Roux-en-Y gastric bypass (RYGB) surgery, but not caloric restriction, increases reward-related genes within the VTA in mice fed a high-fat diet

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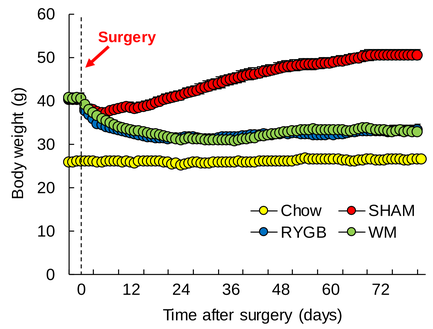
Abstract

Obesity is a strong risk factor for chronic diseases such as diabetes, cancers, and heart diseases. Roux-en-Y gastric bypass (RYGB), a type of bariatric surgery, is one of the most effective treatments for obesity and its comorbidities. After the surgery, patients lose a significant amount of weight and fat mass, mainly through decreased food intake; how this weight loss occurs is poorly understood. Studies show that these individuals experience a decrease in hunger and desire to eat, especially high-calorie and fatty food, indicating changes in dopamine "reward" processing. These changes may explain their reduced food consumption and successful maintenance of weight loss.

To test if RYGB surgery alters the mesolimbic dopamine pathway in the brain, we assessed genes related to reward in the ventral tegmental area (VTA) – a brain region where dopamine neurons are located – from diet-induced obese mice two and twelve weeks after either Sham or RYGB surgery. Sham obese mice displayed lower expression of genes involved in activating dopamine signaling compared to lean, chow-fed controls. These findings are consistent with the reward-deficiency hypothesis, which suggests that obese individuals have diminished dopamine signaling or "satisfaction" making them overeat palatable food in order to increase dopamine transmission. Remarkably, mice after RYGB increased the expression of these genes compared to sham mice, indicating restored dopamine signaling. This may explain lower fat intake in RYGB mice compared to sham mice because they are "satisfied". The lack of these changes in mice that lost the same amount of weight by caloric restriction suggests that these alterations are unique to RYGB surgery and illustrates why dieting may fail.

Collectively, our findings suggest that RYGB surgery, but not caloric restricted-weight loss, alters reward-related genes in the VTA that increase dopamine signaling. This may be one of the mechanisms by which RYGB leads to reduced fat intake and successful weight loss.

1. RYGB lowers body weight of diet-induced obese mice



2. RYGB lowers caloric intake that is restored by day 9

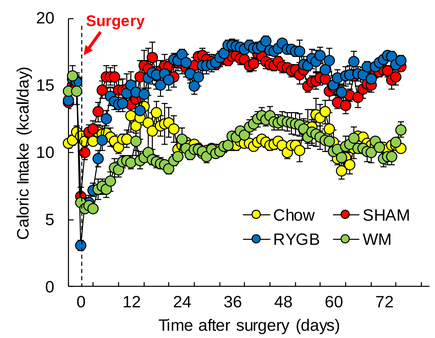
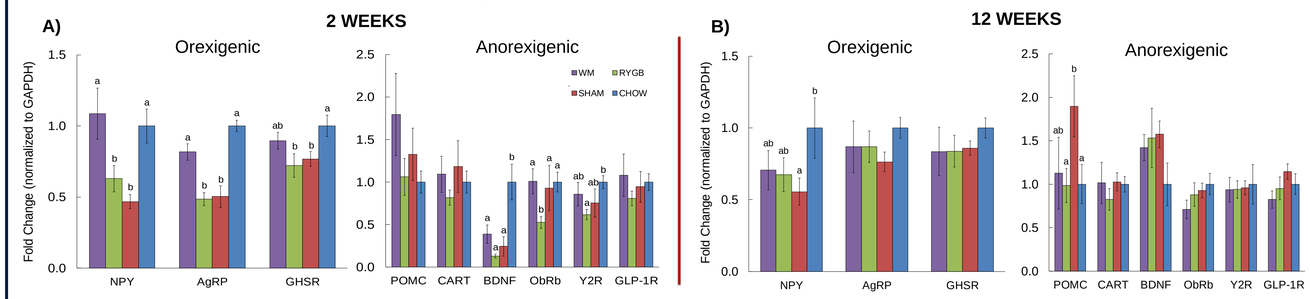


Fig. 1. Effect of RYGB on body weight. Mice were placed on a two-choice diet (chow and 60% HF) for 14 weeks after which they either had Sham or RYGB surgery, or caloric restriction (WM) that is 65% of total intake of RYGB mice to match their body weight. Chow-fed lean mice were added as an additional control group.

Fig. 2. Total daily caloric intake is shown for Sham, RYGB, WM, and Chow groups for 78 days post-surgery.

3. Effects of RYGB on orexigenic and anorexigenic genes in the mediobasal hypothalamus



4. Effect of RYGB on genes related to reward and appetite in the Ventral Tegmental Area (VTA)

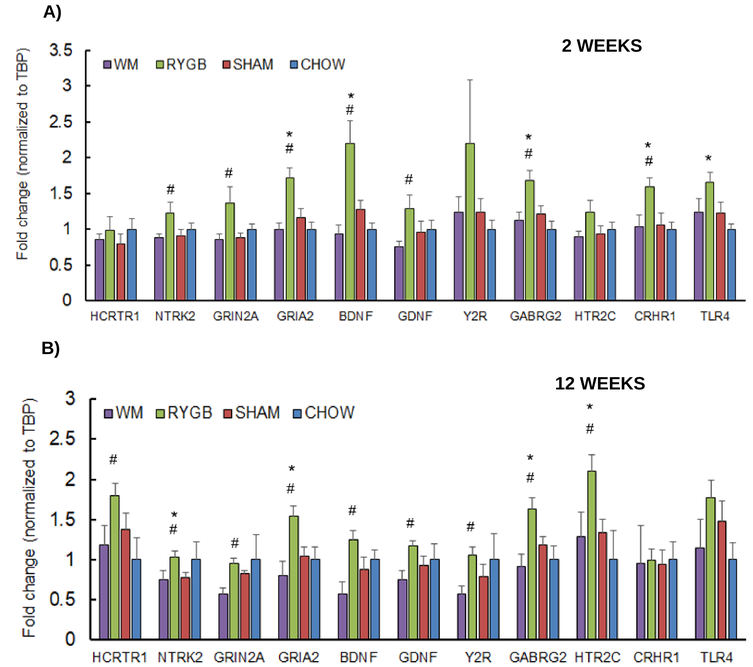
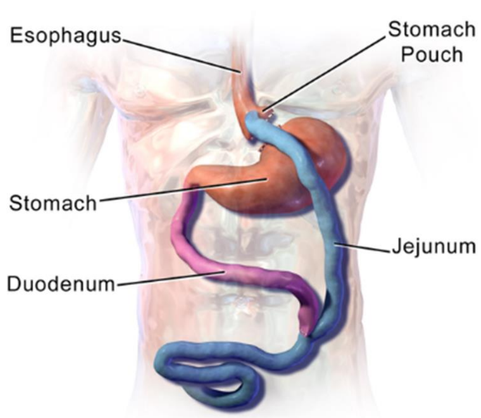


Fig. 3. Expression of oregixenic genes and anorexigenic genes in the mediobasal hypothalamus during **A)** acute "weight-loss" phase or **B)** chronic "weight-maintenance" phase. One cohort of mice was sacrificed at 2 weeks (Acute; Sham surgery (Sham), n=10; RYGB, n=13; no surgery, weight-matched controls (WM), n=8; lean chow-fed controls (Chow), n=6) and the other at 12 weeks (Chronic; Sham, n=10; RYGB, n=9; WM, n=8; Chow, n=4) post-surgically. mRNAs are first normalized to GAPDH and are expressed as fold change from the chow-fed lean control group. Bars that do not share the same letters are statistically significant from each other. Data are presented as Mean±SEM. p<0.05

Fig. 4. Genes related to reward and appetite in the ventral tegmental area (VTA). DIO mice are separated into **A)** 2 weeks and **B)** 12 weeks cohorts (post-surgery). 2 weeks: Sham, n=11; RYGB, n=13; WM, n=7. 12 weeks: Sham, n=10; RYGB, n=9; WM, n=6. These groups were given a choice of regular chow and high-fat diets throughout the experiment. Age-matched, chow-fed lean controls (Chow, n=5) were also included. At the end of either 2 or 12 weeks, mice were sacrificed after 6h fasting. Data are presented as Mean±SEM. *p<0.05 compared to Sham; # p<0.05 compared to WM

RYGB surgery



- ✓ RYGB surgery is widely considered as one of the most effective treatments for obesity and diabetes.
- ✓ RYGB surgery involves reduction of the stomach and attachment of the small pouch directly to the distal part of the small intestine, bypassing the resected stomach and proximal intestine.
- ✓ RYGB surgery is known to decrease food intake and change food preferences which may be a result of altered reward processing.

Conclusions

- ✓ Compared to sham surgery, RYGB surgery increased mRNA expression of reward-related genes in the VTA including Ntrk2, Gabrg2, Gria2
- ✓ Importantly, RYGB mice displayed upregulation of genes associated with increased reward signaling (GDNF, Grin2A, Gria2) compared to WM mice
- ✓ Unlike in calorie-restricted mice, the enhanced reward signaling (positive valence) may allow RYGB mice to feel "satisfied" in lowering and maintaining their body weight without overeating
- ✓ Collectively, these results suggest that RYGB surgery may enhance reward signaling in the brain which may in part explain successful long-term weight loss without overeating, especially fatty food

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