Current Psychiatry Reports (2019) 21: 117
https://doi.org/10.1007/s11920-019-1084-2

EATING DISORDERS (S WONDERLICH AND S ENGEL, SECTION EDITORS)

Recent Advances in the Neurobiology of Altered Motivation Following Bariatric Surgery

Julianna N. Brutman[1] · Sunil Sirohi[2] · Jon F. Davis[1]

Published online: 9 November 2019

Abstract

Purpose of Review There is compelling evidence in the clinical population that long-term weight loss secondary to bariatric surgery is mitigated by the reemergence of maladaptive feeding behaviors and in some cases new onset substance abuse.

Recent Findings A review of the current literature suggests that physical restructuring of the GI tract during WLS alters secretion of feeding peptides and nutrient-sensing mechanisms that directly target the brain's endogenous reward system, the mesolimbic dopamine system.

Summary Post-surgical changes in GI physiology augment activation of the mesolimbic system. In some patients, this process may contribute to a reduced appetite for palatable food whereas in others it may support maladaptive motivated behavior for food and chemical drugs. It is concluded that future studies are required to detail the timing and duration of surgical-induced changes in GI-mesolimbic communication to more fully understand this phenomenon.

Keywords RYGB · VSG · Motivation · Reward · SUD · Dopamine

Introduction

Obesity is a significant unmet health concern that is strongly associated with other comorbidities such as type-2 diabetes, cancer, cardiovascular disease, and hypertension [1–7]. Roughly 6.6% of the population in the USA is considered morbidly obese, classified as having a body mass index of 40 or higher [6]. Presently, we understand obesity as a multietiological disease with primarily genetic, psychological, and environmental roots [8–13]. A large body of work suggests that exposure to highly palatable food augments key neuroendocrine signals, which remodel the brain's reward circuitry to reinforce pathological feeding behaviors [14–17]. However, given our limited understanding of the exact etiology of obesity, our ability to treat the disease is quite limited. Presently, weight loss surgery (WLS) is the most effective way to treat morbid obesity [5, 7, 18–25]. The two most common weight loss procedures are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), with RYGB taking precedence over VSG due to greater effectiveness for long-term, sustained weight loss (Fig. 1) [7, 18, 26–28].

The goal of weight loss surgery is straightforward: restructure the gastrointestinal tract to reduce appetite and metabolic complications, and promote body weight loss [7, 18, 26–28]. An intended consequence of this procedure involves attenuation of food-reinforced behavior, an event that derives from adaptation of brain reward circuits [7, 18, 26–28]. Currently, our understanding of how WLS induces neuroadaptations in the brain's endogenous reward circuit, the mesolimbic dopamine system, is unclear. The goal of this review is to summarize current (2016–present) findings regarding changes in motivation for food and substances of abuse following WLS, as well as the potential mesolimbic and neuroendocrine alterations that underlie these behaviors.

This article is part of the Topical Collection on *Eating Disorders*.

✉ Jon F. Davis
jon.davis@wsu.edu

[1] Department of Integrative Physiology and Neuroscience, College of Veterinary Medicine, Washington State University, 1815 Ferdinand's Lane, Pullman, WA 99164, USA

[2] Laboratory of Endocrine and Neuropsychiatric Disorders, Division of Basic Pharmaceutical Sciences, College of Pharmacy, Xavier University of Louisiana, New Orleans, LA, USA

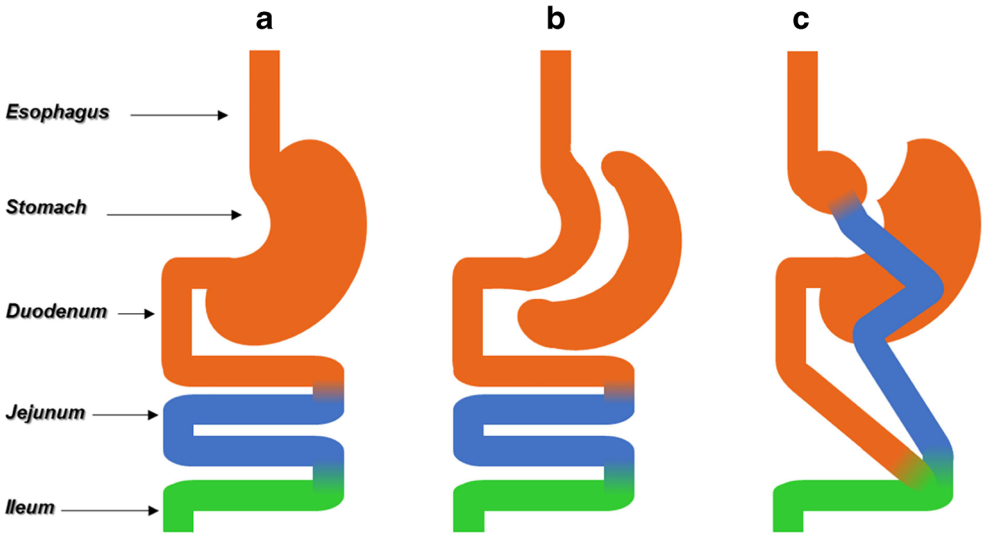

Fig. 1 Basic schematic illustration of the gastrointestinal track before (**a**) and after VSG (**b**) and RYGB (**c**) surgical procedures

WLS-Induced Regulation of Food- and Drug-Reinforced Behavior

Following WLS, the reinforcing properties of food, alcohol, and drugs appear to be reset [19–25]. In the clinical population, hedonic feeding behaviors decrease 2 years following surgery, identified as a decreased preference for sweet foods and increased food restriction patterns in patients that report pathological feeding behaviors prior to surgery [19, 29]. However, it has been observed that these behavioral feeding changes are not permanent in some RYGB patients [29–32]. Specifically, after the 2-year mark, there is a greater potential for recidivism of unhealthy feeding in some patients, which often reverses the weight loss effects obtained by the procedure [29–34]. Thus, understanding how food reinforcement mechanisms adapt to RYGB has become a primary focus, with an emphasis on understanding post-surgical changes in sensory detection of food and altered neuroendocrine signaling.

In this context, work from Geary et al. examined increases in sweet preferences for an artificially sweetened diet (ASD) in RYGB female rats [19]. The goals of this study were to determine (1) if the preference for a low-energy ASD changed in female rats following RYBG and (2) how the presence of estrogen modulated dietary changes and weight loss [19]. These questions pose importance because RYGB and other bariatric procedures are most commonly performed on female patients in the clinical population, yet most of the preclinical work has been completed in male rodents [2, 35]. The results from this study suggest that RYGB increases preference and intake of a low-energy ASD relative to an Ensure maintenance diet 6 months following surgery [19]. When access to the ASD is given prior to surgery, RYGB still increases the amount of ASD intake following surgery, suggesting an innate change in taste preference after RYGB [19]. Interestingly, RYGB rats treated with estrogen (E2) lost the most weight while consuming the most ASD, suggesting the importance of circulating E2 for RYGB success [19]. Notably, exogenous administration of the adipocyte hormone leptin only slightly attenuated the anticipation for ASD in RYGB rats, supporting the notion that hypoleptinemia may contribute to observed differences in diet preference [19]. Collectively, the results establish adaptations in sucrose preference following RYGB and suggest that pre-menopausal women may be better candidates for the surgery compared with women with low circulating estrogen.

Additional work from Mathes and colleagues examined similar changes in dietary preference following RYGB in male rats [20]. Specifically, rats received pre- and post-surgery access to a cafeteria diet paradigm (beans, low-fat/low-sugar; yogurt, low-fat/high-sugar; peanut butter, high-fat/low-sugar; and sugar-fat whip, high-fat/high-sugar; comparable amounts of protein) and changes in macronutrient preference were tracked [20]. RYGB rats decreased fat intake but increased carbohydrate and protein intake. RYGB rats also decreased carbohydrate consumption from sugar, but interestingly, most calories were still obtained from the high-fat/high-sugar option [20]. These studies lend insight into the complexities of macronutrient preference following RYGB. In this regard, new work has established an increase in neuronal activity in response to a high-fat diet (HFD) exposure following RYGB surgery [21]. Interestingly, this change in neuronal activity is region- and time-specific. More specifically, at day 10 post-surgery, but not day 40, eating a voluntary meal induces exaggerated c-Fos expression in the lateral parabrachial nucleus, nucleus tractus solitarius, area postrema, and the central nucleus of the amygdala [21]. These data suggest that brainstem anorexic pathway activation is important in the early stages of RYGB, but the effects may wane as time continues [21]. Future studies that antagonize brain anorectic pathways in

conjunction with assessments of feeding behavior will further elucidate the importance of these signaling mechanisms as regulators of appetite after RYGB.

Separate from the feeding behavior, some RYGB patients are more prone to developing substance abuse disorders (SUD), namely alcohol and opioid abuse [23–25, 36–41]. For example, a body of preclinical work from Davis et al. showed that alcohol use increased following RYGB [36, 37]. In these studies, the authors focused on how the mesolimbic reward pathway adapted to feeding and alcohol intake after RYGB [36, 37]. In recent studies from Sirohi et al., RYGB rats decreased hedonic intake of a highly palatable HFD intake post-surgery, while both SHAM and RYGB rats increased alcohol intake, and preferred lower concentrations of alcohol relative to non-operated pair-fed (PF) controls [23]. In addition, only RYGB rats escalated alcohol intake following acute withdrawal from a liquid alcohol diet that elevated blood alcohol concentration [23].

Similar to increased alcohol intake, roughly 8% of RYGB patients develop chronic opioid use, compared with 3% of the general population [25, 42]. Specifically, recent work from Biegler and colleagues examined intravenous morphine self-administration in RYGB rats using a self-administration task where rats were trained on fixed-ratio lick mode of reinforcement to obtain morphine injection [25]. The results of this study indicate that RYGB rats significantly increased morphine-seeking behavior following training and that RYGB rats consumed significantly more morphine relative to control rats in a time-dependent fashion [25]. Collectively, these results suggest that reinforcement and consumption of morphine increase in RYGB rats. In combination, these studies illustrate the ability of the RYGB procedure to alter preference and reinforcement for palatable food and chemical drugs. Future studies that address the molecular underpinnings of the observed behavioral adaptations will undoubtedly provide more mechanistic insight into this phenomenon. It is worth mentioning that in contrast to RYGB, reduced alcohol has (at least at lower concentrations) been reported following VSG in two recent preclinical studies [24, 43]. In addition to reduced alcohol drinking behavior, hedonic feeding was also decreased and alterations in the ghrelin signaling and/or hypothalamic orexigenic transcripts could mediate these effects [24, 43]. These data suggest that bariatric procedures differentially modulate alcohol intake behavior and particular gut manipulations may carry a reduced risk of developing alcohol use disorders. Studies from Sirohi et al. suggest that reduced mRNA expression of orexigenic peptides including orexin and ghrelin receptor-1a in the hypothalamus may contribute to decreased food intake after VSG [43]; however, further studies are needed to evaluate mechanistic changes that alter alcohol intake.

Presently, the clearest evidence of convergence between clinical and preclinical models of bariatric surgery derives from behavioral outcomes of alcohol intake after RYGB. For example, RYGB stimulates alcohol intake in both patients [122] and rodents [37,41] highlighting the translational validity of this phenomenon. In terms of weight loss, the effect of RYGB on body weight loss is not universally consistent in patients or rodents. The reasons for failed RYGB in patients are multifactorial and involve psychological processes [127] but not post-surgical changes in gastrointestinal signals that control energy balance [123]. In rodents, weight regain after RYGB can derive from genetic deletion of the satiety hormone leptin [125]. Weight regain has also been observed in 25% of obese rats receiving RYGB. In those studies, increased caloric intake coupled with decreased fecal output was concluded to contribute to body weight regain [124]. When viewed collectively, both clinical and preclinical studies have isolated new onset alcohol intake and body weight regain as negative consequences associated with the RYGB procedure. Points of convergence for these outcomes following VSG, especially alcohol-related endpoints, require more data to discern definite trends.

WLS Induces Functional Changes in CNS Circuits That Regulate Food and Drug Reinforcement

Brain reward circuitry plays a critical role in regulating food and drug reward, and alteration in this circuitry could contribute to pathological food and drug intake [49]. Importantly, disorganization in brain reward circuitry has been documented in obesity which may impair decision making and trigger food/drug-reinforced behavior [50–55]. In this context, bariatric surgeries (e.g., RYGB and VSG) have been shown to normalize obesity-induced alterations in the brain reward regions and overall brain functional connectivity, possibly contributing to beneficial or detrimental effects post-surgery [56–65]. For example, a longitudinal study evaluated behavioral, hormonal, and whole-brain fMRI changes 12 months following VSG and compared these data to pre-surgery baseline in 18 human subjects [60]. This study reported improvement in the maladaptive eating behavior and reduction in the feeding peptides (e.g., ghrelin, leptin, insulin) [60]. In addition, baseline brain activity in response to palatable food anticipation in the nucleus accumbens (NAc) and hypothalamus was significantly predictive of 12-month weight loss. Furthermore, a robust improvement in brain activity in the brain reward regions was observed 12-months post-surgery [60]. Another recent fMRI study reported similar VSG-induced reversal of altered brain activity and improved functional connectivity in brain regions (e.g., orbitofrontal cortex, frontal gyrus) implicated in reward, cognitive, and executive functioning [62]. Interestingly, similar normalization in brain activity has also been documented following RYGB. For example, a prospective fMRI study

evaluated brain activity in response to high-calorie foods before and 6 months after VSG and RYGB and compared with weight-stable controls. A positive correlation between fasting ghrelin and ventral tegmental area (VTA) brain activity was observed in both RYGB and VSG groups. In addition, VTA brain activity in response to high-calorie food significantly declined in the RYGB but not in VSG compared with controls [66]. A bold fMRI study assessed neural inhibitory control (go/no-go task) in response to high- and low-calorie food pictures following RYGB and found increased activation of the prefrontal cortex, cingulate cortex, and right inferior frontal operculum during response inhibition to high caloric food [67]. The same group in another bold fMRI study examined food preference and neural activity in response to food images and order of food image presentation before and 2 months after RYGB in human subjects. It was found that RYGB-induced alterations in the frontoparietal brain region (implication in top-down executive control) correlated with the shift in food preference whereas no such correlation was found regarding plasma ghrelin and endocannabinoid concentrations [62].

In addition to functional activity, obesity has been shown to induce structural brain damage. For example, reduction in gray- and white-matter brain volume which was negatively associated with body fat percentage has been documented in obesity [69]. Zang et al. reported for the first-time recouping of structural neuroplasticity in various brain regions (i.e., orbital frontal cortex, corpus callosum, caudate, insula, inferior frontal gyrus, hippocampus, insula, and external capsule) following laparoscopic VSG [64]. A recent study reported similar structural changes in human subjects 1 month following VSG [65] but no such changes were evident approximately 4 months later [70]. These early structural and functional changes caused by bariatric surgeries could pave the foundation for improved brain connectivity, which may rescue impaired hedonic and cognitive response to palatable food as observed in obesity. Overall, these data suggest that normalization in the dysregulated activity of various brain regions implicated in reward processing and cognitive/executive control following bariatric surgeries may mediate post-surgical changes in the food intake and weight loss.

Separate from structural and functional changes, obesity has been linked to alterations in various neurotransmitter systems in brain reward circuitry which may contribute to impairment in food/drug reward under pathological conditions, and possible alterations in these neurotransmitter systems could mediate effects of bariatric surgery [71–73]. The midbrain reward circuitry which primarily involves excitation of VTA dopaminergic neurons causing dopamine (DA) release in the NAc is a critical structure implicated in mediating food/drug-reinforced behavior [74, 75]. Neuroadaptations in the VTA and striatal dopaminergic neurotransmission have been reported following prolonged exposure to palatable food, diet-induced obesity, and alcohol intake [76–80]. For example, obese rats show reduced striatal dopamine D2 receptor (D2Rs) density [80]. Similarly, lower D2/3 receptors availability has been documented in human subjects under obese conditions [81]. Recent studies further provide evidence of hypodopaminergic state–associated with obesity [82, 83]. Whether bariatric surgery can reverse this hypodopaminergic state is less clear. Karlsson et al. did not find alterations in the DR receptors availability following 6-months of bariatric surgery [56]. However, another study reported an increase in striatal dopamine (D2/3R) receptors binding following 2 years of RYGB surgery [84]. Moreover, RYGB surgery has been shown to reduce markers of dopaminergic neurotransmission (tyrosine hydroxylase and DAT) transcripts in the VTA [85]. It is important to note that earlier studies assessing D2 receptor availability at shorter time points have reported increased or no changes 6 weeks following RYGB surgery [86, 87]. A relatively recent preclinical study examined D1-, D2-like receptor and dopamine transporter (DAT) binding in diet-induced (9 weeks on diets) obese rats and found reduced D1-like binding in ventrolateral striatum and NAc core and shell, reduced D2-like binding in all striatal areas, and reduced DAT binding dorsomedial striatum which was reversed following RYGB surgery [88••]. These differences across preclinical studies could be attributed to variation in the surgical procedures and/or relative time of observed outcomes [89].

The opioidergic system is another critical and extensively studied brain neurotransmitter system implicated in food/drug reward [90–93]. Interestingly, a significant decrease in mu-opioid receptors (MOR) availability in the brain reward regions has been documented in morbid obesity [94, 95]. Considering the role of MOR in regulating motivation and reward, decreased MOR availability could stimulate increased hedonic feeding in obesity. Since bariatric surgeries reduce hedonic feeding [23, 96], it is interesting to see how bariatric surgeries impact the central opioidergic system. Using positron emission tomography, Karlsson et al. quantified brain D2R and MOR in the 16 women with obesity before and 6 months after weight loss surgery and also compared the data with 14 lean human subjects. While D2R availability was not altered in any brain region in this study, MORs availability was ~23% higher post-surgery in the brain regions also implicated in the reward [56]. Considering the role of MOR in regulating motivation and reward, decreased MOR availability could stimulate increased hedonic feeding in obesity. Therefore, restored MORs signaling nicely aligns with reduced hedonic feeding behavior observed following bariatric surgery [23, 96]. However, a rodent study examining fat preference, MOR availability, and MOR protein levels in the diet-induced obese rats reported a reduction in fat intake, MOR availability, and protein levels in the brain reward circuitry [97]. It is important to note that the MOR availability assessments in this study were carried out 15–17 weeks post-

operatively which is equivalent to ~9 years of human life. Therefore, the observed discrepancy in the clinical and preclinical studies could be related to the sampling time following surgery, species differences in brain opioid receptor system, and/or surgical procedures [89, 98].

WLS Alters Feeding Peptides and Nutrient Sensing Mechanisms That Regulate Mesolimbic Function

Feeding peptides produced by the gastrointestinal (GI) tract and nutrient-sensing mechanisms communicate extensively with the central nervous system (CNS) to regulate energy balance [14–17]. A key feature of the RYGB procedure is the restructuring of the GI tract to reroute the small intestines to a volume-reduced stomach [6, 7]. Importantly, this process alters the secretion of feeding peptides that target the CNS to regulate mesolimbic dopamine release [99]. This adaptation in GI-CNS communication has been hypothesized to underlie the dramatic changes in feeding- and alcohol-reinforced behaviors that accompany the RYGB procedure [100]. Perhaps the most dramatic example of GI adaptation involves RYGB-induced increases in glucagon-like peptide-1 (GLP-1) secretion. GLP-1 is produced in the small intestines and once released functions to lower blood glucose and reduce food intake [101]. Following RYGB, plasma GLP-1 levels are significantly increased in response to a mixed meal in patients [102] and rodents [103]. In addition, GLP-1 secretion is stimulated by alcohol ingestion in rats [36]. The GLP-1 receptor is expressed in the VTA and NAc key mesolimbic regions that regulate reinforced behaviors [104]. A central application of GLP-1 agonists reduces psychostimulant-induced phasic dopamine release in the NAc [105]. In addition, GLP-1 application in the VTA decreases psychostimulant self-administration in rodents [106]. In combination, these examples suggest that excursions in GLP-1 secretion following RYGB may target the mesolimbic system directly to direct food and drug intake. To our knowledge, data supporting the direct involvement of mesolimbic GLP-1 signaling after RYGB has not been reported and remains an interesting area of inquiry.

Separate from GLP-1, RYGB also dramatically regulates GI ghrelin secretion. Ghrelin is a 28 amino acid protein secreted primarily by the stomach that acts at the ghrelin-1a receptor (GHSR-1a) in the CNS to control feeding behavior [14]. Multiple observations in patients [107] and rodents [23, 37] suggest that the RYGB procedure results in decreased circulating ghrelin levels, a process that is seemingly dynamic. For example, rodent studies indicate that ghrelin production and secretion is elevated 30 days after surgery but that this effect wanes at more distal time points leading to an overall decrease in plasma ghrelin at 90 days after surgery [37]. This becomes important when considering that GHSR-1a surface expression is decreased in conditions of elevated plasma ghrelin [108]. Therefore, acute surges in ghrelin after surgery could have long-lasting impacts on GHSR-1a function. GHSR-1a is expressed in VTA neurons, where it acts to stimulate dopamine release and food- and alcohol-reinforced behaviors [109–112]. Recent work from Sirohi et al. was one of the first studies to link changes in feeding peptides with mesolimbic function and behavior following RYGB [23]. In this study, the authors discovered that GHSR-1a activity controls tonic dopamine release from VTA neurons in male Long Evans rats [23••]. The group further reported that the ability of GHSR-1a antagonism to reduce tonic dopamine was ineffective in RYGB rats that consumed more alcohol relative to controls [23••]. It is important to note here that GHSR-1a displays constitutive activity without the ghrelin ligand present [113] and that this process is functional to control feeding behavior [114]. Thus, one interpretation of the Sirohi data is that GHSR-1a activity in the VTA is increased after RYGB and that this process serves to promote excess alcohol consumption after surgery. It is currently unclear if plasma levels of ghrelin contribute to altered GHSR-1a control of VTA dopamine firing or if a separate process accounts for this observation. Moreover, additional studies that determine the timing and nature of altered GHSR-1a activity in the VTA are required to determine if this phenomenon contributes to adaptations in food and alcohol intake after RYGB.

In terms of nutrient sensing, a recent study indicates that altered lipid sensing may play a significant role in adaptations in mesolimbic function and behavior following RYGB. Oleoylethanolamide (OEA), a lipid species produced in the GI tract, binds the proliferator-associated receptor-α (PPAR-α) to exert biological action [115]. Notably, it has been previously demonstrated that OEA-PPAR-α signaling regulates striatal dopamine release in obese rodents [116]. In a recent study, Hankir et al. reported that OEA is upregulated following RYGB in diet-induced obese rats [117]. In addition, the authors discovered that striatal dopamine levels following an oral meal were increased following RYGB relative to obese sham controls and that this response required intact vagal afferent signaling. Additionally, expression of striatal dopamine-1 receptor (D1R) levels was increased by RYGB in this study. It is well accepted that RYGB shifts preference from high- to low-fat diets in patients [99, 100, 118, 119] and rodent models [20, 23, 119]. A particularly striking discovery from Hankir et al. was the observation that OEA-PPAR-α signaling regulated reductions high-fat preference following RYGB [117••]. Using a series of behavioral pharmacologic manipulations, the authors discovered that attenuation of OEA-PPAR-α signaling in the GI tract or D1R signaling in the dorsal striatum attenuated the decrease in high-fat diet preference in rats receiving the RYGB procedure [117]. The combined results of this study were the first to indicate that adaptations in lipid sensing are transmitted to the mesolimbic

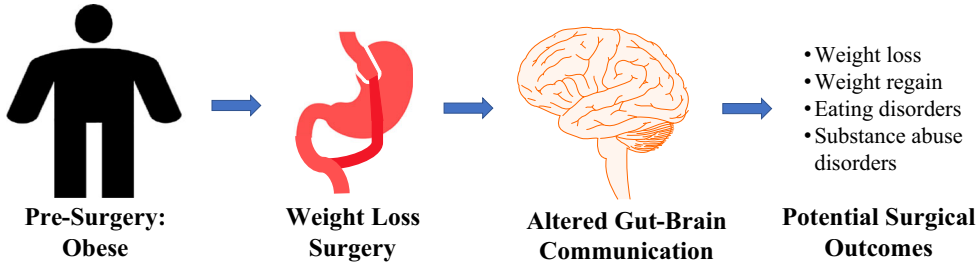

Fig. 2 Proposed adaptation following WLS. WLS is completed on morbidly obese patients facing life-threatening health complications. However, WLS functionally alters the ability of the GI tract to secrete key neuroendocrine hormones, altering neuronal activity in the mesolimbic dopamine system. Recent research suggests that, in some instances, this physiological adaptation rewires the brain to promote maladaptive behaviors such as seeking substances of abuse, including chemical drugs, alcohol, and food. These maladaptive changes may contribute to the maintenance of long-term body weight after WLS surgery. We propose that the surgical restructuring of the gut alters the brain, resulting in behavioral changes that may be of detriment to clinical populations; thus, further preclinical and clinical research is needed to understand these phenomena

dopamine system to control feeding behavior and that OEA-PPAR-α signaling in particular is a positive adaptation that regulates shifts in diet preference to low-fat foods following RYGB.

Efforts to design therapeutic options that target gastrointestinal peptide signaling to treat obesity are an active area of investigation. As new treatments emerge, it will be important to determine if these drugs can enhance post-surgical outcomes following bariatric interventions. A great example of this concept is found in preclinical studies that examined the blood glucose-lowering response of RYGB surgery. Habegger and colleagues were able to demonstrate that obese rats sensitive to the glucose-lowering effects of GLP-1 experienced greater reductions in blood glucose following the RYGB procedure [126]. This is one example of many that leverage knowledge of gut-brain communication to refine surgical interventions aimed at reducing metabolic complications. It is our contention that future approaches of this type will greatly refine the efficacy of bariatric surgery on brain and behavioral function.

Conclusions

In conclusion, it is apparent that restructuring the nature of WLS is capable of altering how the GI tract communicates with mesolimbic circuitry and that this process participates in the control of appetitive and consummatory aspects of ingestive behavior. A significant portion of the recent literature highlights neuroendocrine signals, such as GLP-1, ghrelin, and OEA, as potential signaling mechanisms that facilitate GI communication with the mesolimbic dopamine system. The nature of these modifications for patient success is unclear. In this regard, adaptations within the mesolimbic circuit may aid in reduced appetite and/or bodyweight loss. However, these changes could also provoke harmful behavior such as new-onset alcohol intake or opioid use (Fig. 2). Understanding how the brain adapts to WLS continues to be an important area of inquiry for obesity researchers. In this context, an unexplored hypothesis in the field involves understanding if new set points for appetite and body weight contribute to weight regain and/or substance disorders. Future preclinical research that capitalizes on techniques that enable defined neurocircuit manipulations paired with in vivo imaging will fill critical gaps in knowledge regarding how the brain adapts to a restructured GI tract.

Compliance with Ethical Standards

Conflict of Interest Julianna N. Brutman, Sunil Sirohi, and Jon F. Davis each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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