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Original article

An investigation of the neural mechanisms underlying the efficacy of the adjustable gastric band

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Abstract

Background: The mechanisms via which adjustable gastric band (AGB) surgery provides effective and durable weight loss remain unclear.

Objective: This study defines the role of sensory vagal fibers in the efficacy of the adjustable gastric banding using capsaicin to eliminate unmyelinated afferent fibers in the vagus nerve in a rodent model.

Setting: University.

Methods: A miniaturized AGB was fitted at the gastroesophageal junction of obese rats with either intact or sensory fiber depleted vagus nerves where deafferentation involved intraperitoneal (125 mg/kg) or topical (1% to the stomach) application of capsaicin. The extent of sensory fiber lesion was assessed using c-fiber-mediated reduction in cholecystokinin-induced feeding. Food intake, weight, and composition, as well as shifts in central neural activity (measured by elevation of Fos protein), were assessed after either control or AGB inflation with or without vagal deafferentation.

Results: AGB inflation caused a significant reduction in food intake, weight, and fat mass ($P < .05$) in obese rats. The effect of AGB on these parameters was prevented in capsaicin pre-treated (vagal sensory lesioned) rats. Elevations in neural activity in the nucleus of the solitary tract and parabrachial nucleus after AGB inflation were ameliorated in capsaicin-treated rats.

Conclusion: Vagal sensory fibers are integral to the efficacy of the AGB. (Surg Obes Relat Dis 2016;▮:00–00.) © 2016 Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

Keywords: Bariatric surgery; LAGB; Vagus nerve; Animal model

Severe obesity is a common and serious health problem leading to numerous other diseases, reduced quality of life, and reduced survival. Bariatric surgical options, which include laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and biliopancreatic diversion with or without duodenal switch, are the only current therapies that provide substantial and durable weight loss. Recently published 15-year outcome data for LAGB show a similar sustained long-term weight loss to that achieved with RYGB [1]. No similar long-term efficacy data is available for sleeve gastrectomy. Given that these procedures provide such an important part of the

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antiobesity arsenal, it is essential to better understand the biological mechanisms that underpin their success. This is not only critical to their optimal use but may help to identify ways of achieving satiety and weight loss without surgery.

In the case of the LAGB, there is a longstanding, erroneous assumption that the procedure acts solely by restricting the transit of food into the stomach; this view of a purely restrictive mechanism is now considered overly simplistic [2,3]. In a randomized, blinded, crossover trial, the satiety level of LAGB patients was measured with or without fluid in the band. Optimal adjustment was associated with significantly higher levels of satiety during a fasted period and earlier postprandial satiation levels than with uninflated bands [4]. Although these data are inconsistent with restriction being the sole explanation for band-induced satiety, they leave open the possibility that the essential conduit between gut and brain is neural and/or humoral interaction.

To date, despite repeated attempts to find a humoral contribution to the effectiveness of the band, this has not been forthcoming in measurements made in patient cohorts, although there are isolated instances where gut hormones such as peptide YY (PYY) have been shown to be elevated postprandially after AGB surgery [5]. The most cogent explanation for the satiety-inducing effects of AGB involves the activation of stretch receptors, particularly in the small pouch of the stomach proximal to the inflated band [6]. This is supported by data derived from the authors' rodent model of the AGB [7], showing that band inflation results in activation of neuronal populations in the nucleus of the solitary tract (NTS) consistent with the recruitment of mechanosensitive vagal fibers [8]. This has subsequently been confirmed by others [9].

To better delineate the mechanisms underlying the success of the AGB, an obese rodent AGB model, in which vagal sensory fibers were either left intact or eliminated with capsaicin, was used in the present study. It was hypothesized that vagal sensory fibers are critical to the induction of satiety and hence weight loss after AGB surgery.

Methods

Animals

Adult male Sprague Dawley rats (n = 99, 4–16 weeks, Animal Resources Centre, Perth, Western Australia) were housed under a 12-hr:12-hr light:dark cycle and temperature-controlled environment (24ºC–25ºC). Rats had ad libitum access to either standard laboratory chow (9% kcal from lipids) or high-fat diet (45% kcal from lipids, SF04-001; Specialty Feeds, Western Australia, Australia) and water, unless specified. All experimental procedures were approved by the Monash University animal ethics committee and performed in accordance with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purpose, 8th edition 2013*.

Implantation and inflation of the adjustable gastric band

The AGB used throughout these experiments is a commercially available vascular occluder (OC14, In Vivo Metric, Healdsburg, CA) that has features similar to what is used in human surgeries and has been described previously [7,8]. During postmortem examination, the position and level of inflation of the AGB was verified.

Impact of band inflation on metabolic parameters

To assess the effect of band inflation on a number of metabolic parameters, 4-week-old male Sprague Dawley rats (n = 21) were placed on a high-fat diet for 14 weeks. At the end of the 14 weeks, rats were randomly assigned to AGB or sham surgery, which was followed by a 7-day recovery period. The sham surgery involved all aspects of the AGB other than fitting the band.

Weight and food intake. Weight and food intake were recorded throughout the 75-day treatment period.

Body composition. Total lean, fat, and bone mass were assessed using dual energy x-ray absorptiometry (DEXA) both before surgery and capsaicin/vehicle treatment and at the end of the 75-day treatment period. The fat mass in the individual depots was determined by dissection postmortem at the end of the treatment period where retroperitoneal white adipose tissue (rWAT) and epididymal white adipose tissue (eWAT) were weighed as representative abdominal fat pads.

Capsaicin treatment and assessment of the efficacy of the lesion using a cholecystokinin challenge and postmortem analyses of calretinin immunohistochemistry in the myenteric plexus of the stomach

Systemic administration. Capsaicin (>98% grade; Sigma, St. Louis, MO) was dissolved in a sterile vehicle consisting of Tween 80 (10%), ethanol (10%), and .9% NaCl (80%) to achieve a capsaicin concentration of 50 mg/mL. Capsaicin (or vehicle) was administered in a series of 3 doses (25, 50, and 50 mg/kg) that were injected intraperitoneally over a 48-hour period. Each injection was made under isoflurane (Baxter Healthcare, New South Wales, Australia) anesthesia with .2 mL i.p., atropine sulphate (15 mg/mL saline Sigma-Aldrich, St. Louis, MO) administered 10 minutes before injections. Artificial respiration was required in some rats that experienced respiratory arrest immediately after the first injection of capsaicin. These procedures were adopted from published protocols [10,11] and personal communication Q4 with RC Ritter. Rats were allowed a minimum 2-week recovery period after capsaicin or vehicle treatment. Efficacy of the capsaicin treatment was subsequently assessed by testing the ability of the anorexigenic hormone cholecystokinin (CCK) to reduce food intake (see below).