22 *Emerging Therapies for Treatment of Type 2 Diabetes*

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Abstract: The prevalence of Diabetes is progressively increasing world-wide and the growth of the disease in our country is phenomenal. During the last century the management of Diabetes has improved with the introduction of Insulin and a series of oral hypoglycemic agents. Despite the tremendous strides in the availability of drugs the goal for an adequate and persistent control of glycemia is elusive. In the last decade there has been upsurge in the development of newer drugs and routes of insulin administration.

One of the most significant advances has been the recognition of the gut hormones and glucagon counter regulatory hormones in the control and regulation of blood sugar. A group of drugs like glucagons-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) have been developed. One of the drugs in this category which is available in the form of injection Exenatide and oral drugs in the form of DPP-IV inhibitors such as Sitagliptin have now been approved by the Regulatory Authorities in USA and are available for use in routine practice. The mode of action, side effects, mode of administration and dosage schedule are discussed in the following pages.

The prevalence of diabetes mellitus is increasing world wide and more so in our country. The last century has seen the development of insulin for the management of diabetes mellitus and has remained the most potent hypoglycemic agent available. To date it constitutes an integral component of pharmacologic therapy for type 1 diabetes which is characterized by absolute insulin deficiency resulting from autoimmune destruction of pancreatic beta cells.[1] The implications of tight glycemic control to reduce serious long term vascular complications is well established.[2] The conventional oral agents i.e. sulfonylureas, biguanides, meglitinides thaizolidinediones and alpha glucosidase inhibitors are used in various combinations for adequate control of insulin-resistant Type 2 diabetes mellitus. The available oral hypoglycemic agents with their efficacy and side effects may not be ideal for achieving the goal. The clinical barriers to insulin therapy are hypoglycemia, postprandial hyperglycemia, diurnal glucose fluctuations and excessive weight gain. In non-diabetic individuals glucose homeostasis is maintained through a complex interplay of glucoregulatory hormones including insulin, amylin, glucagon, and insulinotropic incretins: glucagon-like peptide-1(GLP-1) and gastric inhibitory polypeptide (GIP).

The year 2007 will witness the introduction of novel technologies to augment existing therapies for the management of type 2 diabetes. Nasal Insulin, Amylin and Incretin mimetics will offer the potential to intervene in the natural history of type 2 diabetes at an early stage. These agents posses the prospect of getting better glycemic control without weight gain and reduced risk of hypoglycemia. The potential for future molecular manipulation to render the therapy long acting and inventing oral incretin mimetics brings the prospect of weekly or even monthly dosing regimens.

In 1987, it was discovered that a 37 amino acid peptide was secreted with insulin from pancreatic β cells.[3] Amylin's combined effect were suppressing post prandial glucagon, slowing gastric emptying and reduce food intake.[4] Insulin and amylin thus reconciles major fluxes governing post prandial glucose level. Amylin is diminished along with insulin in diabetic patients. Amylin is poorly soluble and has tendency to aggregate. Amylin analogue pramlintide was approved as an adjunctive treatment in patients with type 1 and type 2 diabetes who use meal time insulin to control post prandial hyperglycemia. The neuroendocrine hormone amylin delays the state of gastric emptying, thereby slowing intestinal carbohydrate absorption to match the rate of glucose uptake by peripheral tissues. Amylin also suppresses hepatic glucose output by inhibiting glucagon secretion after meal ingestion.[5] Animal studies have shown that amylin induces postprandial satiety in direct proportion to food intake, the actions are mediated through the central nervous system.

Pramlintide (Fig. 22.1) is a stable, fully active and injectable synthetic analogue of amylin, typically injected within 15 minutes before a meal and like amylin lowers plasma levels of glucacon, slows gastric emptying, increases satiety and facilitates weight loss thus blunting postprandial hyperglycemia.[6] In type 2 diabetes most insulin treated patients are significantly overweight or obese and require large doses of insulin to overcome insulin resistance. In these patients pramlintide improves glycemic control and weight management. Pramilintide reduces caloric intake in obese type 2 diabetes suggesting that its weight-loss effect stems from enhanced satiety and attendant decrease in food consumption rather than appetite suppression.[7] It also increases the incidence of severe insulin induced hypoglycemia and nausea. Properties of pramlintide are summarized on Table 22.1. The neuroendocrine hormone amylin complements the glucoregulatory actions of insulin.

Table 22.1: Properties of pramlintide in type 2 diabetes mellitus

• Lowers plasma levels of glucagon
• Slows gastric emptying
• Suppresses hepatic glucose output
• Increases satiety
• Facilites weight loss
• Blunts postprandial hyperglycemia
• Improves glycemic control

Pramlintide is contraindicated in patients with confirmed diagnosis of gastroparesis and patients who have hypoglycemic unawareness and pediatric patients. The drug should not be mixed with Insulin and must be administered separately. It should not be given in patients taking antiadrenergic agents and alpha glucosidase inhibitors.[8]

An exciting future prospect of reducing post prandial hyperglycemia with amylin analogue is possible. Whereas insulin stimulates uptake of postabsorptive blood glucose into peripheral tissues, amylin attenuates glucose entry into the circulation by slowing gastric emptying, suppressing hepatic glucose output and reducing food intake. Thus pramlintide which is recently approved for adjunctive treatment of diabetic patients who have failed to achieve glycemic control despite optimal therapy with insulin, meal time injection of pramilinitide in the dose ranging between 60 to 120 μg decrease fluctuations of blood glucose, reduce prandial insulin requirements and improve glycemia while facilitating weight control. Patients on pramilintide should be closely monitored for hypoglycemia and nausea during initiation of therapy.

The second molecule which has attracted attention is gut derived incretin hormones. GIP and GLP-1 are the two major incretin hormones in humans.

- GIP is a 42-amino acid peptide derived from a larger protein (ProFGIP) and is secreted by endocrine K cells mainly present in the proximal gastrointestinal (GI) tract (duodenum and proximal jejunum)

- GLP-1 is a 30-amino-acid or 31-amino-acid peptide derived from a larger protein (proglucagon) and is secreted by L cells located predominantly in the distal GI tract ileum and colon) (Fig. 22.2).

The glucose-regulatory actions of GLP-1 and GIP are mediated through the binding and activation of their respective receptors (GLP-1R and GIP-R) located in several tissues, including alpha and beta cells in the pancreatic islets. In the fasting state, plasma levels of GLP-1 and GIP are low, however, the secretion of GLP-1 and GIP rapidly increases after eating a meal.[9] After secretion, GLP-1 and GIP are rapidly metabolized by the enzyme DPP-4. The plasma half-life of these incretins is short (approximately 2 minutes for intact GLP-1 and up to 5 minutes for GIP). Following rapid degradation, the metabolites of GLP-1 and GIP are eliminated through the kidney.

The incretin effect is reduced/ lost in type 2 diabetes patients (Figs 22..3 and Fig. 22.4). While there is GlP hypersecretion in obesity and type 2 diabetes,[10] GLP-1 secretion appears to be slightly reduced in patients who are overweight or patients who have type 2 diabetes.[11] Therefore type 2 diabetes can be viewed, as a state of in cretin deficiency caused by abnormalities in the secretion (GLP-1) and action (GIP) of important gut hormones[12] The action of GLP-1 are:

- Stimulation of insulin secretion in a glucose dependant manner.
- Suppress glucagon secretion and this is associated with reduced hepatic glucose output and suppression of lipolysis and reduced free fatty acid concentration
- Reduce appetite and food intake
- Decelerate gastric emptying
- Stimulates pancreatic β cell neogenesis, growth and differentiation in animal and tissue culture experiments.
- Inhibit β cell apoptosis *in vitro*.

Combination of various actions leads to reduction of both fasting and postprandial glucose level in type 2 diabetic patients. Another advantage is that when euglycemia is achieved, insulin secretion is no longer stimulated and glucagon is no longer suppressed. This avoids risk of provoking hypoglycemia.[12]

Drawback of using GLP-1 (the natural gut hormone) as an antidiabetic agent is its almost immediate proteolytic degradation by dipetidyl peptidase (DPP-4) to the metabolite GLP-1 (9-36 amide) or (9-37) which are biologically inactive.[13] The half life is < 2 min and even after subcutaneous injection, plasma concentration remains elevated for 90 min. DPP- 4 inhibition has shown to prevent the rapid degredation of GLP-1 and GIP to their truncated forms, thereby prolonging the survival of GLP-1(7-36 hr) and GIP (1-42 hr) and their beneficial action in glucose regulation (Fig. 22.5).

Incretin Mimetics and Incretin Enhancers

Incretin minetics (GLP-1 analogue, GLP-1 receptor agonists)are injectable agents that mimic the action of GLP-1 on glucose control. They are able to activate the GLP-1 receptor and have been modified to become resistant to the degradation action of DPP-4. Incretin enhancers are orally effective low molecular weight agents able to inhibit the DPP-4 enzymes (DPP-4 inhibitors). By inhibiting DPP-4, endogenous level of incretins are increased.

This has led to search for agonists at GLP-1 receptor ("incretin mimetics') which can be found in nature such as exendin-4. The available compounds are exenatide or can be derived from the another compound by intentional manipulations to eliminate the recognition site for DPP-4 and to provide attachment sites for free fatty acids (mediation binding to albumin, liraglutide)[14] which have been shown to bind pancreatic endocrine GLP-1 receptors and exert GLP-1 like effects. Properties of incertin mimetics are summarized in Table 22.2.

Table 22.2: Properties of incretin mimetics in type 2 diabetic patients

• Stimulation of insulin secretion

- Suppression of glucagon secretion.
- Hypoglycemia counter—regulation
- Deceleration of Gastric Emptying
- Suppression of Appetite
- Weight loss
- Reduction in fasting and postprandial glucose

The dose of exenatide given SC is 5-10 mg twice daily and liraglutide is upto 2 mg once daily. The drug is indicated as first line therapy in early stages of diabetes and in patients who have OHA failure. The typical adverse effects of incretin mimetics are nausea, vomiting and hypoglycemia. As a gut hormone which reduces gastric motility the effect of GLP-1 therapy and diabetics with subclinical gastroparesis are unknown. The effect of altered gastric emptying on pharmacokinetics of other concomitant therapies are also uncertain.

SUMMARY AND CONCLUSION

Glucose homeostasis involves the interaction of multiple glucoregulatory hormones-including the β-cell hormone amylin, which is coproduced, costored and cosecreted with insulin in response to meals. Whereas insulin stimulated uptake of postabsorpative blood glucose into peripheral tissues, amylin attenuated glucose entry into the circulation by slowing gastric emptying, suppressing hepatic glucose production and reducing food intake. The defects of amylin secretion contribute to postprandial hyperglycemia and wide fluctuation in circulating glucose levels implicated in the development of diabetic complications. By virtue of amylin's mechanism of action, mealtime injection of pramlintide decrease blood glucose fluctuation, reduce prandial insulin requirements and improve glycemia, while facilitating weight control. The main safety concerns associated with pramilintide are insulin-induced hypoglycemia and nausea.

Incretin hormones like GLP-1 and GLP are reduced or lacking in patients with type 2 diabetes. In view of short half life of exogenous GLP-1, incertin mimetics have been developed which are GLP-1 receptor agonists with better stability against proteolytic degradation (DPP-4) and longer half life. They have to be injected s.c. either once or twice daily for desired glycemic control. Sophisticated galenic preparations to reduce the frequency of injections to once every week or month by producing stable circulation concentration will be desirable. Alternatively, inibitors of the proteolytic enzyme DPP-4 which can be administered as tablets is available and other molecules are being evaluated.

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