Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: In the review "A hypothesis that Alpha-amylase Evokes Regulatory Mechanisms Originating in the Pancreas, Gut and Circulation, which Govern Glucose/Insulin Homeostasis ", the authors suggest that bariatric BPD/BPD-DS surgery highlights alpha-amylase-induced, anti-incretin-like regulation of glucose metabolism, which protects the pancreatic beta cells from exhaustion and subsequent failure.The acini-islet-acinar (AIA) axis assumes that insulin intra-pancreatically stimulates alpha-amylase synthesis and alpha-amylase reciprocally inhibits insulin production, thus making alpha-amylase a candidate for being an anti-incretin. This review involves an intersting area whih may be contribute to develop new treatment strategy in the future both on diabetes and obesity based on the new mechanism.

Thank you for the highly professional evaluation of our manuscript. We hope that our responses and the changes we have introduced into the paper will satisfy you and you will find the edited manuscript acceptable for publication. Please find below our responses to your questions.

1, There are many types of bariatric suegery and forms of biliopancreatic diversion, as shown in Fig 2 and Fig 3. So, please discribe the different clinical outcmes in treating diabetes and obesity.

Paragraph added to the manuscript text
With regards to type II diabetes resolution, the following results were published: greatest diabetes remission was observed for patients undergoing biliopancreatic diversion/duodenal switch (95.1% resolved), followed by gastric bypass (80.3%), gastroplasty (79.7%), and then laparoscopic adjustable gastric banding (56.7%) The same pattern was observed even for an excessive weight loss and total body weight loss in the long term perspective (Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009 Mar;122(3):248-256.e5. doi: 10.1016/j.amjmed.2008.09.041. PMID: 19272486). It is worth noticing that Roux-and-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) have very similar outcomes both in short-term excessive weight loss and long-term total weight loss, as well as in type II diabetes resolution and both procedures are superior when compared to the adjustable gastric banding. (Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014 Aug 8;2014(8):CD003641. doi: 10.1002/14651858.CD003641.pub4. PMID: 25105982; PMCID: PMC9028049. Kang JH, Le QA. Effectiveness of bariatric surgical procedures: A systematic review and network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017 Nov;96(46):e8632. doi: 10.1097/MD.0000000000008632. PMID: 29145284; PMCID: PMC5704829. Sudan R, Jain-Spangler K. Tailoring Bariatric Surgery: Sleeve Gastrectomy, Roux-en-Y Gastric Bypass and Biliopancreatic Diversion with Duodenal Switch. J Laparoendosc Adv Surg Tech A. 2018 Aug;28(8):956-961. doi: 10.1089/lap.2018.0397. Epub 2018 Jul 30. PMID: 30059264.)

It should be also taken into consideration that biliopancreatic diversion surgery which was described by Scopinaro (Scopinaro N. Why the operation I prefer is biliopancreatic diversion (BPD). Obes Surg 1991; 1: 307–309) is a historical type of bariatric surgery and it is not recommended to use anymore, while its modification (the biliopancreatic diversion with duodenal switch (BPD-DS) introduced by Hess and Marceau (Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. Obes Surg 1998; 8: 267–282.Marceau P, Hould FS, Simard S et al. Biliopancreatic diversion with duodenal switch. World J Surg 1998; 22: 947–954.) is currently being used. However, despite better outcomes in terms of obesity and obesity-related comorbidities, BPD-DS counts only for ca 2% of bariatric surgeries performed worldwide (Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obes Surg 2013; 23: 427–436.) due to increased risk of complications and development of malnutrition.

2, Is there any difference regarding the distribution of incretins in different part of intestine (duodenum, jejunum, ileum)? Is it related with the different outcomes of the different types of surgery?

The incretins, as well as other gut hormones, are secreted by the enteroendocrine cells (EECs) **Sjölund K**, **Sandén G**, **Håkanson R**, **Sundler F**. **1983**. Endocrine cells in human intestine: an immunocytochemical study. *Gastroenterology* 85:1120–30). It is known that some hormones are produced along the whole length of the gut, while others are produced preponderantly in a particular location. This is the case with incretin, as the majority of GLP-1-producing L cells are located in the distal gut, whereas GIP is synthesised within K cells predominantly localised to the duodenum. There is also a small population of EECs along the gut which produces both hormones (Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. Diabetologia. 2023 Mar 28. doi: 10.1007/s00125-023-05906-7. PMID: 36976349.) One should also consider other hormones secreted along gastrointestinal tract and their possible interactions with GIP and GLP-1 during normal meals containing protein, fat and complex carbohydrates (Rehfeld JF. The Origin and Understanding of the Incretin Concept. Front Endocrinol (Lausanne). 2018 Jul 16;9:387. doi: 10.3389/fendo.2018.00387. PMID: 30061863; PMCID: PMC6054964.).

The possible effects of various types of bariatric surgery on incretin secretion remain under investigated and the messages appearing in the scientific literature are extremely controversial. For example, recently it was shown that β-cell sensitivity to *exogenous* GLP-1 or GIP is diminished after gastric bypass but not after sleeve gastrectomy. Authors consider the blunted sensitivity to GLP-1 as a possible way of β-cell adaptation to massive elevation in GLP-1 secretion following bariatric surgery to protect against hypoglycemia. (Salehi M, Peterson R, Tripathy D, Pezzica S, DeFronzo R, Gastaldelli A. Insulinotropic effect of endogenous incretins is greater after gastric bypass than sleeve gastrectomy despite diminished beta-cell sensitivity to plasma incretins. medRxiv [Preprint]. 2023 Mar 29:2023.03.28.23287755. doi: 10.1101/2023.03.28.23287755. PMID: 37034666; PMCID: PMC10081422.)

3, what is the molecular mechanism for halo phenomenon? And what is the possible molecular mechanisn for alpha-amylase regulating insulin release?

The first studies suggesting the regulation of amylase synthesis on the transcription level by insulin were published in 1972 (Söling HD, Unger KO. The role of insulin in the regulation of -amylase synthesis in the rat pancreas. Eur J Clin Invest. 1972 Jun;2(4):199-212. doi: 10.1111/j.1365-2362.1972.tb00645.x. PMID: 5053831). In two decades, the Insulin-responsive Element in the Pancreatic Enhancer of the Amylase Gen was discovered in and thus the mechanism of transduction of the insulin signal from the cell-surface was clarified (Johnson TM, Rosenberg MP, Meisler MH. An insulin-responsive element in the pancreatic enhancer of the amylase gene. J Biol Chem. 1993 Jan 5;268(1):464-8. PMID: 7678001.)
We have provided a short summary of this finding below:
The amylase regulatory region demonstrates two biological activities: pancreas-specific enhancer activity (associated with PTFl binding) and response to diabetes and insulin in transgenic mice. The amylase gene contains an extended spacer in the PTFl consensus that is several nucleotides longer than that of pancreatic genes that are not regulated by insulin. It is interesting that the PTFI protein can accommodate such a variety of binding sites. This indicates that the amylase spacer has acquired a unique function in mediating the amylase-specific response to insulin. Mutation of the spacer region of the PTF1-binding site had profound effect on regulation, resulting in a high level of residual activity in diabetic mice. The location of the IRE within the PTF1-binding site is consistent with competitive binding of the positive regulator, PTF1, and the putative negative factor, the IRE-binding protein. Competitive binding is the most common mechanism of negative regulation in prokaryotes. Insulin could regulate the competition via post-translational modification of PTFl or the IRE-binding protein, perhaps through the protein phosphorylation cascade that is initiated by insulin binding to the insulin receptor.Since PTFl is believed to regulate many pancreatic genesthat are not repressed in diabetic animals, the IRE-binding protein is a more logical target for specific regulation of amylase. One possible role for insulin would be to maintain the IRE-binding protein in an inactive conformation in normal pancreas, leading to occupation of the amylase regulatory region by PTF1. In diabetic animals with low circulating insulin, activation of the negative regulatory protein would result in displacement of PTFl and loss of amylase expression.
However, no research is currently being performed and this extremely important question remains unclear.

As for possible molecular mechanisms of amylase regulation of insulin secretion and release, we are trying to investigate them in our lab. Some findings related to the potential mechanisms, as an ability of amylase regulate insulin release, cellular glucose intake and its possible effect on expression of glucose transporters GLUT1 and GLUT2 have been already published (Pierzynowska et al., 2020, Pierzynowska et al., 2022)

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The dependency of pancreatic enzyme synthesis on insulin release has been fully studied. In recent years, the influence of pancreatin on

insulin secretion has also been paid more and more attention . Many studies suggest that alpha-amylase can not only digest starch, but also affect insulin secretion through hormone-like action. This has been further confirmed in the study on bariatric surgery, such as biliary-pancreatic bypass, biliary-pancreatic bypass with duodenal bypass, can effectively alleviate type 2 diabetes. Alpha-amylase can reduce blood sugar concentration by inhibiting the absorption of glucose and promoting the synthesis of glycogen, which inhibits the release of insulin. In addition, alpha-amylase can also directly effect pancreatic islets to inhibit insulin secretion, thereby providing protection for pancreatic islet cells. Putting forward the hypothesis that alpha-amylase evokes regulatory mechanisms originating in the pancreas, gut and circulation, which govern glucose/insulin homeostasis. The topic is novel and has great guiding significance for clinical work.

Thank you for the positive professional evaluation of our manuscript.