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Incretins Role in the Pathophysiology of Type 2 Diabetes Mellitus.

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is characterized by the decreased responsiveness of tissues to insulin known as Insulin resistance. There may also be Insulin secretory defects in advanced stages. The insulin secretion is initiated by incretins, the two intestinal hormones namely, Glucose dependant Insulinotropic Polypeptide (GIP) & Glucagon like Polypeptide1(GLP-1). They are secreted when food enters the stomach. These hormones are shown to be reduced in T2DM. Hence, the probable role of Incretins in the pathophysiology of T2DM is reviewed here. Many number of studies have been undertaken on the physiology of Incretins and their role in causation of type2 diabetes mellitus. The literature analysis and compilation of results is given here. The level of incretins are much reduced in type 2 diabetes mellitus leading on to reduction in the secretion of insulin and elevation in the level of glucagon. Incretins are necessary to prevent the occurrence of Type 2 Diabetes Mellitus.

Keywords: Incretins, Insulin resistance, Type II Diabetes Mellitus, pathophysiology.

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INTRODUCTION

Incretins are the gastrointestinal peptide hormones that increase insulin secretion in response to ingestion of food. Glucose in the small intestine stimulates the release of incretin into the blood stream. Incretins enter the pancreatic beta cells and stimulate the beta cells to secrete more insulin in response to the same amount of blood glucose as shown by Perley and Kipnis. They showed, greater (three fold) production of Insulin, earlier (30-60minutes) peak level of plasma insulin and faster (76%) utilisation of glucose following oral ingestion of glucose than after intravenous glucose injection [1]. This incretin effect is blunted in Type 2 Diabetes Mellitus(T2DM) [2].

MATERIALS AND METHODS

Many studies have been carried out in patients with T2DM, diabetes induced animals and cell lines to understand the role of incretins in the initiation of insulin secretion and in pathophysiology of T2DM. These articles discuss in detail & analyse in depth down to the molecular level about the synthesis, functions, mechanism of action etc. So, the literature search was attempted to have an overview of the role of incretins in T2DM and the results of the search are compiled to some extent & presented as a review article.

RESULTS & DISCUSSION

History shows that in 1902, Bayliss & Starling observed a substance secreted from the lining of the gastrointestinal tract stimulating the release of insulin from pancreas [3]. After 30 years, in 1932, Dr. Jean La Barre of Belgium introduced the name "incretin" for the secretion from the gut mucosa that led to increased release of insulin on ingestion of glucose [4]. The insulinotropic effect of incretins was observed by Elrick et al in an experiment comparing the responses of insulin to an oral glucose load with that of intravenous glucose which showed a significantly higher release of insulin after orally ingested glucose [5].

Nauck et al also confirmed the insulinotropic effect of incretins in their study comparing the responses of c-peptide to an oral and intravenous glucose [6]. In 1970, a polypeptide called "gastric inhibitory peptide" was recognized as being an incretin and hence later renamed as "glucose dependent insulinotropic polypeptide" (GIP) [7]. Yet another incretin hormone called "glucagon-like peptide-1" (GLP-1) was identified later [8].

GIP - this 42 amino acid(1-42) peptide is secreted from the neuroendocrine K cells of the duodenum & proximal jejunum [9,10] by post-translational processing of the larger proGIP precursor protein [11]. The secretion is stimulated by oral ingestion of fatty food [12] especially that rich in Long Chain Fatty Acids [13]. In humans, basal circulating GIP levels were measured to be 9 ± 1 pmol/L, and increased to 34 ± 2.8 pmol/L after a meal.[14] *GLP-1* contains 30 amino acids(7-36) and is secreted by the enteroendocrine L cells of the ileum and colon[15] and central nervous system by post-translational processing of the Proglucagon protein[16]. Its secretion is affected by oral ingestion of food[17] and vagal stimulation [18]. Somatostatin inhibits GLP-1 secretion [19]. The normal Fasting plasma levels of bioactive GLP-1 is shown to range between 5 and 10 pmol/L in humans and to increase approximately 2- to 3-fold after a meal [20].

Functions of Incretins:

GLP-1:

- Stimulates the pancreatic *beta cells* of the islets of Langerhans to secrete insulin [21,22].
- Maintains the beta cell insulin stores through increased insulin gene transcription [23].
- Inhibits glucagon release from the alpha cells of the Islets of Langerhans [24, 25].
- Improves insulin sensitivity [26].
- Cytoprotective through decreased expression of active Caspase3, [27] and antiapoptotic action mediated through cAMP & PI3K dependant signalling pathway [28].
- proliferative effects on the beta cells of the islets of Langerhans [29-31] modulate the differentiation of pancreatic ductal precursor cells into insulin-secreting beta cells in rat and human cell lines[32].

GIP:

- Promotes the *islet cells* of the pancreas to secrete insulin [33]
- Does not inhibit glucagon secretion [34].
- Promotes cell proliferation and cell survival in islet cell line studies [35]

Mechanism of action: Action on Insulin:

Incretin hormone release is regulated similar to that of other digestive tract hormones. An increase in the concentration of substance in the lumen of the digestive tract (in this case glucose) acts as the trigger for hormone secretion. The actions of both the incretins are receptor-mediated. There are receptors for GIP in the islets of the pancreas, and also in the stomach, adipose tissue, brain etc [36]. The receptors for GLP-1 are in the islets of the pancreas, lungs, brain, heart, stomach, skeletal muscle and kidney [37]. The incretin hormones elicit their actions through direct activation of distinct G-protein-coupled receptors expressed on islet beta cells³⁸. GLP-1 increases cAMP [23] and acts through protein kinase A (PKA) and the *Exchange Proteins directly Activated by cAMP* (EPAC). EPAC stimulates calcium influx into the islet beta cell, enhancing the release of calcium from intracellular stores and triggering insulin granule exocytosis as presented by Holz G [39].

The signaling pathways that mediate the insulinotropic actions of GIP include PKA-dependent and PKA independent mechanisms & include elevation of cAMP, inhibition of K_{ATP} channel and increases in intracellular Ca^{2+} [40]

Action on Glucagon: Glucagon is the anti-insulin hormone involved in the metabolism of carbohydrates. It acts on the liver to enhance glycogenolysis and gluconeogenesis during periods of fasting to maintain the blood glucose level, thus preventing the development of hypoglycemia [41]. Hence, Glucagon levels increase during periods of fasting and decrease after the ingestion of a meal in patients without diabetes. Like the GLP-1 effect on insulin, this effect on glucagon also is glucose dependent. If glucose levels are high, insulin will be released and glucagon activity will diminish. When the glucose levels approach normal, the actions of GLP-1 stop. In patients with T2DM, this sequence may not be seen because of the lack of insulin.

Role of Incretin in Type II DM:

It is envisioned that GLP-1 is responsible for most of the incretin effect, which is robust in normal people, but is blunted in people with T2DM. This concept was tested in an Europe-based study in which volunteers with T2DM were studied on two distinct days. One day, an infusion of saline was given, and on some other day, an infusion of GLP-1 was given. They fasted on those days during the study. On the day of saline infusion, their blood glucose gradually decreased whereas on the GLP-1 infusion day, their glucose decreased faster and their insulin levels increased. This shows that GLP-1 releases insulin in patients with T2DM also, and can lower blood glucose [42].

In those with diabetes after ingestion of a carbohydrate meal, due to insulin deficiency, glucagon levels rise and enhance the production of glucose through glycogenolysis and gluconeogenesis also. Thus, there are actually two mechanisms by which postprandial hyperglycemia occur in patients with diabetes. But, if they are given an injection of incretin-like exenatide before ingestion of the carbohydrate meal, the rise in glucagon is no longer observed [43]. Thus; GLP-1 mimetics improve glucose control through two glucose dependent mechanisms: an increase in insulin and a decrease in glucagon.

Endoplasmic reticulum (ER) stress within the beta cell may be a contributing factor to the pathogenesis of diabetes in rodents and cell lines as evidenced by increased beta-cell apoptosis and loss of islet mass. ER stress may result from overproduction of proinsulin leading to accumulation of the protein in the ER lumen and misfolding of proinsulin [44- 46] or depletion of ER calcium, [47] or inhibition of the protective, adaptive UPR (Unfolded Protein Response) [48] Incretins with the antiapoptotic action and beta cell proliferative action may be of help in reversing this stress effect.

SUMMARY

The incretins, GLP-1 and GIP are peptide hormones secreted from the gut in response to food. They mainly increase the secretion of insulin from islet beta cells and suppress that of glucagon from islet alpha cells. They also prevent the islet beta cell death and promote proliferation of beta cell mass. The incretin response is reduced in patients with Type 2 Diabetes Mellitus.

CONCLUSION

The incretins are important initiator of insulin secretion from the islet cells of the pancreas. They also suppress the secretion of anti-insulin hormone, glucagon. Incretins promote beta cell proliferation and prevent the islet cell death. The reduction in their activity plays a major role in the pathophysiology of type 2 diabetes mellitus.

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