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Targeting the glucagon receptor family for diabetes and obesity therapy

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ABSTRACT

Diabetes is a debilitating disease characterized by chronic hyperglycemia and is often associated with obesity. With diabetes and obesity incidence on the rise, it is imperative to develop novel therapeutics that will not only lower blood glucose levels, but also combat the associated obesity. The G protein-coupled receptors (GPCRs) for glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and glucagon are emerging as targets to treat both hyperglycemia and obesity. GIP is rapidly released from intestinal K-cells following food intake and stimulates glucose-dependent insulin secretion from β-cells and the storage of fat in adipocytes. Both GIP receptor agonists and antagonists have been demonstrated to display therapeutic potential to treat diabetes and obesity. Similar to GIP, GLP-1 is released from intestinal L-cells following food intake and potentiates glucose-dependent insulin secretion from β-cells. In addition, GLP-1 reduces glucagon levels, suppresses gastric emptying and reduces food intake. As such, GLP-1 receptor agonists effectively lower blood glucose levels and reduce weight. Finally, glucagon is released from α-cells and raises blood glucose levels during the fasting state by stimulating gluconeogenesis and glycogenolysis in the liver. Thus, molecules that antagonize the glucagon receptor may be used to treat hyperglycemia. Given the structural similarity of these peptides and their receptors, molecules capable of agonizing or antagonizing combinations of these receptors have recently been suggested as even better therapeutics. Here we review the biology of GIP, GLP-1 and glucagon and examine the various therapeutic strategies to activate and antagonize the receptors of these peptides.

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1. Introduction

Diabetes mellitus is characterized by chronic hyperglycemia as a result of impaired insulin secretion and/or action (DeFronzo, 1988). The incidence of diabetes is on the rise, perhaps in part due to expanding waistlines as obesity is a major risk factor for the development of diabetes. The global number of patients with diabetes was estimated to be 171 million in 2000 and this number was projected to increase to 366 million by 2030 (Wild et al., 2004). However, a recent analysis reported that the number of patients with diabetes already reached 347 million as of 2008 (Danaei et al., 2011), thus the situation is more serious than we expected. Furthermore, the global number of adults with obesity was estimated to be 396 million in 2005 and was predicted to reach 573 million by 2030 (Kelly et al., 2008). Although more than 80% of patients with type 2 diabetes are obese, only ~10% of obese subjects are diabetic (Harris et al., 1987), signifying the importance of genetic susceptibility and other environmental factors in the development of type 2 diabetes, as well as the remarkable capacity of pancreatic β-cells to typically respond adequately to increasing demands for insulin. The association between obesity and

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diabetes is often attributed to altered secretion of adipokines and non-esterified fatty acids, leading to lipotoxicity and the deposition of ectopic fat in β-cells and insulin sensitive tissues (Kahn et al., 2006b; Unger & Scherer, 2010). Chronic hyperglycemia, if not adequately treated, can cause both microvascular complications (e.g., retinopathy, nephropathy and neuropathy) and macrovascular complications (e.g., coronary artery disease, cerebrovascular disease and other peripheral arterial diseases) (Klein, 1995). These complications significantly decrease the quality of life and ultimately reduce the life span of patients with diabetes. A recent analysis revealed that men with diabetes but without a history of cardiovascular disease at 40, 50, and 60 years of age will die approximately 6.3, 5.8, and 4.5 years, respectively, earlier than men without diabetes (Seshasai et al., 2011). The costs associated with pre-diabetes and diabetes reached $218 billion in 2007 in the U.S. alone, which included $153 billion in medical costs and $65 billion in reduced productivity (Dall et al., 2010), while the costs associated with obesity were estimated to be $147 billion in the U.S. in 2008 (Finkelstein et al., 2009). Given the serious health consequences and enormous economic burden of diabetes and obesity, it is imperative to rapidly develop better treatments and/or find a cure for both conditions. In this regard, the clinical outcome of bariatric surgery is inspiring. A meta-analysis (Buchwald et al., 2004) showed that the mean percentage of excess weight loss was ~60% and complete remission of diabetes is observed in ~77% of cases who underwent bariatric surgery. The superiority of bariatric surgeries to intensive medical therapy on the remission of type 2 diabetes in obese patients has been recently demonstrated by randomized controlled trials (Mingrone et al., 2012; Schauer et al., 2012). Although the exact mechanisms of weight loss and diabetes remission after bariatric surgery are unknown, it is generally believed that gut-derived factors play an important role (Cummings et al., 2004; Karra et al., 2010; Rubino et al., 2010). In this review, we describe the physiology and pathophysiology of two key gastrointestinal hormones, GIP and GLP-1, along with the related peptide glucagon, and discuss strategies to develop agonists and/or antagonists of their receptors to treat diabetes and obesity.

1.1. Incretins and the enteroinsular axis

GIP and GLP-1 are incretin hormones, or factors released from the intestine following ingestion of nutrients that potentiate glucose-stimulated insulin secretion (Kieffer & Habener, 1999; Baggio & Drucker, 2007; Holst, 2007). They comprise a major component of the functional connection between the intestine and pancreatic β-cells, termed the "entero-insular axis" (Unger & Eisentraut, 1969; Kieffer & Habener, 1999). In healthy subjects, intestinal glucose produces a much greater insulin response compared to the same amount of glucose delivered intravenously (McIntyre et al., 1964). Conversely, in patients with diabetes, the oral route fails to substantially increase insulin levels relative to isoglycemic intravenous glucose infusion (Nauck et al., 1986b). The insulinotropic actions of GIP and GLP-1 are estimated to account for ~50–70% of insulin secretion following oral glucose ingestion in healthy individuals (Nauck et al., 1986a). However, the incretin contribution to insulin secretion in response to oral glucose is estimated to be less than 20% in patients with type 2 diabetes (Nauck et al., 1986a). Since the diminished incretin effect associated with type 2 diabetes is not consistently linked to reduced secretion of either GLP-1 or GIP (Meier & Nauck, 2008, 2010), it is possible that the pancreatic β-cells are less sensitive to the incretins. In this regard, genetic factors may play an important role. Carriers of the major type 2 diabetes risk allele TCF7L2 (rs7903146) display a decreased sensitivity to the insulinotropic effects of GIP and GLP-1 (Lyssenko et al., 2007; Schafer et al., 2007; Pilgaard et al., 2009; Shu et al., 2009; Villareal et al., 2010). Furthermore, decreased GIPR and GLP-1R expression was observed in islets from patients with type 2 diabetes as well as human islets treated with siRNA against TCF7L2 (Shu et al., 2009). In addition, subjects carrying the type 2 diabetes risk allele WFS1 (rs10010131) displayed a decreased insulinotropic response to infused GLP-1 (Schafer, et al., 2009). Apart from genetic factors, there is also evidence suggesting that hyperglycemia itself is involved in the diminished incretin effect observed in patients with type 2 diabetes (Lynn et al., 2001; Piteau et al., 2007; Xu et al., 2007; Gupta et al., 2010). It was reported that chronic hyperglycemia decreased the expression of the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R) in pancreatic islets of 90% pancreatectomized rats; incretin receptor expression was recovered by reducing blood glucose levels with phloridzin, a renal glucose transport inhibitor (Xu et al., 2007). Alternatively, it has been postulated that the decreased incretin effect displayed in patients with type 2 diabetes may be an epi-phenomenon of impaired β-cell function, since reduced incretin activity strongly correlates with decreased β-cell function (Meier & Nauck, 2010). Even though patients with type 2 diabetes generally display a decreased incretin response, exogenous GLP-1 action on insulin secretion is relatively well preserved in these patients and its maximum insulin secretory effect at supraphysiological concentrations is comparable to that of normal subjects (Nauck et al., 1993a). However, the insulinotropic action of exogenous GIP is markedly decreased (by ~50%) in type 2 diabetic patients, even at a supraphysiological doses (Nauck et al., 1993a). Currently, incretin-based therapies such as GLP-1 mimetics and dipeptidyl peptidase-4 (DPP-4, a ubiquitous proteolytic enzyme) inhibitors, which inhibit degradation of GIP and GLP-1, are useful for the treatment of hyperglycemia in patients with type 2 diabetes (Chia & Egan, 2008; Lovshin & Drucker, 2009; Verspohl, 2009; Wideman & Kieffer, 2009; Tahrani et al., 2010).

1.2. Importance of α-cell dysfunction

The pancreatic islet of Langerhans is a micro-organ comprised of glucagon-secreting α-cells, insulin-secreting β-cells, somatostatin-secreting δ-cells, ghrelin-producing ε-cells, and pancreatic polypeptide-secreting PP-cells (Edlund, 2002; Prado et al., 2004). The primary function of pancreatic islets is to maintain glucose homeostasis by coordinated secretion of the glucose lowering hormone insulin and the glucose raising hormone glucagon. Normally, increased blood glucose levels after meals stimulate insulin secretion, while glucagon secretion is suppressed following meals, with reciprocal responses during fasting periods (Dunning & Gerich, 2007). Diabetes has been regarded as a bihormonal disorder, characterized by both insulin deficiency and glucagon excess (Unger & Orci, 1975) and it has even been proposed that glucagon excess, rather than insulin deficiency, is the essential component (Unger & Cherrington, 2012). Pancreatic α-cell dysfunction plays an important role in the pathogenesis of type 2 diabetes, with glucagon secretion inappropriately elevated in the presence of hyperglycemia and contributing to the increased basal rate of hepatic glucose production (Baron et al., 1987; D'Alessio, 2011). In addition, a lack of glucagon suppression contributes to the postprandial hyperglycemia seen in patients with type 2 diabetes (Shah et al., 2000; D'Alessio, 2011). Therefore, pharmacological interventions that reduce glucagon secretion or block glucagon receptor (GCGR) signaling are theoretically promising treatment options for diabetes.

1.3. Glucagon receptor family

The G-protein coupled receptors (GPCRs) account for ~2% of the human genome (Lagerstrom & Schioth, 2008) and regulate a wide variety of bodily functions including homeostasis, embryonic development, vision, smell, taste, learning and memory (Ahren, 2009). The ligands that bind these receptors comprise an extremely diverse set of biomolecules, including peptides, amines, lipids, amino acids, steroids and purines and GPCRs are targets of about one third of medicines (Civelli, 2005; Jacoby et al., 2006; Overington et al., 2006). The GPCRs are characterized by an extracellular N-terminal domain, an intracellular C-terminal domain, and seven transmembrane-spanning domains connected by three intracellular and extracellular loops. Despite having a common architecture, GPCRs interact with several different G proteins plus numerous other

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