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New Insights Into the Role of Incretins in the Treatment of Diabetes

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Introduction

Incretin hormones are peptides released from the gastrointestinal tract in response to nutrient ingestion that enhance glucose-dependent insulin secretion from the pancreas and aid in the overall maintenance of glucose homeostasis. The 2 principal incretin hormones are glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are small peptides, 30 and 42 amino acids, respectively, that rapidly stimulate the release of insulin only when blood glucose levels are elevated, thereby enhancing the glucose-sensing and insulin secretory capacity of the endocrine pancreas during postprandial hyperglycemia.[1] GLP-1 and GIP have also been shown in preclinical studies to exert significant cytoprotective and proliferative effects on the islets of Langerhans.[2-4] The incretin hormones elicit their actions through direct activation of distinct G-protein-coupled receptors expressed on islet beta cells.[4,5] There is substantial interest in the therapeutic potential of these hormones for the treatment of diabetes mellitus.[3,6-8]

At the meeting of the European Association for the Study of Diabetes (EASD) in Athens, Greece, there was a significant focus on the role of incretin hormones in the regulation of insulin secretion and the preservation of islet integrity. Additionally, researchers presented data exploring the effects of these hormones on feeding behavior and gastrointestinal function in an attempt to delineate how extrapancreatic actions may contribute to their effectiveness in the treatment of type 2 diabetes. Moreover, because drugs that mimic or potentiate the actions of GLP-1 and GIP are being evaluated in human patients, there was much interest in the new data presented from recent clinical trials.

Native GLP-1 and GIP are rapidly inactivated by the ubiquitously expressed proteolytic enzyme dipeptidyl peptidase (DPP)-IV, which cleaves 2 N-terminal amino acids from both peptides to produce inactive metabolites.[9] The short circulating half-life of bioactive intact GLP-1 and GIP initially limited enthusiasm for the potential use of incretin hormones in the treatment of diabetes. However, incretin analogs have been developed with significantly increased half-lives due to modification of the DPP-IV cleavage site and/or conjugation to large circulating proteins, such as albumin (ie, liraglutide).[10,11] Many of these GLP-1 receptor agonists are being tested in the treatment of type 2 diabetes.

Although both GLP-1 and GIP act as incretin hormones in normal subjects, more focus has been put on the use of GLP-1 to treat type 2 diabetes because diabetes is often associated with a blunted or absent response to GIP. Although it has been suggested that tachyphylaxis may be the cause of the reduced effectiveness of GIP in type 2 diabetes, Dr. M. Nauck and colleagues[12] presented evidence suggesting that tachyphylaxis is not a major contributor to defective GIP action in diabetic patients. However, data presented by members of the laboratory of Dr. F. Pfeiffer demonstrated that the GIP receptor was expressed in fat tissue, and reduced levels of GIP receptor expression were detected in adipocytes from insulin-resistant obese women.[13] The mechanisms for reduced adipocyte GIP receptor expression remain unclear.

Exenatide

Earlier this year, the GLP-1 receptor agonist exenatide (*Byetta*) was approved in the United States for the treatment of type 2 diabetes. The structure of exenatide (synthetic exendin-4) is similar to (~53% amino acid identity) and mimics the biological actions of native GLP-1, but exenatide is resistant to cleavage by DPP-IV. Recent clinical trials demonstrated that exenatide improved glucose tolerance, reduced levels of glycosylated hemoglobin (A1C), and reduced weight in diabetic patients when given alone or during concurrent administration with either sulfonylureas or metformin.[14-16]

The results of ongoing, open-label extension studies of exenatide were reported at the EASD meeting. The effects of exenatide on A1C, glycemic control, and weight loss were maintained for 2 years in human patients.[17-19] Long-term administration of exenatide also produced clinically significant improvements in lipid levels and reduced blood pressure.[20] The most common side effects were gastrointestinal. However, the weight loss that was seen in the exenatide studies was not simply due to nausea and may potentially be explained by new data illustrating that both exenatide and GLP-1 increased postprandial levels of the anorexigenic hormone leptin.[21] In addition to its insulinotropic actions, exenatide has also been shown to stimulate restoration of beta-cell mass in patients with type 2 diabetes. Dr. N. Hanley's group presented data demonstrating that the GLP-1 receptor (GLP-1R) agonist liraglutide could increase beta-cell number during early human embryonic development.[22]

Mechanisms of Action of the Incretins

The mechanisms by which incretins elicit their actions at the level of the beta cell are not well understood. Dr. George Holz[23] reviewed data illustrating a novel cAMP-dependent pathway for GLP-1R-mediated insulin secretion that works independently of protein kinase A (PKA) through the activation of a cAMP-regulated guanine nucleotide exchange factor (cAMP-GEF) called exchange protein directly activated by cAMP (Epac). Epac stimulates calcium influx into the beta cell, potentiating calcium release from intracellular stores and triggering insulin granule exocytosis. Moreover, Dr. S. Hoersch presented data that GLP-1-induced mitogen-activated protein kinase (MAPK) activation is downstream of the GTPase Rap, a known effector of Epac, in INS-1 insulinoma cells.[24]

However, exenatide was also shown to increase levels of PKA in rodent islets, which also may be involved in the cytoprotective effects of GLP-1. Dr. Bernard Thorens[25] presented microarray data from a study performed with insulinoma cell lines. He reported that short-term GLP-1 treatment increased the transcription of genes that is involved in the control of cell growth and the regulation of cell-cycle transition, whereas longer treatment with GLP-1 increased the levels of genes regulating cell survival.[25] GLP-1, at relatively high concentrations, appeared to upregulate the expression of genes that could inhibit GLP-1R signaling, such as the regulators of G-protein signaling, an inhibitor of cAMP response element-binding protein named cAMP-responsive modulatory inducible cAMP early repressor, and a MAPK-specific phosphatase.[25] Additional microarray analysis performed on isolated human islet preparations in the laboratory of Dr. Ricardo Perfetti illustrated that the long-acting GLP-1 analog liraglutide modulated the expression of multiple members of the transforming growth factor-beta pathway.[26]

The mechanism through which the incretin hormones elicit their cytoprotective effects on the beta cell has attracted significant attention because preservation and restoration of beta-cell mass may contribute to the therapeutic potential of the incretins for the treatment of both type 1 and type 2 diabetes. Endoplasmic reticulum (ER) stress within the beta cell, possibly occurring as the result of the overproduction or misfolding of insulin, may be a contributing factor to the increased beta-cell apoptosis and loss of islet mass observed within diabetic patients. Drs. D. Ron,[27] S. Lortz,[28] M. Wheeler,[29] and A. Herchuelz[30] presented data showing that ER and oxidative stress can contribute to beta-cell death and the pathogenesis of diabetes in cell lines and rodents. Moreover, Dr. D. Drucker[31] presented new data suggesting that treatment of insulinoma cell lines with exenatide modulates the ER stress pathway, which may provide an explanation for the effects of GLP-1 on enhancement of insulin biosynthesis and beta-cell survival under conditions of physiologic stress. In addition, GLP-1 was also shown by Dr. F. Lang to protect against dexamethasone-induced apoptosis in INS-1 cells via a PKA-dependent mechanism,[32] suggesting that GLP-1 may alleviate the stress put on the pancreas during glucocorticoid therapy.

The extrapancreatic effects of GLP-1R signaling within skeletal muscle were investigated by members of Dr. M. L. Villanueva-Pencarrillo's laboratory, who showed that GLP-1 stimulated the redistribution of PKC-lambda and -alpha isoforms and suggested that this may play a role in the effects of GLP-1 on glucose transport and metabolism within muscle.[33] They also treated adipocytes isolated from morbidly obese diabetic patients with insulin, GLP-1, and GLP-1 mimetics to monitor the effects of these peptides on glucose uptake and kinase activity. GLP-1 enhanced the activity of specific kinases, including phosphatidylinositol 3-kinase and the p42/p44 MAPKs, but, unlike insulin, did not stimulate glucose uptake in cells from obese patients.[34]

Dr. N. Delzenne's group showed that cerebral administration of exenatide in mice could also regulate insulin secretion, stimulate hepatic glycogen deposition, and prevent glucose utilization and glycogen synthesis in the muscle, whereas administration of the GLP-1R antagonist exendin (9-39) had opposite effects.[35] Of interest, intraperitoneal exendin (9-39) improved glucose tolerance in high-fat-fed insulin-resistant mice, seemingly via its ability to increase muscle glucose transport.

GIP receptor expression has been localized to osteoblasts within bone tissue. Drs. Yamada and Seino investigated the extrapancreatic effects of GIP in bone and showed that bone trabeculae of GIP receptor knockout mice were thinner and the numbers of bone-resorbing osteoclasts were increased compared with wild-type mice.[36] With an osteoblast cell line, GIP was shown to reduce etoposide-induced apoptosis. Thus, GIP may prevent decreases in bone mass through its direct cytoprotective effect on osteoblasts.

Dr. Bernard Thorens[25] presented data from studies with double incretin receptor knockout mice that suggest an additive effect of both GLP-1 and GIP on insulin secretion in response to glucose and illustrate that the beta-cell defect in these mice most likely involves pathways downstream of cell depolarization. In addition, Dr. Thorens suggested that first-phase insulin secretion is primarily regulated by an extrapancreatic GLP-1R-specific portal vein sensor or via central nervous system receptor activation. Although the double incretin receptor knockout mice exhibit a very mild diabetic phenotype, Dr. D. Drucker,[31] who also carried out studies with these mice, suggested that metabolic stress may unmask the importance of incretin receptors for beta-cell function.

Using streptozotocin, an agent known to induce beta-cell apoptosis, researchers in Dr. Drucker's laboratory were able to show that streptozotocin caused significantly more beta-cell damage in mice with genetic ablation of the GLP-1R compared with wild-type controls. Additionally, he showed that many GLP-1R-specific actions within islets are dependent on pancreatic duodenal homeobox-1 transcription factor activity in islet beta cells.[31] Furthermore, studies with rodent islets from a number of laboratories suggest that both GLP-1 and GIP modulate the expression and activity of genes involved in antiapoptotic pathways, such as Bad, Bax, and Bcl-2.[31]

Although the actions of both GLP-1 and GIP on insulin secretion are similar, they also differentially regulate a number of physiologic processes that are involved in energy homeostasis. For example, GLP-1 has been shown to inhibit glucagon secretion, whereas GIP stimulates its release. Using perfused rat pancreases and immunoneutralizing antibodies, members of Dr. J. Holst's laboratory, from Denmark, presented data suggesting that GLP-1, but not GIP, inhibits glucagon secretion indirectly via effects on endogenous somatostatin, which likely acts on the pancreatic alpha cells to inhibit glucagon secretion.[37,38] Small changes in glucagon levels can have significant effects on hepatic glucose production. Thus, in addition to its insulin-stimulating effects, GLP-1 may have the additional benefits of indirectly lowering blood glucose levels via its effects on glucagon and hepatic glucose mobilization.

It has also been suggested that GLP-1 can modulate the differentiation of ductal precursor cells into insulin-secreting beta cells. Dr. Perfetti presented data suggesting that the mechanism by which this occurs may be differential regulation of hedgehog signaling.[39] Treatment of diabetic rats or the ductally derived pancreatic ARIP cell line with GLP-1 caused a significant decrease in sonic hedgehog expression, whereas levels of Indian hedgehog increased. These effects could be reversed by treatment with either exendin (9-39) or cyclopamine, an inhibitor of the hedgehog signaling pathway.

DPP-IV Inhibitors

An alternative approach to using long-acting analogs to extend the biological activity of the incretin hormones is to prevent the degradation of the native peptides. Accordingly, a number of DDP-IV inhibitors are under investigation for the treatment of type 2 diabetes in humans. Vildagliptin (LAF 237) appears efficacious in the treatment of type 2 diabetes in human patients in clinical trials. Recent studies have shown that vildagliptin is effective on its own or as an add-on therapy to metformin.[40,41] A novel DDP-IV inhibitor, PSN9301, which is rapid in onset and short-acting, was also shown to improve glucose tolerance and reduce weight gain in rodent models of diabetes.[42] The compound MK-0431 (sitagliptin) was well tolerated, reduced A1C levels, and decreased fasting glucose in humans.[43,44]

Conclusion

In conclusion, a number of new therapies based on the biological actions of the incretin hormones are being actively investigated. Many of these compounds improve glucose tolerance, lower A1C levels, prevent weight gain (in human studies), and increase beta-cell mass in preclinical experiments. The mechanisms by which the incretin hormones elicit their diverse effects to regulate energy homeostasis remain an active area of research. Ongoing studies promise to provide insight into how these gut hormones regulate the physiology of multiple metabolic processes and how these mechanisms may provide new approaches to the treatment of diabetes.

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