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The effects of bariatric surgery – will understanding its mechanism render the knife unnecessary?

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Abstract

The incidence of obesity is increasing worldwide at a dramatic rate, accompanied by an associated increase in comorbid conditions. Bariatric surgery is the most effective treatment for severe obesity with, until recently, Roux-en-Y gastric bypass (RYGB) being the most commonly performed procedures, yet the underlying mechanisms by which it induces a wide-array of beneficial effects remains obscure. From both basic science as well as clinical standpoints, there are several areas of current interest that warrant continued investigation. Several major focus areas have also emerged in current research that may guide future efforts in this field, particularly with regard to using novel, non-surgical approaches to mimic the success of bariatric surgery while minimizing its adverse side-effects.

Keywords

RYGB; obesity; vagus; vagal reflexes; gastrointestinal

The incidence of obesity is increasing worldwide at a dramatic rate, accompanied by an associated increase in comorbid conditions such as Type 2 diabetes, hypertension and hyperlipidemia. While it is increasingly accepted that obesity in humans is multifactorial in origin involving strong environmental influences, ultimately it is caused by an imbalance in energy intake relative to expenditure. Bariatric surgery is the most effective treatment for severe obesity (defined as BMI>40kg/m²) with, until recently, Roux-en-Y gastric bypass (RYGB) being the most commonly performed procedure. Surgical stapling is used to create a small gastric pouch close to the esophagus, which is then joined to the mid-jejunum, bypassing the distal stomach and proximal small intestine. Following RYGB surgery, patients typically lose 65–70% of excess body weight [4], increase health-related quality of life [9] and longitudinal studies suggest this weight loss is maintained in a significant population of patients for at least 6 years after surgery [1].

RYGB has effects beyond simple weight loss. Numerous studies have reported that glycemic control and cardiovascular function is recovered rapidly following surgery, well in

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advance of significant weight loss [15], suggesting that some of the positive health outcomes associated with RYGB may occur independently of decreased adiposity. Indeed, the most recent consensus statement from the American Society for Metabolic and Bariatric Surgery (ASMBS) concludes that extending bariatric surgery to patients with Class I obesity (BMI 30–35kg/m²) with comorbid conditions such as diabetes may be warranted [4]. Mechanically restricting the size of the stomach certainly increases satiation and restricts the volume of food ingested; recent studies have demonstrated that RYGB has numerous additional effects including alterations in taste processing [7], reward pathways [18] as well as peripheral and central neuroendocrine systems [13].

RYGB and vagal neurocircuits

The gastrointestinal (GI) tract is one of several organs that contribute to the peripheral signaling of food intake and satiety and, increasingly, vagally-mediated reflexes are being recognized as playing a crucial role in the neural mechanisms of satiation [2]. Visceral sensory information from the GI tract is transduced and relayed centrally via the afferent (sensory) vagus nerve the central terminals of which enter the brainstem via the tractus solitarius and terminate on neurons within the nucleus of the tractus solitarius (NTS). NTS neurons integrate this vast volume of visceral sensory information with hormonal and metabolic inputs as well as other neuronal inputs from other brainstem. In particular, NTS neurons have direct or indirect reciprocal connections with several other higher CNS nuclei involved in the longer-term regulation of food intake including the hypothalamus, the amygdala and the nucleus accumbens [16]. NTS neurons relay this integrated signal to the adjacent dorsal motor nucleus of the vagus which provides the motor output back to the GI tract and viscera via the efferent vagus nerve to regulate gastric motility, secretion and emptying [20]. Modulation of vagal neurocircuits, therefore, can have profound influence on both short- and long-term regulation of food intake.

Several studies have demonstrated that the activity, responsiveness and receptor profile of vagal afferent neurons and terminals is altered by diet and obesity. The ability of the gastrointestinal neurohormone cholecystokinin (CCK), for example, to activate vagal afferents is attenuated in diet-induced obese models [5;6;12] while exposure to a high fat diet shifts the receptor profile of these neurons towards an orexigenic phenotype [14]. Several lines of evidence suggest that obesity and diet also alter neuronal function and responsiveness within the CNS including alterations in glucose sensing [19], taste processing [8] and blunted striatal dopamine signaling [21]. The technically demanding nature of making electrophysiological recordings from older or obese rodents has, however, limited investigations into the effects of diet and/or obesity on the behavior of central neurons. Recently, however, we demonstrated that diet-induced obesity also inhibits the excitability of brainstem vagal motoneurons and their responsiveness to gastrointestinal neuropeptides such as CCK and glucagon-like peptide 1 (GLP-1). Importantly, RYGB reversed these effects, restoring the excitability of vagal motoneurons as well as their responsiveness to CCK and GLP-1 [3]. Since previous studies have shown that basal and postprandial levels of GLP-1 increase following RYGB [11], this suggests an additional means by which vagal neurocircuits may respond to the released GLP-1. Furthermore, it appears that the adverse effects of diet and obesity on neuronal function(s) may not be

permanent, at least with respect to vagal neurocircuits, and that these neurons retain a significant degree of plasticity, even following significant periods of insult or injury.

Future directions

Bariatric surgery is, by and large, a safe surgery with few complications and is still the most effective treatment for severe obesity and its associated co-morbid conditions. Nevertheless, some patients still present as a surgical risk and post-surgical complications, including dumping syndrome, dysphagia, altered bowel habits and vitamin and mineral deficiencies are experienced by a significant proportion of patients [4]. Recent clinical reports have also revealed an increased risk for some patients for alcohol consumption [10]. Mimicking the success of RYGB with non-surgical tools, and without its adverse effects, is of significant interest to the field; to do so requires a deeper and more thorough understanding of the mechanism(s) responsible for the beneficial effects of RYGB. The following major focus areas have emerged in current research that may guide future efforts in this field:

- Our initial study, demonstrating the feasibility of recording from central neurons following diet-induced obesity, has opened up several new lines of inquiry. Of immediate interest is determining the temporal nature of the recovery in vagal neurocircuit function(s) following RYGB. In particular, (i) do the adverse effects of diet on vagal neurocircuits precede the development of obesity or do they occur as a consequence of obesity; (ii) does recovery of vagal neurocircuit function(s) after RYGB precede weight loss or is weight loss necessary for recovery of neural functions; and (iii) does RYGB also recover functions within all vago-vagal reflex neurocircuits (vagal sensory neurons, as well as in NTS neurons)?
- The ability of RYGB to rapidly restore glycemic regulation, and its potential use as a therapeutic treatment for Type 2 diabetes, raises questions as to this mechanism of action, whether recovery of glycemic regulation following RYGB is related to restoration of vagally-mediated homeostatic control?
- What contribution do altered gut permeability, transport and microbiota play in improved neuroendocrine and vagal neural functions following RYGB? What role does altered inflammatory signaling after RYGB exert?
- The increased resting and postprandial levels of GI neurohormones such as GLP-1 raises questions as to the extent to which increased vagal signaling contributes to homeostatic regulation of food intake and satiety. Together with restoration of vagal neuronal functions, this should increase the vagally-mediated reflex regulation of GI functions dramatically. While systemic application of GLP-1 analogues such as exendin-4 (Byetta™) can induce adverse side-effects such as nausea and abdominal discomfort, would targeted application/delivery within the distal GI tract be more beneficial? Certainly, peripheral vagal afferents and efferents regulating GI functions present appealing, and more readily available, targets for drug action.
- While bariatric surgery, and RYGB in particular, are exceptionally successful in inducing weight loss in obese patients, longitudinal studies have suggested that a

sub-population of patients regain a significant amount of weight approximately 2 years following surgery. While surgical failures e.g., stretching of the gastric pouch, certainly occur, they do not appear to account for all failures. Future studies targeting this patient population could help with identifying critical eating behavior traits, genetic/epigenetic and metabonomic predictivity markers to target personalized recommendations for alternative therapies.

- Following RYGB, patients voluntarily restrict consumption of calorie-dense, highly palatable foods such as fats, concentrated carbohydrates, ice cream, and sweetened beverages. Such behavioral changes seem to be independent of perioperative counseling of the patients. Recent studies from our and other laboratories using rodents have demonstrated reduced preferences and motivation for high concentrations of sugars and fats in addition to increased neural and behavioral responses to lower, previously non-rewarding, concentrations. Thus, RYGB may improve blunted reward sensitivity observed in obesity. What does this rescuing of reward pathways say about reward in general, and neural rewiring following RYGB in particular?
- Compared to traditional weight loss procedures, the compensatory decrease in energy expenditure in response to body weight loss is absent following RYGB. Future studies focusing on the peripheral signals (gut hormones, altered nutrient/metabolic sensing, or vagal afferent functions), the central integration (e.g., hypothalamic, and hindbrain MC4R regulation of sympathetic tone) are warranted to reveal the cause of this paradox.
- Are the above mentioned side-effects of RYGB surgery (restoration of vagal neurocircuit functions, alterations in gut permeability & microbiota, increasing postprandial GI neurohormone levels, reduced voluntary consumption of highly palatable foods) also apparent if a similar degree of weight loss occurs via calorie or are these effects related to the metabolic and hormonal improvements following surgery rather than the weight loss?
- Despite both procedures inducing a similar degree in recovery of glycemic functions, the effects of RYGB on weight loss appear to last longer than those observed following vertical sleeve gastrectomy [17]; understanding the mechanisms behind these differences may help determine the relative contribution of the foregut vs the hindgut in weight and hormonal improvements following surgery. Additionally, due to its easier surgical approach, recent studies has demonstrated the successful application of vertical sleeve gastrectomies to mice which should allow studies in knock-out/knock-in models which should provide further significant mechanistic advances.

In conclusion, while bariatric surgery, particularly RYGB, has been performed for more than 20 years and is a safe, and extremely effective treatment for severe obesity, the underlying mechanisms by which it induces a wide-array of beneficial effects remains obscure. From both basic science and clinical viewpoints, there are several areas of current interest that warrant new approaches to solve this conundrum. Such efforts may well involve the use of animal models and neuroanatomical investigations but, ultimately, will remain powerless

without human brain imaging studies and novel approaches such as genomic/epigenomic and metabonomic population-based studies to identify predictive biomarkers to improve surgical outcomes and decrease adverse side-effects.

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