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ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS AND DIABETES MELLITUS

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ABSTRACT

Incretin hormones are defined as intestinal hormones released in response to nutrient ingestion, which potentiate the glucose-induced insulin response. In humans, the Incretin effect is mainly caused by two peptide hormones, glucose-dependent insulin releasing polypeptide (GIP), and glucagon-like peptide-1 (GLP-1K cells from small intestine secretes GIP and L cell from distal intestine secretes GLP-1.Actions of GIP and GLP-1 is by binding with the receptors.though part of their biological action may also involve neural modulation. GIP and GLP-1 are both rapidly degraded into inactive metabolites by the enzyme dipeptidyl-peptidase-IV (DPP-IV). GLP-1 exerts other significant actions, including stimulation of insulin biosynthesis, inhibition of glucagon secretion, inhibition of gastric emptying and acid secretion, reduction of food intake, and trophic effects on the pancreas. Glucose homeostasis is regulated by of insulin, glucagon ,Cortisol, Growth hormone, and others like incretins. Insulin causes increased uptake of glucose by peripheral tissues and modulation of hepatic glucose production. Glucagon, maintain fasting glucose levels and preventing hypoglycemia. Cortisol, and Growth hormone causes increased production of glucose from adipose tissues. The Incretin hormones regulates glucose homeostasis via augmentation of insulin secretion, inhibiting glucagon secretions, delaying gastric emptying and other glucoregulatory processes.

KEY WORDS : glucagon-like peptide-1 (GLP-1), Glucose-dependent insulinotropic polypeptide (GIP) . Glucose homeostasis, and diabetes mellitus

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INTRODUCTION

PHARMACOLOGY AND PHYSIOLOGY OF INCRETINS

In 1932, La Barren named the unidentified substances of gut extract thought to exert this effect as “incretin”. In the late 1960s it was further demonstrated that an oral glucose load induced a higher insulin secretion than intravenously administered glucose while blood glucose levels were similar between the two modes of delivery, suggesting that glucose clearance was different and involved different mechanisms leading to the concept of ‘incretins’. The criteria for incretin are, It must be released in response to oral nutrient ingestion, especially glucose, and It must reach physiological concentrations in vivo to cause insulin release. The currently known only incretins are Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

Structure & Source of Incretins

GIP is a 42-amino acid polypeptide. GLP-1 is produced as an inactive 37-aminoacid peptide whose C-terminal end contains glycine. Both GIP and GLP-1 are secreted from specialized gut neuroendocrine cells in response to nutrient ingestion. GIP is secreted by duodenal and proximal jejunal K cells, and GLP-1 is synthesized in L cells found primarily in the distal small bowel and colon.

Secretion of Incretins

Ingestion of nutrients such as carbohydrate, protein and fat, leads to release of GLP-1 as well as GIP; of these, carbohydrate ingestion is the best stimulus for GLP-1 secretion. Only carbohydrate absorption mediated GLP-1 leads to insulin secretion, whereas fat- and protein-mediated GLP-1 do not leads to insulin secretion. Circulating GIP and GLP-1 concentrations rise within 15 minutes following ingestion of nutrients, peak concentrations are attained by 30 minutes, returning to basal value by 2-3 hours.

Metabolism of Incretins

Within 5-7 minutes after release from their intestinal sites, GIP and GLP-1 undergo rapid metabolism in to inactive metabolites by the enzyme Dipeptidyl peptidase-IV (DPP-4) and serine protease.

Incretin receptors

GIP receptors are present in various cell types including pancreatic α and β cells, stomach, adipose tissue and brain. The binding of GIP at the receptor on pancreatic β- cell enhances exocytosis of insulin containing granules. The GIP receptor is a member of the family of G protein-coupled receptors and activation results in the stimulation of adenyl cyclase and Ca^{++} independent phospholipase A_2 and activation of protein kinases A and B. GIP also increases expression of the anti-apoptotic Bcl-2 and decreases expression of the pro-apoptotic Bax., resulting in reduced beta-cell death. In adipose tissue, GIP interacts with insulin to increase lipoprotein lipase activity and lipogenesis. GLP-1 receptors are found on α and β cells of the pancreas, parietal cells of the stomach, pylorus, adipose tissue, lungs and the brain. The mechanism of the insulinotropic action of GLP-1 involves interaction with a specific receptor belonging to the glucagon subfamily of G-protein-coupled receptors, located on the pancreatic β- cells. Binding of GLP-1 to its receptor leads to elevation of levels of cAMP and activation of protein kinase A. GLP-1 synergizes with glucose to stimulate insulin secretion through mechanisms that involve closure of ATP-sensitive K^+ channels (KATP) resulting in subsequent membrane depolarization, causing an increase in intracellular Ca^{++} and potentiation of Ca^{++} induced secretion via direct effects on the β- cell exocytotic machinery.

ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS

The most important property of GIP and GLP-1 is their activity to promote insulin secretion,

maintain glucose homoeostasis without inducing hypoglycaemia.

Effects of Incretins on Glucagon secretion

GLP-1 strongly inhibits glucagon secretion In case of Type 2 diabetes, Increased glucagon secretion and glucagon response occurs after meals.contributes to the hyperglycemia of the patients. So this effect of GLP-1 may be as important clinically as the insulinotropic effects.In patients with type 1 diabetes and complete lack of beta-cell activity (C-peptide negative); GLP-1 is still capable of lowering fasting plasma glucose concentrations, presumably as a consequence of a powerful lowering of the plasma glucagon concentrations. Pancreatic glucagon secretion is either unaffected or increased by GIP.

Effects of Incretins on β-cells mass

GLP-1 has a tropic effect on β-cells, both in terms of enhancing the magnitude of insulin secretion as well as increasing their number of β-cells. GLP-1 increases β-cell mass by stimulating proliferation and induction of islet neogenesis as well as by inhibiting apoptosis. GLP-1 also promotes cell differentiation, from exocrine ductal cells or immature islet progenitors, towards a more differentiated β-cell phenotype. GIP has also been shown to increase β-cell number and mass.

Effects of Incretins on Stomach

Receptors for GIP and GLP-1 are present in the stomach. Stimulation of receptors for GLP-1 in the pyloric sphincter delays gastric emptying and minimizes postprandial Hyperglycemia. By delaying gastric emptying, it also influences the distension of the stomach and peripheral satiety signals. In diabetics, GLP-1 infusion produces a significant decrease in meal related glycemic excursion, even without an increase in plasma insulin secretion due to the inhibitory effects on gastric emptying.

Effects of Incretins on Brain

Although GLP-1 synthesis occurs in the brain, peripheral GLP-1 may bind to regions of the brain where the blood – brain barrier is deficient; these include the Hypothalamus controlling food intake and energy expenditure. GLP-1 may mediate satiety effects at least in part through this mechanism , GIP receptor expression has also been found in the brain. GIP administration in healthy subjects appears to increase food intake and decrease energy expenditure, in contrast to GLP-1. Studies in normal subjects and in patients with Type 2 Diabetes have shown a significant inhibition of short-term food intake with concurrent GLP-1 infusion. A meta-analysis of these studies has concluded that there is a dose-dependent reduction in food intake associated with a reduction of gastric emptying in human subjects.

ROLE OF INCRETINS IN DIABETES MELLITUS

Incretins effects in Type 2 Diabetes

In healthy subjects incretin stimulation of insulin biosynthesis, inhibition of glucagon secretion, inhibition of gastric emptying and acid secretion, reduction of food intake, and trophic effects on the pancreas. In type 2 diabetes patients incretin causes reduced insulin secretion during the oral meal stimulus. Mixed-meal stimulation tests have revealed that postprandial GIP secretion is near normal or slightly impaired, whereas particularly the late phase of the GLP-1 response is significantly reduced in patients with Type 2 Diabetes. Patients with Type 2 Diabetes responded to GLP-1 but were found to be resistant to GIP. Therefore, GLP-1 is being explored as a novel therapy for the treatment of Type 2 Diabetes. In contrast to GLP-1, GIP works poorly in stimulating insulin secretion in Type 2 Diabetes and also stimulates, rather than inhibits, glucagon secretion. Therefore GIP will not be useful in the treatment of type-2 diabetes. Incretin based therapies- GLP-1 analogs (exenatide) and DPP-4 inhibitors (sitagliptin, vidagliptin) have been developed and many analogue are in advanced stages of development. It remains to be seen whether incretin based therapies decrease the morbidity and mortality associated with type 2 diabetes mellitus.

Incretins effects in Type 1 Diabetes

In patients with In case of Type 1 diabetes, Increased beta-cell function and insulin response occurs after meals but little or no improvement in the insulin response to parenteral glucose, suggesting that the incretin function may be important in glycaemic regulation in this phase of diabetes. In patients with Type 1 diabetes mellitus, insulin response to parenteral glucagon-like peptide-1 (GLP-1) is preserved, where as gastric inhibitory polypeptide (GIP) causes lack of stimulation of insulin secretion. Endogenous secretion of insulin in response to meals as demonstrated by blood levels of the insulin-connecting peptide (CP).Glucose homeostasis is maintained by increased glucagon secretion and decreased secretion of human pancreatic polypeptide (HPP) by GLP-1. It was hypothesized that a major component of the glycaemic effect is attributable to the known action of GLP-1 to inhibit gastric emptying and to inhibit glucagon secretion.

NEWER AGENTS (DRUGS) FOR DIABETES MELLITUS

Group-1= Incretinmimetic agents: Eg EXENATIDE, SITAGLIPTIN, VIDAGLIPTIN,
Group-2= AMYLIN ANALOGUE. Eg-PRAMLINTIDE.

EXENATIDE

It is a GLP-1 analogue, it is resistant to DPP-4, so the effect is longer and suitable for using clinically. it acts agonist as mammalian GLP-1 receptors, and produce glucose dependent insulin secretion and reduce post lunch blood glucose and triglyceride levels. It also reduces the glucagon secretion. It delays the gastric emptying. reduce the apatite and weight loss in type-2 diabetes mellitus. It lower the level of HbA1C (1-1.3%). Reduces the risk of heart diseases. Its dose is 5 microgram subcutaneous two times after meals

SITAGLIPTIN

It acts by inhibiting the enzymes DPP-4, It increases the level of GLP-1, it is similar to GLP-1 analogue, Its dose is 100 milligram once a day.

VIDAGLIPTIN : it is orally effective.

LIRAGLUTIDE: it is GLP-1 analogue, it is long acting ,Its dose is once a day.

PRAMLINTIDE: it is modified amylin peptide, its structure is similar to Calcitonin, Its dose is15-60 milligrams subcutaneously,

OTHER AGENTS

ORLISTAT. (used in insulin resistant obese type -2 diabetes)
GUAR GUM. (it reduces the absorption of carbohydrates)
GLUCOMANNAN. (it reduces the apatite and food intake.)

CONCLUSION

Our understanding of incretin biology has expanded exponentially over the past two decades. Both GLP-1 and GIP exert actions on the beta cell which causes insulin secretions and a wide range of analogues of Incretin hormones are being developed for potential therapy of Type 2 Diabetes mellitus and Type 1 Diabetes mellitus.

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