Review Article

Pleiotropic effects of incretins

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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 insulinotropic 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) .

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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

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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 "incrétine."[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 vascularum, 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)
- Vidagliptin (Novartis, approved as Galvus by EU in 2007)
- Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in 2010)
- Linagliptin (Boerhinger 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, Vidagliptin, 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 (metfromin, SU, TZD, alpha-glucosidase inhibitor, miglitinide) 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 dual combination therapy (metfromin, 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_{7-36} amide and GLP-1_{9-36} 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,

however, seems to be related to weight loss. In addition, GLP therapy has 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.[75]

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. *Leptin* is a quantitative marker and product of the *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.[76-78]

The incretins have numerous pleitropic 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 *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.[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 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.[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

if they are overweight or obese, taking into account the profound metabolic benefits.

4. **Increased insulin secretion (improvement in beta-cell health):** GLP-1 analogues improve beta-cell health and insulin secretion. Suggested mechanism includes anti-apoptosis with evidence of increased markers of cell proliferation (Ki67).[85]
5. **Suppression of glucagon:** The alpha-cells have been found to be dysfunctional (loss of glucose sensing mechanism) in T2DM. The liver too seems to be hypersensitive to the stimulatory effects of glucagon. GLP-1 analogues improve alpha-cell health and their glucose sensing ability. Alpha-cells possess GLP-1Rs, and although direct effects on these receptors have been proposed as mechanisms explaining the glucagon's suppressive effects of GLP-1 analogues, indirect suppressive mechanisms (delayed gastric emptying, improved insulin secretion) cannot be ruled out.[86-90]
6. **Hepatosteatosis:** Hepatic insulin resistance contributes to ectopic fat deposition in the liver, resulting in hepatic steatosis known as non-alcoholic fatty liver disease (NAFLD). NAFLD can later progress to non-alcoholic steatohepatitis (NASH) and cirrhosis. GLP-1 has shown to attenuate weight gain and improve insulin resistance. Weight loss has been shown to reduce hepatic steatosis. It has also been demonstrated that GLP-1Rs are hepatoprotective. They can act directly on the hepatocytes and improve hepatic steatosis. In a meta-analysis of the LEAD program, liraglutide and exanatide have shown to improve NAFLD fibrosis score, biochemical transaminitis/fatty liver independent of weight loss.[91-95]

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.[96] 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.[97] Obesity is associated with insulin resistance.

1. An adipocyte that is resistant to the actions of insulin releases *free fatty acids* (FFA) into the circulation, which affects glucose uptake in peripheral tissues in several ways.
   a. FFA directly competes with and inhibits glucose uptake in peripheral tissue (muscle).[98,99]
   b. FFA alters the insulin signaling pathway and down-regulates insulin secretion. It inactivates the intracellular downstream signals involved in the secretion of insulin (phosphoinositide-3-kinase activity).[99-101]
2) Obesity is associated with increased *adipocyte apoptosis* which in turn results in release of inflammatory cytokines (macrophage chemoattractant protein-1, TNF-alpha, IL-6, and IL-1β) locally (fat cell) and systemically (muscle, liver, etc.). The inflammatory cytokines cause serine phosphorylation of insulin receptor substrate-1 (IRS-1; downstream messenger in insulin secretion), which downgrades the cascade of events leading to insulin secretion and function, contributing to a beta-cell dysfunction.[102]

GLP analogues cause significant weight loss (reduce FFA), improve insulin secretion and suppress glucagon. In addition, they directly enhance beta-cell fatty acid oxidation[103] promoting lipolysis within the beta-cell. This promotes breakdown of triglycerides and causes efflux of FFA from the beta-cell, thereby improving insulin signaling. Taking all the findings, it seems clear that by improving insulin resistance, GLP-1 has clear benefits on cardiovascular system indirectly.

Skeletal Effects

A growing body of evidence suggests that by augmenting the incretin system, bone health improves. A study has shown that GLP-1 promotes cellular proliferation and cytoprotection of progenitor bone forming mesenchymal cells. It also prevents these cells from differentiating into adipocytes. NPY has emerged as an important peptide in the regulation of bone remodeling. Central NPY over-expression decreases osteoblastic activity, while on the other hand, specific NYPR1 receptor deletion enhances bone mass. GLP-1 has shown to antagonize the effects of NYP, suggesting that it may help increase bone mass (trabecular and cortical). These effects seem to be dependent mostly on the NPYR1 receptor, with regulatory input from NYPR2 and 4 and the leptin system.[104-107]

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.[108]

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, 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 pleitropic actions.

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