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In This Issue of *Diabetes*

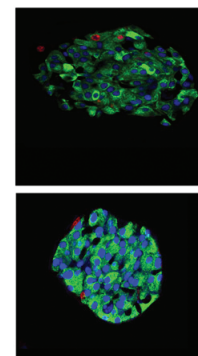
By Max Bingham, PhD

Sleeve Gastrectomy Improves Glycemia Independently of Weight Loss

Sleeve gastrectomy can lead to dramatic weight loss and the normalization of glucose levels in obese individuals. However, whether the weight loss or some other mechanism is responsible for normalizing glucose is not clear. According to Abu-Gazala et al. (p. 1079), it seems likely that improved glycemia is driven by increased hepatic insulin sensitivity but not weight loss. The authors report using the procedure to reduce stomach size in *db/db* mice or a sham surgery to generate a control group. They then tracked the development of the mice over the following days, looking at weight, glucose levels, and various other parameters. One week after surgery, they found that the mice that received the sleeve gastrectomy weighed less and had reduced glucose levels. The controls meanwhile did not lose weight and glucose levels remained at presurgery levels. At 1 month, the sleeve gastrectomy group had put on weight in comparison to before surgery, but glucose levels remained suppressed. The control group carried on putting weight on and glucose levels remained largely constant. Using a pair-feeding approach, they then found that although weight changes did not differ between the groups (as intended), the sleeve gastrectomy group had significantly lower glucose levels, suggesting that surgery, rather than weight loss, accounted for the changes in glucose. Follow-up experiments revealed that sleeve gastrectomy resulted in a significant improvement in muscle and, most notably, hepatic insulin sensitivity. Author Danny Ben-Zvi told *Diabetes*: “The dramatic difference in insulin sensitivity and loss of fatty liver was very surprising, considering the animals did not lose weight. We expected to see a similar improvement in islet functionality but that was not the case. It seems that the surgery somehow rewires liver metabolism to handle lipids and glucose better, and we are hoping to use this model to understand how it does that independently of weight loss.”

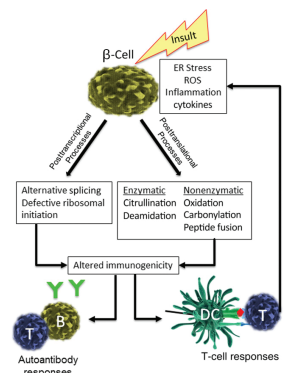
Neopeptides Key to Immune Recognition of β -Cells

Neopeptide generation might be a key link in the autoimmune destruction of β -cells in type 1 diabetes, according to James et al. (p. 1035). Using evidence accumulated in recent years, the authors detail a series of reasons why neopeptides may be central to the process and suggest that with the advent of sophisticated technologies such as single cell proteomics it is likely that novel neopeptides will be identified and that these will form the basis of targets for therapeutic manipulation. They initially describe a series of processes that might be involved in neopeptide generation. They go on to discuss a variety of ways that these neopeptides are then targeted by autoantibodies and T cells and briefly touch on other potential stressors such as viruses, bacteria, and other environmental factors. In short, they say that the formation of neopeptides might be a key step in activating immune cells, which then amplifies a more general antigenic environment toward β -cells and their destruction and eventually type 1 diabetes. Author Eddie A. James said: “Many past studies have identified and studied antigens that are present in β -cells ‘at rest’ and responses to these are certainly relevant, but the formation of neopeptides represents an important new frontier for research. The β -cell proteome is altered in many interesting ways through the effects of diverse processes that reflect both normal and abnormal β -cell physiology. Although the relative importance of phenomena such as citrullination, deamidation, oxidation, carbonylation, and transpeptidation remains to be elucidated, it is increasingly apparent that the such modifications are potentiated by stress and inflammation and can profoundly influence immune recognition. The next challenge will be to pursue a more detailed understanding of the pathways that lead to neopeptide formation and of the role that such responses play within the overall context of disease progression.”



Immunohistochemical staining of pancreata from sham-operated (top) and sleeve gastrectomy-operated (bottom) mice. Sleeve gastrectomy reduces β -cell proliferation back to levels seen in lean mice. Nuclear Ki67 staining marking proliferating cells shown with arrows.

Abu-Gazala et al. Sleeve gastrectomy improves glycemia independent of weight loss by restoring hepatic insulin sensitivity. *Diabetes* 2018;67:1079–1085



Mechanisms of neopeptide formation. The formation of neopeptides arises as a consequence of various types of insults that generate endoplasmic reticulum stress, reactive oxygen species, and/or inflammatory cytokines in the affected tissue. DC, dendritic cell.

James et al. Immune recognition of β -cells: neopeptides as key players in the loss of tolerance. *Diabetes* 2018;67:1035–1042

Glucose Homeostasis Benefits From Oxyntomodulin in Obesity and Diabetes

Oxyntomodulin, a peptide hormone that activates the GLP-1 and glucagon receptors, can improve glucose homeostasis in obese individuals with and without type 2 diabetes, according to Shankar et al. (p. 1105). Moreover, the authors suggest that the effect is likely driven by stimulation of insulin secretion and is independent of any weight loss that the hormone might induce in the longer term. According to the authors, there is scant information regarding the effects of oxyntomodulin on glucose homeostasis in humans. To address the gap, the authors used two randomized placebo-controlled crossover studies to examine the effects of a single administration of native oxyntomodulin on insulin secretion and glycemic excursions. Specifically, they used a procedure called a graded glucose infusion, which sequentially increases glucose infusion rates up to a predefined limit. Each trial focused on 12 individuals who were obese but without diabetes or obese but with type 2 diabetes. In the type 2 diabetes group, the effects of oxyntomodulin were also compared to liraglutide. They found that in both groups 3.0 pmol/kg/min of oxyntomodulin significantly increased insulin secretion rates and reduced glucose excursion in comparison to placebo (saline). In addition, in the trial with the patients with diabetes, the effects of oxyntomodulin were largely comparable to liraglutide, reportedly restoring β -cell responsiveness to levels found in nonobese subjects without diabetes. Author Sudha S. Shankar commented: “The results provide support for the development of more stable peptides with similar profiles as therapeutic options for obesity, type 2 diabetes, and related metabolic conditions. Notably, by quantifying the isolated insulinotropic effect of oxyntomodulin in man, these data enable articulation of the degree of oxyntomodulin-derived weight loss required for the dual effects together to lead to glucose lowering that is superior to that with GLP-1 receptor agonists alone. Results from ongoing clinical trials with long-acting analogs of oxyntomodulin and dual receptor co-agonists are anticipated to provide additional insight regarding the therapeutic potential of these peptides.”

Shankar et al. Native oxyntomodulin has significant glucoregulatory effects independent of weight loss in obese humans with and without type 2 diabetes. *Diabetes* 2018;67:1105–1112

Progress in Pharmacology of Glucose-Responsive Insulins

The pharmacodynamics of a glucose-responsive insulin (GRI) analog are reported by Moore et al. (p. 1173), who suggest that the compound largely works as intended—that is, under low glycemic conditions it had very little potency and was largely excreted, but during hyperglycemia it was at least as potent as regular insulin, stimulating glucose tissue uptake. In short, it may be a step toward insulin with a considerably reduced risk of hypoglycemia. They focused on eight dogs and used a clamp approach to trace the effects and fate of regular insulin and GRI under low and high glycemic conditions. Initially, the dogs received an intravenous infusion of [$^3\text{-H}$]glucose followed by baseline sampling for 30 minutes. After that, there were two study periods (150 min each) administered randomly where glucose was clamped at either 80 mg/dL or 240 mg/dL to represent low and high glycemic conditions. Somatostatin was used to suppress endogenous insulin production while the dogs received regular human insulin or GRI. Reportedly, during the low and high glycemic conditions, whole-body insulin clearance did not differ when human insulin was used but was significantly higher under low glycemic conditions when GRI was administered. Net hepatic glucose output was similar under the low glycemic conditions for both insulin types, whereas under high glycemic conditions GRI was more effective at stimulating glucose uptake in hepatic and nonhepatic tissues than the regular insulin. As a result, the authors conclude that the GRI has potential to improve glycemic control while also reducing the risk of hypoglycemia under low glucose conditions simply because it is not available. Although evidently suggesting that the approach could have potential as a therapy, the authors caution that there is considerable work to be completed, mainly to establish the dosing requirements, as it seems probable that this particular GRI would require large impractical doses if used clinically. They do however allude to further developments with the chemistry that might overcome these issues.

Moore et al. Superior glycemic control with a glucose-responsive insulin analog: hepatic and nonhepatic impacts. *Diabetes* 2018;67:1173–1181

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