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Gut-brain crosstalk regulates craving for fatty food

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Abstract

Patients undergoing Roux-en-Y gastric bypass (RYGB) surgery elicit striking loss of body weight. Anatomical restructuring of the gastrointestinal (GI) tract, leading to reduced caloric intake and changes in food preference, are thought to be the primary drivers of weight loss in bariatric surgery patients. However, the mechanisms by which RYGB surgery causes a reduced preference for fatty foods remain elusive. In a recent report, Hankir *et al* described how RYGB surgery modulated lipid nutrient signals in the intestine of rats to blunt their craving for fatty food. The authors reported that RYGB surgery restored an endogenous fat-satiety signaling pathway, mediated *via* oleoylethanolamide (OEA), that was greatly blunted in obese animals. In RYGB rats, high fat diet (HFD) led to increased production of OEA that activated the intestinal peroxisome proliferation activator receptors-α (PPARα). In RYGB rats, activation of PPARα by OEA was accompanied by enhanced dopamine neurotransmission in the dorsal striatum and reduced preference for HFD. The authors showed that OEA-mediated signals to the midbrain were transmitted *via* the vagus nerve. Interfering with either the production of OEA in enterocytes, or blocking of vagal and striatal D1 receptors signals eliminated the decreased craving for fat in RYGB rats. These studies demonstrated that bariatric surgery led to alterations in the reward circuitry of the brain in RYGB rats and reduced their preference for HFD.

Key words: Roux-en-Y gastric bypass surgery; Dietary lipids; Dopamine D1 receptors; Peroxisome proliferator activated receptor-alpha; Oleoylethanolamide

Core tip: The mechanisms underlying a massive and sustained body weight loss after gastric bypass surgery remain poorly understood. Hankir *et al* describe how a fat-satiety signaling pathway that was greatly blunted in obese rats could be restored by Roux-en-Y gastric bypass (RYGB) surgery. The authors have demonstrated that RYGB rats on high fat diet (HFD) elicited an increased production of oleoylethanolamide (OEA) and activation of PPARα that led to a surge in dopamine release and

activation of D1 in the dorsal striatum. The enhanced dopamine neurotransmission evoked by OEA was obligatorily dependent on intact vagus nerve that had no effect on the production of OEA in the small intestine. The heightened dopamine neurotransmission in the midbrain of RYGB rats was linked to their decreased preference for HFD. These elegant studies have provided a compelling mechanism by which RYGB surgery led to altered gut-brain communication to modify the reward circuitry involved in food preference and obesity. These observations have important clinical implications for the amelioration obesity and its pathological consequences.

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COMMENTARY ON HOT TOPICS

Patients undergoing Roux-en-Y gastric bypass (RYGB) surgery elicit striking loss of body weight. Anatomical re-structuring of the gastrointestinal (GI) tract, leading to reduced caloric intake and changes in food preference, are thought to be the primary drivers of weight loss in bariatric surgery patients. However, the mechanisms by which RYGB surgery causes a reduced preference for fatty foods remain elusive. In a recent report, Hankir *et al*[1] described how RYGB surgery modulated lipid nutrient signals in the intestine of rats to blunt their craving for fatty food. These studies have provided a compelling mechanism by which RYGB surgery led to altered gut-brain communication to modify the reward circuitry involved in food preference and obesity.

Obesity associated diseases represent a looming global healthcare crisis of the 21st century. Although a collusion of genetic, behavioral and environmental factors regulates body mass in humans, its two key drivers are ready accessibility of calorically-dense foods and sedentary lifestyle[2]. Studies aimed at uncovering the Mendelian causes of obesity have revealed that genes encoding leptin or its receptor, or pro-opiomelanocortin and melanocortin-4 receptor are most commonly mutated in genetically obese patients[3,4]. Detailed investigations of monogenic obesity have yielded important insights into the cellular and molecular mechanisms that underpin morbid obesity. However, a key insight emerging from these studies is that a world-wide prevalence of monogenic obesity is rare and a vast majority of cases of obesity are polygenic. The polygenic nature of severe obesity has been most clearly unraveled by genome-wide association studies (GWAS), aimed at deciphering a link between single nucleotide polymorphisms (SNPs) and body mass index (BMI)[5,6]. For example, a recent GWAS in European adults revealed a strong link between 32 common SNPs and severe obesity; it was also notable that individually, none of the 32 SNPs showed significant association with BMI[7].

Severely obese patients, regardless of whether their obesity is monogenic or polygenic in origin, usually engage in overeating and show a preference for fatty diet[8]. Similar to humans, obese rodents also prefer high fat diet (HFD). Although the mechanisms of eating behavior or food preference are poorly defined, they are dependent on reciprocal gut-brain communication, as shown by functional magnetic resonance imaging and positron emission tomography (PET) imaging studies[9-12].

Nutrient-derived signaling pathways play a central role in sensing the hedonic value of food and satiety. Fat, in addition to being a key macronutrient, is vitally involved in gut-brain signaling. The intake and metabolism of fat are closely monitored throughout the gastrointestinal tract[11,13]. The dietary lipids activate taste signals in the mouth to promote eating which is stimulated further by other lipid derivatives (*e.g.,* arachidonoylethanolamide or anandamide) synthesized in the gut[9,11,14]. The small intestine also generates anorexic lipid messengers such as oleoylethanolamide (OEA), an endogenous agonist of peroxisome proliferation activator receptors-α (PPARα). The OEA induced activation of PPARα in the intestine leads to stimulation of vagal afferents that innervate key thalamic and striatal nuclei which constantly appraise the sensation of appetite, eating and satiety[15].

The rewarding and re-enforcing aspects of food and whole body energetics are mechanistically linked to dopamine neurotransmission in the midbrain. Chronic consumption of HFD leads to reduced synthesis of OEA thus blunting the nutrient signaling pathway that enables gauging the hedonic value of food; this deficiency causes enhanced craving for HFD and compensatory overeating[13,16]. A preference for fatty foods in rodents can be reversed by supplementation of OEA in their diet[15]. These studies have spurred a systematic search for weight loss agents that may normalize the eating behavior of obese patients and their affinity for obesogenic diets.

Among the many pharmacological and surgical options for the treatment of obesity, none is more effective than RYGB surgery[17-20]. The physiological and neurological underpinnings of RYGB mediated weight loss are only partially understood. However, recent studies make it abundantly clear that massive and sustained weight loss after bariatric surgery involves several mechanisms[20]; these include a key role of the gut microbiome, as was discussed in an earlier FOV Commentary[21].

A prevailing hypothesis to explain eating behavior of obese patients is that they are deficient in perceiving the reward sensation of food. It is further posited that altered striatal dopamine neurotransmission in these individuals underpins their behavior (compensatory overeating) and physiology (higher metabolic set-point). Several recent studies indicate that after undergoing RYGB surgery, both humans and rodents not only eat less but also develop an aversion for fat-enriched foods. Thus, bariatric surgery leads to normalization of

the putative metabolic set-point and food preference; presumably, this occurs by RYGB-induced changes in gut-brain communication[22].

To explore the mechanistic basis of altered dietary preference associated with bariatric surgery, Hankir *et al*[1], studied diet-induced obese rats that underwent RYGB or sham surgery and were exposed to four different experimental regimens. First group of rats underwent sham surgery and was fed regular low fat chow (Sham-LF). The second cohort of rats received sham surgery and was kept on calorically restricted diet; this group served as body weight matched control (Sham-BWM). The third group of rats with RYGB or sham surgery was subject to complete sub diaphragmatic truncal vagotomy (RYGB-VAG and Sham-VAG). Finally, a group of rats with sham surgery was maintained on HFD (Sham-HFD). The authors found that the cohort of Sham surgery rats gained weight on either LFD or HFD. On the other hand, RYGB rats ate less, showed a reduced preference for HFD and lost weight.

To assess if RYGB led to changes in dietary lipid signaling, Hankir *et al*[1], measured the production of OEA in the biliopancreatic limb, the proximal Roux limb or the proximal common channel of RYGB rats. As assessed by liquid chromatography coupled with mass spectrometry (LC-MS), RYGB rats elicited increased OEA synthesis in the most distal areas of their gut. The OEA is known to signal *via* activation of PPARα that relayed these signals *via* vagus nerve afferents to trigger dopamine neurotransmission in the striatum; this signaling pathway, involved in assessing the hedonic value of food, is dampened in obese animals[15]. Consistent with a putative involvement of OEA signaling pathway, the RYGB rats elicited enhanced dopamine neurotransmission in their striatum. The OEA-mediated surge in dopamine signaling pathway was specific to bariatric surgery alone since enhanced dopamine efflux was not seen in sham-operated rats. Similarly, animals that lost weight by caloric restriction did not elicit changes in dopamine neurotransmission nor showed a reduced preference for HFD. The authors also noted that the OEA-mediated signals did not impinge on satiety pathways regulated by oxytocin, as reported previously[23].

Hankir *et al*[1], experimentally assessed if intestinal OEA-sensory vagal afferent-dorsal striatal dopamine signaling pathway was mechanistically linked to lower appetite for fat in RYGB rats. It has been shown earlier that dopamine D2 and D3 receptor levels in dorsal striatum were not affected by RYGB surgery[24-26]. Therefore, Hankir *et al*[1] investigated the expression of striatal D1 receptors (D1Rs) with [^{11}C] SCH-23390 tracer and small animal PET to show that density of D1R was indeed greater in striatum of RYGB rats, regardless of whether they were maintained on LFD or HFD. The authors infused PPARα specific agonist WY-14643 in the gastrointestinal (GI) tract of Sham-LF and Sham-BWM rats to show that pharmacological activation of PPARα triggered a reduced preference for fat and lower intake of HFD in both groups of animals. Conversely, RYGB associated aversion for fat was neutralized by intestinal infusion of a PPARα antagonist (GW-6471). These experiments validated a key role of OEA signaling and its significant alteration by RYGB surgery.

To investigate if OEA-mediating signaling was mechanistically connected to striatal dopamine neurotransmission, authors carried out additional pharmacological interventions. These experiments revealed that infusion of the mixed dopamine receptor antagonist α-flupenthixol in the dorsal striatum neutralized the effect of bariatric surgery on reduced preference for fat in RYGB rats. The eating behavior of RYGB rats was blocked by a D1R selective antagonist (SCH-23390) thus revealing a specific role of D1R in this process. Finally, a simultaneous intestinal infusion of WY-14643 and delivery of SCH-23390 in the striatum cancelled out the effect of activated PPARα signaling. These experimental observations led Hankir *et al*[1] to surmise that OEA mediated gut-brain signaling pathways that determined food preference and satiety were notably re-configured by bariatric surgery. The RYGB specifically led to enhanced intestinal OEA signaling that was relayed by vagus nerve to trigger dopamine neurotransmission in the dorsal striatum. A motivated reader should consult the original paper[22] for its Graphical Abstract summarizing how food-derived signals from the re-configured GI tract following RYGB travel to the reward centers of the brain and lead to reduced preference for fatty foods.

In summary, the observations of Hankir *et al*[1], have shed important light on how anatomical re-configuration of the GI by bariatric surgery leads to profound changes in gut-brain signaling pathways that regulate the motivational and reinforcing aspects of food. These experiments have also revealed that causal links among the OEA-mediated signaling, food preference and weight loss were not absolute since RYGB rats lost considerable amount of weight despite the vagotomy mediated block in the OEA signaling pathway. These data highlight the notion that although dopamine neurotransmission in the ventral striatum is a key sensor of hedonic reward of the food and satiety, these sensations are regulated by mechanisms that utilize additional nutritional and hormonal signals[20,22,26,27]. It is nearly impossible to assess precise contributions of genetic and environmental factors that dictate eating behavior and food preference in humans. The RYGB rat may be an excellent model system to carry out such studies. Finally, we should note that despite its positive clinical attributes, bariatric surgery is by no means risk-free. The RYGB rats represent an ideal model to search for less invasive methods of weight loss in the future.

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