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Commentary

Does PYY mediate resolution of diabetes following bariatric surgery?

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Bariatric surgeries are far superior to other intensive medical therapies for weight loss and diabetic control [1]. Remarkably, improvements in diabetic control occur prior to substantial weight loss, suggesting that profound alterations in gut physiology have important roles in metabolic adaptations following bariatric surgery. Of the gut factors, the lower gut hormones Peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are often increased in the circulation following bariatric surgery [2,3]. Though enhanced GLP-1 secretion partly mediates the glycemic improvements following Roux-en Y gastric bypass surgery in humans [4], much less is known of the role of PYY in the metabolic benefits of bariatric surgery. Peripheral blockade of both GLP-1 and PYY increased food intake in RYGB subjects [5]. However, an important question is whether PYY is essential for the resolution of diabetes in bariatric subjects.

In this article of *EBioMedicine*, Guida et al. [6], utilize a combination of blood samples from bariatric patients, *ex vivo* pancreatic islet culture, and animal models of bariatric surgery, to determine whether PYY plays a role in resolving diabetes following bariatric surgery. The authors initially confirm that the reduction in circulating PYY concentrations in obese are restored to normal levels in bariatric subjects. They next show that serum from bariatric patients increased insulin content in pancreatic islets and, importantly that immunoneutralization of PYY, but not GLP-1 receptor blockade, attenuated glucose-induced insulin secretion from human islets. Further, both human and mouse islets show a delayed increase in PYY secretion in response to propionate, but not other volatile fatty acids, and with a bile acid receptor agonist stimulating PYY release from mouse but not human islets. A novel finding is that circulating concentrations of the cytokine IL-22 are increased in bariatric patients, and that IL-22 stimulates PYY secretion from both human islets and colon cultures.

The role of PYY in post-bariatric energy homeostasis has traditionally focused on the lower gut and central neuronal targets. The current paper [6], together with others [7], shifts the focus from the intestine to pancreas, with pancreatic PYY likely playing a key role in restoring insulin secretion post-bariatric surgery. However, to define whether pancreatic PYY is physiologically important for resolving diabetes in bariatric surgery, then similar to criteria needed for a physiological satiety signal [8], it is important to demonstrate at a minimum that: *i*) exogenous PYY-isoforms at doses that mimic local pancreatic concentrations stimulates insulin secretion, improves glycemic control and peripheral insulin resistance, and *ii*) PYY immune and receptor blockade, and targeted deletion of PYY in islets, attenuates such improvements *in vivo*, in bariatric subjects or relevant animal models. Though administration of the PYY(3–36) isoform improves glycemic control and enhances insulin-induced disposal of glucose in peripheral tissues of mice [9], it's unclear whether such effects occur at physiological doses and independent of weight loss. A key finding in the current study is that PYY sequestration with an antibody attenuates insulin secretion from islets [6]; however, it remains to be determined whether immunoneutralization of circulating PYY decreases insulin secretion, worsens glycemic control and exacerbates peripheral insulin resistance post-bariatric surgery in humans or animal models. Though the expression of PYY Y2 receptor is low in the pancreas [7], yet, it is well known that PYY inhibits pancreatic exocrine secretion in humans and rodents [10,11] partly through a through a Y2 dependent mechanism in rats [11]. It is unknown whether endogenous PYY isoforms act through similar mechanism to modulate endocrine pancreatic secretions in bariatric subjects.

Among the gut microbial products, the short chain fatty acids stimulate PYY secretion from the gut in humans [12]. The authors extend these findings and show that of these fatty acids, only propionate stimulates PYY secretion from the islets, which would make sense given that majority of butyrate is metabolized by the gut and some propionate may very likely reach pancreatic circulation. Apart from fatty acids, the cytokine IL-22 has been reported to stimulate PYY secretion, with Y2 receptor blockade attenuating the hypophagic effects of IL-22 in mice [13]. Guida et al. [6] now show that IL-22 secretion is robustly upregulated in bariatric subjects and that it also stimulates pancreatic PYY. The stimulatory effects of IL-22 occur at ~6000-fold higher concentrations than circulating concentrations, and hence, whether IL-22 is a PYY-secretagogue at physiological concentrations remains to be studied.

In summary, the current study contributes significantly to our understanding of the role of pancreatic PYY in enhancing insulin secretion in bariatric surgery. Future studies should define whether PYY secreted from the intestine and islets is necessary and sufficient to improve diabetic control following bariatric surgery. If PYY does indeed prove to be a key player in resolving diabetes in bariatric subjects, then it could lead

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to the development of novel PYY-based therapeutics for treating diabetes.

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Conflicts of interest

There are no conflicts of interest to disclose.

Author contributions

P. K. Chelikani wrote the article.

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