# Gut Hormones in Glucose Homeostasis and Current Treatment Approach in the Control of T2DM: A Succinct Review

## ABSTRACT

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| 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 enteroendocrine cells located in the epithelium of the stomach, small bowel, and large bowel. Gut hormones activate neural circuits to signal peripheral organs for overall energy intake and assimilation coordination. Incretins, Leptin, CCK, Oxyntomodulin, PYY, and Gastrin are the major gut hormones involved in glucose metabolism. A group of gut peptides that are secreted after nutrient intake and stimulate insulin secretion together with hyperglycemia 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). Currently 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. 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. Pleiotropic actions of leptin reported to lower glucose is also, an area of investigation for hyperglycemia. Studies have proved that these hormonal actions are a possible platform for therapeutic development in T2DM management. |

*Keywords: Gut hormones; glucose homeostasis; 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. Bayliss and Starling (1902) described the first gastrointestinal (GI) hormone, secretin, establishing the role of the GI tract as an endocrine organ”. “Considerable evidence is available on the important biological role of these endogenous hormones with direct bearing on glucose homeostasis. Incretins, Leptin, Cholecystokinin (CCK), Oxyntomodulin (OXM), PYY and Gastrin are the gut hormones responsible for glucose homeostasis. 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 function resulting in 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” (Nauck et al.1986, Muscelli et al. 2008, Knop et al. 2007). Leptin primarily produced in the adipose tissue does not increase insulin levels, can potently increase insulin sensitivity (Lin et al.2002, German et al.2010, Denroche 2012) and “participates in regulation of glucose absorption. CCK released from intra-islet neurons (Rehfeld et al.1980) along with GLP-1 (glucagon-like peptide-1) enhances insulin secretion. Oxyntomodulin (OXM) another 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 dipeptidyl peptidase-4 (DPP-4) may also regulate glucose homeostasis by improving insulin sensitivity” (van den Hoek et al.2004).” Gastrin may contribute to incretin effect in combination with other hormones. Gastrin peptides are reported to stimulate insulin secretion independent of glucose levels” (Rehfeld and Stadil 1973, Rehfeld et al.1980). These hormonal actions are now being viewed as possible platform for therapeutic development in T2DM management (Drucker 2024). Incretin-based therapy has clearly emerged as one of the most sought out strategy in managing type 2 DM (Phung et al. 2010). The paper is a focus on basic physiology with clinical relevance. The paper is a concise review on the role of 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 the hormonal substance that stimulated upper gut mucosa i.e., islet secretions of the pancreas” (La barre 1932, Rehfeld 2018). "Oral glucose elicits a higher insulin response than intravenous glucose at identical plasma glucose (PG) profiles (isoglycaemia) is termed as incretin effect” (Mc Intyre et al.1964, Elrick et al.1964). Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1(GLP-1) are the two incretin hormones from the upper (GIP, ‘K’ cells) and lower (GLP-1, ‘L’ cells) gut (Holst and Gromada 2004). “The secretion of these incretins vary with individuals with same trend (Nauck et al.2004, Calanna et al.2013). Thus, incretins are the [gut hormones](https://www.sciencedirect.com/topics/medicine-and-dentistry/gastrointestinal-hormone) that potentiate [insulin secretion](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/insulin-release) after meal [ingestion](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ingestion) in a glucose-dependent manner. While, GIP and GLP-1 are two major incretins, gastrin and CCK may also play a minor role 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” (Asmar et al. 2010). Reduced incretin effect is a consequence of the diabetic state and not a primary event in the development of type 2 diabetes (Knop et al.2007). "Incretin effect is also reported to be reduced in type 1 diabetes subjects and normal fasting glucose levels” (Nauck et al.1986, Meier and Nauck 2006,Bagger et al.2011). Glucagon-producing α-cells, play a key role in glucose counter-regulation to avoid hypoglycemia. GLP-1 issecreted from the ‘L’-cells located in the gut epithelium (Solcia et al.1980) with enteroendocrine cells distributed throughout the jejunum, ileum, and colon (Hansen et al.2013). GLP1 circulates in two equipotent forms as GLP17-37 and GLP17-36 amide (Wettergren et al.1998), but most circulating GLP1 in humans is GLP17-36 amide (Orskov et al.1994). “GLP-1 enhances the differentiation of new *B*-cells from progenitor cells in the pancreatic duct epithelium” (Zhou et al.1990) “stimulating cell proliferation (Xu et al.1999, Butler Alexandra 2013, Bai et al.2005). GLP-1 is capable of inhibiting apoptosis of *B*-cells” (Farilla et al.2003) to “maintain a balance between apoptosis and proliferation (Bonner-Weir Susan 2000). GIP cells are found in the small intestinal mucosa” (Mortensen et al.2003) secreted from specific endocrine cells, known as ‘K’ cells in response to glucose, amino acids, and lipids (Falko James et al.1975, Buchan Alison et al.1978).

**Table 1. Gut hormones in glucose homeostasis**

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| **Hormone** | **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](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/glucagon-release), inhibits gastric emptying, food intake, and maximizing [nutrient absorption](https://www.sciencedirect.com/topics/medicine-and-dentistry/nutrient-absorption) | (Holst 2019) |
| GIP | Secreted in intestinal mucosa from endocrine cells, called K cells | Mediates the postprandial potentiation of insulin secretion | (Falko et al. 1975, Mortensen et al. 2003) |
| Ghrelin | 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 | (Kojima et al.1999) |
| Leptin | A peptide hormone containing 167 amino acids primarily produced in the adipose tissue | Regulates absorption of glucose both directly through [leptin receptors](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/leptin-receptor) and indirectly via the hypothalamic receptors of [central nervous system](https://www.sciencedirect.com/topics/medicine-and-dentistry/central-nervous-system). | (Zulfia and Junaid 2017) |
| Gastrin | The main site of production gastrin in adults is the antroduodenal G-cells | Contributes to an incretin effect in combination with other hormones | (Edkins 1905,Wank et al.1992) |
| PYY | Peptide YY is a short (36-[amino acid](https://en.wikipedia.org/wiki/Amino_acid)) peptide released from cells in the [ileum](https://en.wikipedia.org/wiki/Ileum) and [colon](https://en.wikipedia.org/wiki/Colon_(anatomy)) in response to feeding. | Increases postprandial insulin and glucose response and also regulate glucose homeostasis through peripheral effects distinct from its interaction with islets | (Tatemoto and Mutt 1980,Cox et al.2010) |
| Cholecystok-inin (CCK) | I-cells in duodenal mucosa, particularly with multiple molecular forms | Moderates postprandial glycemia by slowing down gastric emptying. CCK along with incretin hormone GLP-1 enhances insulin secretion. | (Ivy and Oldberg 1928) |
| Oxyntomod-ulin (OXM) | Oxyntomodulin 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 | (Bataille et al.1981) |

“GIP is a 42 amino acid peptide stimulating insulin together with GLP-1. Late phase of the insulinotropic response is particularly impaired in T2DM” (Meier and Nauck 2006). However, insulin resistance is independent of decreased GLP-1 (Rask Eva et al.2001, Muscelli et al.2008). 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 hyperglycemia (Christensen et al.2011). “Women who had a history of gestational diabetes are at high risk of developing type 2 diabetes as the GIP effect was reported to be preserved” (Meier et al.2005). “The enteroglucagon peptides expressed by proglucagon gene, primarily in the ‘L’ cells of the distal intestine are glicentin and OXM” (Sinclair and Drucker 2005)

“Glicentin is considered as only a discarded metabolite of proglucagon after the cleavage of GLP-1 and GLP-2” (Sinclair and Drucker 2005). OXM is similar to GLP-1, a peptide of 37-amino acids secreted from the intestine following nutrient ingestion originating from the same proglucagon precursor (Cohen et al.2003). “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, reducing postprandial glucose levels by glucagon action thus a key peptide in therapeutic development” (Pocai 2012). 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 (Rehfeld et al.1980) with two receptors, CCKAR (CCK1R) and CCKBR (CCK2R). “CCKBR is reported to mediate the effect of CCK on the control of glucose homeostasis by the pancreas. CCK moderates postprandial glycemia by slowing down gastric emptying. CCK, along with incretin hormone GLP-1 enhances insulin secretion. CCK has been shown to stimulate glucagon release from human islets *in vitro*. Studies *in vitro* elucidate that glucagon is released by CCK from islets and stimulates insulin in a glucose-dependant manner in mice models. Infusion of CCK-8 increases plasma insulin concentration and reduces glucose excursion following meal ingestion in normal and T2DM subjects” (Ahren and Holst 2000). “CCK has proliferative role on pancreatic *β* cells while CCK-8 can promote regeneration of *β* cells” (Kuntz et al.2004). “Short CCK peptides, CCK-4, CCK-5, and CCK-8 have been shown to release insulin in humans and in the isolated perfused porcine pancreas” (Kaneto et al.1969, Rehfeld et al.1980). “Gastrin as a humoral mediator of gastric acid secretion proposed in 1905” (Edkins 1905). However, physiological proof of an acid-stimulating hormone from the gastric antrum was presented in 1948 (Grossman et al.1948), and later isolation, structure, and physiological functions were determined (Gregory 1974). Gastrin may contribute an incretin effect in combination with other hormones as evident in mouse model under gastrin and GLP-1 dual agonist ZP3022 (Fosgerau et al. 2013). Gastrin, when co-administrated with glucose, produced a more pronounced insulin release, which was evidenced supporting incretin effect (Rehfeld and Stadil 1973). The main production site of gastrin in adults is the antroduodenal G-cells targeting G-protein coupled receptors (Reubi et al.2003, Dufresne et al.2006). Human islet cells are well equipped with gastrin receptors (Kopin et al.1992). Gastrin is likely to induce β -cell proliferation, neogenesis and stimulate the secretion of insulin postprandially (Rehfeld 1976). Gastrin peptides are reported to stimulate insulin secretion independent of glucose (Rehfeld and Stadil 1973, Rehfeld et al.1980). “Gastrin enhances islet mass from transdifferentiated exocrine pancreatic tissue” (Rehfeld 1976) and “induces the expression of glucagon genes in α-cells (Leung-Theung-Long et al.2005). Gastrin is expressed in fetal and neonatal pancreatic islets” (Larsson et al.1976).

“Ghrelin is a 28–amino acid hormone is produced in the fasting state promoting hunger sensation” (Ibrahim Abdalla 2015). “Ghrelin is a endogenous ligand for the growth hormone secretagogue receptor (GHSR)1a, capable of stimulating growth hormone (GH) release from the anterior pituitary gland” (Kojima et al.1999). “Secreted primarily in the enteroendocrine cells as pro-hormone by P/D1 closed-type cells in gastric fundus” (Date et al.2000). “Ghrelin to 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” (Zhao et al.2010). “GHSR1a expressed by *a*-cells of the pancreatic islet are likely to contribute to the ability of GH to directly stimulate glucagon secretion” (Chuang et al.2011). Acylated bioactive ghrelin (AG) produced in *ε* cell of pancreatic islets (Prado et al.2004), “acts on *β-*cells of the isletspromoting calcium release (Ca2+) as a messenger signal”. “Ghrelin inhibition of insulin secretion is reported in most animal studies” (Qader et al.2005). “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” (Dezaki et al.2006). An inverse relationship between circulating ghrelin levels and insulin resistance is reported (Tschop et al.2001,Flanagan et al.2003). “AG increases glucose levels by suppressing insulin secretion and UAG may counteract AG’s diabetogenic effects and improve insulin sensitivity” (Broglio et al.2004, Gauna et al.2006, Barzzoni et al.2007). “Investigations reveled that ghrelin administration increase plasma levels of glucose and decrease plasma levels of insulin” (Tassone et al.2003) with plasma concentration of glucose regulating ghrelin secretion from *a*-cells to stimulate insulin secretion (Toshinai et al.2001).

In 1994, the human obese (*OB*) gene located on chromosome 7 and its product leptin were identified and characterized (Green et al.1995).“Leptin a peptide hormone containing 167 amino acids is primarily produced in the adipose tissue and in in small amounts in tissues of the stomach, mammary epithelium, placenta and heart” (Klok et al.2007). Direct role of Leptin on glucose metabolism independent of body weight and food intake is demonstrated in leptin deficient mice (Louis 1997). Similarly, *in vitro* studies have shown mechanism and regulatory role of leptin in glucose absorption (Gutierrez-Jaurez et al.2004, Balthasar et al.2004, Pereira et al.2023). “Although leptin does not increase insulin levels, it can potently increase insulin sensitivity as seen in animal models of T1DM” (Denroche et al.2011).The glucose lowering actions of leptin are largely facilitated through its role in many metabolic pathways due to its pleirotropic actions (Anna et al.2017). An increase in adipocyte leptin expression and circulating leptin is reported after overfeeding in healthy humans (Kolaczynski et al.1996). Circulating leptin levels show a diurnal pattern influenced by gender, age, exercise, and glucose uptake (Ostlund et al.1996). Shanta and Gavin (2014) reviewed the potential role of peptide tyrosine tyrosine (PYY) in Glucose homeostasis. “Gut hormone Peptide YY (PYY) with 36 amino acids was first isolated from porcine intestine” (Tatemoto and Mutt 1980) and “its 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 increases postprandial insulin and glucose responses” (Batterham and Bloom 2003). “PYY may also regulate glucose homeostasis through peripheral effects distinct from its interaction with islets”(Chandarana et al.2013). “In addition, PYY3–36 from PYY1-36 processed by DPP-4 may also regulate glucose homeostasis by improving insulin sensitivity” (van den Hoek et al.2004).

**4. GUT HORMONES AND T2DM CONTROL STRATEGIES**

Synergistic effect of gut hormone combinations for glucose metabolism is seen as a better alternative. Combination effects of GLP-1 and GIP with CCK and gastrin peptides are of clinical interest now for glucose metabolism (Rehfeld 2016, Pathak et al.2018). GLP-1 due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), which has a very short half-life of 1.5 to 5 min in plasma, is a major limitation (Mentlein et al.2014). “Currently 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. GLP-1 receptor agonists proved to be weight-negative anti-diabetes treatment option (Collins et al.2025). Exenatide is a synthetic form of a natural peptide found in the saliva of Gila monster-*Heloderma suspectum,* the first analogue GLP-1 receptor agonist” (Kleinman et al.1992). “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” (Herman et al.2006), “resulting in elevated plasma levels of GLP-1 without side effects (Vilsboll and Krarup 2001). DPP-4 inhibitors are small-molecules called gliptins are also been demonstrated to be effective devoid of any major adverse events. Presently, there are five DPP-4 inhibitors available viz., sitagliptin (2006), vildagliptin (2007), saxagliptin (2009), linagliptin (2011) and alogliptin (2013). Four more gliptins, namely teneligliptin, anagliptin, omarigliptin, and trelagliptin are approved and available in the Japanese and Korean markets. Generally, the DPP-4 inhibitors are eliminated primarily via the kidney” (Herman et al.2005, Covington et al.2008, He et al.2009,Graefe-Mody et al.2012), except linagliptin, which is eliminated via the biliary pathway (Gallwitz 2019, Deacon 2019). DPP-4 inhibitors are clinically proved to be safe and no dose escalation requirement is reported. They are also, reported to be safe in large cardiovascular outcome trials but were not found to have cardio-protective effects except the case of saxagliptin which may cause heart attack (Orime and Terauchi 2020, Subrahmanyan et al.2021). “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.Similarly, inhibition of post-transcriptional octanoylation by the enzyme ghrelin O acyltransferase (GOAT) can be a target to get improved glycemic control” (Yang et al.2008). LEAP2, Quinazolinone and Triazole are the presently known antagonists of GHSR1a.

“Proton pump inhibitors (PPIs) are a group of drugs that decrease stomach acid production and can raise serum gastrin concentration significantly to affect glucose metabolism through promoting β-cell regeneration/expansion and enhancing insulin secretion” (Bodvarsdottir et al.2010).PPI lansoprazole increased serum gastrin which is associated with improved glycemia and increased pancreatic insulin content in rat models (Kirchner et al.2012).Gastrin with GLP-1 dual agonist showed incretin effect in animal models can be an area for investigation (Suarez-Pinzon et al.2008,Fosgerau et al.2013). “The duodenal–jejunal bypass liner (DJBL; EndoBarrier; GI Dynamics, MA, USA) is a 60-cm-long impermeable sleeve-like device, suggested potential hormonal mechanism for diabetes improvement needs further confirmations” (De Moura et al.2012, Patel et al.2013). Although insulin therapy restores circulating leptin levels in type 1 diabetic patients (Soliman et al.2002),“addition of leptin provides more glycemic control, with less-frequent insulin dosing. However, leptin and insulin co-therapy has a potential danger of hypoglycemia” (Soliman et al.2002, Denroche et al.2011). “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” (Claudia Guida et al.2019).GLP-1, PYY, and CCK combination therapy was reported to improve post-prandial glycemic control similar to that of RYGB patients (Behary et al.2019).However, use of PYY as a potential treatment needs further investigation (Batterham and Bloom 2003). Infusion of CCK as a promising therapy for glycemic control and obese is reported but for its short circulating half-life (Bataille et al.1981, Pocai 2013,Holst 2019).

**5. 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 therapy, as gut hormones play role not only in glucose homeostasis but act on other physiological actions, cardiovascular system and brain. 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**

It is not applicable.

**ETHICAL APPROVAL**

It is not applicable.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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