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Unraveling the role of gut hormone PYY in diabetes remission and pancreatic islet function following Roux-En-Y gastric bypass

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Roux-En-Y gastric bypass (RYGB) results in long-lasting remission from type-2 diabetes (T2D) in most cases. Improvements in glucose homeostasis occur within days of surgery, but the mechanisms involved remain unclear. Although pancreatic islets play a fundamental role in glucose homeostasis, the impact of RYGB on islet architecture and secretory properties has not been studied thoroughly. T2D is a bihormonal disease characterized by both insufficient insulin secretion and impairment in glucagon regulation. RYGB can correct both hormonal secretory defects remain unexplored. Using the Goto-Kakizaki (GK) rat model of T2D, we have explored whether RYGB affects islet structure and glucose-stimulated insulin secretion (GSIS) and glucagon release. RYGB restored distorted islets from diabetic rats to spheroidal shape as in healthy animals. Compared to the sham-operated animals, RYGB normalized glucose-dependent glucagon and insulin secretion. Thus, islets from RYGB rats exhibited markedly enhanced insulin secretion at 20 mM glucose and complete restoration of glucose-induced suppression of glucagon release. Culture of isolated islets with serum from RYGB animals resulted in improved insulin and glucagon secretion, in support of a humoral factor which remains conserved in serum. These effects were reversed following immuno-neutralization of the gut hormone peptide tyrosine (PYY) but persisted in the presence of a glucagon-like peptide-1 (GLP-1) receptor antagonist. Chronic (60-72 h) treatment of islets with synthetic PYY enhanced GSIS in a NPY1-receptor-dependent manner. PYY application also restored GSIS and normalized impaired glucose-induced glucagon release in islets from severely diabetic GK rats and human donors with T2D. These data provide a novel mechanistic insight on the effect of RYGB in diabetes and highlight that the mechanism behind the improvement of islet function is dependent on PYY and not GLP-1. These findings imply that a pharmacological agent enhancing PYY release or its action could provide an effective and non-surgical therapy for T2D.

Biography

Reshma Ramracheya is investigating the regulation and failure of the insulin-secreting beta-cell and glucagon-secreting alpha-cell in normal health and diabetes respectively. As an islet Physiologist, she intrigued by how pancreatic islet cells, despite being biochemically similar, are able to respond to nutrients and drugs differently.

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