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OBESITY

Beneficial effects of bariatric surgery are mediated by FXR signalling

The crucial contribution of nuclear receptor FXR, bile acids and the gut microbiota to the beneficial effects of vertical sleeve gastrectomy (VSG) have been demonstrated in a study published in *Nature*. The study by Randy Seeley and colleagues provides further evidence that changes in gut physiology are what drives the weight loss and metabolic improvements seen after bariatric surgery.

"The role that gut hormones such as PYY and GLP-1 play in causing weight loss after bariatric surgery transformed the thinking from the dogma that these operations work through restriction and malabsorption to the idea that they work by enhancing how the gut talks to the brain. We are now discovering that traditional gut hormones do not explain the entire picture…" explains Carel le Roux, an independent expert from University College Dublin.

Previous work identified a substantial increase in enterohepatic circulation of total bile acids after VSG and Roux-en-Y gastric bypass, and that bile acids bind to FXR and contribute to the regulation of metabolic processes (in addition to their role in lipid digestion and absorption). "In light of this role, we hypothesized that FXR-signalling links altered bile acid homeostasis to postoperative changes in metabolism and gut microbial communities, thereby contributing to the maintenance of weight loss and improvements in glucose control observed following VSG," the authors explain.

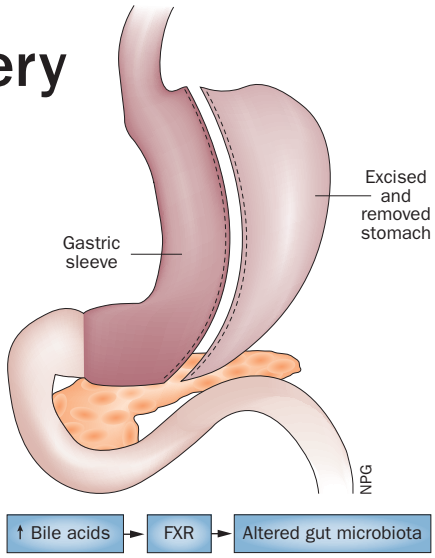
The first step was to identify key pathways in the terminal ileum that VSG altered. RNA was collected from the terminal ileum of VSG mice and sham-operated, pair-fed controls; mRNA was sequenced and an unbiased pathway analysis of the genes that were differentially regulated (fold change ≥1.5) performed.

Among the differentially regulated genes in the 'nuclear receptors in lipid metabolism and toxicity' pathway—one of the top five pathways enriched in VSG mice—was *Nr1h4*, which encodes FXR. A role for gut microbiota was indicated by differential regulation of genes in another three of the top five pathways: 'glutathione-mediated detoxification', 'metapathway biotransformation' and 'type II interferon signalling'.

Next, FXR knockout (KO) mice were generated. KO mice and their wild-type (WT) littermates were given a high fat diet for 10 weeks before undergoing VSG or sham surgery. WT-VSG and KO-VSG mice initially lost weight after surgery, but only the WT-VSG mice maintained the weight loss over the course of the experiment. At 11 weeks post-surgery, WT-VSG mice had 50% of the body fat of WT-sham mice, but KO-VSG mice and KO-sham mice had equivalent body fat.

The researchers then investigated why KO-VSG mice regained their body weight and found that FXR changes feeding behaviour after VSG. In the first week after surgery, KO-VSG and WT-VSG mice consumed fewer calories than their sham-operated counterparts. WT-VSG mice ate significantly less food than WT-sham mice for 3 weeks after surgery and didn't go on to compensate for this deficit; their cumulative food intake was 15% less than that of WT-sham mice 8 weeks after surgery. By contrast, KO-VSG mice compensated for their reduced intake—from week 4 after surgery they consumed more than KO-sham mice and at week 8 their cumulative food intake was equivalent. Compared with WT-sham mice, WT-VSG mice had a reduced preference for fat; the authors note that KO-sham mice also had a reduced preference for fat, but this was not reduced further in KO-VSG mice.

FXR was also found to contribute to improved glucose tolerance after VSG. The fasting blood glucose level was reduced by 20% in WT-VSG mice, but was increased by 24% in KO-VSG mice. After intraperitoneal injection of dextrose into fasted mice, glucose tolerance improved in WT-VSG mice, but not in KO-VSG mice.



Finally, the effect of FXR deficiency plus VSG on the gut microbiota was studied. Mice were sacrificed 14 weeks after surgery and the caecal microbiota composition analysed. "Importantly, we observed changes in key bacterial groups that have been previously linked to the risk of type 2 diabetes, and these changes were related to FXR and bile acids," explains Karen Ryan, lead author.

So, how might these findings impact clinical practice? "Instead of trying to achieve optimal 'anatomical results', such as a tight VSG, surgeons can focus on how to use the changes in anatomy to optimize the 'physiological results' (i.e. more postprandial bile acid secretion)," says le Roux.

"We now need to identify the key FXR populations responsible and the FXR target genes that are critical to mediate these effects," says Seeley. "We hope this leads to new therapies that can mimic the effects of surgery but are less invasive and more scaleable to help more people."

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Original article Ryan, K. K. *et al.* FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature* doi:10.1038/nature13135

Further reading Miras, A. D. & le Roux, C. W. Mechanisms underlying weight loss after bariatric surgery. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 575–584 (2013)