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Review Article

Incretins- in the care of Type 2 Diabetes Mellitus

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Abstract: The ever increasing incidence of Type2 Diabetes Mellitus (T2DM) in our population calls for a variety of agents to combat this disorder. T2DM is the resultant of Insulin deficiency or the reduced activity of available insulin. Incretins viz. "Glucose dependant Insulinotropic Polypeptide" (GIP) and "Glucagon like Polypeptide-1" (GLP-1) are the intestinal hormones secreted in response to ingestion of food and they increase the secretion of Insulin. Reduced efficacy of these hormones is seen in T2DM. This review analyses the role of Incretins in the therapy of T2DM. A number of studies have been going on to analyse and utilize the beneficial effects of these incretins. Some such studies are reviewed here to give an overall picture of the efficacy of incretins in the care of Type 2 diabetes mellitus. Results and discussion of these studies show that the bioactivity of incretins is short lived as they are easily degraded by the enzyme, Dipeptidyl peptidase 4. A drug that could prevent the incretin degradation and prolong their bioavailability was found to be beneficial. An incretin analogue that could increase the insulin secretion was also studied to be really useful in the treatment of T2DM. In Conclusion Incretin being the initiator of insulin secretion is effective in the care of Type 2 diabetes mellitus as synthetic analogues or as inhibitors of degradative enzyme, dipeptidyl peptidase 4.
Keywords: Type2 Diabetes Mellitus, Incretin analogue, Dipeptidyl Peptidase4 inhibitor.

INTRODUCTION:

Type 2 diabetes mellitus is a disorder of insulin deficiency either in the quantity or activity. Generally the tissue response to insulin is very much reduced, may be because of the reduction in the number of insulin receptors or defect in the receptor action. This is also called insulin resistance. The amount of insulin can be replenished by insulin injection, or the secretion of insulin can be augmented through incretins which induce the glucose dependant insulin secretion. The two peptide hormones, "Glucose dependant Insulinotropic Polypeptide" (GIP) and "Glucagon Like Polypeptide-1" (GLP-1) secreted from the gut on ingestion of food, stimulate the beta cells of the pancreatic islets of Langerhans to secrete more amount of insulin [1, 2]. But, the availability of these incretins is also reduced in T2DM [3]. The enzyme, Dipeptidyl Peptidase4 degrades incretins to cause the reduction in their level[4]. So, the substance which can prevent the degradation of incretins and prolong the life of incretins will be of much help in treating T2DM.

MATERIALS & METHODS:

Numerous studies on the intestinal hormone, incretin and T2DM in animals, cell lines and patients have been undertaken in the recent past worldwide and the outcome published in various journals revealing a rich source of knowledge for the management of T2DM. The results of such studies are discussed in this review.

RESULTS & DISCUSSION:

Natural GLP-1 and GIP are rapidly inactivated by the proteolytic enzyme dipeptidyl peptidase (DPP)-IV, which cleaves 2 N-terminal amino acids from both peptides to produce inactive metabolites [4]. The half-life of intact biologically active GIP was found to be less than 2 minutes in rodents, [5] whereas in human, it was about 7 minutes in healthy subjects and 5 minutes in type 2 diabetic patients [6]. The half-life of bioactive GLP-1 in the circulation is less than 2 min [7].

GLP-1 treatment modified the factors regulating the transition of cell-cycle. This was reported by Bulotta et al in his study performed with cultured pancreatic ductal epithelial cells. GLP-1 increased the transcription of β cell specific genes, resulting in loss of ductal cell expression and promotion of islet cell expression [8].

Considering the experiment where individuals with diabetes fasted and received either an infusion of saline or GLP-1, as the blood glucose approached normal fasting level, glucagon level started rising [9]. This result endorses the valid therapeutic use

of GLP-1 mimetic, because their actions stop in the presence of low glucose level. Thus, the risk for hypoglycemia is extremely low.

Therapeutic use of Incretins:

The identification of the potential use of incretin hormones, GLP-1 and GIP in the treatment of diabetes was encouraging. But, the short circulating half-life of these was the cause for concern & led to the development of drugs that can prolong their bioactivity. Now, there are incretin analogs with significantly increased half-lives due to modification of the DPP-4 cleavage site and/or conjugation to large circulating proteins, such as albumin.

The two classes of medications that take advantage of the incretins to treat diabetes are GLP-1 receptor agonists and DPP-4 inhibitors. "GLP-1 receptor agonists" or,"GLP-1 agonists" work by activating the GLP-1 receptors. DPP-4 inhibitors act by inactivating the enzyme DPP-4 and increase the duration of incretin effects resulting in better control of blood glucose. The types of drugs have glucose lowering effect, they do not cause hypoglycemia & both have some side effects. They differ in their effect on body weight and cardiovascular parameters. GLP1 receptor agonist seems to be a better choice [10].

GLP1 agonist:

Exendin-4, a naturally occurring peptide & structurally similar to GLP-1 was originally isolated from the salivary secretions of the Gila monster, a poisonous lizard. It is resistant to DPP-4 inactivation due to the substitution of certain critical amino acids in its structure. The structural similarity to GLP-1 is such that it interacts with the GLP-1 receptor and simulates its actions. This finding led to the production of the GLP-1 mimetic exenatide (synthetic exendin-4), which can be administered as a twice-daily injection [11]. Patients who received either 5 µg or 10 µg of exenatide twice daily showed a greater decrease in HbA_{1c} levels and body weight than patients treated with a placebo [12]. The effect was sustained over 82 weeks [13]. Studies have shown that the effects of exenatide wane when treatment is terminated [14]. Because of this discovery, other analogues of GLP-1 that can bind to a ligand to prolong the half-life were also developed. Eg: liraglutide. It binds to albumin through a fatty acid side chain and is metabolized slowly. So, this GLP-1 analogue can be injected only once a day. A long-acting release form of exenatide that can be injected once-weekly instead of twice daily, for glycemic improvements were also tried and results have been presented [15]. CNTO736, a GLP-1 receptor agonist, proved to be effective in enhancing the insulin action in diet induced insulin resistance mice and also reduced production of VLDL [16].

DPP-IV Inhibitors

Vildagliptin is effective as monotherapy or as an add-on therapy with metformin. A rapid onset, short-acting, novel DDP-IV inhibitor, PSN9301 also improved glucose tolerance and reduced weight gain in rodent models of diabetes. The compound MK-0431 (sitagliptin) was tolerated well, decreased HbA_{1C} levels, and reduced fasting glucose in humans [17].

Thus, many drugs acting like the incretins and/ or promoting the longevity of incretins are successfully utilized in the therapy of Type 2 Diabetes Mellitus.

The other side of Incretin therapy: Recent developments show that there could be cause for concern with incretin therapy in the form of some long term ill effects as shown in certain studies on animals & patients. Acute pancreatitis, pancreatic cancer, thyroid carcinoma etc were reported in some patients treated for a prolonged period with incretin analogues & drugs that prolong the half life of incretins [18]. This may be due to the uncontrolled amplification of incretin action like preventing cell apoptosis and promoting proliferation of cells, by the synthetic analogues. But, these are still under debate as T2DM by itself can lead to occurrence of acute pancreatitis [18-20].

Further research in a large population of long term users of Incretin analogue is warranted to endorse the harmless efficacy of these drugs.

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 and so drugs mimicking incretin action could be of use to improve glycaemic control. Incretins are metabolized by the enzyme, dipeptidyl peptidase-4, and those drugs which selectively inhibit this enzyme also increase the concentration of incretins in blood. An incretin analogue that cannot be cleared by dipeptidyl peptidase-4 also gives a similar effect. There is a controversial opinion about the safety of these drugs due to the development of acute pancreatitis, pancreatic cancer & thyroid carcinoma in some patients on incretin therapy.

CONCLUSION:

The importance of incretins, the initiator of insulin secretion, in improving the glycaemic control in Type2 Diabetes mellitus where there is insulin deficiency, is elucidated by the enormous number of scientific studies undertaken around the world. There are also studies debating the safety of this therapy. Hence, further research is needed to prove the harmless efficacy of the incretin therapy.

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