, leading to a deficiency of insulin and consistently requires therapeutic replacement of insulin. Autoimmune destruction of β-cells have multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Whereas the Type 2 diabetes (T2D) or non-insulin-dependent diabetes mellitus (NIDDM) is the most common form of diabetes and is primarily characterized by resistance to insulin action, increased hepatic glucose production (e.g., From glycogen degradation), decreased insulin-mediated glucose transport into muscle and adipose tissues and impaired β-cell function leading to loss of the early phase of insulin release in response to hyperglycemia stimuli. The higher blood glucose levels would be expected to result in even higher insulin values if β-cell function is normal. However, in the event of higher insulin secretion the hyperglycemia is found to be uncontrolled due to insulin resistance. Thus, higher insulin secretion is insufficient to compensate for insulin resistance [3, 4]. In normal human being blood glucose level is maintained between 70 mg/dl and 110 mg/dl before meals (fasting plasma glucose, FPG) and under 140 mg/dl (7.8 mmol/L) at two hours after eating (oral glucose tolerance test, OGTT). Diabetes is diagnosed with FPG greater than 126 mg/dl (7.0 mmol/L) and OGTT greater than 200 mg/dl (11.1 mmol/L) [5].
The diagnosis of diabetes is primarily dependent on measurement of blood glucose levels, but in order to understand further details of disease status other parameters are also now available viz. Estimation of glycosylated hemoglobin (HbA_{1c}) and levels of C-peptide. The levels of HbA_{1c} determine the blood glucose flow and the levels of C-peptide along with insulin level are helpful to determine insulin secretion capability of the patient. HbA_{1c} is glycosylated hemoglobin and its test serves as a marker for average blood glucose levels over the preceding 2-3 months prior to the measurement. For normal glucose levels, HbA_{1c} should be around (<6.0% or ~135% mg/dl) [5] but as glucose level increases the value of HbA_{1c} crosses its normal range. Another parameter of diabetes diagnosis is measurement of C-peptide to monitor insulin production, thereby determines β-cell activity and cause of hypoglycemia [6]. During insulin biosynthesis C-peptide (connecting peptide) is cleaved off from the proinsulin molecule.

C-peptide and insulin are eventually released in equimolar amounts into the portal circulation. Any insulin that the body does make will be reflected in the C-peptide level. Range of C-peptide in normal person is 0.5 to 2.0 or 3.0 ng/mL.

Insulin and glucagon has been the central theme of controlling glucose homeostasis in humans and other vertebrates [7]. Insulin is secreted in response to the increase in plasma glucose following a meal. Insulin is a peptide hormone composed of 51 amino acid residues of two chains connected via intermolecular disulphides with a molecular weight of 5808 Da, secreted from the β-cells of pancreatic islets of Langerhans. The storage of carbohydrate and lipids, and synthesis of protein is promoted by insulin. The three main target tissues which insulin acts on are the liver, muscle, and adipose tissue. Insulin stimulates both glycolysis and glycogen synthesis in the liver and in muscle, insulin increases glucose transport, glucose metabolism, and glycogen synthesis. Glucagon plays a major role in maintaining normal glucose levels in blood via increasing it when blood glucose levels begin to fall below the normal range. Glucagon is a linear peptide of 29 amino acids is synthesized as proglucagon in the intestinal L-cell and proteolytically processed to yield glucagon within α-cells of the pancreatic islets. Glycogen breakdown and gluconeogenesis is stimulated by glucagon and it also inhibits glycogen synthesis and glucose oxidation. Glucagon is secreted in response to hypoglycemia or low blood concentrations of glucose and its secretion is inhibited by high levels of blood glucose. Metabolic actions on target tissues of glucagon are thus the opposite of those of insulin. This fine balance between insulin and glucagon action provides a key factor in the control of blood glucose.

In addition to insulin and glucagon several other endogenous substances are discovered that directly or indirectly control glucose metabolism. In 1987, the discovery of amylin (figure 1) has expanded the understanding that a variety of different hormones contribute to glucose homeostasis. Amylin is a 37-amino acid peptide, a β-cell hormone which is co-secreted with insulin from the pancreatic β-cell and is therefore deficient in individuals with diabetes [7]. Amylin has been shown to delay gastric emptying and inhibit meal-stimulated glucagon secretion, thereby influencing the rate of glucose appearance in the circulation. It is also known to reduce food intake and body weight. Human Amylin is liable to aggregate and form amyloid fibrils, which may play a part in β-cell destruction in type 2 diabetes, making it unsuitable for therapeutic use. Therefore, synthetic analogues have been developed that are devoid of aggregating properties. Pramlintide is a synthetic analog of Amylin (Figure 1) which is approved by the FDA for treatment of types 1 and 2 diabetes in patients who use mealtime insulin.

2. Significance of Incretin effect and enteroinsular axis for diabetes control

The control of diabetes remains unabated due to non availability of diabetes therapy resulting in cure of diabetes. The therapy developed so far is basically focused on the stimulation of insulin secretion from β-cells viz. secretagogues and sensitizing the insulin actions known as insulin sensitizers.

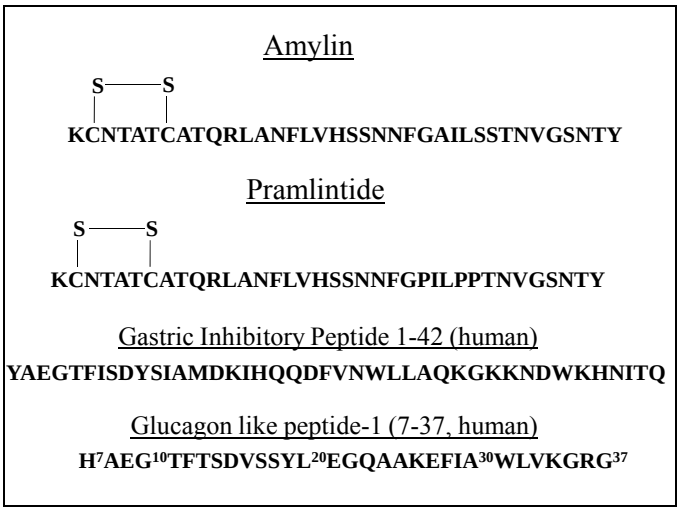

Fig 1: Structure of peptides secreted by the pancreas (Amylin, GIP and GLP-1) and Amylin analog Pramlintide

In both the cases β-cells are stressed resulting in poor β-cell health leading to further complications of disease. In late 90's extensive efforts were made to understand the disease progression, which led to identification of a network called enteroinsular axis controlled by non pancreatic substances that are responsible for maintaining β-cell health as well as secretion of insulin. Search for gastrointestinal effects on hormonal system started in 1929 when Zunz and La Barre hypothesized that gastrointestinal factors stimulate insulin secretion after a meal [8]. In 1932, La Barre introduced for the first time the name "incre´tine" (incretin) for a substance extracted from the upper gut mucosa, which lowers the blood glucose level of normal rabbits and dogs if given intravenously, subcutaneously and by oral routes [9]. The incretin effect is believed to be mediated almost equally by the two incretin hormones. Perley and Kipnis [10] estimated that 50% of the insulin secreted after an oral glucose load was released by gastrointestinal factors. Unger and Eisentraut [11] coined for this system the term enteroinsular axis. Incretin hormones are mediators of postprandial insulin secretion forming the basis of 'enteroinsular axes. Creutzfeldt [12] suggested that this axis encompasses nutrient, neural, and hormonal signals from the gut to the islet cells secreting insulin, glucagon, somatostatin, or pancreatic polypeptide. The criteria for fulfillment of the incretin part of the enteroinsular axis are that incretin hormone must be released by nutrients, particularly carbohydrates, and it must stimulate insulin secretion in the presence of elevated blood glucose levels.

First incretin was isolated and sequenced by John C. Brown from intestinal mucosa (in search for a gastrone) a new peptide which he named gastric inhibitory polypeptide (GIP) because of its inhibitory effect on gastric acid secretion in dog's

duodeno-jejunal mucosa [13, 14]. In 1973 with John Dupre´, he demonstrated the insulinotropic action of GIP in man. [15] Graeme Bell *et al.,* were the first to isolate a mammalian pancreatic preproglucagon cDNA [16]. Mammalian preproglucagon cDNA contained three glucagon-related peptides arranged in tandem, glucagon and glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) as named by Dr. Bell and colleagues. Cloning of the hamster cDNA led to rapid isolation and sequencing of the human glucagon gene [17]. Linda Lopez and Grady Saunders reported the isolation of bovine preproglucagon cDNA and Heinrich *et al.,* characterized the rat preproglucagon cDNA. [18] As late as 1985, insulinotropic effect of GLP-1(7-36)-NH_2, identified by cloning of preproglucagon, was found and an even stronger insulinotropic effect suggested for the truncated GLP-1(7-36)-NH_2. [19] Therapeutic potential of these peptides shows that incretins can be used as effective therapy for diabetes. Treatment based on GLP-1 has further therapeutic, but GIP is not found to be as effective treatment for diabetes, as GIP-based derivatives studied shown to be resistant to DPP-IV enzyme, but less potent as compared to native GIP [20].

3. Glucagon Like Peptide-1 (GLP-1) a novel incretin hormone

GLP-1 (7-37) -NH_2 is a 30 amino acid peptide released from the L-cells in the intestine in response to food intake and promotes the release of insulin from the β-cells in the pancreas. Major regulators of the GLP-1 secretion include nutrients (glucose and fatty acids), gastrointestinal hormones (gastric inhibitory polypeptide (GIP), gastrin-releasing polypeptide (GRP) and the vagal nerve dependent release of acetylcholine [21-23]. These hormones do not have insulinotropic activity at glucose concentrations that are too low to elicit insulin secretion (4 mM and lower). GLP-1 is a product of the preproglucagon gene, which is generated by tissue-specific post-translational processing of proglucagon. The gene is expressed in α-cells of the pancreas, L-cells of the small intestine and the hypothalamus. Proglucagon is processed by 2(PC2) enzyme in the pancreatic islet α-cells (to release mainly glucagon), and by prohormone convertase 1/3 (PC1/3) in the intestinal L cells (to produce mainly GLP-1, GLP-2) [24]. In the pancreas, the main GLP-1 related products are GLP-1(7-36)-NH_2 and glycine-extended GLP-1(1-37). The GLP-1(7-36)-NH_2 and GLP-1(7-37) are active forms of GLP-1 where GLP-1(7-36)-NH_2 is predominant form and exists in approximately 75% and the glycine-extended GLP-1(7-37) is present in approximately 25% of the total enterogastrone GLP-1 [25].

The effects of GLP-1 are mediated via specific G-protein-linked transmembrane receptors. GLP-1 receptor is a member of the seven membrane-spanning G-protein-coupled receptor from the B family also referred to as the secretin/glucagon family [26]. The GLP-1 receptors are present in brain, lung, pancreatic islets, stomach, hypothalamus, heart, intestine, and kidney [27, 28]. The GLP-1(7-36)-NH_2 and GLP-1(7-37) produce powerful incretin effects in response to food intake for insulin signaling and secretion. GLP-1 has another beneficial effect of controlling diabetes as well as disease progression. GLP-1 has a unique property of regulation of β-cell mass that include-stimulation of replication and growth, inhibition of apoptosis of existing β-cells and neogenesis of β-cells from duct precursor cells which is absent in other drug therapies for diabetes cure [29-32]. GLP-1 has a number of other functionally important effects viz. stimulation of insulin biosynthesis, restoration of glucose sensitivity to the islets, and stimulation of increased expression of the glucose transporter GLUT-2 and glucokinase [33-35]. GLP-1 inhibits glucagon secretion which leads to reduced hepatic glucose output [36]. In the gut, GLP-1 is a potent inhibitor of motility and gastric emptying and has also been shown to inhibit gastric acid secretion [37, 38]. The inhibition of gastric emptying leads to decreased food intake and reduced body weight [39-41].

The primary advantage of GLP-1 over other antihyperglycaemic drugs is that it does not induce hypoglycemia, which is one of the main side effects associated with insulin secretagogues used for diabetes treatment. These properties provide a new hope for control and cure of diabetes.

4. Incretin effects of GLP-1

GLP-1 stimulate insulin secretion from pancreatic β-cells via incretin effect that underlies a different mechanism compared to already known insulin secretagogues namely sulfonylureas etc. Food intake provokes the secretion of several hormones involved in digestion and gut motility. These hormones also include secretion of gut hormones that facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas. The observation that enteral nutrition provided a more potent insulinotropic stimulus compared with isoglycaemic intravenous challenge led to the development of the incretin concept [10]. The term incretin, first used by La Barre in 1932, refers to gut derived hormones that stimulate insulin secretion in response to nutrients. The incretin effect is considered responsible for the higher insulin release in response to food intake or an oral glucose load compared to intravenous glucose load. A diagrammatic presentation of incretin effect on insulin secretion is shown in Figure 2.

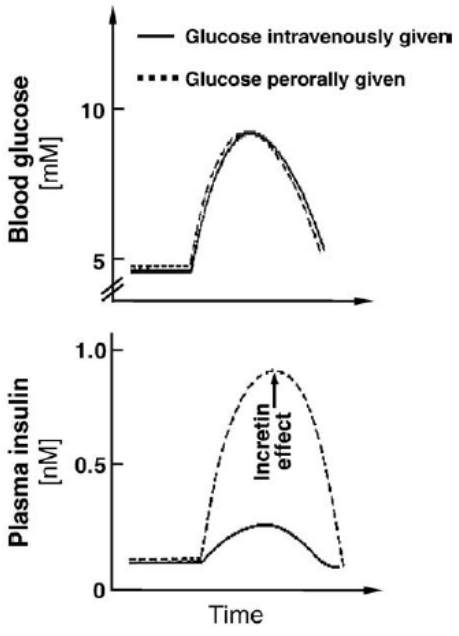

Fig 2: Incretin effect (schematically shown differences in curves after i.v. and per os application of glucose)

The incretin effect is one of the vital components of endocrine signalling from the gut affecting pancreatic islet physiology and function. This incretin effect is believed to be mediated by mainly two incretin hormones: GIP and GLP-1. Both hormones enhance insulin secretion to an extent that can fully account for the incretin effect. It has been shown that in normal healthy subjects GLP-1 is several times more potent

than GIP on a molar basis at equivalent glycemic conditions. The incretin hormone GLP-1 has been found to be highly beneficial for the development of novel alternate therapeutic approach for diabetes. Available treatment for diabetes is often associated with several undesired effects viz. weight gains and stressing β-cells which result in progressive β-cell failure in T2D and eventually leading to type-1 diabetic situation. This new innovative concept for treatment of T2D comprising incretin based approach where the possibility of weight gain is not only eliminated but these therapeutic approaches also help in reducing body weight by decrease in apatite and delay in gastric emptying.

5. Therapeutic potential of GLP-1

During 1990s the promising therapeutic potential of GLP-1 as a pharmacological tool for treating T2D was proposed, along with characterization of the incretin effect [42, 43]. GLP-1 has also been tested both in normal human subjects as well as in subjects with either type-1 or type-2 diabetes [44, 45]. Surprisingly, it has also been shown to be active in subjects with type-1 diabetes by lowering the amount of insulin required, because of its capability of decreasing gastric motility and inhibiting glucagon secretion. In patients with type-2 diabetes, continuous infusion of exogenous GLP-1 via either the intravenous or the subcutaneous route was reported to nearly normalize glycemia by enhancing glucose-mediated insulin secretion, suppressing glucagon secretion and slowing gastric emptying [42, 46, 47]. Unexpectedly, the effects of a single subcutaneous injection of GLP-1 were disappointing. Although high plasma levels of immunoreactive GLP-1 were achieved, insulin secretion rapidly returned to pretreatment values and blood glucose concentrations were not normalized [48]. Nevertheless, the effect of repeated subcutaneous administration on fasting blood glucose is as good as that of intravenous administration [49] while continuous subcutaneous administration for 6 weeks reduces fasting and postprandial glucose concentrations and lowers HbA_{1c} concentrations [50]. The insulinotropic action of GLP-1 were shown to be glucose-dependent therefore, long-term exogenous GLP-1 therapy would not be expected to induce hypoglycemia when administered alone [51]. It is evident from the above descriptions that GLP-1 and other incretin mimics have great potential for the development of safe and effective treatment of diabetes.

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