**The Incretin Effect And Its Significance – Basic To Applied Physiology**

**Solomon Sathishkumar\*, Rashmi Vyas\*\***

\*Associate Professor, Associate Professor, Department of Physiology, \*\*Professor, Department of Physiology; Core educator, Medical Education Unit; Convener, MCI Regional Centre for National Faculty Development

Christian Medical College, Vellore

**Abstract**: The gastrointestinal tract releases several hormones in response to oral food intake and absorption. The increased secretion of insulin in response to oral glucose administration when compared to intravenous glucose administration is called the Incretin effect. This is due to release of certain gut hormones which in turn cause an increased glucose stimulated insulin secretion. The incretin effect is due to two main hormones: Glucose-dependent Insulinotropic Polypetide (GIP) and Glucagon-like Peptide – 1 (GLP-1). The insulinotropic effect of GLP-1 is preserved in type 2 diabetic patients. Since GLP-1 is rapidly degraded by the plasma enzyme Dipeptidyl Peptidase IV (DPP-IV), GLP-1 receptor agonists and DPP-IV inhibitors are now being used to treat type 2 diabetes.

**Author for correspondence:** Solomon Sathishkumar, Associate Professor, Department of Physiology, Christian Medical College, Vellore-632002, Tamil Nadu, India, E Mail: [solomon@cmcvellore.ac.in](mailto:solomon@cmcvellore.ac.in)

**Introduction:** Intake of food is associated with release of several hormones from the gastrointestinal mucosa1. These hormones exert several physiological effects and thus play important roles in maintaining normal homeostasis1. Knowledge of the structure, stimulus for release, mechanism of action and functions of these gut hormones is crucial for understanding normal physiology, patho-physiology and planning treatment strategies for various disease conditions. Among various gut hormones, a few of them affect insulin secretion and thus play a role in diabetes mellitus2,3,4.

Type 2 diabetes is a major health problem all over the world5. The incidence of type 2 diabetes in India is on the increase6. Effective management of this disease is essential in order to avoid the multiple complications associated with it. Novel treatment strategies are being researched in order to treat this disease satisfactorily. This non-systematic or journalistic review focuses on the incretin effect and the inroads it has made in the treatment of type 2 diabetes mellitus. The journal articles that were reviewed were accessed using the PubMed search engine and the inter-library loan policy.

**Incretin effect:** In the early 1960s, experiments were conducted to compare amount of insulin secretion in response to oral versus intravenous glucose administration7,8. These experiments revealed that oral glucose caused greater insulin secretion when compared to glucose given intravenously7,8. This increased amount of insulin secretion with orally administered glucose when compared with intravenously administered glucose is called the ‘**Incretin effect**’7,9. There is approximately two to three fold increase in insulin secretion due to the incretin effect in normal people8. Research was further extended to find out the cause for the incretin effect. This led to the possibility that oral glucose caused release of certain gut hormones which in-turn stimulated insulin secretion. Studies done as early as the 1960s proved this hypothesis right2,3. The gut hormones responsible for the incretin effect are called **incretin hormones**10.

**Incretin hormones:** The main gut hormones which are responsible for the incretin effect were found to be **Glucose-dependent Insulinotropic Polypetide (GIP)**2 also called Gastric Inhibitory Polypeptide and **Glucagon-like Peptide – 1 (GLP-1)**11. They are both responsible equally for the incretin effect12. They are peptide hormones and are released in response to absorption of food. The fasting plasma level of these hormones is less than 10 pmol/L and increases to about 50 pmol/L following food ingestion thus bringing about the incretin effect. Both hormones have a very short half life (ie about 2 minutes for GLP-1 and about 5 minutes for GIP) and are rapidly degraded or cleaved by Dipeptidyl Peptidase IV (DPP-IV) which is a plasma enzyme, and later cleared by the kidneys12.

Glucagon-like Peptide – 1 (GLP-1) is released by ‘L’ cells, mainly in the mucosa of the distal ileum and colon. It is released in response to absorption of glucose, protein and fat in the diet. GLP-1 exists as two important potent forms i.e. GLP-17-37 amide and GLP-17-36 amide. GLP-1 receptors are located on beta cells, alpha cells and in other tissues12.

Glucose-dependent Insulinotropic Polypetide (GIP) is released by ‘K’ cells mainly in the duodenal mucosa in response to glucose and fat absorption. GIP receptors are located on beta cells and to a lesser proportion in other tissues12. The principle physiological effects of GLP-1 and GIP are summarized in table 112, 13, 14, 15, 16.

**Table 1: Structural and functional aspects of incretin hormones: Glucagon-like Peptide – 1 (GLP-1) and Glucose-dependent Insulinotropic Polypetide (GIP)12, 13, 14, 15, 16.**

|  |  |  |
| --- | --- | --- |
| **Incretin hormones** | **GLP-1** | **GIP** |
| Chemical nature | Peptide | peptide |
| Different forms | GLP-17-37,GLP-17-36 amide. | GIP |
| Produced in the gastrointestinal mucosa by | ‘L’ cells, mainly in the mucosa of the distal ileum and colon | ‘K’ cells mainly in the duodenal mucosa |
| Stimulus for secretion | absorption of food in the diet with special References to glucose, protein and fat | absorption of food in the diet with special References to glucose and fat |
| Effect on  insulin gene transcription and synthesis | Increases | Increases |
| Effect on glucose stimulated insulin secretion | Increases | Increases |
| Effect on insulin sensitivity | Increases | Increases |
| Effect on beta cell proliferation or neogenesis | Increases | Increases |
| Effect on beta cell mass | Increases | Increases |
| Effect on glucose disposal | Enhances | Not known |
| Effect on food intake | Decreases | Not known |
| Effect on satiety | Increases | Not known |
| Effect on gastric emptying | Decreases | No effect |
| Effect on glucagon secretion | Decreases | No effect |
| Effect on body weight | Decreases | Not known |

*Principal action of incretins:* The principal action of the incretin hormones is to augment glucose-stimulated insulin secretion17. GLP-1 and GIP hormone receptors are situated on beta cells as well as in other tissues12. Animal studies on mice with inactivated GIP or GLP-1 receptors revealed a marked reduction in the glucose-stimulated insulin secretion and showed an impaired glucose tolerance18,19. This proves that incretin hormones are important hormones for glucose homeostasis.

Both GIP and GLP-1 increase insulin synthesis, increase beta cell proliferation and reduce apoptosis12. Experimental evidence suggests that GLP-1 increases insulin sensitivity, slows gastric emptying and glucose absorption, inhibits glucagon secretion, reduces food intake and enhances satiety12,14.

*Mechanism of action producing the incretin effect:* The incretin hormones increase glucose-stimulated insulin secretion from the beta cells by acting on G protein coupled receptors and activating adenylyl cyclase, thus increasing cAMP levels. This causes increased calcium entry into the beta cells which in turn causes exocytosis of the insulin granules causing insulin release12.

**What happens to the incretin effect in Type 2 Diabetes Mellitus?** The main features of Type 2 diabetes include insulin resistance and impaired glucose stimulated insulin release17. The incretin effect was studied in type 2 diabetic patients in order to find the possible causes for the impaired glucose stimulated insulin release. Human clinical studies revealed a marked *decrease in the incretin effect* in type 2 diabetic patients20. This decrease in the incretin effect in type 2 diabetic patients contributes to the impaired glucose tolerance seen in these patients.

Further studies were carried out to see if the decrease in incretin effect seen in type 2 diabetic patients was due to a decrease in incretin hormone secretion or decrease in the incretin hormone function. Studies in type 2 diabetic patients revealed that GIP secretion was near normal post meals but GLP-1 secretion was markedly reduced21.

Studies were conducted to assess if the insulinotropic effect of GLP-1 was preserved in diabetic patients, even though the secretion of GLP-1 was reduced. These studies revealed that the insulinotropic effect of GLP-1 was preserved but slightly reduced in type II diabetic patients but the insulinotropic effect of GIP was greatly reduced22.

Since the insulinotropic effect of GLP-1 was preserved in type 2 diabetic patients further studies were done to assess the effectiveness of GLP-1 in treating type 2 diabetes mellitus. In a study done, intravenous infusion of GLP-1 completely normalized plasma glucose in patients with long-standing type II diabetes23. However, continuous intravenous infusion is not practical as a long term treatment modality. Though GLP-1 has promising effects, it is rapidly degraded/ cleaved by the enzyme Dipeptidyl Peptidase IV (DPP-IV) and thus cannot be used clinically in the form of GLP-1 per se.

Therefore research was focused on finding GLP-1 receptor agonists which would function as GLP-1 but not get degraded by DPP-IV. Research was also focused on preserving GLP-1 by identifying inhibitors for the enzyme DPP-IV.

**GLP-1 receptor agonists:** GLP-1 receptor agonists bind to the GLP-1 receptors and bring about the effects of GLP-1 as described previously. They do not get degraded by the enzyme DPP-IV. A prominent GLP-1 receptor agonist identified is Exendin-424. It is a peptide isolated from saliva of Gila monster (Heloderma suspectum) 25. It has 50% sequence homology to GLP-1 and is stable against DPP-IV17.

Exenatide is a synthetic form of exendin-426. Studies done on type 2 diabetic patients comparing Exenatide and placebo injections as an additional treatment to previously prescribed treatment revealed a significant reduction in HbA1C and significant decrease in body weight with Exenatide27. Thus Exenatide plays an important role in the control of type 2 diabetes as a GLP-1 receptor agonist28. Exenatide is used clinically as a twice daily subcutaneous injection at a dose of 10 μg29. A longer acting form of Exenatide has been developed30.

Another GLP-1 receptor agonist that has reached the market is Liraglutide31, 32. Clinical trials with Liraglutide have shown a decrease in HbA1C levels and a decrease in body weight of diabetic patients, thus playing an important role in glycaemic control33.

**DPP-IV inhibitors:** The inhibitors of the enzyme DPP-IV play an important role as they prevent early degradation of the incretin hormones, thus preserving the incretin effect34. Animal studies revealed that DPP-IV inhibitors had a protective effect on both native and exogenous GLP-1, and enhanced the glucose-stimulated insulin release35. Numerous human clinical trials have proved the effectiveness of DPP-IV inhibitors36,37.

DPP-IV inhibitors in the market now include Sitagliptin and Vildagliptin36, 37. They are oral anti-diabetic agents. Since the action of these drugs last for a long duration, Sitagliptin is given once a day and Vildagliptin twice a day17. There is improved control of blood sugars when these drugs are given along with other anti-diabetic medications17. Recent reviews have concluded that both Sitagliptin and Vildagliptin are well tolerated34,38.

**Conclusion:** Incretin effect refers to the increased glucose-stimulated insulin secretion due to hormones secreted from the gastrointestinal tract. The two main incretin hormones are GLP-1 and GIP. Though the incretin effect is severely reduced in type 2 diabetic patients, the insulinotropic effect of GLP-1 is preserved. As GLP-1 is degraded rapidly by the plasma enzyme DPP-IV, GLP-1 receptor agonists and DPP-1V inhibitors enhance glycaemic control in type 2 diabetic patients.

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