**ABSTRACT**

Drugs that augment the incretin system [glucagon like peptide (GLP) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] represent a novel class of anti-hyperglycemic agents that have shown to improve the health and survival of beta-cells (improvement in postprandial hyperglycemia) and suppress glucagon (improvement in fasting hyperglycemia). The incretins represent a large family of molecules referred to as the “glucagon superfamily of peptide hormones” of which more than 90% of the physiological effects of incretins are accomplished by GLP-1$_{7-37}$ and GLP1$_{7-36}$ amide and gastric insulinoctropic peptide (GIP). GLP-1 mediates its effects via the GLP-1 receptor, which has a wide tissue distribution [pancreas, lung, heart, vascular smooth muscle cells, endothelial cells, macrophages and monocytes, kidney, gastrointestinal tract (stomach and intestine), central nervous system (neoortex, cerebellum, hypothalamus, hippocampus, brainstem nucleus tractus solitarius) and peripheral nervous system]. This would imply that the incretin system has effects outside the pancreas. Over time data has accumulated to suggest that therapies that augment the incretin system has beneficial pleiotrophic effects. The incretins have shown to possess a cardiac-friendly profile, preserve neuronal cells and safeguard from neuronal degeneration, improve hepatic inflammation and hepatosteatosis, improve insulin resistance, promote weight loss and induce satiety. There is growing evidence that they may also be renoprotective promoting wound healing and bone health.

**Key words:** Extrapancreatic, gliptins, glucagon like peptide analogues, glucagon like peptide, incretin mimetics, incretins, pleiotrophic

**INTRODUCTION**

More than 50% of patients with type 2 diabetes mellitus (T2DM) have a glycosylated hemoglobin (HbA1c) level of >7% and are inadequately controlled.[1] Drugs such as metformin and sulfonylurea (SU) have traditionally been the mainstay of therapy despite the knowledge that the combination may be cardiac unfriendly (UKPDS) and may result in a progressive decline in (beta)-cell function, and by 3 years, up to 50% of diabetic patients can require an additional pharmacological agent to maintain the HbA1c to <7.0% (UKPDS).[2-4] Moreover, these drugs do not address the pathogenesis of T2DM, except metformin that helps improve insulin resistance (hepatic more than peripheral).

Drugs that augment the incretin system [glucagon like peptide (GLP) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] represent a novel class of anti-hyperglycemic agents that have shown to improve the health and survival of beta-cells (improvement in postprandial hyperglycemia), suppress glucagon (improvement in fasting hyperglycemia), improve insulin resistance (modest effect) and influence energy intake (augment satiety signal) with minimal, if at all, any side effects (weight neutral and non-hypoglycemic). The incretins address most of the proposed pathogenetic mechanisms involved in the development of T2DM.[2]

Over time, these agents have shown to have a cardiac-friendly profile, preserve neuronal cells and safeguard from neuronal degeneration, improve hepatic inflammation and hepatosteatosis, improve insulin resistance, promote weight loss and induce satiety.[5] There is growing evidence that they may also be renoprotective and help with wound healing.

**GUT PEPTIDES/INCRETINS**

In 1902, Bayliss and Starling identified the first gut
hormone called “secretin” and suggested that it may be involved in glucose homeostasis. In 1930, crude secretin was successfully divided into two fractions by a Belgian physiologist named Jean La Barre. One fraction was shown to stimulate exocrine pancreatic secretion (secretin) and the other was shown to lower plasma glucose (incretin). In 1932, La Barre coined the term “incretine.”[6-8]

Incretins, namely, GLP-1 and gastric insulotropic peptide (GIP), have shown to dispose glucose far more efficiently following an oral mixed meal (incretin effect).[9] They represent a large family of molecules referred to as the “glucagon superfamily of peptide hormones.” More than 90% of the physiological effects of incretins are accomplished by GLP1$_{7-37}$ and GLP1$_{7-36}$ amide and GIP.

GLP-1 circulates as two equipotent forms, GLP1$_{7-37}$ and GLP1$_{7-36}$ amide, and is secreted by neuroendocrine L-cells present in the distal small intestine in response to a carbohydrate/fat meal. GLP1$_{7-36}$ constitutes 80% of circulating GLP-1. It is rapidly cleared by the kidney and degraded by DPP-4 (a type II membrane peptidase resembling CD26) even before it leaves the gastrointestinal tract. DPP-4 was discovered in 1996. The half-life of circulating native bioactive GLP-1 is less than 2 minutes. Gliptins work by inhibiting DPP-4 and raising the concentration of circulating GLP-1 as many as twofold to threefold. Incretin mimetics (exanatide, liraglutide) work by stimulating the GLP-1 receptor (GLP-1R) directly. GIP is secreted by neuroendocrine K-cells present in stomach and proximal small intestine and has a half-life of approximately 7 minutes in healthy individuals and 5 minutes in patients with T2DM, being degraded by DPP-4 also. GIP is rapidly cleared through the kidney.[9-17]

GLP-1 has a wide tissue distribution and acts via the GLP-1R that belongs to the class B family of 7-transmembrane–spanning, heterotrimeric G-protein–coupled receptors functionally associated with adenylate cyclase. It has been identified in pancreas, lung, heart, vascular smooth muscle cells, endothelial cells, macrophages and monocytes, kidney, gastrointestinal tract (stomach and intestine), central nervous system (brain) and peripheral nervous system. The brain and cardiac tissue express the same GLP-1R as is expressed on pancreatic tissue, in contrast to peripheral human tissue (skeletal muscle, adipose tissue, liver) where the receptors bear some degree of homology to pancreatic GLP-1R.[12-16] In the brain, the GLP-1R is found only on neurons and not on glial cells. It is present on mainly large output neurons such as pyramidal neurons, dentate granule neurons and Purkinje cells. GLP-1Rs are found on dendrites in and around synapses, suggesting that they directly modulate synaptic activity and plasticity. In the brainstem, GLP-1R is mostly distributed in the brainstem nucleus (caudal part of nucleus tractus solitarius). Hypothalamus [dorsomedial (DMN), paraventricular (PVN), ventromedial (VMN), lateral and arcuate (ARC) and supraoptic nuclei], sensory circumventricular organs such as the subfornical organ, organum vasculare, laminae terminus, and the area postrema express GLP-1R in high density. Other areas that express GLP are neocortex, cerebellum and hippocampus. Although it is believed that the liver (hepatocyte) possesses the GLP-1R, it is clearly different compared to the native GLP-1R. Simulation of the liver GLP-1R results in anabolic effect, an action opposite to that seen with glucagon (neoglucogenesis and glycogenolysis). It is thus believed that although GLP-1R truly exists on hepatocytes, it must be different from the known GLP-1R, produced either by an unidentified gene locus encoding a second GLP-1R, or it may be an alternatively spliced receptor related to the superfamily of glucagon-related peptide receptors.[18-20]

**Currently Available Gliptins and Incretin Mimetics**

**Gliptins**
- Sitagliptin (Merck Sharp and Dohme Corp., approved as Januvia by US FDA in 2006)
- Vildagliptin (Novartis, approved as Galvus by EU in 2007)
- Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in 2010)
- Linagliptin (Boehringer Ingelheim, approved as Tradjenta by US FDA in 2011)
- Alogliptin (developed by Takeda Pharmaceutical Company Limited, approved for use in Japan)
- Dutogliptin (being developed by Phenomix Corporation)
- Gemiglaptin (being developed by LG Life Sciences)
- Sitagliptin, Vildagliptin, Saxagliptin are approved for use in India

**Incretin mimetics**
- Exanatide (EliLilly, approved as Exanatide by US FDA in 2005)
- Liraglutide (Novonordisk, approved as Victoza by US FDA in 2010)
- Exanatide, Liraglutide are approved for use in India

**Current Position of Drugs that Work on the Incretin Axis in the Management of T2DM**

Amongst all currently available anti-diabetic agents, gliptins address most of the “pathogenetic octet” components of T2DM, as proposed by Ralf Dfranzo. They have found...
themselves occupying a unique position in the management of T2DM based on the fact that they are weight neutral (gliptins) or weight reducing (incretin mimetics) and virtually free of hypoglycemia. For this very reason, they are commonly advised as second-line therapy along with an insulin sensitizer. They are indicated and approved for use as follows:

1. First line in patients with HbA1c <7%
2. Second line as add-on therapy to pre-existing monotherapy (metformin, SU, TZD, alpha-glucosidase inhibitor, miglitol) for uncontrolled T2DM with HbA1c >7%. Caution is advised along with the use of SU, as it may potentiate its action and cause hypoglycemia. Dose titration of SU (reduce to half existing dose) is recommended when used along with gliptin or GLP-1 analogue.
3. Third line as add-on therapy to pre-existing combination therapy (metformin, SU, TZD, alpha-glucosidase inhibitor, miglitinide).

NICE UK recognizes the enormous potential of the drugs (weight neutral and virtually free of hypoglycemia) and states that the drugs should be continued as long as they can maintain an HbA1c reduction of greater than 0.5% over a 6-month period. This might change in the future assuming the profound non-glycemic benefits that they have shown to possess.[21-23]

**Pleiotropic Effects**

**Cytoprotection**

GLP-1R stimulation has been associated with cytoprotection and anti-apoptosis in all tissue types bearing the receptor. The trophic actions are probably mediated via protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K) signaling. GLP-1R stimulation has been associated with suppression of pro-apoptotic protein, Bax, and stimulation of anti-apoptotic protein, Bcl-2; thereby favorably modifying the Bax/Bcl-2 ratio, supporting cell survival. Pancreas, brain and heart have been shown to express exactly the same GLP-1R type and it would only be appropriate to suggest that the cytoprotective benefit would in least extend to these tissue types as they bear the same receptor type.[24-26]

**Cardiovascular Effects**

Both intact GLP-1 and amide have demonstrated GLP-dependent cardioprotective effects in preclinical studies. Studies have also demonstrated cardioprotective effects following use of GLP-1R agonists in GLP-1R knockout mice [Glp1r(−/−)] suggesting GLP-1 independent effects. Furthermore, mice lacking the GLP-1R were reported to have lower heart rates, worse left ventricular (LV) diastolic function, greater LV wall thickening, and impaired LV contractile function.[27-29]

The proposed mechanisms to explain the cardiac benefits are as follows:

1. The human heart usually uses fats as metabolic fuel in the normoxic state. When acutely stressed (ischemic), it switches from lipid metabolism to carbohydrate oxidation, which is although adaptive initially, eventually leads to insulin resistance and a loss of metabolic flexibility, which is detrimental to the heart. GLP-1R stimulation helps improve insulin sensitivity and shifts cardiac metabolism in favor of cardioprotection.[30-32]
2. Pre-clinical studies have shown that GLP-1 up-regulates the expression of glucose transport protein (GLUT)-2 and -4, which in turn improves insulin resistance. GLUTs represent a family of proteins that help facilitate the transport of glucose across the plasma membrane. In the myocyte, GLUT-4 is found predominantly distributed between sarcolemmal and T tubule membranes. GLUT-4 expression is markedly reduced in T2DM. GLP-mediated GLUT-4 translocates to the myocyte surface to increase glucose uptake. GLUT-2 is the most abundant isoform in liver and pancreatic B-cells, which when up-regulated improves peripheral glucose uptake.[33-34]

3. GLP-1 has shown to decrease pyruvate and lactate concentrations both in normoxic and ischemic conditions of the heart, suggesting cardioprotective effects.[35]
4. Anti-apoptosis of cardiac myocyte – GLP-1 seems also to reduce infarct size in rats, when given either prior to ischemia (as a preconditioning mimetic) or directly at reperfusion. Other potential cardioprotective markers enhanced by GLP-1 agonists are Bcl-2 family proteins (anti-apoptosis) and heme oxygenase-1 (antioxidant gene, shown to reduce LV fibrosis and remodeling and improve LV function post myocardial infarction).[36-39]

**Potential benefits**

1. **Ionotropic:** GLP-1 agonists have shown to limit infarct size and improve LV function. In a study that assessed LV function following a myocardial infarction, a significant improvement in ejection fraction (from 29 ± 2% to 39 ± 2%) and regional functional recovery in the peri-infarct zone was observed, which were independent of changes in blood pressure or heart rate, suggesting cardioprotection.[40-41]

2. **Blood pressure:** In humans, the use of GLP-1 analogues (exenatide and liraglutide) and gliptins (sitagliptin) has shown a significant reduction in both systolic and diastolic blood pressure when compared with placebo. The main mechanism for this antihypertensive effect,
GLP-1 agonists have been shown to have a natriuretic/diuretic effect (inhibiting sodium reabsorption in the proximal tubule and angiotensin II), peripheral vasodilatory effect and endothelial function stabilizing effect in preclinical studies, all shown to contribute to improvements in blood pressure.\[42-48\]

3. **Vascular endothelium:** GLP-1R agonists have shown to inhibit monocyte/macrophage accumulation in the arterial wall, inhibit expression of inflammatory marker [tumor necrosis factor-alpha (TNF-alpha)], inhibit hyperglycemic-mediated induction of expression of plasminogen activator inhibitor type-1 (pro-coagulant), adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1)] and promote vascular relaxants (nitric oxide). The same results have been replicated by gliptins (sitagliptin) that have shown to improve inflammatory cytokines [monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, IL-12, IL-12] at the level of adipose tissue (improved insulin resistance) and systemically. The net result seems to be amelioration of endothelial function and stabilization of fatty plaques, which should eventually translate into direct protective effects of GLP-1 on the progression of atherosclerosis.\[49-54\]

4. **Dyslipidemia:** GLP-1 agonists have been shown to increase high-density lipoprotein (HDL) and reduce triglyceride, apolipoprotein B48 (apoB48, a component of chylomicrons, rich in triacylglycerol, produced after fat ingestion). Most of these effects, however, have been shown to be related to weight loss rather than the direct effect of the drugs. Improvements in postprandial lipemia are seen with both DPP-4 inhibitors and GLP-1 agonists. However, the mechanism seems unclear. Postprandial lipemia has been shown to be atherogenic. It may, therefore, be extrapolated that use of GLP-1 agonists may have an anti-atherosclerotic effect.\[55-57\]

5. **Weight loss:** As little as a 5% reduction in weight can improve glycemic control, blood pressure and lipid levels. In a prospective study, the effect of intentional weight loss on mortality in overweight individuals with diabetes was studied. It was seen that a weight loss of 34% was associated with a 25% reduction in total mortality and a 28% reduction in cardiovascular disease (CVD) and diabetes mortality. An intentional weight loss of 20–29 lb was associated with the largest reduction in mortality (~33%). GLP-1 agonists have been associated with an average weight loss of approximately 1–10 kg over a 1-year period in studies carried out in both controlled and real life setting. A retrospective analysis of patients treated with GLP-1R agonists showed that weight reduction was associated with a favorable cardiovascular risk profile.\[58-63\]

**Effects on the Nervous System**

Patients with T2DM are predisposed to the development of neurodegenerative disorders like Alzheimer’s disease and the association has been referred to as type 3 diabetes mellitus. Desensitization of insulin receptors has been observed in the brains of patients with Alzheimer’s disease, and any process (GLP-1 analogues or DPP-4 inhibitors) that can up-regulate the insulin receptors should theoretically have the potential to improve the clinical course.\[64-67\] Augmentation of the incretin system has demonstrated the potential advantage of preservation of neuronal cells. GLP-1 may gain access to the brain via either local production of GLP-1 within the brain or uptake of intestinally derived GLP-1 in the circulation. There is some skepticism with regard to GLP-1’s central actions derived from the gastrointestinal tract as it has a very short circulating life, being rapidly inactivated by DPP-4. GLP-1 inhibits eating responses (taste aversion, satiety) via its action on GLP-1R.

The proposed mechanisms to explain these benefits include the following:

1. **Modulation of peripheral taste sensation:** GLP analogues can directly influence the taste receptors. Human GLP-1 is found in mammalian taste cells (type 2 and type 3). The weight loss observed with GLP receptor agonists has been associated with reduction in food intake and weight loss in rats. GLP-1 may help modulate taste sensation which may further contribute to its anorexigenic effect.\[68\]

2. **Central modulation of energy intake:** Preclinical studies indicate enhanced expression of c-Fos in the nucleus tractus solitarii, area postrema and central nucleus of the amygdale in response to GLP, which are central regulators of energy metabolism. Specific hypothalamic nuclei (DMN, PVN, ARC and VMN) serve as control centers for appetite. The ARC nucleus lies outside the blood–brain barrier and is the major target for peripheral hormones that regulate appetite, like GLP. The ARC contains two distinct types of neurons, anorexigenic [neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)] and orexigenic [neuropeptide Y (NPY) and agouti-related protein (AgRP)]. There exist several NPY-receptors (NPY-R); NPYR1- and Y5-receptor activation appears to stimulate appetite, while NPYRY2- and Y4-receptor activation suppresses food intake via presynaptic inhibition of NPY release. GLP-1 has shown to antagonize the orexigenic effects of NPY. Central GLP-1 augmentation results in an anorexigenic effect with a reduction in appetite by 12% approximately for the subsequent meal.\[69-74\] Also, corticotropin-
releasing hormone and thyrotropin-releasing hormone are anorexigenic peptides expressed in the PVN nuclei of hypothalamus. GLP-1 has shown to increase the release of corticotropin in the hypothalamus, further contributing to appetite suppression.\textsuperscript{[79]}

3. **Peripheral modulation of energy intake in concert with central mechanisms**: In response to food and nutrients in the proximal gastrointestinal tract, signals are carried from the lamina propria via the vagal afferents (parasympathetic system) to the center. The nucleus tractus solitarius primarily receives afferents from the vagus. Studies have shown that the caudal neurons of the nucleus of the solitary tract containing GLP-1 project to the PVN nucleus of the hypothalamus (satiety center) to cause central suppression of appetite and food intake, participating in the regulation of energy intake. Efferents from the center are also generated to project back to the gastrointestinal tract, resulting in gastric slowing by a mechanism called “ileal-break.” Preclinical studies have also shown that the production of GLP-1 is dependent on the presence of an intact autonomic nervous system, without which weight gain results. It is tempting to speculate that this may constitute a prandial satiety signal. \textit{Leptin} is a quantitative marker and product of the \textit{ob} gene in white adipose tissue. The leptin receptor has been found on the membrane of the GLP-1 secreting intestinal L-cells. Leptin can stimulate GLP-1 secretion from fetal rat and human intestinal L-cells in a dose-dependent manner. Leptin has been shown to activate the hypothalamic circuits, leading to the inhibition of food intake. T2DM and obesity is associated with leptin receptor resistance leading to reduced GLP-1 secretion and hypothalamic activation in favor of increased energy intake.\textsuperscript{[76-78]}

The incretins have numerous pleiotropic effects with clear benefits to the neuronal system. Central augmentation of the incretin system has been shown to protect neuronal cells (neuroprotection), influence neurobehavioral changes (enhanced learning, cognition, spatial orientation) and regulate food and energy intake (weight loss). This adds a new dimension to the use of GLP-1 augmenting therapies for patients with diabetes.

**Gastrointestinal and Hepatobiliary Effects**

GLP-1 has shown to improve beta-cell health and suppress glucagon, thereby improving postprandial and fasting hyperglycemia, respectively. As explained above, in concert with the central nervous system, GLP-1 augmentation results in central appetite suppression, weight reduction with secondary benefits on dyslipidemia (reduction in triglyceride, apoB48 and increase in HDL). It has been shown that when fatty acids are applied directly to fetal rat intestinal cell cultures, they stimulate GLP-1 secretion. Incretins are released within 5–15 minutes of food ingestion, the time that is insufficient for food to directly stimulate the more distally placed neuroendocrine secreting incretin cells. It is thus believed that there exists a regulatory loop.

The proposed mechanisms for GLP-1 release are as follows:

1. **Proximal–distal neuro-enteral regulatory loop**: As explained above, release of GLP-1 from the distal ileum is stimulated in response to nutrients in the proximal gastrointestinal tract. An \textit{indirect} influence of nutrients on the release of GLP-1 is mediated via the autonomic nervous system (vagus, myenteric) wherein afferent signals (vagus nerve) carry impulses to higher centers in the brain (hypothalamus, area postrema, amygdala) in order to modulate feeding, inducing satiety or anorexia (food aversion). The parasympathetic system (vagus) is also hypothesized to carry efferent signals to directly influence the release of GLP-1.\textsuperscript{[74]}

2. **Direct stimulatory effect of nutrient related GIP release on GLP-1 release by L-cells**.

**Potential benefits**

1. **Appetite suppression**
2. **Delayed gastric emptying causing prandial satiety**
3. **Weight reduction/anti-obesity**: This results from the cumulative effect of central appetite suppression, modulation of peripheral taste sensation and gastric slowing (prandial satiety). A \textit{meta-analysis} has suggested that use of GLP-1 analogues is associated with an average weight loss of approximately 4.76 kg compared to patients receiving insulin therapy. GLP-1 analogues cause reduction in both visceral and subcutaneous (abdominal circumference) adipose tissue. For every 1 cm increase in waist circumference, the relative increase in cardiovascular risk equals approximately 2%. It is well established that intentional weight loss has cardiovascular benefits. Weight loss of approximately less than 20 lb is associated with reduction of diabetes-associated mortality by 32%. Even a modest loss of weight (<10%) significantly improves blood pressure, cholesterol levels and glycemic control.\textsuperscript{[79,84]} GLP-1 analogues are an effective weight management tool that delays the onset of type 2 diabetes. Although not approved for obesity alone, drug therapy that exploits the GLP-axis seems like a potential strategy to counter both obesity and diabetes. With its vast pleiotropic effects, the incretin mimetics threaten to become the mainstay of therapy in patients with diabetes, especially...
Insulin Resistance

Insulin resistance is associated with an increased risk of metabolic abnormalities (dyslipidemia, T2DM). In one study, waist circumference and body mass index (BMI) were independently associated with CVD risk factors (such as hypertension, metabolic syndrome, and dyslipidemia) in both men and women. GLP-1 has shown to reduce insulin sensitivity through restoration of insulin signaling and by reduction of hepatic gluconeogenesis. Enhanced insulin secretion causes increased uptake of glucose in the muscle and adipocyte and reduced outpouring of glucose from the liver. Obesity is associated with insulin resistance.

Wound Healing

Gliptin (linagliptin) has shown to influence positively macrophage-mediated inflammation response and tissue remodeling, which may have benefits with regard to suppression of vascular inflammation and improvement in wound healing.
Nephroprotection

Gliptin (sitagliptin) has shown to reduce albuminuria in a small pilot study, without affecting the glomerular filtration rate, most likely due to its beneficial effect on blood sugar, blood pressure, and inflammation.109

Conclusion

Augmentation of the incretin axis by use of either GLP-1 agonists or DDP-4 inhibitors represents a novel therapeutic concept that is not only anti-hyperglycemic but has substantial pleiotropic effects. Benefits extend to virtually every organ system, providing cardiovascular stability (anti-ischemic, anti-hypertensive, ionotropic, antiatherosclerotic) weight loss, neuronal-protection, liver stability (anti-ischemic, anti-hypertensive, ionotropic, anti-atherosclerotic) weight loss, neuronal-protection, liver and skeletal health and improvement in insulin resistance. Incretin agonism clearly represents the future of anti-diabetes therapy given its impressive pleiotropic actions.

References

1. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: A preliminary report. Diabetes Care 2004;27:17-20.
2. Defronzo RA. Baniting Lecture: From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773-95.
3. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963-72.
4. UK Prospective Diabetes Diabetes Study Group. UKPDS 28: A randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. Diabetes Care 1998;21:87-92.
5. Charbonnel B, Cariou B. Pharmacological management of type 2 diabetes: The potential of incretin-based therapies. Diabetes Obes Metab 2011;13:99-117.
6. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. J Physiol 1902;28:325-53.
7. La Barre J, Still EU. Studies on the physiology of secretin. Am J Physiol 1930;91:649-53.
8. La Barre J. Sur le possibilité d’un traitement du diabète par l’incretine. Bull Acad R Med Belg 1932;12:620-4.
9. Drucker DJ. The biology of incretin hormones. Cell Metab 2006;3:153-65.
10. Drucker DJ, Nauck MA. The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705.
11. Meier JJ, Nauck MA. Incretins and the development of type 2 diabetes. Curr Diab Rep 2006;6:194-201.
12. Holst, Jens J. The physiology and pharmacology of incretins in type 2 diabetes mellitus. Diabet Obes Metab 2008;10(Suppl 3):14-21.
13. Deacon, Carolyn F, DPP4IV and diabetes. Clin Chem Lab Med 2008;46:A18.
14. Martin JH, Deacon CF, Gorrell MD, Prins JB. Incretin-based therapies: Review of the physiology, pharmacology and emerging clinical experience. Intern Med J 2011;41:299-307.
15. Rasmussen HB, Branner S, Wiberg FC, Wagtmann N. Crystal structure of human dipeptidyl peptidase IV/CD26 in complex with a substrate analog, Nat Struct Biol 2003;10:19-25.
16. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: A comparative review. Diabet Obes Metab 2011;13:7-18.
17. Hopsu-Havu VK, Glenner GG. A new dipeptide naphthylamide hydrolyzing glycyyl-prolyl-[*beta*]-naphthylamide. Histochemistry 1966;7:197-201.
18. Kinzig KP, D’Alessio DA, Seeley RJ. The diverse roles of specific GLP-1 receptors in the control of food intake and the response to visceral illness. J Neurosci 2002;22:10470-6.
19. Larsen PJ, Tang-Christensen M, Holst JJ, Ørskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. Neuroscience 1997;77:257-70.
20. Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, et al. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. Hepatology 2010;51:1584-92.
21. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. Endocr Pract 2009;15:540-59.
22. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
23. NICE diabetes treatment algorithm. Available from: http://www.nice.org.uk/guidance/CG66. [cited in 2010].
24. Drucker DJ. Glucagon-like peptides: Regulators of cell proliferation, differentiation, and apoptosis. Mol Endocrinol 2003;17:161-71.
25. Ban K, Kim KH, Cho CK, Sauvé M, Diamandis EP, Backx PH, et al. Glucagon-like peptide (GLP)-1(9-36)amide-mediated cytoprotection is blocked by exendin(9-39) yet does not require the known GLP-1 receptor. Endocrinology 2010;151:1520-31.
26. Li Y, Tweedie D, Mattson MP, Holloway HW, Greig NH. Enhancing the GLP-1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J Neurochem 2010;113:1621-31.
27. Nathanson D, Zethelius B, Berne C, Lind L, Andrén B, Ingelsson E, et al. Plasma levels of glucagon like peptide-1 associate with diastolic function in elderly men. Diabet Med 2011;28:301-5.
28. Ban K, Kim KH, Cho CK, Sauvé M, Diamandis EP, Backx PH, et al. Glucagon-like peptide (GLP)-1(9-36)amide-mediated cytoprotection is blocked by exendin (9-39) yet does not require the known GLP-1 receptor. Endocrinology 2010;151:1520-31.
29. G ros R, You X, Baggio LL, Kabir MG, Sadi AM, Mungrue IN, et al. Cardiac function in mice lacking the glucagon-like peptide-1 receptor. Endocrinology 2003;144:2242-52.
30. Taegtmeyer H. Cardiac metabolism as a target for the treatment of heart failure. Circulation 2004;110:894-6.
31. Randle PJ, Garland PB, Hales CN, Neoholme EA. The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785-9.
Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. Diabetes 2010;59:1030-7.

Liu H, Dear AE, Krudsen LB, Simpson RW. A long-acting glucagon-like peptide-1 analogue attenuates induction of plasminogen activator inhibitor type-1 and vascular adhesion molecules. J Endocrinol 2009;201:59-66.

Nystöm T, Gutniak MK, Zhang Q, Zhang F; Holst JJ, Ahrén B, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. Am J Physiol Endocrinol Metab 2004;287:E1219-E1225.

Nystöm T, Gutniak MK, Zhang Q, Zhang F; Holst JJ, Ahrén B, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. Am J Physiol Endocrinol Metab 2004;287:E1209-15.

Dobrian AD, Ma Q, Lindsay JW, Leone KA, Ma K, Coben J, et al. Dipeptidyl peptidase IV inhibitor sitagliptin reduces local inflammation in adipose tissue and in pancreatic islets of obese mice. Am J Physiol Endocrinol Metab 2011;300:E410-21.

Dobrian AD, Ma Q, Lindsay JW, Leone KA, Ma K, Coben J, et al. Dipeptidyl peptidase IV inhibitor sitagliptin reduces local inflammation in adipose tissue and in pancreatic islets of obese mice. Am J Physiol Endocrinol Metab 2011;300:E410-21.

Horton ES, Silberman C, Davis KL, Bertha R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes Care 2010;33:1759-65.

Bunch MC, Cornèr A, Eliasson B, Heine RJ, Sharagian RM, Wu Y, et al. One-year treatment with exenatide vs. insulin glargine: Effects on postprandial glycemia, lipid profiles, and oxidative stress. Atherosclerosis 2010;212:223-9.

Ahrén B, Foley JE. The islet enhancer vildagliptin: Mechanisms of improved glucose metabolism. Int J Clin Pract Suppl 2008;159:8-14.

Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 2000;23:1499-504.

Drucker DJ, Buse JB, Taylor K, et al. and DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: A randomised, open-label, non-inferiority study. Lancet 2008;372:1240-50.

Charbonnel B, Cariou B. Pharmacological management of type 2 diabetes: The potential of incretin-based therapies. Diabet Obes Metab 2011;13:99-117.

DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092-100.

Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2008;31:2628-35.

Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083-91.

Luchsinger JA, Tang MX, Shea S, Mayeux R. Hypersinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187-92.

Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer’s disease: Shared pathology and treatment. Br J Clin Pharmacol 2011;71:365-76.

Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004;82:510-29.
Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 2004;490:115-25.

Egan JM, Margolskee RF. Taste cells of the gut and gastrointestinal chemosensation. Mol Interv 2008;8:78-81.

Larhammar D. Structural diversity of receptors for neuropeptide Y, peptide YY and pancreatic polypeptide. Regul Pept 1996;65:165-74.

Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of AgRP and NPY in fasting-activated hypothalamic neurons. Nat Neurosci 1998;1:271-2.

Inui A. Neuropeptide Y feeding receptors: Are multiple subtypes involved? Trends Pharmacol Sci 1999;20:43-6.

Furuse M, Matsumoto M, Mori R, Sugahara K, Kano K, Hasegawa S. Influence of fasting and neuropeptide Y on the suppressive food intake induced by intracerebroventricular injection of glucagon-like peptide-1 in the neonatal chick. Brain Res 1997;764:289-92.

Kim GW, Lin JE, Valentino MA, Colon-Gonzalez F, Waldman SA. Regulation of appetite to treat obesity. Exp Rev Clin Pharmacol 2011;4:243-59.

Turtur MD, O’Shea D, Gunn I, Beck SA, Edwards CM, Meenan K, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 1996;379:69-72.

Tauchi M, Zhang R, D’Alessio DA, Stern JE, Herman JP. Distribution of glucagon-like peptide-1 immunoreactivity in the hypothalamic paraventricular and supraoptic nuclei. J Chem Neuroanat 2008;36:144-9.

Layer P, Holst JJ. GLP-1: A humoral mediator of the ileal brake in humans? Digestion 1993;54:385-6.

Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763-70.

Schwartz MW, Seeley RJ, Campfield LA, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest 1996;98:1101-6.

Freemantle N, Holmes J, Hockley A, Kumar S. How strong is the association between abdominal obesity and the incidence of type 2 diabetes? Int J Clin Pract 2008;62:1391-6.

Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, Düring M, et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabet Obes Metab 2009;11:1163-72.

Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in Type 2 diabetes: Systematic review and meta-analysis. J Am Med Assoc 2007;298:194-206.

De Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: Meta-analysis of the LEAD program. Diabetologia 2010;53:1552.

Bulchandani D, Nachnani JS, Eaton C, Hamburg M. Association of exenatide with liver enzymes in patients with type 2 diabetes. Endocrinologist 2009;19:114-5.

Chen G, Liu C, Chen F, Yao J, Jiang Q, Chen N, et al. Body fat distribution and their associations with cardiovascular risk, insulin resistance and [beta]-cell function: Are there differences between men and women? Int J Clin Pract 2011;65:592-601.

Lee YS, Shin S, Shighara T, Hahn E, Liu MJ, Han J, et al. Glucagon-like peptide-1 gene therapy in obese diabetic mice results in long-term cure of diabetes by improving insulin sensitivity and reducing hepatic gluconeogenesis. Diabetes 2007;56:1671-9.

Martyn JA, Kaneki M, Yashara S. Obesity-induced Incretin resistance and hyperglycaemia: Etiological factors and molecular mechanisms. Anesthesiology 2008;109:137-48.

Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes 1997;46:3-10.

Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, et al. Effects of free fatty acids on glucose transport and IRS-1 in type II diabetics. Diabetes 1987;36:274-83.

Hare KJ, Vilbell T, Asmar M, Deacon CF, Knop FK, Holst JJ. The glucagonostatic and insulinotropic effects of glucagon-like peptide 1 contribute equally to its glucose-lowering action. Diabetes 2010;59:1765-70.

Van Dijk G, Lindskog S, Holst JJ, Steffens AB, Ahrén B. Effects of glucagon-like peptide-1 on glucose turnover in rats. Am J Physiol 1996;270:E1015-21.

Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: Effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. J Clin Endocrinol Metab 1996;81:327-32.

Tomas E, Wood JA, Stanojevic V, Habener JF. Glucagon-like peptide-1(9-36)amide metabolite inhibits weight gain and attenuates diabetes and hepatic steatosis in diet-induced obese mice. Diabet Obes Metab 2011;13:26-33.

Tomas E, Wood JA, Stanojevic V, Habener JF. Glucagon-like peptide-1(9-36)amide metabolite inhibits weight gain and attenuates diabetes and hepatic steatosis in diet-induced obese mice. Diabet Obes Metab 2011;13:26-33.

Gupta NA, Mells J, Dunham RM, Grakoui A, Handjyi J, Saxena NK, et al. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. Hepatology 2010;51:1584-92.
E. Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow. Am J Physiol Endocrinol Metab 2010;298:E634-43.

106. Lee NJ, Nguyen AD, Enriquez RF, Doyle KL, Sainsbury A, Baldock PA, et al. Osteoblast specific Y1 receptor deletion enhances bone mass. Bone 2011;48:461-7.

107. Baldock PA, Lee NJ, Driessler F, Lin S, Allison S, Stehrer B. Neuropeptide Y knockout mice reveal a central role of NPY in the coordination of bone mass to body weight. PLoS One 2009;4:e8415.

108. Ta NN, Li Y, Schuyler CA, Lopes-Virella MF, Huang Y. DPP-4 (CD26) inhibitor alogliptin inhibits TLR4-mediated ERK activation and ERK-dependent MMP-1 expression by U937 histiocytes. Atherosclerosis 2010;213:429-35.

109. Hattori S. Sitagliptin reduces albuminuria in patients with type 2 diabetes. Endocr J 2011;58:69-73.

Cite this article as: Gupta V. Pleiotropic effects of incretins. Indian J Endocr Metab 2012;16:S47-56.

Source of Support: Nil, Conflict of Interest: None declared.