

Incretins or Anti-Incretins? A New Model for the “Entero-Pancreatic Axis”

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- pancreatic islets

Abstract



The role of incretins in glucose homeostasis is well known. Yet, in recent years, the sustained weight loss and rapid glycemic control following bariatric surgery has challenged our understanding of the intestinal-pancreatic interaction. This in turn led to the introduction of metabolic surgery, an innovative medical discipline in which a surgical manipulation of the gastrointestinal tract (e.g., through a Roux-en-Y gastric bypass, RYGB, or Bilio-Pancreatic-Diversion, BPD) yields a sustained remission of diabetes mellitus. The pathophysiological background of this metabolic effect is, amongst other things, based on the anti-incretin theory. This theory postulates that in addition to the well-known incretin effect, nutrient passage through the GI-tract could also activate negative feedback mechanisms (anti-

incretins) to balance the effects of incretins and other postprandial glucose-lowering mechanisms (i.e., suppression of ghrelin, glucagon, and hepatic glucose production via activation of nutrient sensing). This in turn prevents postprandial hyperinsulinemic hypoglycemia. The bypass of the duodenum, the entire jejunum and the first portion of the ileum by BPD induce normalization of peripheral insulin sensitivity, while the bypass of a shorter intestinal tract by RYGB mainly improves the hepatic insulin sensitivity. In addition, RYGB greatly increases insulin secretion. Therefore, metabolic surgery highlights the important role of the small intestine in glucose homeostasis, while until few years ago, it was only the pancreas and the liver that were thought to represent the regulatory organs for glucose disposal.

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Bibliography

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In the early 1900s, Bayliss et al. postulated that certain factors produced by the intestinal mucosa in response to nutrient ingestion could stimulate the release of substances from the endocrine pancreas, thereby reducing blood glucose levels [1]. In 1969, Unger and Eisentraut introduced the term “entero-insular-axis” to define the multiple stimulating and inhibiting interactions between the gut and the pancreatic islet cells [2].

The key functional connection between the small intestine and the endocrine pancreas was unmasked after it was shown that the insulin response to orally digested glucose is substantially stronger than that which follows the intravenous administration of the same amount of glucose [3]. This observation was named “the incretin effect” and led to the discovery of “incretins”, namely gastric inhibitory polypeptide (GIP) [4] and later glucose-dependent insulinotropic polypeptide-1 (GLP-1) [5]. These gut-hormones enhance the release of insulin from the pancre-

atic β -cells in a glucose-dependent way after ingestion of food.

In addition to a role in the secretion of insulin, the gut can also play an important role in the regulation of insulin sensitivity and energy homeostasis through a variety of mechanisms that have become the focus of intense research in recent years. For instance, the gut microbiota, a term used to collectively describe all the microorganisms that inhabit the human digestive tract, has been implicated in the development of obesity, insulin resistance, and diabetes [6,7]. Furthermore, bile acids can also influence glucose and lipid metabolism and play a role in the overall regulation of energy homeostasis. Bile acids facilitate the absorption of fatty acids and lipid-soluble vitamins, contribute to cholesterol clearance, act as metabolic signaling molecules [8] and are also involved in incretin secretion [9,10].

The most compelling evidence for the importance of the role of the gastrointestinal (GI) tract in the regulation of energy homeostasis however, derives from observations of the dramatic clinical effects of gastrointestinal operations that go under the name of “bariatric” and now “metabolic” surgery [11].

These procedures in fact have been shown to induce long-term weight loss and sustained remission of type 2 diabetes mellitus (T2DM) [12, 13] as well as improvement of other metabolic conditions including hypertension, sleep apnoea, and dyslipidemia [14, 15].

There are several surgical procedures used for the treatment of morbid obesity. Roux-en-Y gastric bypass (RYGB) and the Bilio-Pancreatic Diversion (BPD) appear to evoke the greatest effect on the regulation of metabolism. From an anatomical point of view, RYGB involves the creation of a small stomach pouch and an exclusion of the proximal small intestine (all of duodenum and a large segment of jejunum), while BPD involves a gastric resection and diversion of the biliopancreatic juice to the terminal ileum that significantly reduces the absorption of nutrients [16]. Other bariatric procedures include gastric banding and vertical sleeve gastrectomy, which both reduce the volume of the stomach without bypass of the small intestine. While all procedures reduce body weight and result in variable degree of improvement of T2DM, results of randomized clinical trials suggest that procedures involving intestinal rerouting, like BPD and RYGB, have the greatest effect on diabetes [17, 18] and that longer intestinal bypass (such as in BPD) is associated with greater rates of remission of hyperglycemia [12]. Long term control of glycemia and improved levels of glycosylated hemoglobin have been observed in obese diabetic patients in series for up to 14 years follow-up [19] along with long-term reduction of micro- and macrovascular complications of diabetes [20].

Examining the mechanisms by which surgery can improve diabetes may help understand the physiology and pathophysiology of diabetes [21]. There is evidence that various GI procedures change the pattern of secretion of various gastrointestinal hormones, including GLP-1, PYY-3-36, glucagon, GIP, and ghrelin [22–24], which may provide a relatively straightforward explanation for the effects of surgery on insulin secretion and appetite suppression.

In particular, the “hindgut hypothesis” holds that the mechanism by which RYGB improves diabetes would be through an enhancement of GLP-1 secretion due to the accelerated delivery of nutrient to the L-cell-rich distal small bowel [25, 26]. Increased postprandial GLP-1 levels would in turn enhance the incretin effect and result in greater insulin secretion and improved glucose tolerance [27]. Lindqvist et al. recently reported a doubling of β -cell mass and islet number in 4 RYGB-treated pigs suggesting that this surgery can influence both secretion of insulin and β -cell growth [28]. This effect has been also attributed to the enhancement of endogenous GLP-1.

The “hindgut hypothesis” and the role of GLP-1, however, have recently come into question owing to evidence from both human and animal studies showing that blockage of GLP-1 action only modestly reduces the effect of surgery on glucose tolerance and diabetes control. For instance, the effects of RYGB on body weight and glucose metabolism are not substantially reduced when the operation is performed in genetic mice models with attenuated GLP-1 secretion and in GLP-1-receptor deficient mice [29]. Furthermore, suppression of glucose production and stimulation of glucose disappearance were unaltered in RYGB subjects after administration of exendin-9,39, a competitive

antagonist of GLP-1 at its receptor [30], therefore questioning the hindgut hypothesis and the role of incretins as the sole explanation to the improvement of diabetes after surgery [31–33]. An alternative hypothesis for the effect GI surgery has on diabetes is that alterations of the physiologic mix of bile and nutrients and their contact with intestinal mucosa, typical for procedures that involve duodenal-jejunal exclusion, may reduce production of diabetogenic signals (“foregut hypothesis”) [34–36].

The foregut hypothesis is one of the predictions made by the anti-incretin theory. This theory was developed by one of us (FR), originally reported in 2002 [37] and progressively refined [38–40] to provide a theoretical model that is coherent with observations of physiologic response to nutrient ingestion as well as with the effects of gastric bypass surgery. This theory postulates that in addition to the well-known incretin effect, nutrient passage through the GI-tract could also activate negative feedback mechanisms (anti-incretins) to balance the effects of incretins and other postprandial glucose-lowering mechanisms (i.e., suppression of ghrelin, glucagon, and hepatic glucose production via activation of nutrient sensing), thus preventing postprandial hyperinsulinemic hypoglycemia.

In fact, incretins enhance insulin secretion, insulin action, as well as β -cell function and growth. If there were no control mechanisms, these effects would expose to the risk of postprandial hyperinsulinemic hypoglycemia and uncontrolled β -cell proliferation (i.e., nesidioblastosis and insulinomas). These are, in fact, quite uncommon, suggesting that the action of incretins must be physiologically balanced by hormonal, metabolic, and/or neural mechanisms [anti-incretin(s)] to maintain normal glucose homeostasis.

The anti-incretin theory may provide a rational theoretic model to explain physiology and pathophysiology of glucose metabolism as well as the effects of various interventions, including gastrointestinal surgery and diet.

In fact, according to the anti-incretin theory, an excess of anti-incretin signals, possibly stimulated by specific macronutrient composition of modern diet or chemical additives, could cause insulin resistance, reduced insulin secretion, and β -cell depletion, leading to T2DM. Conversely, reduction of anti-incretin signals below thresholds necessary to control incretin-driven responses might result in postprandial hypoglycemia and uncontrolled β -cell proliferation [40].

Reduction of nutrient stimuli on the gut by drastic decrease in food intake (i.e., very low calorie diet), expedited gastro-intestinal transit (i.e., such as after sleeve gastrectomy), or, more radically, through the exclusion of large portions of the upper small bowel from nutrient transit (i.e., RYGB, duodenal-jejunal bypass, biliopancreatic diversion) could reduce excess anti-incretin and restore appropriate incretins/anti-incretins balance, thus explaining improvement and remission of T2DM.

Disruption of GI continuity, however, (i.e., RYGB and certain anatomic reconstructions after gastrectomy for ulcer/cancer) may reduce anti-incretin signals below minimal thresholds to compensate for incretin actions and result in postprandial hypoglycemia or alterations of β -cell proliferation, which have both been reported as rare but possible complications of RYGB.

A number of recent studies provide preliminary evidence in support of the various predictions made by the anti-incretin theory and the foregut hypothesis.

Salinari et al. performed resection or bypass of different intestinal segments in diabetic Goto-Kakizaki and normal control animals followed by an oral glucose tolerance test 2 weeks after

surgery [41]. Baseline and post stimulation levels of glucose, insulin, GLP-1, GIP, and insulin sensitivity were measured. In this study, stomach-sparing duodenal-jejunal bypass (DJB) and jejunectomy (which bypass/remove a segment of proximal small intestine) did not change GIP or GLP-1 levels, but were able to improve glucose tolerance more than ileectomy, a procedure that is associated with expedited nutrient delivery to areas rich in L-cells but does not involve duodenal exclusion. These findings support the hypothesis that excluding duodenum and jejunum from nutrient transit has specific antidiabetes effects [37,42,43] and that this is not due to changes in GLP-1, but possibly due to the reduction of factors with negative influence on insulin sensitivity.

In another study by the same group, protein extracts from the duodenum and/or jejunum of diabetic rodents and humans were found to be able to induce insulin resistance in cell-based assays and in vivo [44]. This observation supports the hypothesis that the proximal small bowel of subjects with type 2 diabetes may produce diabetogenic factor(s), consistent with one of the predictions made by the anti-incretin theory.

A recent study by Lindqvist et al. [28] found increased β -cell mass in pigs that had undergone RYGB. In this study, however, the experiments with RYGB were performed in pigs with normal glucose homeostasis at baseline, suggesting that the effect of this surgery is not due to an enhancement of defective incretin mechanisms but rather the consequence of the disruption of physiologic mechanisms that control β -cell proliferation and maintain normal β -cell mass. This is consistent with the predictions made by “the anti-incretin-theory” [36] suggesting the existence of factor(s) in the small proximal intestine that act as regulators of β -cell growth along with incretins, but in the opposite direction.

The current model of the entero-pancreatic axis is insufficient to explain a number of observations about the physiology of glucose homeostasis and the effects of gastrointestinal surgery. Although the anti-incretin theory remains to be demonstrated at a molecular level, it provides an alternative theoretical framework for the link between diet, insulin resistance, diabetes, and its reversal after gastrointestinal surgery. The anti-incretin theory may inspire new research approaches aimed at a deeper understanding of the physiology and pathophysiology of glucose homeostasis.

Conflict of Interest



The authors declare that they have no conflict of interest in the authorship or publication of this contribution.

References

- 1 Bayliss WM, Starling EH. The mechanism of pancreatic secretion. *J Physiol* 1902; 28: 325–353
- 2 Unger RH, Eisentraut AM. Entero-insular axis. *Arch Intern Med* 1969; 123: 261–266
- 3 Goke B, Fehmann HC, Schirra J, Hareter A, Goke A. The intestinal hormone glucagon-like peptide 1 (GLP-1): from experiment to the clinic. *Z Gastroenterol* 1997; 35: 285–294
- 4 Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin Endocrinol Metab* 1973; 37: 826–828
- 5 Kreyman B, Ghatei MA, Williams G, Bloom SR. Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet* 1987; 2: 1300–1304
- 6 Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care* 2010; 33: 2277–2284
- 7 Graessler J, Qin Y, Zhong H, Zhang J, Licinio J, Wong MOL, Xu A, Chavakis T, Bornstein AB, Erhart-Bornstein M, Lamounier-Zepter V, Lohmann T, Wolf T, Bornstein SR. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. *Pharmacogenomics J* 2013; 13: 514–522
- 8 Hansen M, Sonne DP, Knop FK. Bile acid sequestrants: glucose-lowering mechanisms and efficacy in type 2 diabetes. *Curr Diabetes Rep* 2014; 14: 482
- 9 Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochem Biophys Res Commun* 2005; 329: 386–390
- 10 Thomas C, Gioiello A, Noriega L, SStrehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Mataka C, Pruzanski M, Pellicciari M, Auwerx J, Schoonjans K. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab* 2009; 10: 167–177
- 11 Rubino F. From bariatric to metabolic surgery: definition of a new discipline and implications for clinical practice. *Curr Atherosclerosis Rep* 2013; 15: 369
- 12 Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; 366: 1577–1585
- 13 Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012; 366: 1567–1576
- 14 Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, de Ramon RA, Israel G, Dolezal JM, Dohm L. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995; 222: 339–350 Discussion 332–350
- 15 Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, vella A, Chuang L-M, Bessler M, Sarr MG, Swain JM, laqua P, Jensen MD, Bantle JP. Roux-Y gastric bypass vs. intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013; 309: 2240–2249
- 16 Scopinaro N, Gianetta E, Civalieri D, Bonalumi U, Bachi V. Bilio-pancreatic bypass for obesity: II. Initial experience in man. *Br J Surg* 1979; 66: 618–620
- 17 Lee WJ, Lin YH. Single-Anastomosis Gastric Bypass (SAGB): Appraisal of Clinical Evidence. *Obes Surg* 2014; 24: 1749–1756
- 18 Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ESH, Nissen SE, Kashyap SR; for the Stampede Investigators. Bariatric surgery versus intensive medical therapy for diabetes – 3-year outcomes. *N Engl J Med* 2014; 370: 2002–2013
- 19 Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; 273: 219–234
- 20 Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, Bouchard C, Carlsson C, Karason K, Lönroth H, Näslund I, Sjöström E, Taube M, Wedel H, Svensson P-A, Sjöholm K, Carlsson LMS. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014; 311: 2297–2304
- 21 Bourdages H, Goldenberg F, Nguyen P, Buchwald H. Improvement in Obesity-associated Medical Conditions following Vertical Banded Gastroplasty and Gastrointestinal Bypass. *Obes Surg* 1994; 4: 227–231
- 22 Halverson JD, Kramer J, Cave A, Permutt A, Santiago J. Altered glucose tolerance, insulin response, and insulin sensitivity after massive weight reduction subsequent to gastric bypass. *Surgery* 1982; 92: 235–240
- 23 Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes* 2011; 60: 2308–2314
- 24 Malin SK, Samat A, Wolski K, Abood B, Pothier CE, Bhatt DL, Nissen S, Brethauer SA, Schauer PR, Kirwan JP, Kashyap SR. Improved acylated ghrelin suppression at 2 years in obese patients with type 2 diabetes: effects of bariatric surgery vs. standard medical therapy. *Int J Obes* 2014; 38: 364–370
- 25 Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol* 2014; 2: 152–164

- 26 Rubino F, Schauer PR, Kaplan LM, Cummings DE. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. *Ann Rev Med* 2010; 61: 393–411
- 27 Laferrere B. Effect of gastric bypass surgery on the incretins. *Diabetes Metab* 2009; 35: 513–517
- 28 Lindqvist A, Spegel P, Ekelund M, Vaz EG, Pierzynowski S, Gomez MF, Mulder H, Hedenbro J, Groop L, Wierup N. Gastric bypass improves beta-cell function and increases beta-cell mass in a porcine model. *Diabetes* 2014; 63: 1665–1671
- 29 Mokadem M, Zechner JF, Margolskee RF, Drucker DJ, Aguirre V. Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. *Mol Metab* 2014; 3: 191–201
- 30 Shah M, Law JH, Micheletto F, Sathananthan M, Man CD, Cobelli C, Rizza RA, Camilleri M, Zinsmeister AR, Vella A. Contribution of endogenous glucagon-like peptide 1 to glucose metabolism after Roux-en-Y gastric bypass. *Diabetes* 2014; 63: 483–493
- 31 Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, Eid GM, Mattar S, Ramanathan R, Barinas-Mitchel E, Rao RH, Kuller L, Kelley D. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surgery* 2003; 238: 84–85 Discussion 465–484
- 32 Pories WJ. Diabetes: the evolution of a new paradigm. *Ann Surg* 2004; 239: 12–13
- 33 Briatore L, Salani B, Andraghetti G, Sferrazzo E, Scopinaro N, Adami GF, Maggi D, Cordera R. Restoration of acute insulin response in T2DM subjects 1 month after biliopancreatic diversion. *Obesity (Silver Spring, Md)* 2008; 16: 77–81
- 34 Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, Nanni G, Castagneto M, Calvani M, Migrone G. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* 2006; 55: 2025–2031
- 35 Bikman BT, Zheng D, Pories WJ, Chapman W, Pender JR, Bowden RC, Reed MA, Cortright RN, Tapscott EB, Houmard JA, Tanner CJ, Lee J, Dohm GL. Mechanism for improved insulin sensitivity after gastric bypass surgery. *J Clin Endocrinol Metab* 2008; 93: 4656–4663
- 36 Rubino F. Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. *Diabetes Care* 2008; 31 (Suppl 2): S290–S296
- 37 Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. *Ann Surg* 2002; 236: 554–559
- 38 Rubino F, Moo TA, Rosen DJ, Dakin GF, Pomp A. Diabetes surgery: a new approach to an old disease. *Diabetes Care* 2009; 32 (Suppl 2): S368–S372
- 39 Rubino F, R'Bibo SL, del Genio F, Mazumdar M, McGraw TE. Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. *Nat Rev Endocrinol* 2010; 6: 102–109
- 40 Rubino F, Amiel SA. Is the gut the “sweet spot” for the treatment of diabetes? *Diabetes* 2014; 63: 2225–2228
- 41 Salinari S, le Roux CW, Bertuzzi A, Rubino F, Mingrone G. Duodenal-jejunal bypass and jejunectomy improve insulin sensitivity in Goto-Kakizaki diabetic rats without changes in incretins or insulin secretion. *Diabetes* 2014; 63: 1069–1078
- 42 Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. *Ann Surg* 2004; 239: 1–11
- 43 Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, Castagneto M, Marescaux J. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. *Ann Surg* 2006; 244: 741–749
- 44 Salinari S, Debard C, Bertuzzi A, Durand C, Zimmet P, Vidal H, Mingrone G. Jejunal proteins secreted by db/db mice or insulin-resistant humans impair the insulin signaling and determine insulin resistance. *PLoS One* 2013; 8: e56258