

FGF15 Deletion Displays Metabolic Changes in Murine Model of Vertical Sleeve Gastrectomy

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Background

Obesity is a fast growing problem in the United States. Bariatric surgeries such as vertical sleeve gastrectomy (VSG) are the methods of choice in case of morbid and severe obesity. In addition to the weight reduction, the effects of bariatric surgeries go beyond what can be explained by the weight loss alone. Recently it has been shown that stimulation of nuclear factor farnesoid-X-receptor (FXR), by bile acids is crucial for the development of positive effects associated with VSG including weight loss, decreasing glucose resistance, and a reduction in non-alcoholic steatohepatitis (NASH). However, the mechanisms of known FXR modified genes have not yet been delineated. One such downstream FXR effector in the ileum is fibroblast growth factor 15 (FGF15) whose specific role in VSG is unknown.

Materials and Methods

Using our VSG murine model, we assessed the role FGF15 played in the VSG-FXR dependent pathway by comparing common metabolic variables in a wild type Sham mouse (WT Sham) (n=6), FGF15 deletion Sham mouse (FGF15 KO Sham) (n=5), wild type VSG mouse (WT VSG) (n=5), and a combined FGF15 knockout VSG mouse (FGF15 KO VSG) (n=7). The mice were fed a high fat diet for 8 weeks to induce obesity. Then, the surgeries were performed. The mice were sacrificed after 7 weeks. Some values measured included glucose/insulin ratios, weight, body fat, and fibroblast growth factor 21 (FGF21), a related hormone. The tests were performed using commercially available kits. FXR-related gene expression was assessed by PCR.

Results

The FGF15 KO mice that underwent VSG did not display the body weight rebound seen in the other mice groups. While WT VSG mice returned to their pre-surgery threshold (-1.30±1.04 g), FGF15 VSG mice plateaued at the lower weight (-4.51± 0.98 g). FGF15 KO VSG mice were more insulin resistant when compared to the other groups by the finding an increased glucose/insulin ratio (p<0.05). In addition, WT mice saw reduced FGF21 after VSG while FGF15 KO mice did not see this decrease. Bile acid metabolism is unchanged between WT VSG and FGF15 KO VSG.

Conclusion

VSG surgery on mice lacking an intact FGF15 pathway is effective in producing and sustaining weight loss. This result suggests that the FGF15 pathway should be a therapeutic target to maintain weight loss. However, the increase in insulin resistance and the FGF15/FGF21 dysregulation suggest the FGF15's role is more complicated than previously realized.

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