**INCRETINS: ANTIOBESITY AND ANTIDiABETIC BLOCKBUSTERS**

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**ABSTRACT**

Incretins are a group of specialized hormones secreted in gastrointestinal tract (usually post-meal) that play crucial role in feeding behavior directly or indirectly. They stimulate a decrease in blood glucose levels. Incretins increases insulin release from the beta cells of the islets of Langerhans of pancreas, post meal so that blood glucose levels remains in check. They also minimize the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake by providing a feeling of satiety. Their gastric emptying delay also causes slower entry of glucose in blood. They also inhibit glucagon release from the alphacells of the Islets of Langerhans. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (also known as: glucose-dependent insulinotropic polypeptide or GIP) are two major candidate molecules that fulfill criteria for an incretin. Both GLP-1 and GIP are rapidly inactivated by enzyme dipeptidyl peptidase-IV (DPP-IV). This led to the concept of DPP-IV inhibitors as anti diabetic agents. Few insulinotropic activity possessing incretins which are available in marker for treatment of diabetes are exenatide, liraglutide, exenatide (extended-release). There are reports of incretins being explored for their role in management of obesity. This article summarizes potential role of incretins in discovery of antidiabetic and antiobesity molecule. Article also throws light on recent developments in incretin research.

**KEYWORDS:** Incretins, GLP-1, Amylin, Exenatide, Gila monster, Diabetes, Obesity, DPP-4 inhibitors.

**INTRODUCTION**

Incretins are gut-derived peptide molecules secreted post meal to act on food.[1] The major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)¹. GLP-1 is secreted by neuroendocrine L cells of the ileum and colon and GIP is
produced by K cells of the duodenum and jejunum. GLP-1 and GIP stimulate insulin release from pancreatic beta cells in a glucose-dependent fashion. GLP-1 also lessens secretion of glucagon, a hormone that causes conversion of glycogen into glucose (responsible for opposing the effects of insulin and amylin) in liver. GLP-1 also slows down gastric emptying and makes person feel full for an extended time. In this way he consumes less. The incretin hormones; GLP-1 and glucose-dependent insulinotropic polypeptide GIP are now widely recognized as important contributors to the maintenance of glucose homeostasis. This class of drugs is not very old and much of the research work is focused on incretins as researchers are exploring them from antiobesity point of view also. This article reviews currently available GLP-1 analogues (GLP-1 mimetics) which mimic incretins e. g. Exenatide, DPP – IV inhibitors (sitagliptin), and closely related category, amylin.[3] Latest in the domain of incretins is also being discussed here.

**GLP-1/Incretin mimetics**

Two incretin hormones identified first are GIP and GLP-1. Levels of these hormones rise post prandial and shown to rise rapidly shortly after nutrient intake and then fall suddenly shortly thereafter as a result of inactivation by the enzyme DPP – IV. GLP-1 is secreted in greater concentrations.[4] GLP-1 has been reported to enhance glucose-dependent insulin secretion, suppress postprandial glucagon secretion from pancreatic alpha-cells, slow gastric emptying, and reduce food intake and body weight. It may also preserve/enhance beta-cell mass, by promoting beta-cell proliferation, and by decreasing beta-cell death.[5] In addition to its effects on the core defects in type 2 diabetes, GLP-1 also appears to have direct effects on other body tissues.[6-11] The first synthetic agonist at GLP-1 receptor is Exenatide. Exenatide (a drug available with the brand name Byetta) is a synthetic analogue of a substance (exendin-4) found in Gila monster (*Heloderma suspectum*) saliva, led to healthy sustained glucose levels and progressive weight loss among type 2 diabetics who took part in a three-year study. Gila monster is a large venomous lizard native to the southwestern United States and northwestern Mexico. The lizard hormone is about 50 percent identical to GLP-1. It was approved by the USFDA in April 2005 to treat type 2 diabetes in patients who were finding it difficult to lower their raise blood glucose level despite of using couple of oral hypoglycemic agents. GLP-1 receptor agonists are the among the newest categories of anti diabetic drugs. Exenatide (manufactured by Amylin Pharmaceuticals Inc. in collaboration with Eli Lilly and Company, comes in a prefilled pen. The reptile version of this hormone remains effective much longer than the human version and thus its synthetic form helps diabetics keep their
blood sugar levels from getting too high. Exenatide also slows the emptying of the stomach and causes a decrease in appetite, which is how it leads to weight loss. John Eng, an endocrinologist at the Bronx Veterans Affairs Medical Center in New York City, was looking at studies of people who developed pancreatitis after being bitten by venomous animals. Eng wanted to find the connection, so he procured various animals’ venoms, including that of the Gila monster. He explored these venoms for their effect on pancreas. Then he concluded that Gila monster secretes a hormone in its saliva called exendin-4. This hormone, which aids digestion in the lizard, is similar to a human digestive hormone called GLP-1. This finding encouraged researchers to develop more successful agonists of GLP-1. The beauty of Exenatide is that it is resistant to DPP-IV degradation, and is cleared by kidneys.

**Dipeptidyl Peptidase - IV Inhibitors (DPP – IV inhibitors)**

Physiological incretins are short-lived owing to their rapid degradation by the enzyme DPP-IV. DPP-IV is widely available in body and circulates in a soluble form. Endogenous GLP-1 has a short half-life (2 minutes). Inhibitors of DPP – IV are available to prevent the inactivation of GLP-1 and lengthen the activity of the endogenously released hormone. The drugs currently available are sitagliptin, saxagliptin, and vildagliptin as sole agents and also combined with metformin. They act on other bioactive peptides like neuropeptide Y, gastrin releasing peptide, substance P, and various chemokines. Oral inhibitors of DPP - IV are recommended for patients with type 2 diabetes mellitus. They decrease the activity of the enzyme close to 80% for up to 24 hours. By doing this they enhance post meal circulating level of GLP-1 and GIP. Unlike GLP-1 mimetics, DPP – IV inhibitors increase effective incretin levels into a more physiological range. They increase insulin secretion in response to dietary glucose and suppress glucagon secretion.
As the boxes clearly indicate only two broad categories are there neurotransmitters augmenting agents and agents reducing the digestion and absorption (Only orlistat)

*Got positive response from USFDA on 09/09/2014, but final approval is still not granted, marketing authorization may be granted very soon. Novo Nordisk is looking to get Saxenda approved for chronic weight management in patients with either a BMI of $\geq 30$ kg/m$^2$, or a BMI of $\geq 27$ kg/m$^2$ plus at least one weight-related comorbid condition.
Current options and mode of action of antidiabetics drugs

**Alpha-glucosidase inhibitors**
- They delay the digestion and absorption of carbohydrates; hence reduce the blood sugar elevation after a meal.
- E.g. Acarbose, Miglitol.

**PPAR agonists**
- E.g. Saroglitazar
- Agonist action at PPARα lowers high blood triglycerides, and agonist action on PPARγ improves insulin resistance and consequently lowers blood sugar.

**Sulphonylureas**
- They increase insulin secretion.
- E.g. Tolbutamide, Chlorpropamide, Glibenclamide, Glipizide, Gliclazide, Glimiperide.

**Thiazolidinediones**
- E.g. Rosiglitazone, Pioglitazone activate PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, with greatest specificity for PPARγ (gamma).

**Biguanides**
- E.g. Metformin

**Meglitinides**
- E.g. Repaglinide, Nateglinide are secretagogues that stimulate rapid insulin production by the pancreas and reduce both post-prandial blood glucose and HbA1c by 0.5–2%.

**Glucagon like peptide (GLP-1) analogues**
- Mimics incretins, the peptides that are secreted when a person eats; incretins stimulate insulin production and help the person feel full by delaying emptying of the stomach.
- E.g. Exenatide

**Amylin (Islet Amyloid Polypeptide (IAPP)) analogues**
- E.g. Pramlintide functions as a synergistic partner to insulin, with which it is cosecreted from pancreatic beta cells in response to meals.

**SGLT-2 inhibitors**
- Block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine.
- E.g. Canagliflozin, Dapagliflozin

**Dipeptidyl peptidase-4 (DPP-4) inhibitors**
- E.g. Sitagliptin
- DPP-4 inhibitors reduce glucagon and blood glucose levels by blocking DPP-4, which breaks down GLP-1.

**Insulin shots**

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Amylin analogues

Amylin is a peptide neurohormone that is synthesized and released by beta cells of the pancreas with insulin. Patients without active beta cells are deficient in both insulin and amylin. Secretion of amylin, like GLP-1, is stimulated by the presence of food in the gut. The physiological effects of amylin are also akin to those of GLP-1 but it is not an incretin hormone. Amylin is similar to the incretins, but one exception is there; amylin does not cause insulin secretion, but it does all of the other things that the incretins do to prevent the shoot in glucose level after food is taken.\(^\text{[21]}\) Amylin represses glucagon secretion, holdups gastric-emptying, and acts centrally in the area postrema of the hindbrain to induce feeling of fullness (satiety). Amylin slows the entry of glucose into the circulation while insulin stimulates cellular uptake of glucose to reduce glucose concentrations.\(^\text{[22, 23]}\) By augmenting endogenous amylin, pramlintide (drug available on a prescription) aids in the cellular absorption and regulation of blood glucose by delaying gastric emptying, promoting feeling of stuffed stomach via hypothalamic receptors (not GLP-1 receptor), and inhibiting inappropriate secretion of glucagon.

DISCUSSION AND CONCLUSION

Increased occurrence of type 2 diabetes mellitus and obesity has elevated the medical need for new agents to treat these metabolic ailments. Resistance to the hormones insulin and leptin are characteristic of both type 2 diabetes and obesity. Drugs that can mitigate this resistance should be effective in treating these two.\(^\text{[24]}\) Type 2 diabetes mellitus is estimated to affect more than 5% of the adult population in Western societies (figures for children population also alarming), and its occurrence is expected to further boost considerably in the future, in particular owing to the remarkable increase in obesity. Hyperglycaemia, the prominent and easiest diagnostic symptom, is associated with flawed insulin production and peripheral insulin resistance, and leads to the development of a range of signature complications of diabetes mellitus. Incretin based pharmacognosy is youngest among USFDA approved, which mimic the activity of natural glucoregulatory peptides.\(^\text{[17]}\) Various implication and ways of bringing these incretin in use for other metabolic disorders are being studied. A latest paper published in Science Translational Medicine has shown that an under trial diabetes drug that targets two members of the incretin family of hormone receptors may have superior metabolic effects than approved diabetes drugs such as exenatide (Byetta; Amylin) and Liraglutide.\(^\text{[25]}\) Incretins are gut hormones that potentiate insulin secretion post meal. The two best-studied incretins so far, GIP and GLP-1 exert their insulinotrophic actions
through G-protein-coupled receptors highly expressed on islet β cells. These two incretins are really incredible, because they are addressing not only diabetes mellitus but may also show exhibit potential as antiobesity molecule in various ongoing studies in various laboratories. This later effect may be due to the fact that GLP-1 and GIP receptors are also widely expressed in nonislet cells and also exert indirect metabolic events. Two ways have been identified to use these incretins. Inhibition of DPP - IV, the enzyme which causes for N-terminal cleavage and inactivation of GIP and GLP-1. A second class of incretin-based therapies is comprised of injectable GLP-1R. The glucagon-like peptide 1 receptor is a human gene, resting on chromosome 6. A member of the glucagon receptor family of G protein-coupled receptors is expressed by this gene.

The insulinitropic properties of GIP and GLP-1 were came to fore more than 25 years ago; however, new dimensions of incretin hormones will continue mesmerize and happify scientists, as our understanding of underlying mechanism of diabetes grows, pharmacotherapy will further be explored. GLP - 1 receptor agonist are also being used in treatment of obesity in some part of world (off label use). Pharmacotherapy using DPP-4 inhibitors has few side effects and does not affect wait. Animal studies support their use in prediabetes. GLP-1 receptor agonist effects are also apparent in non-diabetic obese individuals. A paper published in International Journal of Obesity (Nature) in 2013 reviews around 130 references and reported various conclusions drawn by earlier researches on feeding behavior apropos to incretins namely GIP and GLP-1. It says Results from studies in both experimental animals and humans have indicated that GLP-1 has a key role in satiation signaling. In the periphery, satiation-inducing effects of GLP-1 are most probably mediated by vagal afferents originating in the intestine in combination with other mechanism that may involve circumventricular organs, and peripheral GLP-1 appears to activate CNS nuclei that are involved in satiation, including the PVN, the central nucleus of the amygdala and possibly the nucleus accumbens. Intrinsic to the CNS, a GLP-1 pathway arising in the NTS (nucleus of the solitary tract) is also involved in satiation. ICV (intracerebroventricular) administration of GLP-1 receptors in the CNS reduces food intake. Circulating levels of GLP-1, including responses to meals, are decreased in obese individuals. Weight loss associated with diet and exercise or bariatric surgery is associated with increased GLP-1 levels, and it has been suggested that elevated satiation signaling mediated by GLP-1 may contribute to weight loss in both the settings. In another study it has been found that weight loss induced by GLP-1 analogues is dose dependent and progressive. Liraglutide has
shown to cause a mean weight loss of around 6.0 kg (more than thirty five percent of the subjects achieving more than or equal to ten percent reduction) of weight. Longer acting version of Exenatide has been found to improve bodyweight with an average weight reduction of around 3 kg.\(^{[36-37]}\) The most recent update about upcoming antiobesity molecule based on incretin is Liraglutide. USFDA may give its final nod to this molecule (Saxenda\(^{®}\)) which is already in market as anti diabetic drug by Novo Nordisk.\(^{[38,39]}\) US FDA panel endorsed on September 09, 2014 Liraglutide as obesity treatment but not given final nod for launching into market. It is suggested and reported that incretin based molecule should not be used for shedding extra pounds of fats, especially not in nondiabetic patients, until it emerges as foolproof antiobesity molecule associated with no potential cardiovascular risks and other major side effects in long run, but still few GLP-1 agonists are being consumed by people for decreasing wait. Other antiobesity options, still in infancy, are superabsorbent hydrogel, temporary controllable gastric pseudobezoars (pseudobezoar is an indigestible material administered intentionally into the digestive system).\(^{[40, 41]}\)

In summary, incretin therapy appears to offer an effective choice to the currently available hypoglycaemic agents and it potential to serve diabetics for a long time with an added advantage of weight reduction. Weight regain remains a major limitation among patients who are on antiobesity medication. Though simultaneous options are there, indeed they are warranted for effective output of pharmacotherapy, like lifestyle modification and surgical interventions, but most subjects suffer from wait gain after certain period of time or after finishing prescribed medicament regimen. Here incretins may play a crucial role and may fill the gap, as none of the incretin analogues are in practice (recommended by regulatory bodies) for antiobesity effect around the world. Chances might be there for approval of specifically designed incretins for treatment of obesity in years to come. Incretin-based analogues may be effective in preventing progression of prediabetes and GLP-1 agonists if modified properly may have potential for use in the treatment of obesity. As per Dr. Daniel Drucker, a senior instigator at Lunenfeld Tanenbaum Research Institute (LTRI), Mount Sinai Hospital, Toronto; and a pioneer in diabetes and obesity research from view point of incretins (chiefly GLP – 1) “since enhanced gut hormone action may be beneficial in diabetes, obesity and inflammatory bowel disorders, these analogues have real potential to lead to new and better treatments for diseases that afflict millions of people worldwide”. It will not be an hyperbole to expect whopping sale of a molecule based on incretin approach, which can address both obesity and diabetes without major side effects because WHO report says that over 347
million people in the world are afflicted with diabetes type 2 and number for obese people is also disturbing. Problem with obesity treatment is that they are adjunct to a reduced-calorie diet and increased physical activity (with shunning away from sedentary life style), if patient wants to see some significant weight loss. Very rightly told by Larry Page, co-founder of Google, “If the past is any indicator of our future success, today’s big bets won’t seem so wild in a few years’ time”.

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