**GLUCOREGULATORY ACTIONS OF INCRETINS/ANTI-INCRETINS**

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**INTRODUCTION**

Diabetes mellitus (DM) is a major lifestyle disease and is unquestionably the most challenging public health problem of 21st century with a worldwide prevalence of 387 million (8.3%) and predicted to be 592 million by 2035. India, on one occasion known as the ‘diabetes capital of the world’ was home to 61.3 million patients with Type 2 Diabetes mellitus (T2DM) in 2011 with prophecies of 101.2 million diabetics by 2030. [1]

The vast majority of cases of diabetes fall into four broad etio-pathogenetic categories. First category: Type 1 DM, in which the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can frequently be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. Second category: T2DM is much more prevalent; the cause is a combination of resistance to insulin action and an insufficient compensatory insulin secretory response. Categories third and fourth: Other specific types and gestational DM respectively. [2]

**TYPE 2 DM AND INCRETIN- ANTI-INCRETIN THEORY**

The concept of ***incretins*** is at least a century old (Table 1).

**TABLE 1: Milestones in Diabetology with special reference to Incretin/Anti-incretin Theory.**

|  |  |
| --- | --- |
| Year | The Development of Incretin-Based Therapies |
| 1906 | The role of a gut-derived hormone to treat diabetes was first alluded to. |
| 1921–1922 | Extraction of insulin from pancreas and its potential to treat type 1 diabetes was shown. |
| 1932 | The term “incretin” was used for the first time to refer to a substance derived from the gut, presumably a hormone, which regulates insulin secretion after eating. |
| 1964–1967 | Clinical proof that a gut-derived factor positively modulated insulin secretion. |
| 1971 | The first incretin, Gastro Intestinal Peptide (GIP), was isolated and sequenced. |
| 1985 | The second incretin, Glucagon-Like Peptide-1 (GLP-1), was described. |
| 2002 | Exendin-4, a GLP-1 receptor agonist extricated from Gila monster lizard saliva, was shown to powerfully stimulate insulin secretion in a glucose-dependent manner in subjects with and without T2DM. |

Gastro Intestinal Peptide (GIP) was the first incretin and Glucagon-Like Peptide-1 (GLP-1) the second and final incretin to be characterized. [3] ***Incretins*** are gut hormones that potentiate insulin secretion after ingestion of meal in a glucose-dependent manner. [4] In response to ingestion of food, they are released from the gut into the bloodstream and they then modulate the insulin secretory response to the products within the nutrients in the food. Therefore, by definition, incretin hormones are insulinotropic (i.e., they induce insulin secretion) at normal physiological concentrations seen in the plasma after ingestion of food. [3] The two best-studied incretins are: 1) GIP and 2) GLP-1. They employ their insulinotropic actions through distinct G-protein-coupled receptors, which are highly expressed on islet β cells and non-islet cells and also exert indirect metabolic actions. [4]

The β-cell secretion of insulin is greater after the oral administration of glucose than after the intravenous administration, expressed as C-peptide levels. This difference in insulin secretion is referred to as the “incretin effect” [5,6], which may be responsible for 50% to 70% of the total insulin secreted following oral glucose intake. [7]

The ***anti-incretin*** theory postulates that the nutrient passage through the GI-tract also activates another set of hormones known as anti-incretins. They suppress the secretion and action of insulin through negative feedback mechanisms to balance the effects of incretins and other postprandial glucose-lowering mechanisms (like suppression of hepatic glucose production via stimulation of nutrient sensing, glucagon, and ghrelin) [Figure: 1] [8].

 

Healthy individuals are in a state of incretin/anti-incretin balance. [9, 10]. The ‘anti-incretin’ theory postulates the subsistence of nutritionally stimulated, gastrointestinal, neuroendocrine signals that antagonize the effects of incretins. A normal, physiologic balance between incretins and ‘anti-incretins’ ensures normal excursions of blood glucose and proper functioning of β-cells. This theory suggests that an increase or untimely production of the anti-incretin signal might disrupt the incretin–anti-incretin homeostatic mechanism and eventually affects the functions of a number of organs that are involved in the regulation of metabolism (like β cells, adipose tissue and brain). This theory also predicts that in patients with T2DM, gastrointestinal bypass surgery could prevent the release of excess of anti-incretins, which reinstates the proper incretin–anti-incretin balance, and ultimately results in the improvement of T2DM. [11] The outcome of certain types of bariatric surgery which resulted in rapid amelioration of glucose tolerance, lead to conclude that dopamine acts as an “anti-incretin” signal that counterbalances the stimulatory effect of GLP-1. [12]

**BIOCHEMICAL ASPECTS OF INCRETINS**

***Gene structure and synthesis***

The first incretin hormone described was GIP. Human GIP is a single 42-amino acid peptide derived from the post- translational processing by PC1/3 of proGIP, a 153-amino acid precursor that is encoded by a 459-bp open reading frame and whose gene: the *gip* gene is localized to chromosome 17q. GIP is amember of a family of structurally related hormonesthat includes secretin, glucagon, and vasoactive intestinal peptide. [3] In addition to encoding glucagon, the *proglucagon* gene encodes two glucagon-like peptides, that have nearly 50% amino acid homology to glucagon, designated GLP-1 and glucagon-like peptide-2 (GLP-2, which is not insulinotropic, does not have glucose-lowering properties, and is consequently not an incretin). [3]

***Stimulants and Secretion***

GIP exerts glucose-dependent stimulatory effects on insulin secretion, thereby ensuring rapid insulin mediated uptake of glucose into tissues.It is synthesized in and released in response to nutrients from enteroendocrine cells (called K cells) primarily in the proximal small intestine (duodenum and jejunum). [3]

GLP-1 potently stimulates glucose dependent insulin secretion, is a second peptide with incretin activity. [3] It is synthesized in and secreted from enteroendocrine L cells found throughout the small and large intestine, after posttranslational processing of proglucagon by prohormone convertase 1/3 (PC1/3). More L cells are located in the distal ileum and colon than in the duodenum and jejunum, in contrast to GIP-secreting K cells. K/L cells seem most abundant in terminal ileum. Within few minutes after oral glucose in humans, plasma levels of GLP-1 increase rapidly. [4] After meal ingestion, release of GLP-1 occurs bi-phasically, with an early phase (15–30 min) and a prolonged late phase (1–2 h); GIP has a similar secretion profile. [3, 6]

***Mechanism of action***

Both GIP and GLP-1 are ubiquitous hormones. They act by binding to their specific G-protein–coupled receptors. [5,6] Their receptors are distributed within several organs including: brain, duodenum, kidneys, liver, lungs, pancreas, and stomach. [5] The GIP receptor is found in pancreatic β-cells, central nervous system, and adipose tissue, whereas the GLP-1 receptor (GLP-1R) is expressed in islet α- and β-cells, the central nervous system, gastrointestinal tract, heart, kidney and lung. [6]

***Degradation***

Both GLP-1 and GIP are proteins that are rapidly degraded by dipeptidyl peptidase 4 (DPP-4). [7]

**BIOCHEMICAL ASPECTS OF ANTI-INCRETINS**

In addition to its recognized neuronal functions, dopamine (DA) has additional regulatory functions outside the nervous system (whereby it is synthesized by and released from non-neuronal tissues). [12] The existence of a second (gut-based) layer of regulation of glucose homeostasis is suggested by the kinetics of release of GLP-1 and DA. [12] β-cells of islet in humans exploit an autocrine DA-mediated inhibitory circuit to regulate insulin secretion. β-cells also express the DA active transporter and the large neutral amino acid transporter (heterodimer) permitting them to import circulating DA or L-3,4 dihydroxyphenylalanine (L-DOPA), its biosynthetic precursor. The capacity to import DA or L-DOPA from the extracellular space probably indicates that DA may be an endocrine signal as well. In humans, after a mixed meal stimulus there are contemporary serum excursions of incretins, DA and L-DOPA, recommending that DA may act as an anti-incretin as postulated by the foregut hypothesis proposed to explain the early effects of bariatric surgery on T2DM. DA mediates a glucose-stimulated insulin secretion (GSIS) inhibitory circuit in human β-cells is recent evidence that researchers have provided. Based on their data and previous studies, authors have conjectured the existence of a second layer of glucose homeostasis, with endocrine signaling originating in the gut upon mixed meal stimulation. During GSIS, DA and insulin are released and dopamine receptor (D2R) is delivered to the cell surface, where it binds DA. DA signaling through D2R is a dominant inhibitor of glucose-dependent insulin secretion. [13]

Glucose-stimulated insulin secretion from pancreatic islets is down-regulated by dopaminergic signaling. In this negative feedback loop, DA that is synthesized in the β-cells from circulating L-DOPA, serves as an autocrine signal that is co-secreted with insulin, and prompts a tonic inhibition on glucose-stimulated insulin secretion. Cells in the GI tract produce L-DOPA, and following a mixed meal its concentration increases in the blood plasma. [12] A substantial amount of work has shown that the components necessary for DA synthesis and secretion are all present in the β-cell.

The idea of a second layer of regulation of glucose homeostasis originates in the foregut and hindgut hypotheses postulated to explain the effects of bariatric surgery on T2DM. According to the hindgut hypothesis, the rapid delivery of nutrients to the distal intestine leads to the secretion of “incretins” which enhance insulin release and/or action, causing a subsequent decrease in blood glucose levels. [12] An alternate foregut hypothesis was also posited; according to which bypass of the upper small intestine resulted in the removal or diminution of a hyperglycemia-promoting (“anti-incretin”) signal. GLP-1 derived from the L-cells (found in the ileum and colon) is now recognized as the major factor responsible for this incretin effect. As described above, dopamine and/or L-DOPA fulfill several requirements of such an anti-incretin posited by the foregut hypothesis. [12]

**HOW THIS THEORY CHANGES THE WAY WE THINK ABOUT T2DM**

It has long been understood that the pathophysiology of T2DM is founded on the triad of: 1) progressive decline in insulin-producing pancreatic β-cells, 2) an increase in insulin resistance, and 3) increased hepatic glucose production. It is now evident that other factors also play a significant role in pathogenesis of T2DM. These factors are: 1) Defective actions of the GI incretin hormones: GLP-1 and GIP, and 2) Excess of anti-incretin signals. [7]

As per the predictions of anti-incretin theory, excess of anti-incretin signals, conceivably stimulated by macronutrient composition or chemical additives of modern diets, may cause insulin resistance, reduced insulin secretion, and β-cell depletion, leading to T2DM. Contrariwise, reduction of anti-incretin signals below thresholds essential to control incretin-driven responses may result in postprandial hypoglycemia and uncontrolled β-cell proliferation. Changes in the anti-incretin/incretin balance may explain benefits and complications of gastric bypass surgery.[8] Another explanations propositioned for the impaired incretin effect are: 1) The reduction in overall β-cell function and mass, which occurs during the natural disease history and 2) The defective secretory capacity of β-cells in response to incretin stimuli. [14]

Although the mechanisms underlying the reduced β-cell response to GIP remain unclear, more current studies suggest that hyperglycemia alters the physiological response as a result of down-regulation of GIPR expression/activity [3] and/or attenuation of receptor signaling. Loss of GIPR expression and GIP responsivity was associated with ubiquitination and GIP receptor degradation under conditions of hyperglycemia in both rodent and human islets. [4]

While GIP concentration is normal or moderately increased in patients with T2DM, the insulinotropic actions of GIP are significantly diminished or absent. [3,7] Thus, T2DM patients have an impaired responsiveness to GIP that most likely results in worsening of insulin secretion. However, T2DM seems unlikely to result from deficient incretin secretion. One of the reasons repetitively given for using Exenatide or DPP-4 inhibitors is that they lead to normalization of incretin levels that are allegedly reduced compared with non-diabetic subjects. [3] In contrast to GIP, diminished secretion of GLP-1 results in reduced levels of this incretin hormone in patients with T2DM, [15] whereas the insulinotropic actions of GLP-1 is maintained to a great extent. [14] Thus, it is clear that the incretin effect of GLP-1 is better preserved in T2DM, in contrast to that of GIP. [3]

**PROOF OF CONCEPT**

***Bariatric/metabolic surgery*** highlights the important and significant role of the small intestine in glucose homeostasis, while until few years ago; it was only the pancreas and liver that were thought to represent the regulatory organs for glucose disposal. Studies have revealed that the sustained weight loss and rapid glycemic control occur following a number of GI operations: bariatric surgery [9] and they have also been shown to cause remission of T2DM as well as improvement of hypertension, dyslipidemia and reduction of cardiovascular disease and death associated with diabetes and obesity. [8] This, in turn, guided to the introduction of metabolic surgery, an innovative medical discipline in which a surgical manipulation of the GI tract (e. g., through a Roux-en-Y gastric bypass [RYGB] or Bilio-Pancreatic-Diversion, BPD) yields a sustained remission of DM. This in turn prevents postprandial hyperinsulinemic hypoglycemia. BPD surgery (the bypass of the duodenum, the entire jejunum and the first portion of the ileum) induces normalization of peripheral insulin sensitivity, while the bypass of a shorter intestinal tract by RYGB mainly improves the hepatic insulin sensitivity. RYGB also significantly increases insulin secretion. The pathophysiological background of this metabolic effect is based on the anti-incretin theory. [9]

Hence, bariatric/metabolic surgery appears to be an effective treatment for obesity and its related comorbidity, T2DM. Reversal of hyperglycemia in 83% of patients was seen by Pories et al over a decade ago in his 10-year follow up study on the effects of bariatric surgery in T2DM. [13] Numerous human investigations have shown that RYGB and other procedures can improve T2DM by a variety of GI mechanisms, including changes in: 1) gut hormones: In humans, RYGB causes a three to fourfold increase in postprandial levels of GLP-1, an incretin hormone that stimulates insulin release from the pancreas and also exerts anti-apoptotic effects on the β-cells. Increased expression of islet GLP-1 receptor after RYGB could contribute to increased β-cell mass; 2) bile acids metabolism; 3) intestinal micro-biota, nutrient sensing; 4) reprogramming of intestinal glucose metabolism. This demonstrates a critical and previously underappreciated role of the gut in glucose metabolism and underscores the importance of further research on the mechanisms of action of GI surgery; 5) In particular, RYGB restores first-phase insulin response and results in hypersecretion of C-peptide and insulin following nutrient ingestion, suggesting enhancement of β-cell function. Studies have been done that add support to the hypothesis that RYGB can stimulate β-cell growth. Immune-reactive cells for GLP-1 receptor were also 3.8-fold higher after RYGB. The authors concluded that increased β-cell mass can explain improved glucose tolerance after RYGB. [8]

The hindgut hypothesis proposes that nutrient delivery to the distal intestine results in the secretion of “incretins,” which enhances insulin release and/or action. The foregut hypothesis posits that GI bypass reduces the secretion of upper GI factors that normally defend against hypoglycemia and antagonizes the effects of incretins by decreasing insulin secretion and/or promotes insulin resistance. [13]

Overall, it is conceivable that bypass and/or partial resection of organs known to store and produce significant amounts of insulin secretion inhibitor (DA) from nutritional sources would move the organism to a more glucose-tolerant state. [12]

**PHARMACOLOGICAL AND CLINICAL ASPECTS**

Recognition and a better understanding of the role of the incretins and the enzyme involved in their degradation has resulted in the clinical development of a variety of agents for the treatment of DM. [7,15] The clinical use of incretins in their natural forms has been hampered by the fact that they have a short half-life because of fast inactivation by DPP-4, and a continuous infusion is impractical. [6] Two incretin-based treatment strategies comprehending potentiation of incretin receptor signaling for the treatment of type 2 diabetes are: 1) The GLP-1 receptor agonists (degradation-resistant synthetic/chemically modified peptides) that bind GLP-1Rs and mimic the action of naturally occurring GLP-1 (incretin mimetics), which possess many of the glucoregulatory actions of incretin peptides [6, 7] and 2) the DPP-4 inhibitors: which by inhibiting the enzyme decrease the degradation of endogenous incretin hormones (both GIP and GLP-1) [6,14], and thus prolong the activity of endogenous incretin hormones by diminishing their degradation (incretin enhancers). Several incretin-based therapeutic agents are: Exenatide, Liraglutide, and Exenatide long-acting release (LAR); Albiglutide and Taspoglutide (GLP-1 agonists); and Sitagliptin, Saxagliptin, Vildagliptin, and Alogliptin (DPP-4 inhibitors). [6]

Studies have shown that long-acting glucagon-like peptide-1 receptor agonists (LA-GLP-1RAs) might deliver extra therapeutic benefits over other available incretin-based therapies. Compared with other incretin-based therapies, LA-GLP-1RAs yield greater improvement in hemoglobin A1C (HbA1C) and fasting plasma glucose. They provide lesser effect on postprandial glucose, result in a potentially favorable adverse event profile and similar reduction in body weight compared with Exenatide twice daily. [16]

Incretin-based therapies have revolutionized the medical management of T2DM. There are several unique therapeutic benefits of incretin-based therapies: 1) Significant reduction of HbA1C when used as monotherapy and in combination regimens, 2) Low risk of hypoglycemia, 3) Favorable effects on body weight, 4) Enhanced efficacy with other anti-diabetics in combination regimens for glycemic management. Their safety and tolerability are similar to other anti-diabetic medications. [17]

**INCRETIN-BASED THERAPY IN THE PRE-DIABETIC AND FRANK DIABETIC STAGE**

Evidence exists that the period between the initial abnormalities of glucose metabolism and the onset of diabetes is long and that a many individuals with prediabetes are likely to progress to diabetes or to remain in the abnormal glycemic state. Consequently, various intervention strategies to prevent advancement to overt disease have been sought. Limited evidence regarding incretin-based therapy in prediabetes seems to indicate some advantage, but it appears that the treatment needs to be of long duration. Current ADA, EASD, and other association guidelines for the management of T2DM encourage initial lifestyle changes (to decrease weight and increase physical activity) and Metformin early after diagnosis to triumph glycemic goals. Barring contraindications, Metformin is the preferred first therapy for most patients. Recent studies reveal that metformin modulates components of the incretin axis also; it increases expression of the GLP-1 receptor, and increases GLP-1 concentration by enhancing preproglucagon expression. However, in certain situations (e.g. when hypoglycemia or weight gain constitute a problem, and when metformin is contraindicated or not tolerated), incretins should be considered as a treatment option. In the second step, treatment augmentation with incretin mimetics and DPP-4 inhibitors is applicable when one drug alone is not sufficient to achieve glycemic goals. Basically, four options are there: adding incretin mimetics to i) metformin, ii) pioglitazone (at present the only available drug of the TZD class), iii) a sulfonylurea, or iv) Insulin. When used in connotation with metformin or pioglitazone, the chief advantages of incretins are pathophysiological. These two drugs are insulin sensitizers (in muscle, adipose tissues, and liver as in the case of TZDs), whereas incretins target different pathological mechanisms (as discussed above), and consequently potentiate the glucose-lowering action. When combined with metformin, avoidance of hypoglycemia and better weight control are the key benefits of incretins. The addition of incretin mimetics or DPP-4 inhibitors to metformin is of particular advantage in patients who need an increase in endogenous insulin secretion, but who would be at high risk for hypoglycemia from sulfonylureas. Both incretins and TZDs are believed to have beneficial effects on β-cells by improving and preserving their function and probably increasing β-cell mass. The complementary effect of incretin-based therapies and insulin on fasting and postprandial glucose control provides a basis for association of these agents in the management of T2DM.

At the third stage of treatment intensification, a triple drug combination may be contemplated for patients that do not achieve satisfactory glycemic control on double therapy, and when insulin treatment is not the preferred choice. At this stage, the best alternative might be to associate incretin-based agents with metformin and a TZD, principally when insulin resistance is the main concern. Exenatide, liraglutide, and sitagliptin are accepted for use in triple combination with metformin and sulfonylurea/TZD. [14]

**CLINICAL OUTCOMES**

Both the GLP-1 receptor agonists and the DPP-4 inhibitors have established safety and efficacy in the management of hyperglycemia in patients with T2DM. [7] There are other elements also that distinguish these two classes of drugs, apart from their different mechanisms of action, which can help clinicians identify patients who would almost certainly benefit from the therapeutic intervention with either of them. First is the route of administration: GLP-1R agonists require subcutaneous administration, whereas DPP-4 inhibitors are taken as oral tablets, and this difference could be significant in terms of expediency of use and adherence to therapy. Second is the influence on body weight: GLP-1R agonists cause sustained and significant weight loss, however DPP-4 inhibitors are weight neutral, so obese subjects are more likely to benefit from therapy with a GLP-1R agonist. Third is the occurrence of side effects: therapy with GLP-1R agonists is associated with a higher incidence of adverse GI effects predominantly nausea, whereas with DPP-4 inhibitors infections seem to be more frequent. [6]

**CONCLUSIONS AND FUTURE PERSPECTIVES**

An improved understanding of the roles played by GIP and GLP-1in the pathogenesis of T2DM might provide clinicians with important details considering the therapeutic application of incretin-based therapies, including the GLP-1 receptor agonist exenatide and the DPP-4 inhibitors. Antidiabetes agents whose development is based on the numerous pharmacologic effects of incretin hormones, can address the multifaceted nature of T2DM and overcome some existing limitations of traditional therapies, particularly those related to weight. This becomes more convincing given the close link among T2DM, obesity, and increased cardiovascular risk. [7] At present, incretin-based therapies are most extensively used as add on to metformin to provide satisfactory glycemic control after metformin failure. However, early in the disease course they are also recommended as monotherapy, and later in triple combination. In pre-diabetic subjects also, these agents may be a promising therapeutic tool. [14]

Surgical manipulation of total body dopamine content accompanied by stimulation of GLP-1 secretion, might be responsible for the rapid improvement in glucose tolerance and enhanced insulin secretion observed before weight loss following RYGB. Alternatively, since blocking the dopaminergic feedback increases insulin secretion, therefore the dopamine receptor, or one of the steps downstream of its activation, is a potential target for new drugs to treat T2DM. [12]

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