Diabetes remission after bariatric surgery explained by the AIA axis theory. Is amylase a key to postoperative glucose regulation? – research hypotheses

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Key Messages

- Besides insulin, amylase is a further important regulator of glucose metabolism.
- There is a hitherto unrecognised reciprocal regulation within the pancreas: insulin stimulates the secretion of amylase and other pancreatic enzymes, while amylase inhibits insulin secretion (acino-insulo-acinare (AIA) axis).
- Amylase, in addition to its digestive function, has a strong down-regulatory effect on insulin secretion - both mediated via blood and from the gut.
- The alpha-amylase of the pancreas causes the anti-incretin effect with limitation of insulin secretion, which thus generally counteracts hypoglycaemia and at the same time protects the beta cells from depletion.
- Bariatric surgery provides duodenal exclusion from food passage and thus eliminates the incretin-dependent vicious cycle in obese patients.
- AIA axis action is a comprehensive explanation for diabetes remission following bariatric surgery.

ABSTRACT

The concept of the AIA axis postulates that insulin stimulates amylase synthesis ("halo phenomenon") and amylase in turn inhibits insulin production. Additionally, both intestinal and plasma amylase from the pancreas and other sources directly influence the appearance of dietary glucose in the blood and accordingly lower the glucose peak after intravenous or oral glucose load tests. Amylase thus apparently has a protective influence on the depletion of the pancreatic insulin-producing beta cells.

The regulation described can be transferred with particular significance to postoperative glucose regulation after bariatric bypass surgery. The interaction of salivary

amylase at the alimentary limb and pancreatic amylase exclusively at the common channel results in an immediate metabolic effect that leads to a significant reduction in incretin-induced hyperinsulinaemia and a marked improvement in glucose action on insulin production. As a result, both pancreatic beta cells and acinar cells are effectively protected from depletion.

The findings from a previous animal study clearly support the above statements: Disruption of AIA feedback due to amylase production arrest by acinar cell destruction (pancreatic duct-ligated (PDL) porcine model of EPI) causes hyperinsulinaemia and hyperglycaemia, thus leading to a diabetogenic status, and vice versa.

The above emphasize the importance of the close collocation of the anatomical structure of the acini and islet cells in the pancreas, which have a mutual and interdependent function. The pancreas is therefore the coherent organ with mutual functional units in the regulation of glucose homeostasis, also in post-bariatric glucose regulation.

INTRODUCTION

The evolution of knowledge on the physiological role of the pancreas as the organ combining both an exocrine and an endocrine function has been puzzling for many years. The relationship between the pancreas and the development of diabetes was established as early as in 1889 by Oscar Minkowski and Joseph von Mering in their studies on the dog model.[1] From that time until World War I, studies were conducted on the possible treatment of diabetes with administering pancreatic extracts. Even though crude extracts of whole pancreas were shown to diminish glycosuria, the islets of Langerhans were still considered as the main source of regulatory molecules.

However, the role of serum amylase activity in the development of diabetes has been lively discussed, and assumptions have been made about a possible correlation between serum amylase activity and blood glucose concentrations.[2 3] Nevertheless, the Nobel Prize-winning extraction and purification of insulin by Banting and Best in 1921-1922 and its subsequent successful introduction into clinical practice made the possible role of amylase in glucose homeostasis fade and eventually be forgotten.

Studies on the interdependence of pancreatic enzymes on insulin synthesis began 60 years ago and led to the discovery of the so-called "halo phenomenon".[4-8]

For several years now, we have been studying this mutual regulation of insulin release and pancreatic enzyme secretion and its potentially role in the interaction in glucose metabolism.[9] Our studies indicate a local as well as a peripheral dependency of insulin secretion on pancreatic amylase.

Amylase may be involved in the inhibition of glucose absorption from the gut [10 11] and in beta cells *in vitro*, leading to a decrease in insulin production.[12] Whether amylase is administered intraduodenally (id) or intravenously (iv), it consistently stimulates the conversion of glucose to glycogen in enterocytes (Fig. 1)

Due to the already described inhibition of glucose absorption leading to a reduced appearance of glucose in the blood, this would correspond to an insulin response according to an intravenous administration of glucose. This renders corroboration of the assumed reciprocal regulation within the pancreas: insulin stimulates the secretion of amylase and other pancreatic enzymes, while amylase inhibits insulin secretion, as suggested by Pierzynowski et al. [13]

In fact, chronic hyperinsulinemia not only leads to insulin resistance, but equally to the devastation of pancreatic acinar cells and thus to the development of exocrine pancreatic insufficiency.[14]

The above observations were confirmed in several *in vitro* and *in vivo* studies .[12 13 15-17]

Both the reciprocal AIA local interactions in the pancreas, as well as the remote interactions (originating from gut and blood) of amylase influencing insulin secretion, belong to the group of structural metabolic and anti-incretin regulations. These are intrinsic persisting interactions, while incretin-dependent regulations strongly and directly rely on the composition of food when it is ingested and consequently is there for rapid and transient. These structural regulations and counter-regulations appear to protect both pancreatic beta and acinar cells from overproduction and thus ongoing depletion.

PANCREATIC ENZYME THERAPY AMELIORATES EPI- DEPENDENT HYPERINSULINEMIA IN DIABETIC STATUS

Exocrine pancreatic insufficiency (EPI) is frequently diagnosed in both DMT1 and DMT2 patients (Radinger et al, 2020).[14] It additionally may influence in such procedures the reduction of digestion and the subsequent absorption.

Our own studies on streptozotocin (STZ) – induced diabetes[12] and on EPI[15] pig models have clearly shown that both iv administration of amylase of microbial origin (Amano, Japan) and the oral administration of pig pancreatic enzymes (enteric coated pancrelipase -Abbot Healthcare Products Ltd, Southampton, UK) lower insulin and glucose levels in the iv-glucose tolerance test (IvGTT).

Moreover, studies from 2016 on healthy pigs have shown that particularly pancreatic-like enzymes of microbial origin (Sigma-Aldrich) after oral administration differently affect insulin release; amylase lowers it, while protease enhances insulin release during an IvGTT, lipase did not exhibit any effect on insulin realise.[9] The aforementioned studies in EPI and STZ pigs thus enabled the investigation on the efficacy of amylase-induced long-term structural regulation of glucose homeostasis, while demonstrating the protective effects of enteral- and blood amylase on pancreatic beta cell survival. Enteral or parenteral amylase, both of microbial and of porcine origin, lower blood levels of insulin and glucose during IvGTT and oral glucose tolerance tests (OGTT). Undoubtfully, in this scenario high levels of amylase - independently of origin in the gut and blood - should be treated as a factor which protects pancreatic beta cells from metabolic failure.

However, the key question remains how amylase signals from the intestinal lumen and from the blood are transferred to beta and acinar cells? Due to the nature of the portal vascular system in the pancreas, local peri-islet insulin levels are very high compared to systemic levels.[18 19] The supraphysiological doses of iv infused amylase under study conditions were much higher than physiological amylase level and thus could possibly increase the amylase level in the peri-islet circulation, inhibiting insulin release.[15] The inhibitory action of amylase on insulin from the gut lumen requires the existence of a gut-pancreas amylase-dependent anti-incretin reflex which ends in the peri-islet interstitial tissue. More physiological, however, is direct action of amylase or amylase-derived peptides on gut

glucose absorption or on enterocyte metabolism stimulating glycogen formation and glucose storage.[12 17]

Pancreatic amylase, which is synthesized in the acinar cells, and then appears in the pancreatic juice, is also obviously leaking to the periinsular interstitial fluid and in such way can downregulate insulin secretion. Additionally, digesta entering the AL stimulates behavioural reflexes responsible for insulin and enzyme secretion to a lower extent, since in the proximal jejunum the number of incretins and other gastrointestinal hormones receptors is markedly decreased when compared to the duodenum.

To complete this intriguing postulation, it is necessary to perform *in vivo* studies on direct infusion of amylase alone and/or as a mixture with other pancreatic enzymes, to the *arteria pancreatica magna* during iv glucose loading. Inhibition of insulin release will finally confirm the role of amylase in the protection of beta cells from the overproduction of insulin.

In the schema presented below (Fig. 2 A, B) we suggest possible pathways of amylase-dependent structural regulations of insulin secretion and their integration with food-related regulations of insulin secretion. These are usually eliminated or at least ameliorated by successful bariatric surgery.

EFFECTS OF BARIATRIC SURGERY ON ACINI-ISLETS INTERACTIONS AND BETA CELL PROTECTION

There are currently three main types of bariatric surgery being performed across the world, the sleeve resection (SG), the Roux-en-Y gastric bypass (RYGB) and the one-anastomosis gastric bypass (OAGB) (Fig. 3). The mode of action of bariatric procedures is based mainly on restriction (reduction of gastric volume - all procedures) and duodenal exclusion with varying lengths of the adjacent jejunum (bypass procedures).

SG is a resective procedure that is only performed on the stomach and thus reduces its volume (restriction). In the classic RYGB (Fig. 3) and its possible modifications in limb

lengths (Fig. 3), duodenal exclusion (Bypass) is achieved by creating a small gastric pouch from the genuine stomach, which then is anastomosed with the transposed jejunum in a Roux-en-Y reconstruction (AL, BPL, CC), whereas the recreation of the food passage in the OAGB is achieved by a Billroth II reconstruction (BPL, CC, but no AL). All those procedures result in a significant reduction of body weight and improvement or even remission of DMT2. Surgical manipulation of gastrointestinal anatomy has profound effects. These metabolic acting bariatric procedures can result in normo-glycemia and normo-insulinemia and interventions reduce body weight by decreasing hunger, increasing satiation and satiety, change food preferences and energy expenditure.

Contribution of duodenal exclusion to the mode of action

In the SLEEVEPASS randomized clinical trial, gastric bypass appears to be associated with greater percentage excess weight loss and better diabetes remission at 5 years compared with sleeve gastrectomy, although without static significance.[20] However, the rapidity of recovery from DMT2 was not taken into consideration.

Nevertheless, considering the outstanding results of biliopancreatic diversion procedures on DMT2 remission (up to 95 %), a procedure that is very rarely performed today because of its extremely pronounced malabsorptive effects (short bowel syndrome), it becomes most obvious that the anatomical alteration of the small intestine must have major effect on glucose homeostasis (Fig. 4).[21]

Obviously, certain types of bariatric surgery (bypass procedures) indicate more clearly than purely restrictive procedures the likelihood of structural regulations of insulin secretion due to rapid observed and apparently weight loss-independent improvement in comorbid DMT2 (metabolic effect). Based on the above facts, this can be conclusively

explained by the partial loss of incretin action on insulin release, anatomically implemented by creating a biliopancreatic limb (BPL) and thus excluding the duodenum.

Attenuation of incretin response, due to the absence of chyme contact with the duodenal mucosa, results in lower insulin release. At the same time, the passage of food along the AL is responsible for slight stimulation of pancreatic enzyme secretion. Since the pancreas secrets amylase into the BPL (duodenal exclusion) it thus cannot be involved in carbohydrate digestion there. In the BPL, other properties of amylase can therefore be emphasised, such as the anti-incretin-effect.

Whole or partially digested amylase molecules can attenuate glucose absorption and improve the conversion of glucose to glycogen (Fig. 1).[16] At the same time, the local interference of AIA (amylase from the acini surrounding the pancreatic islets) can additionally moderate insulin release, which can be recognized as the anti-incretin action. These factors altogether are most likely responsible for achieving DMT2 remission after bariatric surgery.

Importantly, the pharmacological duodenal exclusion of incretin action with GLY-200 polymer mimicking bariatric (metabolic) surgery is being studied in a clinical trial and the duodenojejunal bypass liner (DJBL) can be considered as an endoscopically implantable model for duodenal exclusion.[22] In clinical use, it showed a comparable effect to RYGB on a comorbid DMT2.[23]

Both strategies assume the exclusion of incretin action and the mechanical prevention of contact of duodenal mucosa and food (duodenal exclusion), when AIA thesis, including the anti-incretin action of amylase, is in full effect.

Additionally, the superior clinical effectiveness of bariatric surgery has promoted recognition and encouraged scientific investigation of the gut as a major endocrine organ.

Research inspired by these exciting results has contributed to the further development of GLP-1 analogues, which are now firmly established in the treatment of DMT2 and obesity. However, their efficacy and safety in terms of long-term beta cell protection is not yet fully elucidated, as in contrast to bariatric surgery the primary goal of GLP-1 analogues is to stimulate and thus increase insulin secretion.[24]

Nevertheless, it is worth noting that despite the exclusion of food passage from the duodenum, small amounts of gastric juices can enter there, which can still cause some incretin effect.

Contribution of the remnant stomach to the mode of action

To clarify the mode of action of bariatric surgery, it should be considered that the residual or even absent secretion of gastric juice (varies from person to person, depending on the type of surgery and the patient) is probably an important factor contributing to the complete success of bariatric metabolic surgery. The role of amylase in the AIA regulations with complete isolation of the stomach from the BPL has been experimentally proven both in the pig model of biliopancreatic diversion and in *in vitro* experiments, [13 16] confirming the direct inhibition of amylase on insulin release from insulinoma cell line BRIN-11.[12]

Lack of gastric juices entering to the BPL as a consequence of bariatric surgery minimizes the release of GLP-1.[25] This in turn has additional effect on reducing insulin secretion. However, even negligible amounts of gastric juice entering the BPL can evoke a cascade of incretin secretion from the duodenum and thus, stimulate large amounts of insulin released, which may explain the nocturnal hypoglycemic episodes observed with postoperative hyperinsulinemic hypoglycemia (PHH) in late dumping syndrome (LDS).

Contribution of the remnant stomach to hyperinsulinemic hypoglycemia (PHH) in the context of late dumping syndrome (LDS)

Generally, if the anti-incretin effects of amylase meet a non-diabetic and catabolic status, PHH can appear, which is still defined as LDS. This situation is often observed in patients after RYGB.[26] Nocturnal and especially food-independent hypoglycaemic episodes occur regular and are so far without any explanation.

Basically, luminal and circulating amylase further inhibit glucose absorption and stimulates enterocytes to store glucose in the form of glycogen, thus limiting the passage of glucose to the blood, while insulin ensures transport of blood glucose to tissues. Thus, in principle the unwanted status of hyperinsulinemia and hypoglycaemia is achieved. Additionally, glucose absorbed from the alimentary and common limb stimulates insulin release and at the same time, the incretins originating from the BPL amplify this insulin response making it extraordinarily high. In such case, the local, intrapancreatic protective effect of acinar amylase on insulin release, which is normally achieved via AIA regulation, is attenuated because the amylase from the peri-islets is already excreted with the pancreatic juice and thus less amylase is locally available.[27] This hypothesis is in line with the observations on the improvement or elimination of LDS by injection of incretins or percutaneous feeding, via a tube placed in the stomach remnant.[28] A small amount of liquid food pre-prandially infused to the remnant stomach of LDS patients, before a meal, moderately stimulates (activates) the incretin system prior to the meal thus allowing for realisation of insulin release and duodeno-pancreatic reflexes and simultaneously stimulating the exocrine pancreas.

Based on the same principle, the therapeutical dosage of GLP1 could stimulate timely insulin secretion. Thus, during a meal, the pancreas already partially empties of insulin

(GLP1 application) and amylase (CC). Case reports already indicates that this principle has an impact and PHH can be ameliorated or even eliminated. [29 30]

In consequence of the AIA, the cause of the frequently observed nocturnal hypoglycaemias can therefore be conceivably explained as possibly inadvertently secreting gastric juices (including proteins) from the rest of the stomach into the BPL during the night, thereby stimulating the release of incretins in the duodenum. Consequently, insulin concentration is elevated, by stimulation of pancreatic enzyme secretion. The interacting effects of insulin and amylase in such a situation would lead to a rapid lowering of blood glucose levels and hypoglycaemia without dietary trigger, thus developing even in this fasting state.

Therefore, the role of the remnant stomach after bariatric surgery may have been significantly underestimated. In the pathophysiological understanding of the development of PHH, especially in the context of the concept of AIA function and its consequent protection of pancreatic beta cells.

CONCLUSIONS

Thus, for the first time, it has been possible to reveal and track these amylase-dependent structural regulations of insulin secretion and glucose metabolism, in the main based on studies in the EPI pig model and bariatric surgery studies.

In summary, it is suggested that special type of bariatric surgery (gastric bypass) is one of the most efficient treatments which protects beta cells from exhaustion following (pre) -diabetic status. It’s mode of action is based on the elimination of the incretin-dependent vicious cycle in obese patients. Food stimulates the synthesis of insulin and amylase in parallel. Amylase synthesis is extraordinarily stimulated by insulin, which is known as the halo phenomenon. In turn, amylase, through its ability to inhibit glucose absorption,

stimulates the conversion of glucose to glucagon and directly downregulates insulin release,[12] thus limiting hyperglycaemia and hyperinsulinemia to a certain degree.

Data from studies on EPI and STZ-induced diabetes porcine models prove the concept of the importance of amylase from the pancreatic acini, as well as peripheral (gut and blood) amylase on the regulation of insulin secretion.

However, in further studies pancreatic proteinase alone and together with amylase should be tested to finally evaluate role of pancreatic enzymes on glucose homeostasis, insulin secretion and protection of beta-cells and objectify the key role of amylase (duodenal exclusion) in the context of diabetes improvement following bariatric surgery.

Contributorship statement

SGP conceived and wrote the review; CS and KP wrote the review and prepared the figures

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Ethical approval Not applicable.

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Figure Legends

Figure 1. Glycogen granules in enterocytes from proximal jejunum of healthy pigs treated with amylase for 10 days. Amylase diluted in saline was iv-infused before and after the morning and evening meals (25 mg x 2 x 2, Amano), while intraduodenal administration of amylase was given together with the morning and evening meals respectively (4500 mg x 2) Data are presented as Median ± IQR. A p value of < 0.05 was considered significant. (Pierzynowska & Pierzynowski – data not yet published).

Figure 2. A schematic view of AIA- and incretin-dependent pathways involved in the regulation of glucose metabolism before (A) and after (B) metabolic bypass surgery. Incretin-dependent, quick stimulatory pathways (black) and AIA – dependent, structural regulatory pathways of insulin secretion that regularise glucose homeostasis (orange and green).

Figure 3. Main types of bariatric surgery from the left to the right: Sleeve gastrectomy, Roux-en-Y gastric bypass, One-anastomosis gastric bypass (© Dr Levent Efe, courtesy of IFSO).

Figure 4. Forms of biliopancreatic diversions from the left to the right: Biliopancreatic diversion, Biliopancreatic diversion with duodenal switch (© Dr Levent Efe, courtesy of IFSO).

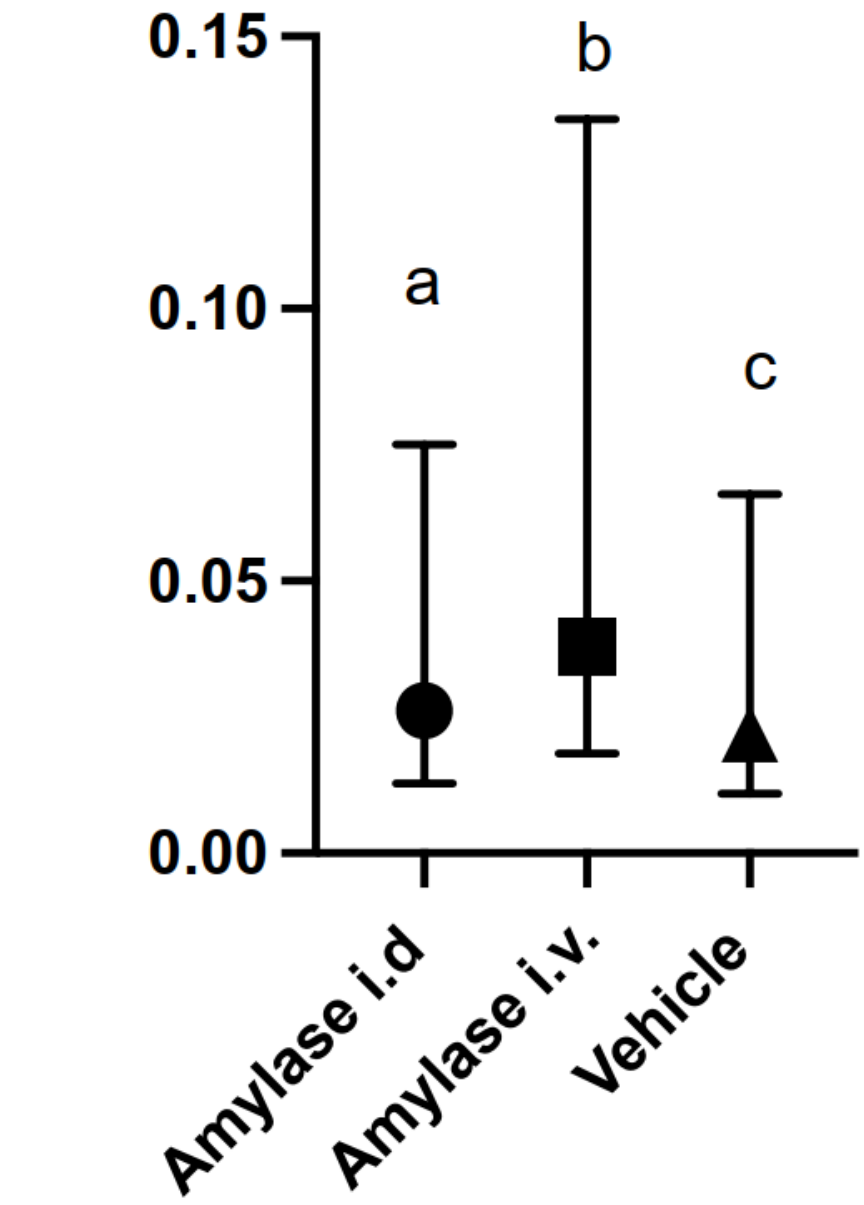
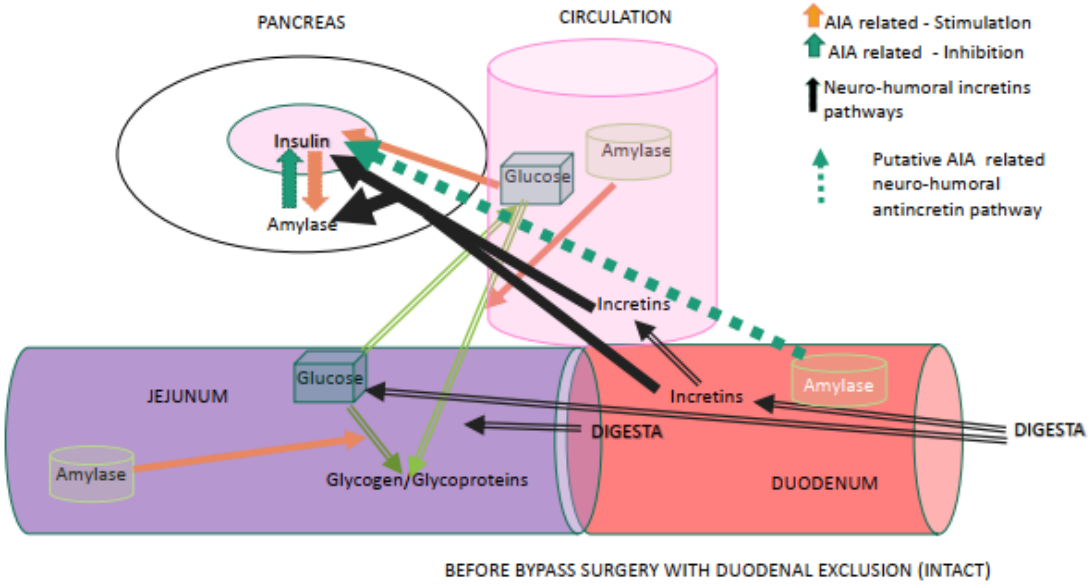

Area of glycogen granules, μm2
0.15
0.10
0.05
0.00
a
b
c
Amylase i.d
Amylase i.v.
Vehicle

Fig.1

A


PANCREAS
CIRCULATION
AIA related - Stimulatlon
AIA related - Inhibition
Neuro-humoral incretins pathways
Putative AIA related neuro-humoral antincretin pathway
Insulin
Amylase
Glucose
Amylase
Incretins
JEJUNUM
Glucose
Incretins
Amylase
DIGESTA
DIGESTA
Amylase
Glycogen/Glycoproteins
DUODENUM
BEFORE BYPASS SURGERY WITH DUODENAL EXCLUSION (INTACT)

B

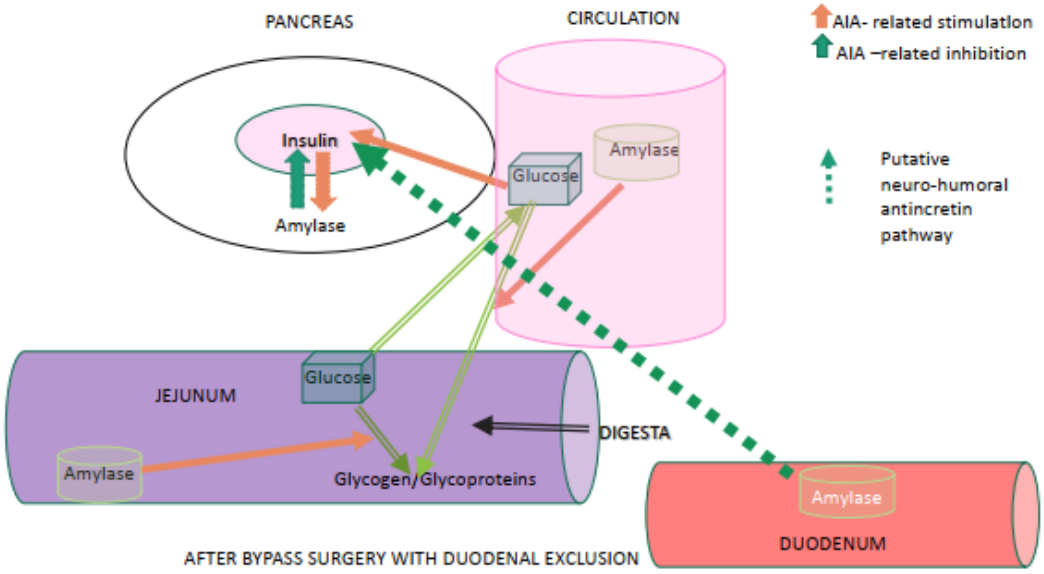

PANCREAS
CIRCULATION
AIA- related stimulatlon
AIA –related inhibition
Putative neuro-humoral antincretin pathway
Insulin
Amylase
Glucose
Amylase
JEJUNUM
Glucose
DIGESTA
Amylase
Glycogen/Glycoproteins
Amylase
DUODENUM
AFTER BYPASS SURGERY WITH DUODENAL EXCLUSION

Fig. 2

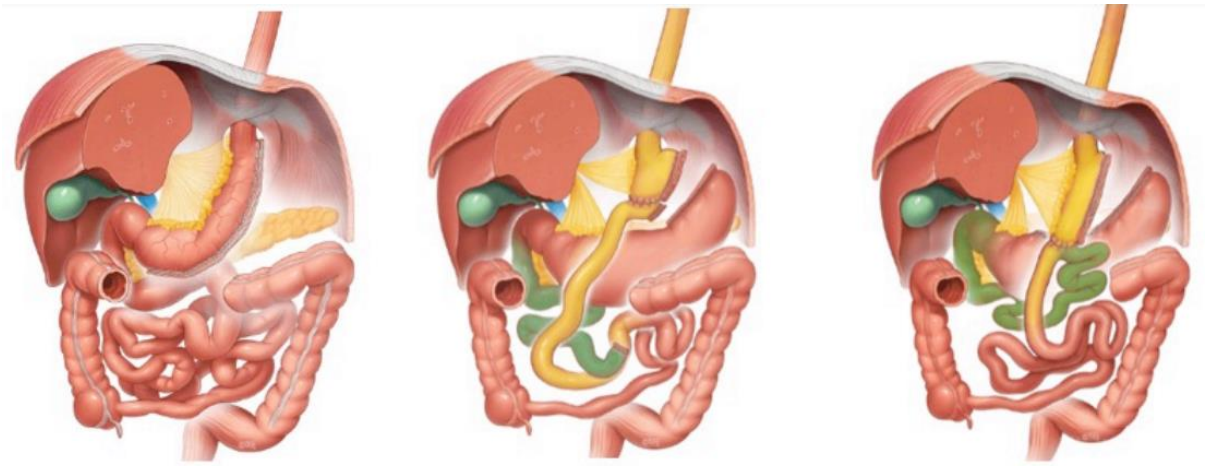


Fig. 3

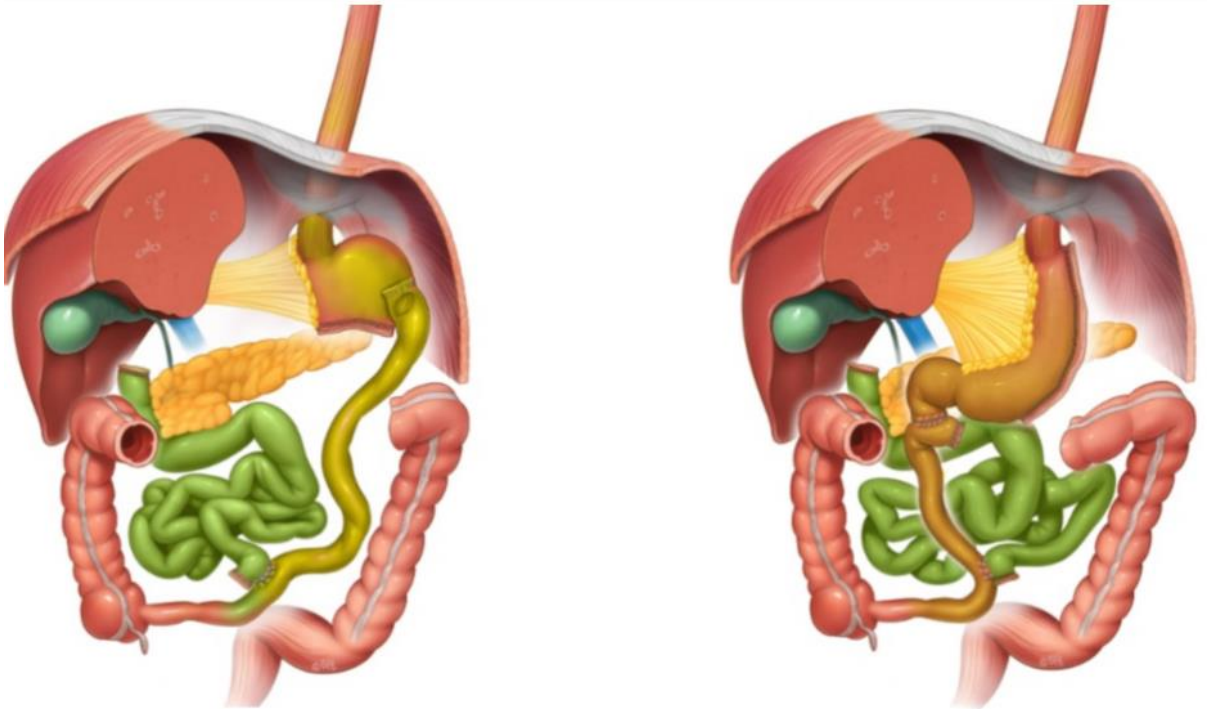


Fig.4