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 Polypeptide (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

Introduction: Intake of food is associated with release of several hormones from the gastrointestinal mucosa[1]. These hormones exert several physiological effects and thus play important roles in maintaining normal homeostasis[1]. 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 mellitus[2,3,4].

Type 2 diabetes is a major health problem all over the world[5]. The incidence of type 2 diabetes in India is on the increase[6]. 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 administration[7,8]. These experiments revealed that oral glucose caused greater insulin secretion when compared to glucose given intravenously[7,8]. 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 people[8]. 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 right[2,3]. 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 Polypeptide (GIP)**[2] also called Gastric Inhibitory Polypeptide and **Glucagon-like Peptide – 1 (GLP-1)**[11]. They are both responsible equally for the incretin effect[12]. 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 kidneys[12].

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-$1_{7\text{-}37}$ amide and GLP-$1_{7\text{-}36}$ amide. GLP-1 receptors are located on beta cells, alpha cells and in other tissues[12].

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 tissues[12]. The principle physiological effects of GLP-1 and GIP are summarized in table 1[12, 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-1_{7-37}, GLP-1_{7-36} 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 secretion[17]. GLP-1 and GIP hormone receptors are situated on beta cells as well as in other tissues[12]. 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 tolerance[18,19]. 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 apoptosis[12]. Experimental evidence suggests that GLP-1 increases insulin sensitivity, slows gastric emptying and glucose absorption, inhibits glucagon secretion, reduces food intake and enhances satiety[12,14].

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 release[12].

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 release[17]. 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 patients[20]. 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 reduced[21].

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 reduced[22].

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 diabetes[23]. 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-4[24]. 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-IV[17].

Exenatide is a synthetic form of exendin-4[26]. 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 Exenatide[27]. Thus Exenatide plays an important role in the control of type 2 diabetes as a GLP-1 receptor agonist[28]. Exenatide is used clinically as a twice daily subcutaneous injection at a dose of 10 μg[29]. A longer acting form of Exenatide has been developed[30].

Another GLP-1 receptor agonist that has reached the market is Liraglutide[31, 32]. Clinical trials with Liraglutide have shown a decrease in HbA_1C levels and a decrease in body weight of diabetic patients, thus playing an important role in glycaemic control[33].

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 effect[34]. Animal studies revealed that DPP-IV inhibitors had a protective effect on both native and exogenous GLP-1, and enhanced the glucose-stimulated insulin release[35]. Numerous human clinical trials have proved the effectiveness of DPP-IV inhibitors[36,37].

DPP-IV inhibitors in the market now include Sitagliptin and Vildagliptin[36, 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 day[17]. There is improved control of blood sugars when these drugs are given along with other anti-diabetic medications[17]. Recent reviews have concluded that both Sitagliptin and Vildagliptin are well tolerated[34,38].

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.

Acknowledgement: The authors thank the faculty and staff of the Department of Physiology for their support.

Referencess

1. Yamada T. Gut hormone release induced by food ingestion. *Am J Clin Nutr* 1985; 42(5 Suppl):1033-1039.
2. Dupre J, Ross SA, Watson D, et al. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab. 1973; 37(5):826-828.
3. Orskov C. Glucagon-like peptide-1, a new hormone of the entero-insular axis. Diabetologia. 1992; 35(8):701-711.
4. Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009; 297(1-2):127-136.
5. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J 2012; 27(4):269-273.
6. Shetty P. Public health: India's diabetes time bomb. Nature. 2012; 485(7398):14-16.
7. Elrick H, Stimmler L, Hlad CJ Jr., et al. Plasma Insulin response to oral and intravenous glucose administration. The Journal of Clinical Endocrinology & Metabolism.1964; 24:1076-1082.
8. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. J Clin Invest. 1967; 46(12):1954-1962.
9. Creutzfeldt W, Ebert R. New developments in the incretin concept. Diabetologia. 1985; 28(8):565-573.
10. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007; 132(6):2131-2157.
11. Kreymann B, Williams G, Ghatei MA, et al. Glucagon-like peptide-1 7-36: a physiological incretin in man. The Lancet. 1987; 8571:1300-1304.
12. Girard J. The incretins: from the concept to their use in the treatment of type 2 diabetes. Part A: incretins: concept and physiological functions. Diabetes & Metabolism. 2008; 34(6 Pt 1):550-559.
13. Kieffer TJ, Habener JF.The glucagon-like peptides. *Endocrine Reviews*. 1999; 20(6):876-913.
14. Gautier JF, Choukem SP, Girard J. Physiology of incretins (GIP and GLP-1) and abnormalities in type 2 diabetes. Diabetes Metab. 2008; 34 Suppl 2:65-72.
15. Starich GH, Bar RS, Mazzaferri EL. GIP increases insulin receptor affinity and cellular sensitivity in adipocytes. Am *J* Physiol.1985; 249(6 Pt 1):E603-607.
16. Nauck MA Unraveling the science of incretin biology. The American Journal of Medicine. 2009; 122(6 Suppl):S3-S10.
17. Vilsbøll T, Hare KJ, Bagger JO, et al. Glucagon-like peptide-1 and diabetes treatment. International Diabetes Monitor. 2009; 21(1): 1-7.
18. Miyawaki K, Yamada Y, Yano H, et al. Glucose intolerance caused by a defect in the entero-insular axis: a study in gastric inhibitory polypeptide receptor knockout mice. *PNAS*.1999; 21; 96(26):14843-14847.
19. Cani PD, Holst JJ, Drucker DJ, et al. GLUT2 and the incretin receptors are involved in glucose-induced incretin secretion. *Molecular and Cellular Endocrinology,* 2007; 276(1-2):18-23.
20. Nauck M, Stöckmann F, Ebert R, et al. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986; 29(1):46-52.
21. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. The *Journal* of *Clinical Endocrinology* & *Metabolism* 2001; 86(8):3717-3723.
22. Nauck MA, Heimesaat MM, Orskov C, et al. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. The *Journal* of *Clinical Investigation*. 1993; 91(1):301-307.
23. Nauck MA, Kleine N, Orskov C, et al. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993; 36(8):741-744.
24. Göke R, Fehmann HC, Linn T, et al. Exendin-4 is a high potency agonist and truncated exendin-(9-39)-amide an antagonist at the glucagon-like peptide 1-(7-36)-amide receptor of insulin-secreting beta-cells. *Journal of Biological Chemistry,* 1993; 268(26):19650-19655.

25. Furman BL. The development of Byetta (exenatide) from the venom of the Gila monster as an anti-diabetic agent. Toxicon. 2012; 59(4):464-471.
26. Degn KB, Brock B, Juhl CB, et al. Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. Diabetes. 2004; 53(9):2397-2403.
27. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007; 298(2):194-206.
28. Shin J, Chang JS, Kim HS, et al. Effects of a 6-Month Exenatide Therapy on HbA1c and Weight in Korean Patients with Type 2Diabetes: A Retrospective Cohort Study. Diabetes Metab J. 2012; 36(5):364-370.
29. Robles GI, Singh-Franco D. A review of exenatide as adjunctive therapy in patients with type 2 diabetes. Drug Des Devel Ther. 2009; 21(3):219-240.
30. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study.The Lancet. 2008; 372(9645):1240-1250.
31. Fujishima Y, Maeda N, Inoue K, et al. Efficacy of liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, on body weight, eating behavior, and glycemic control, in Japanese obese type 2 diabetes. Cardiovasc Diabetol. 2012; 14; 11:107.
32. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. The Lancet. 2012 S0140-6736(12)61267-7.
33. Vilsbøll T, Zdravkovic M, Le-Thi et al. A long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care. 2007; 30(6):1608-10
34. Karagiannis T, Paschos P, Paletas K, Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ. 2012; 12; 344:e1369.
35. Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. Diabetes. 1998; 47(5):764-9.
36. Muscelli E, Casolaro A, Gastaldelli A, et al. Mechanisms for the antihyperglycemic effect of sitagliptin in patients with type 2 diabetes. J Clin Endocrinol Metab. 2012. 97(8):2818-26.
37. Bluher M, Kurz I, Dannenmaier S, et al. Efficacy and safety of vildagliptin in clinical practice-results of the PROVIL-study. World J Diabetes. 2012. 15;3(9):161-9
38. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008: 16;(2):CD006739.