Anti-incretin Effect: A Missing Link between Obesity, Diabetes, and Metabolic Surgery

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Abstract

The exact changes in physiology of individuals undergoing metabolic surgery are still under investigation. According to the foregut hypothesis, surgical bypass of certain parts of the gastrointestinal (GI) tract leads to the downregulation of biological factors that are secreted by the upper GI system, and compete against incretin actions (anti-incretins). Those molecules have a negative effect on insulin secretion, action, and sensitivity. Various biological factors have been hypothesized to exert anti-incretin properties, including dopamine, ghrelin, enterostatin, and oxyntomodulin. Disruption of the balance between incretins and anti-incretins could be considered as a pathway leading to the development of obesity and insulin resistance.

Keywords

Incretins · Anti-incretins · Type 2 diabetes · Obesity · Insulin resistance · Metabolic surgery

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Introduction

Incretins are gut hormones which play a key role in the preservation of glucose homeostasis in humans. Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) amplify the glucose-dependent secretion of insulin by the pancreatic beta-cells, presenting at the same time extrapancreatic actions. GLP-1 is known to inhibit postprandial glucagon secretion and delay gastric emptying, duodenal, and small intestine motility, thus resulting in delayed sugar absorption (Seino et al. 2010; Karras et al. 2012). Incretins mediate the well-described incretin effect, according to which orally digested glucose triggers a stronger insulin response than that resulting from the intravenous administration of the same amount of glucose (Rehfeld and Stadil 1973). The incretin effect has been recognized to be reduced in people with type 2 diabetes (T2D) compared with healthy controls, although it is debated whether this is a cause or a consequence of the diabetic state (Knop et al. 2007).

Changes in incretin biodynamics have been recognized as part of the mechanisms explaining the positive effects of metabolic surgery on obesity and T2D. Several studies have established increased concentrations of both GLP-1 and GIP after bariatric surgery procedures (Bose et al. 2010; Honka et al. 2018), related to improved insulin secretion and lower insulin resistance (IR). However, the exact changes in the physiology of individuals undergoing metabolic surgery are still under investigation and intensive research is currently being conducted to elucidate the full spectrum of the implicated mechanisms (Karras et al. 2019).

According to the foregut hypothesis (Rubino and Gagner 2002), surgical bypass of certain parts of the gastrointestinal (GI) tract leads to the downregulation of biological factors that are secreted by the upper GI system, and compete with incretins actions (anti-incretins). Those molecules have a negative effect on insulin secretion, action, and sensitivity (Rubino and Amiel 2014).

The Anti-incretin Theory

The anti-incretin theory suggests that the presence of food in the GI tract, apart from activating the cascade of incretin-related biological actions, also stimulates a negative feedback adaptation, which is the release of anti-incretins (Kamvissi et al. 2010). Anti-incretins aim to balance the glucose-lowering effects of incretins, in order to prevent excessive insulin release, potentially leading to hypoglycemia (Rubino and Gagner 2002; Kamvissi et al. 2010; Rubino and Amiel 2014).

Incretins also stimulate beta-cell proliferation (Lavine and Attie 2010; Lindqvist et al. 2014). A similar phenomenon occurs with modern GLP-1 analogues such as liraglutide, which inhibits beta-cell apoptosis through stimulation of PI3-kinase-dependent AKT

phosphorylation (Kapodistria et al. 2018). Albeit protective (Lavine and Attie 2010), these responses might be potentially harmful in case of unlimited proliferation, due to the absence of appropriate regulatory mechanisms. Animal studies have showed that Roux-en-Y gastric bypass (RYGB) results in increased beta-cell mass postoperatively (Lindqvist et al. 2014), suggesting that RYGB abolishes gut-derived signals that prevent excessive growth of beta-cells, in face of elevated incretins (Rubino and Gagner 2002; Holst 2007; Rubino and Amiel 2014).

Early Response to Dysglycemia after Bariatric Surgery

Up to 89% of bariatric patients experience early T2D remission (Wickremesekera et al. 2005). As this appears during the first postoperative days, weight loss cannot play a significant role. Surgical exclusion of specific parts of the GI tract from nutrient transit, could abolish anti-incretin signals, thus resulting in improved insulin action and sensitivity (Rubino and Gagner 2002; Kamvissi et al. 2010; Rubino and Amiel 2014).

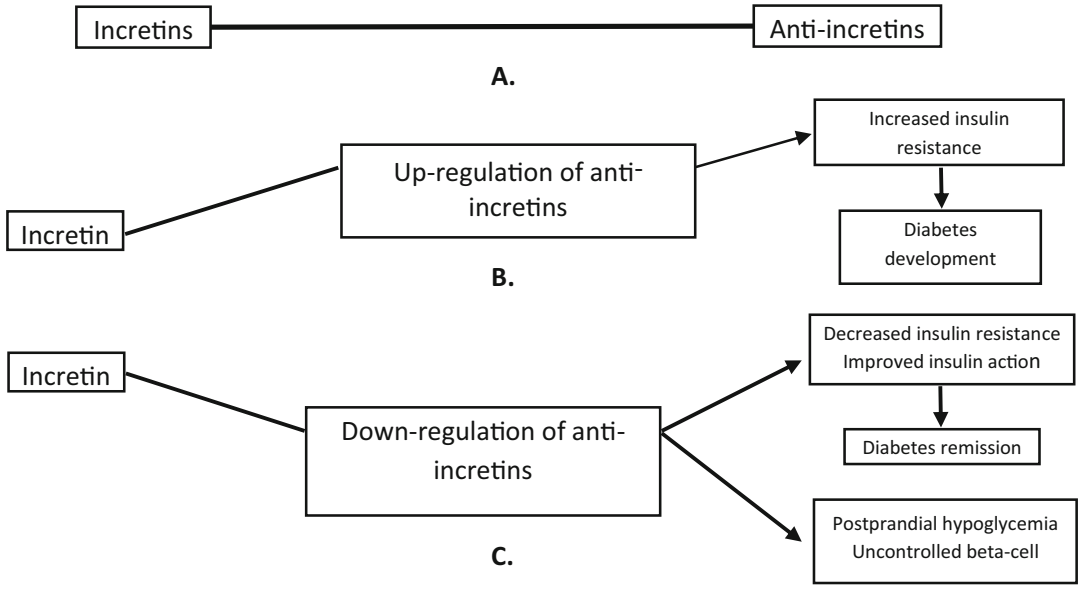

Fig. 15.1 A schematic overview of the balance between incretins and anti-incretins. (**A**) The normal state, in which the balance between the two mechanisms results in the preservation of normal glucose homeostasis, (**B**) Type 2 Diabetes, where an exaggeration of the anti-incretin effect could contribute to the development of insulin resistance and hyperglycemia, (**C**) Following metabolic surgery, where down-regulation of anti-incretins could lead to diabetes remission, and rarely to postprandial hypoglycemia and unrestricted beta-cell growth

Post-bariatric Hypoglycemia

On the other hand, postprandial hypoglycemia possibly linked to unrestrained beta-cell proliferation, occasionally occurs after RYGB (Cummings 2005). It is also postulated that Western-pattern diets or food additives might promote the overexpression of anti-incretins and through this pathway, to deteriorate beta-cell function and sensitivity (Rubino and Gagner 2002; Kamvissi et al. 2010). Figure 15.1 summarizes current knowledge about these shifts.

Potential Pathways and Molecules

Any anti-incretin should gather a number of features, including: (a) downregulation of insulin production and release from the pancreatic beta-cells, (b) production by an enteroendocrine source as a result of exposure to nutrients, and c. response to fasting or carbohydrate restraint (Alfa et al. 2015).

Dopamine

Dopamine exerts regulatory effects on glucose metabolism, given that it has the ability to downregulate incretin-mediated enhanced glucose-dependent phosphoprotein signaling procedures, as well as to inhibit *in vitro* GLP-1-promoted islet and beta-cell proliferation (Maffei et al. 2015). Tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis, is highly expressed in parietal and ileal epithelial cells, as well as Lieberkuhn crypts (Kozicz and Arimura 2002). Of note, D2-like receptors which are believed to be the key mediators of dopamine-related suppression of insulin secretion, are expressed in beta-cells (Rubi et al. 2005). As shown in a study conducted with a rodent beta-cell line (INS-1 832/12), insulin secretion was amplified following the knock-out of the aforementioned receptors (Wu et al. 2008), further supporting the implication of dopamine in an autocrine circuit of neurotransmitter regulation, which acts as a limiting factor of glucose-

stimulated insulin secretion (Chaudhry et al. 2016). There is an experimental evidence that diet-derived tyrosine, a precursor of L-DOPA and dopamine, participates in postprandial glucose homeostasis. This circuit could be involved in protection against hypoglycemia via inhibition of glucose-stimulated β-cell insulin secretion, a response consistent with the anti-incretin hypothesis (Korner et al. 2019).

Ghrelin

Ghrelin has been also postulated to play an anti-incretin role, albeit relevant data are more limited here. Ghrelin has been demonstrated to prevent GLP-1-mediated stimulation of cyclic adenosine monophosphate signaling and insulin secretion in beta-cells (Damdindorj et al. 2012), and suppress the production of adiponectin (Cummings 2009), whereas synthetic ghrelin administration in humans can restrain insulin secretion (Tong et al. 2010). However, the effect of metabolic surgery on ghrelin is controversial, with both increase and stability being observed (Cummings 2009).

Other Molecules

The amino acid sensor G protein receptor 142 (GP142) integrates anti-incretin properties, since it stimulates pancreatic glucagon secretion, but also exerts adjusting effects on insulin-mediated glucose uptake in fat and muscle, and hepatic glucagon-mediated glucose production (Lin et al. 2018).

Oxyntomodulin has been also reported to upregulate glucagon secretion both *in vitro* and *in vivo* (Baldissera et al. 1988), having at the same time the ability to decrease glucagon secretion through the activation of the GLP-1 receptor (Holst et al. 2018a, b). Those GP142 and oxyntomodulin actions could be considered as part of the physiological response antagonizing incretin-induced hypoglycemia and preserving normal glucose levels, through the modulation of glucagon hepatic production, peripheral glucose utilization, and perhaps other mechanisms (Karras et al. 2019).

Correlation with Diabetes and Obesity Remission Following Metabolic Surgery

Salinari et al. (2017) investigated the impact of metabolic surgery (biliopancreatic diversion) on glucose homeostasis variables. Participants with obesity exhibited lower insulin sensitivity, whereas in normal individuals, insulin sensitivity was lower during oral compared to intravenous glucose administration. The more robust difference between oral and intravenous insulin sensitivity in obese individuals was attenuated following biliopancreatic diversion. It was predicted that hypoglycemia would occur during an OGTT, in case insulin sensitivity remained in the range of intravenous glucose administration, particularly in case of obesity and IR. According to the anti-incretin model, postprandial amplification of IR protects against hypoglycemia, following the elevation of insulin levels as a result of food intake.

In an experimental study (Salinari et al. 2014), nonobese, diabetic Goto-Kakizaki rats were subjected to resection or bypass of various intestinal segments. Duodenal-jejunal bypass (DJB) as well as jejunectomy, although improving insulin sensitivity, did not have an impact on GIP and GLP-1 concentrations, indicating no role for elevated incretin levels. Downregulation of specific duodenum- and jejunum-derived molecules that negatively affect insulin sensitivity might be responsible instead. It could also be hypothesized that an exaggerated anti-incretin effect is a component of T2D pathophysiology, even in the absence of obesity.

Enhancement of Pancreatic Beta-cell Mass

Lindqvist et al. (2014) achieved improvements in glycemic homeostasis following RYGB in a porcine model, driven by an increase in beta-cell

mass, islet number, and number of extra islet beta-cells, suggesting that the operation resulted in the suppression of signals that inhibit beta-cell proliferation. This is in agreement with the anti-incretin theory, albeit different studies have failed to demonstrate an increased beta-cell mass after bariatric procedures (Meier et al. 2006). Inappropriately, improved beta-cell function, rather than changes in beta-cell mass, might explain the post-operative hypoglycemia occasionally seen in people subjected to RYGB.

A different study (Salinari et al. 2013), assessed the effects of protein extracts, derived from the duodenum-jejunum conditioned-medium (CM) of diabetic rodents on insulin sensitivity, both *in vitro* and *in vivo*. Jejunal proteins negatively affected muscle insulin signaling, through promotion of Akt ^{473}Ser phosphorylation in L6 cells, possibly via mTOR Complex 2 (mTORC2) or TSC activation, and Akt recruitment to plasma membrane. The authors indicated the proximal small bowel of animals with diabetes as a source of diabetogenic factors that have the potential to impair peripheral insulin sensitivity; however, these interesting findings need to be replicated by studies in humans.

Future Perspectives

The idea that T2D and obesity could be effectively managed or even put into remission following metabolic surgery is gaining popularity, due to increasing evidence supporting the effectiveness of surgical approaches, not only in reducing weight loss and improving glucose outcomes (Batterham and Cummings 2016), but also in preventing obesity-related macrovascular complications (Yan et al. 2019). The exact mechanisms mediating the effects of bariatric surgery are still hotly debated, as these are complex and involve interactions between numerous physiological and pathogenetic pathways (Karras et al. 2019).

The anti-incretin theory provides an alternative theoretical framework to explain the mechanisms behind the effects of metabolic surgery on T2D, and highlights the significance of the GI tract in the homeostatic regulation of food intake and energy balance in humans. Disruption of this two-way feedback loop, could be considered as an additional pathway leading to the development of obesity and IR.

Obviously, the anti-incretin theory should be studied in the context of other mechanisms that explain the impact of bariatric surgery on metabolic outcomes. For example, changes in incretin bioavailability (Holst et al. 2018a, b), differentiation of the vagus nerve anatomy (de Lartigue et al. 2014), altered expression of bile acids (Penney et al. 2015), and modified gut microbiome (Liou et al. 2013), have been all shown to contribute to the metabolic benefits of bariatric surgery.

Anti-incretin molecules and pathways, as well as genetic, molecular or biochemical markers able to monitor such phenomenon in obesity and diabetes, are worthwhile topics for future research (Karras et al. 2019).

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