Review Article

Gut hormones in glucose homeostasis and current treatment approach in the control of T2DM - A succinct review

ABSTRACT

Gut–brain axis plays a key role in the regulation of energy homeostasis and glucose metabolism through various hormones. Gut hormones are peptides synthesized by specialized cells of enteroendocrine located in the epithelium of the stomach, small bowel and large bowel. Gut hormones activate neural circuits to signal peripheral organs for coordination of overall energy intake and assimilation.Incretins, Leptins, CCK, Oxyntomodulin, PYY and Gastrin are the major gut hormones involved in glucose metabolism. Group of gut peptides that are secreted after nutrient intake and stimulate insulin secretion together with hyperglycaemia are known as incretin hormones. Certain gut hormones like cholecystokinin (CCK) and gastrin are reported to activate pathways that promote islet neogenesis and improve glucose homeostasis in type 2 diabetes mellitus (T2DM). First-generation gut hormone treatments-GLP-1 analogues (incretin mimetics) are now available for the treatment of T2DM.Presently, hormonal synergy is of therapeutic interest for treatment of diabetes mellitus. Augmenting the biological activity of the "incretin" hormones to address many of the pathophysiological problems of diabetes is an effort in this direction. Gut hormones such as OXM, ghrelin and PYY play crucial role in the regulation of glucose. Pleirotropic actions of leptin reported to lower glucose is also, an area of investigation for hyperglycemia.Research has proved that these hormonal actions are a possible platform for therapeutic development in T2DM management.

Keywords: Gut hormones,glucosehomeostasis,T2DM,GLP-1 receptor agonists,DPP-4 inhibitors

1.INTRODUCTION

The diverse actions of gut peptides play an important role regulating the control of various physiological actions like satiety, gut motility, digestion and absorption of nutrient, disposal and energy storage. Gut hormones play role to initiate several physiological processes in multiple metabolically active tissues hence, attracted as therapeutic targets in the treatment of type 2 diabetes mellitus. In 1902 Bayliss and Starling described the first gastrointestinal (GI) hormone, secretin, establishing the role of the GI tract as an endocrine organ [1]. Considerable evidence is available on the important biological role of these endogenous hormones with direct bearing on glucose homeostasis.Incretins, Leptins, CCK, Oxyntomodulin, PYY and Gastrin are the gut hormones responsible for glucosehomeostasis.GIP and GLP-1 two major incretins along with gastrin, secretin, and

cholecystokinin play a key role in the pathophysiology of type 2 diabetes. Failure of pancreatic β-cell functioning cause insulin depletion as well as insulin resistance in organs is a pathophysiological disorder in Type 2 diabetes (T2DM). Impaired regulation of incretin hormones which reduce BG levels is another fundamental defect in the pathogenesis of Type 2 diabetes [2-4].Leptin primarily produced in the adipose tissue although does not increase insulin levels, can potently increase insulin sensitivity [5-7] and participates in regulation of glucose absorption. CCK released from intra-islet neurons [8] along with GLP-1 (glucagon-like peptide-1) enhances insulin secretion.Oxyntomodulin (OXM) anther peptide secreted post-prandially is a dual agonist of the GLP-1 receptor and the glucagon receptor combining the effects of both hormones.PYY3–36 from PYY1-36 a satiety hormone processed by DPP-4 may also regulate glucose homeostasis by improving insulin sensitivity [9].Gastrin may contribute to incretin effect in combination with other hormones. Gastrin peptides are reported to stimulate insulin secretion independent of glucose [8,10].These hormonal actions are now being viewed as possible platform for therapeutic development in T2DM management [11,12]. Incretin-based therapy has clearly emerged as one of the most sought out strategy in managing type 2 DM [13]. The paper is a concise review on gut hormones in glucose metabolism and the current therapeutic development to reduce hyperglycemic condition in T2DM subjects.

2. INCRETINS IN GLUCOSE METABOLISM

The term “incretin” was coined in 1932 to describe hormones that stimulated upper gut mucosa i.e., islet secretions of the pancreas[14,15]. Oral glucose elicits a higher insulin response than intravenous glucose at identical plasma glucose (PG) profiles (isoglycemia) is termed as incretin effect [16,17].Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1(GLP-1) are the two major incretin hormones from the upper (GIP, ‘K’ cells) and lower (GLP-1, ‘L’ cells) gut [18]. The secretion of these incretins vary with individuals with same trend of secretion in both the hormones [19,20].Thus, incretins are the gut hormones that potentiate insulin secretion after meal ingestion in a glucose-dependent manner. While, GIP and GLP-1 are major incretins, gastrin and cholecystokinin may also have minor roles to play in the pathophysiology of type 2 diabetes. GLP-1 and GIP enhance the effects of insulin, suppress glucagon release, and decrease hepatic gluconeogenesis to maintain BG levels in healthy subjects [21]. Reduced incretin effect is a consequence of the diabetic state and not a primary event in the development of type 2 diabetes [4,20,22].Incretin effect is also, reported to be reduced in type 1 diabetes subjects and normal fasting glucose levels [2,23-25]. Glucagon producing α-cells, play a key role in glucose counter-regulation to avoid dangerous hypoglycemia. Glucagon-like peptide-1 (GLP-1) issecreted from the ‘L’-cells located in the gut epithelium [26] with enteroendocrine cells distributed throughout the jejunum, ileum and colon [27].GLP1 circulates in two equipotent forms as $GLP1_{7-37}$ and $GLP1_{7-36}$ amide [28,29,30], but most circulating GLP1 in humans is $GLP1_{7-36}$ amide [31]. GLP-1enhances the differentiation of new *B*-cells from progenitor cells in the pancreatic duct epithelium [32] also, stimuling cell proliferation [33-35].GLP-1 is capable of inhibiting apoptosis of *B*-cells [36] to maintain a balance between apoptosis and proliferation [37].Glucose-dependent insulinotropic polypeptide (GIP) cells are found in the small intestinal mucosa [38] secreted from specific endocrine cells, known as ‘K’ cells in response to glucose, amino acids, and lipids [39,40]. GIP is a 42 amino acid peptide stimulating insulin together with GLP-1.Late phase of the insulinotropic response is particularly impaired in type 2 diabetes[22].However, insulin resistance is independent of decreased GLP-1 [3,41]. GIP contains an alanine at position 2 and is a substrate for enzymatic inactivation by DPP4, an aminopeptidase. Insulinotropic actions of GIP are more prominent during hyperglycaemia [42].GIP effect was preserved in women who had a history of gestational diabetes and are therefore at high risk of developing type 2 diabetes[43].The

enteroglucagon peptides expressed by proglucagon gene, primarily in the 'L' cells of the distal intestine are glicentin and oxyntomodulin (OXM).

Table 1: Gut hormones in glucose homeostasis

Harmone	Site of secretion	Mode of action	Reference
GLP-1	Secreted from the L-cells located in the gut epithelium	Augmentation of insulin, inhibition of glucagon secretion, inhibits gastric emptying,food intake, and maximizing nutrient absorption	[144]
GIP	Secreted in intestinal mucosa from endocrine cells, called K cells	Mediates the postprandial potentiation of insulin secretion	[38,39]
Gherlin	Secreted primarily in the enteroendocrine cells as pro-hormone by P/D1 closed-type cells in gastric fundus.	Growth hormone secretagogue that stimulates pituitary release of growth hormone and stimulates hypothalamic centers to increase appetite Effects mediated through vagus nerve	[69]
Leptin	A peptide hormone containing 167 amino acids primarily produced in the adipose tissue	Regulates absorption of glucose	[94]
Gastrin	The main site of production gastrin in adults is the antroduodenal G-cells	Contributes to an incretin effect in combination with other hormones	[54,59]
PYY	Peptide YY is a short (36-amino acid) peptide released from cells in the ileum and colon in response to feeding.	Increases postprandial insulin and glucose response and also regulate glucose homeostasis through peripheral effects distinct from its interaction with islets	[107]
Cholecystokinin (CCK)	I-cells in duodenal mucosa, particularly with multiple molecular forms	Moderatespostprandial glycemia by slowing down gastric emptying. CCK along with incretin hormone GLP-1 enhances insulin secretion.	[142]
Oxyntomodulin	Oxyntomodulin (OXM) is a peptide hormone released from the gut in postprandial state.	Decreases food intake by suppressing appetite, enhances glucose stimulated insulin secretion and inhibits glucagon release, thereby reducing postprandial glucose levels	[143]

Glicentin is considered as only a discarded metabolite of proglucagon after the cleavage of GLP-1 and GLP-2 [44].OXM **s**imilar to GLP-1, a peptide of 37-amino acid secreted from the intestine following nutrient ingestion originating from the same proglucagon precursor [45]. OXM is a dual agonist of the GLP-1 receptor and the glucagon receptor combining the effects of both hormones. Like GLP-1,OXM decreases food intake by suppressing appetite,inhibits gastric emptying, enhances glucose-stimulated insulin secretion and inhibits

glucagon release, thereby reducing postprandial glucose levels by glucagon action thus a key peptide in therapeutic development [46-49].Activated glucagon receptor (GCGR) can increase hepatic glucose production, but the overall metabolic effect of OXM is balanced toward improving glycemic control.

3. OTHER GUT HORMONES IN GLUCOSE METABOLISM

Cholecystokinin (CCK) peptides are released from intra-islet neurons [8] with two receptors, CCKAR (CCK1R) and CCKBR (CCK2R), CCKBR mediating the effects of CCK on the control of glucose homeostasis by the pancreas. CCK moderatespostprandial glycemia by slowing down gastric emptying which otherwise leads to poor glycemic control. CCK along with incretin hormone GLP-1 enhances insulin secretion.CCK has been shown to stimulate glucagon release from human *islets* in vitro. In vitro studies elucidate glucagon release by CCK from *islets*, and stimulation of insulin in a glucose-dependant manner in mice model. Infusion of CCK-8 increases plasma insulin concentration and reduces glucose excursion following meal ingestion in normal and T2DM subjects [50]. CCK has proliferative role on pancreatic *β* cells while CCK-8 can promote regeneration of *β*cells [51].Short CCK peptides, CCK-8, CCK-5, and CCK-4 have been shown to release insulin in humans and in the isolated perfused porcine pancreas [8,52,53].Gastrin as a humoral mediator of gastric acid secretion proposed in 1905 [54]. However, physiological proof of an acid-stimulating hormone from gastric antrum was presented in 1948 [55] and later isolation, structure and physiological functions were determined [56]. Gastrin may contribute an incretin effect in combination with other hormones as evident in mouse model under gastrin and GLP-1 dual agonist ZP3022 [57].Gastrin when co-administrated with glucose more pronounced insulin release was evidenced supporting incretin effect [10].The main site of production gastrin in adults is the antroduodenal G-cells targeting G-protein coupled receptors [58.59]. Human islet cells are well equipped with gastrin receptors [60,61].Gastrin is likely to induce β-cell proliferation, neogenesis and stimulate the secretion of insulin postprandially [62].Gastrin peptides are reported to stimulate insulin secretion independent of glucose [8,10].Gastrin enhances islet mass from transdifferentiated exocrine pancreatic tissue [63]and induces the expression of glucagon genes in α-cells [64].Gastrin is expressed in fetal and neonatal pancreatic islets [65]

Gherlin is a 28–amino acid hormone is produced in the fasting state promoting hunger sensations [66-68].Gherlin is a endogenous ligand for the growth hormone secretagogue receptor (GHSR)1a, capable of stimulating growth hormone (GH) release from the anterior pituitary gland [69]. Secreted primarily in the enteroendocrine cells [69-71] as pro-hormone by P/D1 closed-type cells in gastric fundus. Gherlinto act on its own receptors, the growth hormone secretagogue receptor (GHSR 1a) must be cleaved and post-transcriptionally acylated by the enzyme ghrelin O acyltransferase (GOAT) a member of the membrane bound O acyltransferase (MBOAT) family [69,72-76].GHSR1a expressed by *a*-cells of the pancreatic islet are likely to contribute to the ability of GH to directly stimulate glucagon secretion [77].Acylated bioactive ghrelin (AG) produced in *ε* cell of pancreatic islets [78],acts on *β*-cells of the *islets* promoting calcium release (Ca2+) as a messenger signal [79].Ghrelin inhibition of insulin secretion is reported in most animal studies [80,81].Blocking the function of endogenous ghrelin with GHSR1a showed low fasting glucose concentrations suggesting an inhibitory role for ghrelin in the control of insulin secretion [82].Ghrelin secretion reported to be on peak during fasting [83]. Plasma ghrelin and insulin levels are negatively correlated [84,85],with an inverse relationship between circulating ghrelin levels and insulin resistance [86]. While,AG is responsible for the decrease in insulin with a consequent rise in glucose levels [87] with UAG able to antagonize the effects of AG on insulin secretion [88,89]. Investigations reveled that ghrelin administration increased plasma levels of glucose and decreased plasma levels of insulin [90,91] with plasma concentration of glucose regulating ghrelin secretion from *a*-cells to stimulates insulin secretion [92].

In 1994, the human obese (*OB*) gene located on chromosome 7 and its product leptin were identified and characterized [93,94].Leptin is a peptide hormone containing 167 amino acids primarily produced in the adipose tissue and in in small amounts in tissues of the stomach, mammary epithelium, placenta and heart [95]. Direct role of Leptin on glucose metabolism independent of body weight and food intake is demonstrated in leptin deficient mice [96]. Similarly, *in vitro* studies have shown mechanism and regulatory role of leptin in glucose absorption [97-99].Although leptin does not increase insulin levels, it can potently increase insulin sensitivity as seen in animal models of T1DM [100-102].The glucose lowering actions of leptin are largely facilitated through its role in many metabolic pathways due to its pleirotropic actions [103]. An increase in adipocyte leptin expression and circulating leptin is reported after overfeeding in healthy humans [104], with circulating leptin levels showing a diurnal pattern influenced by gender, age, exercise and glucose uptake [105].Shanta and Gavin (2014) reviewed the potential role of peptide tyrosine tyrosine (PYY) in Glucose homeostasis [106]. Gut hormone Peptide YY (PYY) with 36 amino acids was first isolated from porcine intestine [107] and the biological activity is dependent on the presence of an amide group at the C-terminus. PYY a satiety hormone released from the enteroendocrine L cells. PYY increased postprandial insulin and glucose responses [108].PYY may also regulate glucose homeostasis through peripheral effects distinct from its interaction with *islets* [109]. In addition, PYY3–36 from PYY1-36 processed by DPP-4 may also regulate glucose homeostasis by improving insulin sensitivity [9].

4. GUT HORMONES AND T2DM CONTROL STRATEGIES

Synergistic effect of gut hormone combinations for glucose metabolism is seen as better alternative. Combination effects of GLP-1 and GIP with CCK and gastrin peptides are of clinical interest now for glucose metabolism [110-112]. GLP-1 due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), which has very short half-life of >2 min in plasmais is a major limitation [113,114].DPP-4 resistant GLP-1 receptor agonists (incretin mimetics), and inhibitors of DPP-4 activity (incretin enhancers) are being successfully used clinically for treatment of T2diabetes mellitus currently. GLP-1 receptor agonists proved to be weight-negative anti-diabetes treatment option. Exenatide is a synthetic form of a natural peptide found in the saliva of Gila monster-*Heloderma suspectum* first analogue GLP-1 receptor agonists [115]. Liraglutide, Dulaglutide, and Semaglutide are other GLP-1 receptor agonists.DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion by elevating endogenous GLP-1 concentrations without an intrinsic hypoglycaemia risk. DPP-4 inhibitors raise only the proportion of active GLP-1 postprandial concentration [116],resulting in elevated plasma levels of GLP-1 does not produce GLP-1-related side effects [117,118]. DPP-IV inhibitor are small-molecules (gliptins) also demonstrated to be effective in antihyperglycemic state devoid of any major adverse events. Presently there are five DPP-4 inhibitors available vie., sitagliptin (2006),vildagliptin (2007),saxagliptin(2009),linagliptin (2011) and alogliptin (2013). Four more gliptins, namely teneligliptin, anagliptin, omarigliptin, andtrelagliptin are approved in the Japanese and Korean markets. Generally, the DPP-4 inhibitors are eliminated primarily via the kidney[119-123], except linagliptin which is eliminated via the biliary pathway [124,125].Inhibition of ghrelin can be a potential therapeutic target to regulate hyperglycemia opening a new avenue for type-2 diabetes subjects. The ghrelin receptor, growth hormone secretagogue receptor (GHSR1a) is expressed in a wide variety of tissues suggesting diverse biological activity. GHSR1a antagonism could be a promising therapy in the treatment of T2DM. Inhibition of post-transcriptional octanoylation by the enzyme ghrelin O acyltransferase (GOAT) can be a target to get improved glycemic control [126,127].LEAP2,Quinazolinone and Triazole are the presently known antagonists of GHSR1a.

Proton pump inhibitors (PPIs) are a group of medicines that decrease stomach acid production and can raise serum gastrin concentration significantly to affect glucose metabolism through promoting β-cell regeneration/expansion and also enhancing insulin

secretion [128].PPI lansoprazole increased serum gastrin which is associated with improved glycemia and increased pancreatic insulin content in rat models [129].Gastrin with GLP-1 dual agonist showed incretin effect in animal models can be a area to be investigated [130,131].The duodenal–jejunal bypass liner (DJBL; EndoBarrier; GI Dynamics, MA, USA) is a 60-cm-long impermeable sleeve-like device, suggests potential hormonal mechanisms for diabetes improvement needs further confirmations [132,133].Although insulin therapy restores circulating leptin levels in type 1 diabetic patients [134], addition of leptin provides more glycemic control, with less-frequent insulin dosing. However,leptin and insulin co-therapy has a potential danger of hypoglycemia [134,135].PYY also, represents as a therapeutic tool after establishment of its role as anti-obesity and anti-diabetic effects. PYY is a key effector of the early recovery of impaired glucose-mediated insulin and glucagon secretion in bariatric surgery establishes principles in development of new non-surgical therapy for T2D correction [136].GLP-1, PYY, and oxyntomodulin combination therapy was reported to improved post-prandial glycemic control similar to that of RYGB patients[137].However, use of PYY as a potential treatment needs further investigation (Batterham*et al*., 2003).Infusion of oxyntomodulin a promising glucose-lowering and obese and therapy well-tolerated in human studies is also, reported but for its its short circulating half-life [138-141].

CONCLUSIONS

Gut–brain axis has a key role in the regulation of energy homeostasis and glucose metabolism. A better understanding of the gut–brain axis perhaps may the key for the development of successful therapies to manage diabetes and related metabolic disorders.Caution must be taken to avoid side effects when developing therapies, as gut hormones play role not only in glucose homeostasis but act on other physiological actions. Similarly, more attention is required towards comorbidity linked to diabetes. Bariatric surgery has given a new thinking on exploiting hormonal changes to target future medical therapies for Type 2 diabetes mellitus. It may be possible to reset metabolism and reverse diabetes taking the advantage of knowledge gained from bariatric surgery.

CONSENT (WHERE EVER APPLICABLE): Not applicable

ETHICAL APPROVAL (WHERE EVER APPLICABLE): Not applicable

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