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Review

Neuroendocrine adaptations to bariatric surgery

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ABSTRACT

The global epidemic of obesity and its related disease in combination with robust physiological defence of intentional weight loss generates a pressing need for effective weight loss therapies. Bariatric surgery, which works very effectively at delivering substantial sustained weight loss, has been an enigma with respect to mechanism of action. Naive concepts of restriction and malabsorption do not explain the efficacy of the most commonly used bariatric procedures. This century has seen increased interest in unravelling the mystery of the mechanisms underlying surgery associated weight loss with a focus on integrative gastrointestinal (GI) physiology, gut–brain signalling, and beyond weight loss effects on metabolism. GI interventions, some very minor, can alter GI wall stretch and pressure receptors; a range of GI hormones affecting hunger and satiety; bile acid metabolism and signalling; the characteristics of GI microbiome; portal vein nutrient sensing; and circulating concentrations of amino acids. Understanding the mechanisms involved should present targets for less invasive effective therapies.

Contents

1. Introduction

This century the prevention and management of the combined epidemics of obesity and type-2 diabetes will provide the greatest public health challenge (Ng et al., 2014; Unwin et al., 2010). The

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determinants generating this epidemic are complex, involving both biological and environmental factors, and are proving very difficult to tackle (McAllister et al., 2009; Stunkard et al., 1990). A common perception is that two factors heavily related to personal choice, sedentary behavior and overconsumption of palatable energy dense foods, have generated the problem – but it appears to be far more complex (McAllister et al., 2009). So many aspects of the way we live have changed over recent decades and many of these are strongly associated with obesity and its related comorbidity and complications (McAllister et al., 2009). Indeed, a wide range of the determinants of *weight trajectory for life* appear to be set in very early life – perhaps the most important 4 years are those prior to a child's 3rd birthday (Gluckman and Hanson, 2008; Kerr et al., 2014; Leong, 2013). Early life, including preconception and intrauterine, can establish predictive adaptation and programming whereby a mismatch between fetal expectation and the actual post natal environment develops, generating obesity and related metabolic disorders. There is clear evidence that both low and high extremes of weight for gestation at birth, babies conceived using in-vitro fertilisation and the offspring born to mothers with type-2 diabetes and gestational diabetes are at risk of obesity and its related metabolic disorders (Dyer and Rosenfeld, 2011; Nadif et al., 2015; Sparano et al., 2013). There is also growing interest in the immediate post natal environment and its subsequent influence on weight trajectory and propensity to develop weight related disease (Kerr et al., 2014; Seach et al., 2010). Preventing obesity will not be achieved by attempting to change individual behaviors with reliance on will power and compliance (Atkinson, 1997). It will require tackling a range of environmental determinants of obesity on a whole of society basis, but this can only be achieved with a better understanding of the relative contribution of putative factors, and proven public health strategies that effectively address these. Hence we have pressing need to develop effective management strategies to treat those most affected by this global epidemic. Currently, bariatric surgery provides the best sustained method of weight loss and therefore presents an opportunity for looking at mechanisms for weight loss that are effective in humans.

1.1. Bariatric surgical procedures

There are four bariatric procedures that are currently considered established and conventional and, of these, three procedures dominate global usage: (i) sleeve gastrectomy (SG), (ii) Roux-en Y gastric bypass (RYGB) and its single anastomosis variant, the mini-gastric bypass (MGB), and (iii) the adjustable gastric band (AGB) (Fig. 1a–c). The fourth, biliopancreatic diversion (BPD) and its duodenal switch variant (BPD-DS), are truly malabsorptive procedures and despite a long established history, uptake and utilisation remains below 2% (Buchwald and Oien, 2009; Buchwald and Williams, 2004). Surveys by the International Federation for the Surgery of Obesity (IFSO) and the first IFSO global registry demonstrated major variance in both regional and temporal trends in the choice of procedures (Buchwald and Oien, 2009; Buchwald and Williams, 2004; Welbourn et al., 2014). Some European countries perform RYGB almost exclusively while some South American countries perform Sleeve Gastrectomy almost exclusively and differences represent surgeon training and choice rather than regional difference in outcomes. All procedures impart substantial long-term weight loss, but the mean weight loss varies with the procedure, and the individual variability in response to all procedures is considerable (Hatoum and Kaplan, 2013; Sjostrom, 2013). The summary of the characteristics for the 4 procedure groups is shown in Table 1. Substantial weight loss accompanied by bariatric surgical procedures brings major improvements in weight related comorbidities, psychological wellbeing and quality of life, and reduces cardiovascular, cancer and diabetes related mortality (Adams et al., 2007; Dixon et al., 2011; Sjostrom et al., 2007).

This review will address two key questions, and put on notice a third, regarding the neuro-endocrine effects of bariatric surgery:

- How does surgery generate weight loss?
- What is the evidence for a beyond weight loss effect on type 2 diabetes?
- How could the targeted mechanisms adversely influence health?

2. How does surgery generate weight loss?

Strangely, and perhaps surprisingly, an overwhelming focus of many of those working on the mechanism of action of bariatric–metabolic surgery has been an obsession with the beyond weight loss benefits of 'metabolic' surgery, without sufficient regard to how the surgery generates weight loss and its accompanying benefits. Perhaps the attraction is that people without weight issues could have metabolic disorders such as type 2 diabetes treated successfully with little or no weight loss. To date weight loss

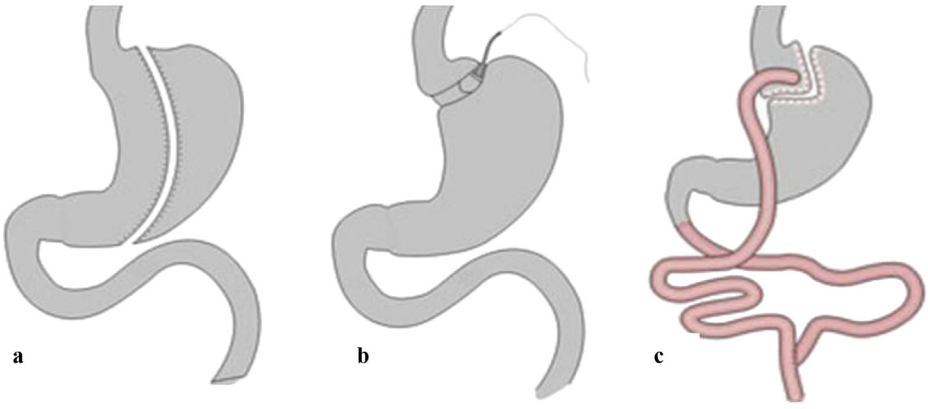

Fig. 1. The three bariatric surgical procedures: (a) Sleeve gastrectomy (SG) involves removing the greater portion (80%) of the fundus and body of the stomach, reducing its volume from about 2.5 l to about 250 ml. Gastric satiety signalling pathways may be accompanied by an intestinal component. (b) Laparoscopic adjustable gastric banding (LAGB) involves placing an adjustable silicone band around the stomach cardia immediately below the gastroesophageal junction. The band can be tightened and loosened over time to alter the pressure generating satiety signalling without excessive restriction. (c) Roux-en-Y gastric bypass (RYGB) is a combination of a small gastric pouch (~15 ml) and GI diversionary procedure in which food bypasses much of the stomach, duodenum and first portion of the jejunum. A range of gastric and intestinal satiety signalling pathways are likely to be involved.