Enhancement of the incretin pathway in response to bariatric surgery is important for restoration of beta cell function

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To the Editor: In a recent paper, Salinari and colleagues reported normalisation of glucose metabolism associated with improved pancreatic beta cell sensitivity to nutrients derived from a mixed meal, 1 week after malabsorptive bariatric surgery (bilio-pancreatic diversion), in morbidly obese patients with type 2 diabetes [1]. This was observed before the patients had lost a significant amount of weight. On the basis of timed serum insulin, C-peptide, NEFA and plasma glucose measurements, they calculated the effects of NEFA and glucose on the insulin secretion rate (ISR). The plasma glucose level was decreased to within the normal range after the surgery, but the serum NEFA level was unchanged. Using a mathematical model, the authors concluded that the improved ISR after bariatric surgery was due to the restoration of normal NEFA oxidation in the beta cell, which enhanced ISR despite the significant decrease in the plasma glucose level. This study is of great interest to us because we consider the malonyl-CoA pathway and the resultant NEFA augmentation of insulin exocytosis to be vital for glucose-stimulated insulin secretion (GSIS), especially for the replenishment of the readily releasable pool of insulin granules during second-phase secretion [2, 3]. Prior to the visual demonstration and molecular elucidation of intracellular granule trafficking, this process was known conceptually as ‘potentiation’ [4], ‘augmentation’ [5] or ‘amplification’ [6].

The paper makes no mention of factors other than glucose and NEFA that are also involved in meal-induced insulin secretion, such as incretins [7], parasympathetic input and amino acids, to name but a few. Of note, an increase in the serum level of the incretin glucagon-like peptide 1 (GLP-1) is documented 1 week after bilio-pancreatic diversion, and this is thought to be responsible for long-term effective weight reduction through satiety [7]. GLP-1 acts on the beta cells to increase the level of cAMP, leading to replenishment of the readily releasable pool of insulin granules during GSIS. This is an ATP-sensitive K^+ channel-independent insulinotropic [8]. Interestingly, NEFA augments GSIS also in the ATP-sensitive K^+ channel-independent manner [5].

Salinari et al. use a mathematical model of glucose–NEFA comodulation to estimate the ISR [1]. Therefore, given the lowered basal glucose, lowered glucose excursion after the meal, unchanged NEFA and increased ISR, they will naturally

conclude that the effect of NEFA has been enhanced/amplified. However, in our opinion, the increased beta cell potentiation [8], achieved through the GLP-1–cAMP pathway after surgery, is expected in their patients, in line with previous findings in patients who underwent the same operation, at the same postoperative time-point [7]. A different conclusion might have been reached if the incretin effect had been taken into account. The inclusion of the positive effect of the incretin pathway would have at least reduced, and at most cancelled out, the calculated effect of restored β-oxidation on ISR after surgery [1].

In conclusion, by not considering factors other than glucose and NEFA in meal-induced insulin secretion, Salinari et al. [1] may have overestimated the effect of restored NEFA oxidation on ISR after bariatric surgery. The data itself is very important and has considerably expanded our understanding of the physiology of bariatric surgery. However, a more comprehensive analysis of the ISR, one that at least takes account of the incretin effect, would be desirable.

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

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