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Original article

Sleeve gastrectomy leads to weight loss in Magel2 knockout mouse

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Abstract

Background: Prader-Willi syndrome (PWS) is a genetic disorder characterized by hyperphagia, obesity, cardiopulmonary diseases, and increased mortality. Although successful weight loss improves health in PWS, few treatments cause sustained weight loss in obese patients let alone obese individuals with PWS.

Objectives: The present study uses the Magel2 knockout (KO) mouse, an animal model of PWS, to conduct a preclinical study on the efficacy of sleeve gastrectomy (SG) in PWS.

Setting: Academic research laboratory, United States.

Methods: We performed sham or SG surgeries in 24- to 28-week-old male Magel2 KO and wild-type littermate control mice (WT) who had been maintained on a high-fat diet for 10 weeks. We monitored weight, food intake, and fat and lean mass pre- and postoperatively. Fasting glucose, glucose tolerance, and counter-regulation were measured postoperatively.

Results: Magel2 KO animals had similar recovery and mortality rates compared with WT. SG resulted in similar weight loss, specifically loss of fat but not lean mass, in both Magel2 KO and WT mice. SG also resulted in significantly lower fasting glucose levels and a reduction in fat intake in both Magel2 KO and WT mice. We also found that Magel2 KO mice failed to increase their food intake in response to the glucoprivic agent 2-deoxy-D-glucose, suggesting impaired glucose counter-regulation, but this occurred regardless of surgical status. All results were considered significant when $P < .05$.

Conclusion: We find in this mouse model of PWS, SG is a well-tolerated, effective strategy for weight and fat loss. (Surg Obes Relat Dis 2016;▮:00–00.)

Keywords: Bariatric surgery; Glucose regulation; Obesity; Sleeve gastrectomy

Prader-Willi syndrome (PWS) is a complex genetic condition associated with intellectual and behavioral deficiencies as well as excessive hunger and progressive, life-threatening obesity in adulthood. The obesity associated with PWS leaves individuals at greater risk for mortality [1] and for obesity-associated co-morbidities [2]. Although dietary intervention can somewhat restrain obesity in PWS, such lifestyle interventions have limited long-term efficacy in non-PWS obese patients. Indeed, we currently have limited options for treatment of obesity in non-PWS patients, let alone patients with PWS.

Currently, the most effective treatment for obesity is bariatric surgery. Sleeve gastrectomy (SG) is one such surgical procedure, in which ~80% of the stomach is

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removed along the greater curvature, and, unlike in Roux-en-Y gastric bypass (RYGB), there is no intestinal rearrangement. Yet SG leads to significant and sustained reductions in body mass, specifically because of reduced adiposity, and improves glucose and lipid metabolism.

Interestingly, SG also reduces meal size and shifts macronutrient preference away from fat [3–5]. These potent effects of bariatric surgery on feeding behavior suggest that surgery could be a viable options for patients with PWS. In the past, some studies have tested the effectiveness of bariatric surgical procedures in obese individuals with PWS but have not found the anticipated health advantages [6]. Overall, these studies concluded that bariatric surgical procedures did not lead to significant weight loss in PWS and may in fact be associated with an increased risk of complications [6]. However, since these publications, bariatric surgical procedures have had great technologic advancements that have contributed to greater reliability and reduced complications [7,8]. Given the simplicity of the SG procedure and the reduced need for vitamin replacement but high degree of weight loss and metabolic improvements, this surgery may be an effective strategy for obese individuals with PWS.

PWS is complex syndrome in which multiple genes on chromosome 15 q11–q13 are inactivated [9]. Of these genes, MAGEL2 has emerged as a strong candidate for many aspects of the PWS phenotype after the discovery of children carrying mutations only in MAGEL2 with a PWS-like phenotype [10–12]. Mice with a mutation in the homolog Magel2 exhibit many characteristics of PWS, including elevated adiposity, decreased physical activity, increased leptin and insulin levels, and deficits in reproduction [13–15] and metabolism [16,17]. This model offers an opportunity to determine the potential for bariatric surgery to compensate for this genetic defect and lead to a well-tolerated, effective strategy for both weight loss and improvement in the obesity-associated co-morbidities in PWS.

Materials and methods

Animals

Female heterozygous Magel2 knockout mice (C57 BL/6-Magel2 tm1 Stw/J, the Jackson Laboratory stock #009062) were received from Dr. Rachel Wevrick (University of Alberta) and bred in-house at the University of Cincinnati to male wild type (WT) C57 Bl/6 J mice. Male heterozygous *Magel2* knockout mice were used for the following experiments along with their wild type littermate controls. As in human PWS, imprinting silences the maternally inherited *Magel2* allele, so that heterozygous mice carrying a paternally inherited *Magel2* deletion allele are effectively *Magel2*-null [15]. At 14–18 weeks old, all mice were placed on a high-fat diet (45% fat, 4.54 kcal/g, D12451 Research Diets, New Brunswick, NJ). Over the next 8 weeks, measurements of weight, food intake, and activity were performed on a subset of mice (n = 10–12/genotype) whereas lipid analysis and all other measures were performed on all mice (n = 15–21/genotype). Mice underwent SG (see later) at 24–28 weeks of age, after 10 weeks on the high-fat diet. Postoperative weight, food intake, and glucose regulation were measured over the 10 weeks after surgery. All mice had *ad libitum* access to food and water at all times, unless noted later. Mice were individually housed within temperature-controlled rooms with a 12 h:12 h light cycle with lights on at 6 AM. All studies were approved by and performed according to the guidelines of the Institutional Animal Care and Use Committee of the University of Cincinnati.

Sleeve gastrectomy

SG and sham surgeries and postoperative care were performed as previously described [5,18]. All mice remained on the high-fat diet after the surgery.

Locomotor activity, energy expenditure

Animals were singly housed and placed into an automated system to measure data in increments of 5 minutes (Phenotyping Systems International Group, Chesterfield, MO). Activity counts were measured via horizontal beam break over the course of the 4–7 days. Energy expenditure was calculated by indirect calorimetry and expressed as average kcal/hour in 12-hour bins. Because of limitations in the number of animals we could run at one time, a subset of mice from each group (4–5/group) was chosen at random to receive activity and energy expenditure data collection.

Glucose tolerance test

All animals were fasted for 4 hours before the glucose bolus. Dextrose (25%, 2 mg/kg) was delivered either orally (oral glucose tolerance test [GTT]) or via intraperitoneal injection. Blood glucose was measured by glucometer before glucose injection (time 0), and then 15, 30, 45, 60, and 120 minutes postinjection. Blood was collected from the tip of the tail by cutting a small amount of the tail and gently massaging the blood out.

Insulin tolerance test (ITT)

Insulin (500 mU/kg) was delivered intraperitoneally. Blood glucose was measured by glucometer before insulin injection (time 0), and then 15, 30, 45, and 60 minutes postinjection. Blood was collected from the tip of the tail by cutting a small amount of the tail and gently massaging the blood out.