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In Vivo Models for Incretin Research: From the Intestine to the Whole Body

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Incretin hormones are produced by enteroendocrine cells (EECs) in the intestine in response to ingested nutrient stimuli. The incretin effect is defined as the difference in the insulin secretory response between the oral glucose tolerance test and an isoglycemic intravenous glucose infusion study. The pathophysiology of the decreased incretin effect has been studied as decreased incretin sensitivity and/or β-cell dysfunction *per se*. Interestingly, robust increases in endogenous incretin secretion have been observed in many types of metabolic/bariatric surgery. Therefore, metabolic/bariatric surgery has been extensively studied for incretin physiology, not only the hormones themselves but also alterations in EECs distribution and genetic expression levels of gut hormones. These efforts have given us an enormous understanding of incretin biology from synthesis to *in vivo* behavior. Further innovative studies are needed to determine the mechanisms and targets of incretin hormones.

Keywords: Incretins; Enteroendocrine cells; Bariatric surgery

INTRODUCTION

In the early nineteenth century, physicians found that oral glucose administration was superior to intravenous glucose infusion in terms of reduced systemic glucose excursion [1]. Several decades ago, the concept of incretin was proposed [1]. Incretin hormones are a component of the enteroinsular axis, and are synthesized in the intestine [1-3]. Until now, two incretin hormones have been discovered: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretin hormones are synthesized by enteroendocrine cells (EECs) and stimulate insulin secretion from pancreatic β-cell [2-4]. Due to the incretins' insulinotropic and extrapancreatic effects, incretin-based therapy has been widely used for antidiabetic treatment [5]. In addition, a GLP-1 analogue was proposed as an anti-obesity drug [6] because GLP-1 enhanced satiety and reduced appetite [3]. Although outstanding scientific knowledge is increasing, the actions and pathophysiological role of incretin are not totally understood. In this review, we overview the key experiments in incretin research, from the level of the intestine to the whole body.

INCRETIN FROM INTESTINE

GLP-1 and GIP are produced by L-cell in the distal small intestine and K-cell in the proximal small intestine, respectively. L-cell produces GLP-1, GLP-2, peptide-YY (PYY), and oxyntomodulin [7]. These L-cell hormones exert paracrine and endo-

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crine effects such as intestinal proliferation [8] and energy homeostasis [9,10]. Interestingly, when the distal intestine was transposed to proximal jejunum, EECs which were supposed to be L-cell expressed both GLP-1 and GIP and were termed K/L-cell [11]. The co-expression of more than two peptides in a single EEC can be easily observed with immunohistochemistry [12]. For this process, the intestines were marked to identify its proximal-to-distal axis. For example, we harvested jejunum (10 cm distal from the ligament of Treitz) and ileum (5 cm proximal from the ileocecal valve) from rats, and each proximal site was tagged with a non-absorbable suture. To evaluate the density of EECs, we cut the intestines into longitudinal or cross-sectional sections and then counted the number of EECs per villus. However, it is hard to obtain the whole thickness of the intestine in human subjects. Therefore, mucosal biopsies were used in human experiments and the number of EECs per mucosal area was counted [13]. In this human study, regional differences of EECs were also observed and could be an important mechanism in metabolic/bariatric surgery.

A recent study showed that GLP-1 signaling is critical for intestinal growth [14]. One-month treatment with exendin-4, a GLP-1 receptor agonist, increased small bowel weight and length and crypt number, but these effects were diminished in GLP-1 receptor knockout mice [14]. Therefore, histological changes such as villus growth and cellular proliferation are important indicators of local incretin action. Similar to GLP-1, another L-cell hormone, PYY showed intestinotrophic effects [15], and GLP-2 improved intestinal integrity [16]. These paracrine effects can be assessed simply by measuring of villus length and muscle thickness [11,17,18], and more precise stereological analyses can be adopted [19]. These changes at the level of the intestine might be a clue as to whether incretin or other gut hormones are working.

INCRETIN EFFECT

Insulin secretion is higher after glucose ingestion than intravenous administration of glucose, even though the blood glucose levels are identical, the difference thus being caused by the contribution of incretin hormones [20]. To quantitate this incre-

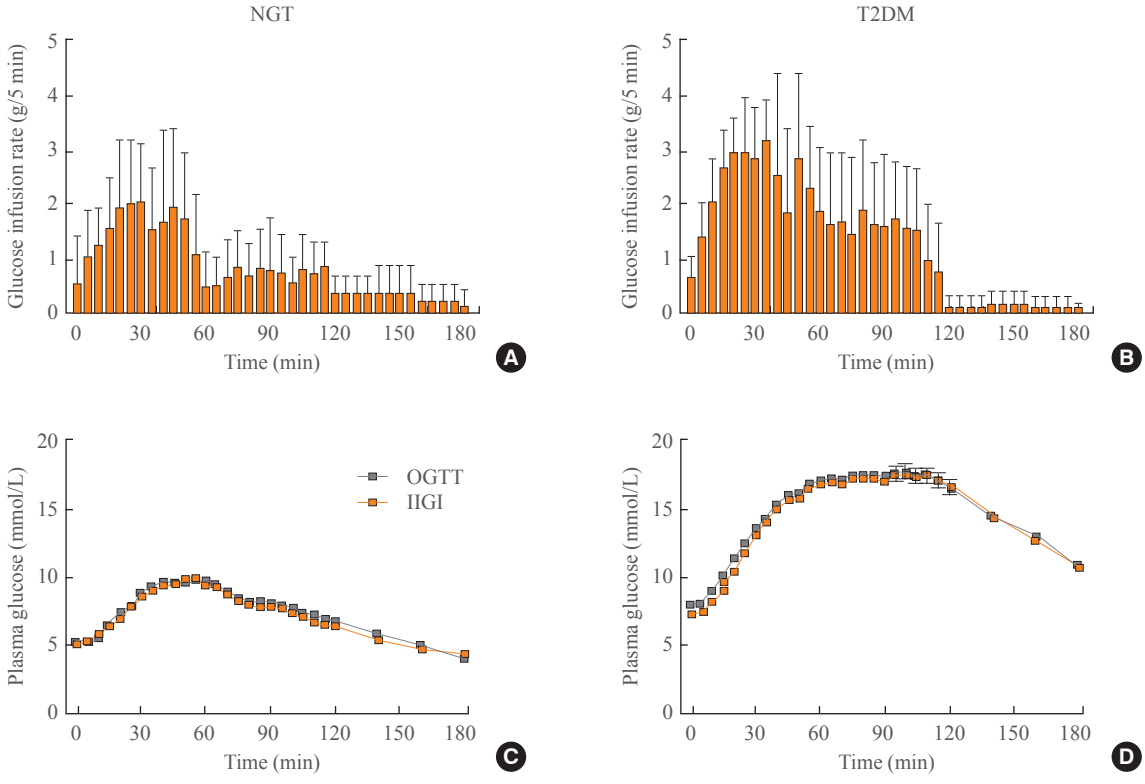

Fig. 1. Intravenous glucose infusion rates during an isoglycemic intravenous glucose infusion (IIGI) study in subjects with (A) normal glucose tolerance (NGT) or (B) type 2 diabetes mellitus (T2DM). Plasma glucose profiles of oral glucose tolerance test (OGTTs) (filled symbol) and IIGI studies (open symbol) in subjects with (C) NGT or (D) T2DM. Adapted from Oh et al. [21], with permission from John Wiley and Sons.

tin effect, two separate glucose challenge studies are performed: an oral glucose tolerance test (OGTT) and an isoglycemic intravenous glucose infusion (IIGI) study. Plasma glucose levels are obtained at 5-minute intervals during standard OGTT procedures, and IGII studies were followed. In the IIGI studies, a gradual increase in dextrose infusion and frequent adjustment of the infusion rate are very important because plasma glucose levels should not be exceeded. In our experience [21], the amount of glucose infused during the initial 5 minutes is ~0.6 g both in healthy volunteers and type 2 diabetes patients. During the next 5 minutes, 1.0 and 1.4 g of glucose was needed to be infused in healthy volunteers and type 2 diabetes patients, respectively, to copy the glucose profiles of the 75-g OGTTs (Fig. 1). We developed mathematical models to calculate the glucose infusion rate [22], but further validation is needed. After both OGTTs and IIGI studies, the plasma levels of C-peptide and insulin are measured. The incretin effect is calculated using the area under the curve (AUC) value for C-peptide or insulin. The formula is $100\times(AUC_{OGTT}-AUC_{IIGI})/AUC_{IIGI}$ [23].

The above-mentioned method to calculate the incretin effect has been widely adopted in human studies, can be applied with various dosages of glucose (25, 50, 75, 100, and 125 g) [21,23-26] and can be repeated before and after therapeutic interventions (e.g., to test the effect of medications or procedures) [27-29]. However, it is hard to apply the method to rodent models because of the complicated nature of the procedure, the frequent sampling and the precise adjustments of the infusion rate. Indirectly, the IIGI study can be substituted by an intraperitoneal glucose tolerance test (IPGTT) in rodent models. During the IPGTT, theoretically, endogenous incretin secretion and neural signaling of the "enteroinsular axis" are not stimulated like with intravenous glucose. Therefore, the difference in insulin secretion between the OGTT and IPGTT could denote the incretin effect. However, the glucose profiles of the OGTT and IPGTT are not identical, so there is a large limitation in the estimation of the incretin effect with these two procedures. In summary, OGTTs and IIGI studies have been used to calculate the incretin effect, but there are some drawbacks: a substantial trial-and-error stage is required, and the application to rodent models is very tricky.

INCRETIN SENSITIVITY

A large body of evidence has indicated that alterations in incretin secretion is not the key pathophysiological mechanism of type 2 diabetes [30,31]. Attenuation of the incretin effect, rather than decreases in incretin secretion, might be the important pathophysiological mechanism of type 2 diabetes, especially in Caucasians [23]. A diminished incretin effect without diminished secretion of incretin hormones could indicate decreased incretin sensitivity. Similar to insulin sensitivity, which is analyzed with a hyperinsulinemic euglycemic clamp, incretin sensitivity is evaluated using a hyperglycemic clamp with incretin infusion [32]. During hyperglycemic clamp, endogenous incretion secretion is blocked and insulin secretion is augmented by exogenously administered incretin hormones. For example, after infusion of a physiological dose of GIP, insulin secretion was lower in subjects with type 2 diabetes than in subjects with normal glucose tolerance [32]. This result indicated that GIP sensitivity is decreased in subjects with type 2 diabetes. Interestingly, GIP sensitivity was partially recovered after near-normalization of blood glucose levels with intensive insulin therapy, which was calculated by insulin secretion during hyperglycemic clamp with GIP infusion before and after the treatment [33]. Although the hyperglycemic state is not physiological, hyperglycemic clamp and incretin infusion study is a good model to evaluate incretin sensitivity, as both blood glucose levels and endogenous incretin secretion are controlled.

In rodents, we have a simple way to estimate incretin sensitivity: intraperitoneal injection of incretin followed by IPGTT. For example, exendin-4 was injected intraperitoneally or infused intravenously and then an IPGTT was performed [34]. This procedure did not augment endogenous incretin secretion but reflected the action of exogenously administered GLP-1. Higher insulin secretion represented higher incretin sensitivity during the exendin-4 and IPGTT study. However, severe β-cell dysfunction could mask the insulinotropic effect of GLP-1 [35]. Thus, we assessed incretin sensitivity under consideration of β-cell function, even though it is not conclusive whether β-cell dysfunction influences incretin sensitivity [36].

INCRETIN RESPONSE AFTER METABOLIC/BARIATRIC SURGERY

Changes of the intestinal configuration after metabolic/bariatric surgery produced alterations in gut hormone secretion [37]. In particular, L-cell hormones were robustly increased after Roux-en-Y gastric bypass (RYGB) [38]. Rapid stimulation of the small intestine (intestinal roux limb) with chyme from the directly anastomosed gastric pouch was found to be a key component of the enhanced secretion of L-cell hormones [39]. Ileal transposition (IT) and duodenal jejunal bypass (DJB) surgery

Table 1. The Intestinal mRNA Levels of Proglucagon and Peptide-YY after Metabolic Surgery

Study	Subject/Animal	Surgery	Proglucagon	Peptide-YY
Strader et al. (2005) [44]	Long-Evans rat on a high-fat diet	Ileal transposition	↑	↑
Patriti et al. (2007) [45]	GK rat	Ileal transposition	↑	NA
Nausheen et al. (2013) [46]	SD rat	Sleeve gastrectomy	↔	↔
Nausheen et al. (2013) [46]	SD rat	Ileal transposition	↔	↑
Mencarelli et al. (2013) [47]	Wistar rat	Ileal transposition	↑	NA
Hansen et al. (2013) [43]	Wistar rat	RYGB	↑	↑
Ramzy et al. (2014) [48]	SD rat	Ileal transposition	↑	↑
Rhee et al. (2015) [13]	Type 2 diabetes patients	RYGB	↑	↔

GK, Goto-Kakizaki; NA, not available; SD, Sprague-Dawley; RYGB, Roux-en-Y gastric bypass.

shared this component of RYGB [40], so GLP-1 levels were consistently increased after RYGB [38], IT [17,41], and DJB [11,40]. Interestingly, sleeve gastrectomy, which does not change the configuration of the distal ileum, also enhanced GLP-1 secretion [42]; this effect was partially explained by acceleration of gastric emptying [37]. To summarize, metabolic/bariatric surgery is a good model with which to evaluate the metabolic effects of increased endogenous GLP-1.

After metabolic/bariatric surgery, the number of L-cell hormone-positive cells and the genetic expression of each hormone were dramatically changed in small intestine (Table 1) [13,43-48]. For example, the number of GLP-1-positive cells and the level of proglucagon mRNA were found to be increased in the alimentary and common limbs in obese patients [13] and rats [18,43] after RYGB. This cellular change could be one mechanism for the increased plasma levels of GLP-1 [13], another one being the enhanced exposure of L-cell-rich intestinal section to nutrients. In animal models, the number of cells co-expressing GIP and GLP-1 was increased in the jejunum after DJB [11] and in the transposed ileum after IT [17]. However, the increased number of K/L cells did not increase the plasma levels of GIP [11,34]. In addition, the level of proglucagon mRNA was not consistently increased in various metabolic surgery models [44-46,49]. Post-translational modification of incretin hormones, such as the regulation of prohormone convertase 2, might be important. Furthermore, glucose lowering effect was still observed in GLP-1 receptor knockout mice underwent RYGB [50] and sleeve gastrectomy [51], which result doubt the role of GLP-1 in metabolic/bariatric surgery. Further study is needed to shed light on the expression of incretin hormones after metabolic/bariatric surgery, from synthesis to modification, secretion, and biological action.

NOVEL APPROACHES

Incretin hormones are produced by EECs, and EECs exhibit dynamic changes during differentiation. In addition, more than one peptide is frequently expressed in a single EEC [12]. This pluripotent nature has been studied using a green fluorescent protein tagging system [12]. Novel signals that induce EEC differentiation into GLP-1 secreting cells could be a potential treatment target for type 2 diabetes and obesity. In addition, mRNA expression changes in the intestine will give us new insights into the mechanisms causing diabetes remission after metabolic/bariatric surgery [52].

CONCLUSIONS

Incretin hormone-producing EECs are scattered through the entire intestine, and the gut has been thought to be "the largest endocrine organ in the body" [53]. To understand incretin physiology, we need to investigate from intestines to whole body. At the level of the intestine, identification of incretin-producing cells and assessment of intestinal expression of related genes would be fundamental. At the level of the whole body, calculation of the incretin effect, measurement of the blood levels of incretin hormones and analysis of incretin sensitivity were widely studied. In the future, an in-depth understanding of incretin physiology coupled with creative methodology will give us a new treatment target for diabetes and obesity.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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