Reducing Hyperglycemia without Over-Stimulation of β-cells: Prevention rather than Cure Type 2 Diabetes

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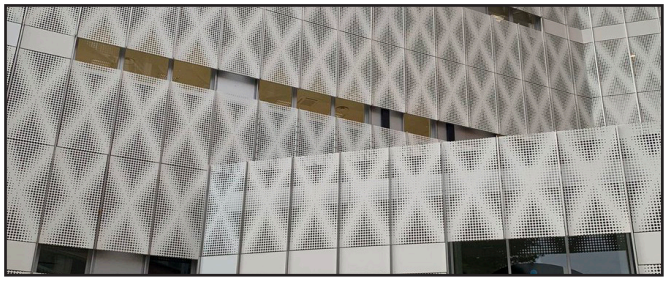
Abstract:

Alimentary overload has been described as a key factor that induces persistent hyperglycemia. Similarly, circulating glucose is the main factor that induces insulin secretion. In the presence of sustained hyperglycemia, the pancreas is forced into a state of compensatory hyperinsulinemia to control glucose levels in the blood. The hyperinsulinism is maintained until a point at which further over-secretion is no longer possible due to impair of β-cell function. Thus, hyperinsulinism has been proposed as an independent predictive factor for the development of Type 2 Diabetes Mellitus (T2D). However, the molecular mechanisms underlying the progressive decline in β-cell mass and functions remain controversial. β-cells adjust their mass according to demand and rises in β-cells number have been observed only during situations of increased metabolic demand, such as pregnancy or obesity. In conditions of induced β-cell stress, these cells undergo a dedifferentiation process, losing the expression of crucial signature genes such as Nkx6.1, which is a key driver of insulin biosynthesis and glucose metabolism in mature cells. Metabolic surgery achieves a consistent long-term control of glycemia in T2D. However, the mechanisms of action mediating the remission of diabetes after surgery remain still elusive. Therefore, there are doubts that whether metabolic surgery improves only hyperglycemia in T2D or whether it modifies the disease's progression. For this reason, we hypothesized that surgery is able reducing glucotoxicity (by intestinal mechanisms) without over-stimulation of β-cells. For this purpose, we used a Goto-Kakizaki (GK) rat model that spontaneously develops T2D during life due to a progressive loss in β-cell. We choose a duodenal jejunal exclusion bypass (DJB) as surgical technique and we performed the surgery at different weeks of life (12, 16 and 20 weeks of age), which correspond to early, intermediate and late stages of T2D progression. Sham operated GK rats served as controls. We found that DJB in GK rats resulted in a marked reduction in postprandial glucose excursion and decreased



plasma insulin levels compared to the sham operated rats in all stages.

Biography:

Lorea Zubiaga (MD -2006- PhD -2015- "Miguel Hernández" University, Spain) is a digestive surgeon trained in SECO-Spanish system (Spanish Society for obesity and metabolic diseases) who developed her scientific thesis on metabolic surgery for Type 2 Diabetes (T2D). She began her postdoc in Lille, on May 2017 in the European Genomic Institute for Diabetes in U-1190. The aim of her postdoc project is to unveil new hypothesizes on T2D treatment associated to the intestinal mechanism of absorption, specifically related with gluco-transporters activity in the gut. To address this idea, she is performing 3 specific projects: (1) to asses the importance of the gut reprogramming after surgery to prevent the pancreatic damage in T2D (2) to demonstrate the physiological and pathophysiological relevance of the gluco-transporters in different animal models regarding the effect of bariatric surgery (3) to demonstrate the physiological and pathophysiological relevance of these findings to evaluate pharmacological molecules which could be able to imitate the surgery effects.

Publication of speakers:

1. 1.Erion, K. & Corkey, B.E. beta-Cell Failure or beta-Cell Abuse? Frontiers in endocrinology 9, 532 (2018).

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