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A Rat Model of Restrictive Bariatric Surgery with Gastric Banding

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Background: Gastric banding is a well established weight reduction operation that is effective in the treatment of severe obesity. Its metabolic and endocrine mechanisms of action, however, remain unclear. The aim of this study was to establish a rat model of gastric banding that would replicate the procedure performed in human obese patients.

Methods: Male Wistar rats were submitted either to gastric banding (n=5) or sham gastric banding (n=4), and were followed for 21 days. Detailed description on how to perform gastric banding in rats are herein described.

Results: The Wistar rats submitted to gastric banding showed a decrease in weight gain and food intake when compared to sham-operated rats. The cumulative weight gain during the 21 days after the surgical procedure was 143 ± 2.58 g for the gastric banded rats and 162 ± 2.48 g for the sham-operated animals (*P*=0.001). The cumulative food intake was 329 ± 0.53 g for the gastric banded rats and 380 ± 15.22 g for the sham-operated animals, also statistically significant (*P*=0.025).

Conclusion: A rat model to study gastric banding is described. This model can now be used for experimental investigation of biochemical and molecular mechanisms of weight loss resulting from this type of surgery.

Key words: Obesity, gastric banding, bariatric surgery, food intake, rat

Introduction

The prevalence of obesity is accelerating worldwide. The obesity epidemic is recognized by the World Health Organization as one of the top 10 global health problems.[1] Obesity is associated with increased prevalence of hypertension, dyslipidemia, diabetes type 2, cardiovascular disease, non-alcoholic steatohepatitis, sleep apnea, osteoarthritis and depression.[1] The high morbidity rate is costly, both for the individual and the health-care system.[2-4] Weight loss improves or resolves the co-morbidities.[5,6]

Bariatric surgery, by restrictive or malabsorptive methods, is the only treatment sustaining weight loss.[5] Gastric banding, a restrictive type of bariatric surgery, is a well established weight reduction operation,[7] although the precise mechanisms leading to weight reduction are not fully understood.[5] In general, bariatric surgery is considered to induce weight loss by reduction of gastric capacity and by decrease in appetite, both leading to diminished food intake.[2] If and how such a surgical procedure interferes with appetite and satiety is difficult to demonstrate in humans. Thus far, there are no experimental studies to support this interpretation. Further investigations on the sustained weight loss that follows gastric banding may enable a better understanding of the appetite-satiety pathways, and also the development of new and more successful medical treatments of obesity.

There is a need for an animal model that will allow the testing of putative mechanisms whereby surgical procedures lead to a decrease in food intake and body weight, that are known to be regulated by the interaction between the gastrointestinal tract and the hypothalamus.[2] We have, therefore, investigated whether gastric banding would lead to weight loss in Wistar rats in a way that would resemble what occurs in the human after gastric banding. In the current preliminary report using a small number of

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rats, we document that there are significant differences between rats submitted to gastric banding and sham-operated controls with regards both to food intake and body weight.

Materials and Methods

Nine male Wistar rats (125-150 g) purchased from the commercial breeder Charles River, Barcelona, were maintained in individual cages under controlled temperature (21-23˚C), humidity, and light (12h light, 12h dark, lights on at 0800 h) with *ad libitum* access to standard rat chow (A04, Panlab, s.l., Barcelona, Spain) and tap water. All procedures were approved by the local Ethics Board for Animal Research, and followed the European Union laws on animal protection (86/609/EC). Animals were acclimatized to the local facilities for 7 days before surgery and only healthy growing animals were used in the experiments.

After an overnight 12h fast, rats were anesthetized by intra-peritoneal injection of a mixture of ketamine 60 mg/kg (Imalgene 1000, Merial, Portugal) and xilazine 12 mg/kg (Rompun, Bayer, Portugal) according to body weight. A midline abdominal incision was made, and the stomach was exposed. For the gastric banding, the surgical technique consisted in placing a 14-mm long and 2-mm wide silicone band, custom-made, at the glandular portion of the gastric fundus immediately below the rumen, partially restraining the stomach volume and creating upper and lower pouches in the stomach. To keep the band from sliding and from dislocation, two vertical stitches (Prolene 5/0, Ethicon, Edinburgh) were placed in the anterior stomach wall near the lesser and the greater curvatures (Figure 1A and B). The abdominal wall was closed with reabsorbable sutures (Vycril 3/0, Ethicon, Edinburgh).

As controls, a sham-operated group of four rats was included. These rats were submitted to the same procedure described above, except for the placing of a non-restraining band in the same location which was removed immediately before closure of the abdominal wall. Both groups of animals were given 5 ml sterile warmed saline subcutaneously to avoid dehydration and allowed to recover spontaneously from anesthesia and the surgery.

Rats were returned to their home cages which contained a pre-weighed amount of food. Body weight was measured daily at 0900 h using a scale (Monobloc, Metterr, Toledo, Spain), recording to the nearest 1 g and the remaining food in the hopper was reweighed at the same time using a scale (Kern, KB 5000-1, Balingen, Germany) recording to the nearest 0.1 g, which allowed daily food intake to be calculated.

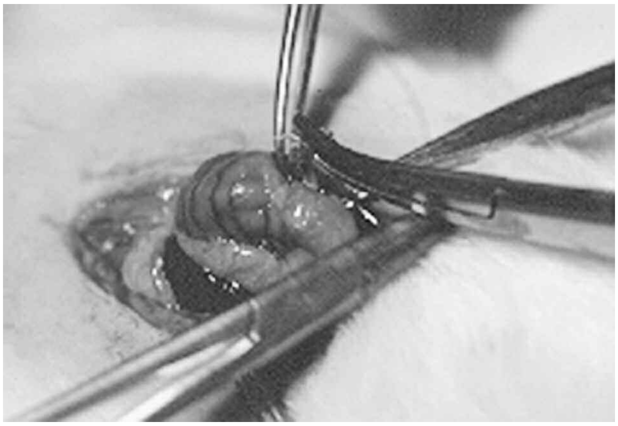

Figure 1A. Surgical placement of a gastric band around the stomach of a Wistar rat, just below the rumen of the animal.

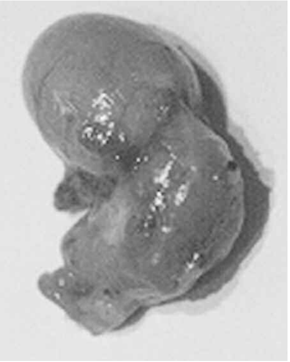

Figure 1B. The stomach of a Wistar rat after being submitted to gastric banding.

Results are shown as means ± SE, unless otherwise specified. Unpaired *t*-test was used for comparison of the means between the two unpaired treatment groups; $P<0.05$ was considered to be statistically significant.

Results

Male Wistar rats were submitted either to gastric banding (n=5) or sham gastric banding (n=4), as described above, and were followed for 21 days after the surgical procedure. All animals submitted to surgery recovered successfully and survived until the end of the experiment. Baseline mean body weight was comparable in the two groups of animals before treatment: gastric banded (156.6 ± 4.04 g) and sham-operated (152.5 ± 4.87 g) rats, respectively (P=0.53).

After surgery, gastric banded rats showed a decrease in weight gain compared to sham-operated animals (Figure 2). The cumulative weight gain 21 days after the procedure was 143 ± 2.58 g for the gastric banded rats and 162 ± 2.48 g for the sham-operated animals, a significant difference (P=0.001).

During the first days after surgery, there was also a decrease in food intake in gastric banded rats in comparison to sham-operated ones. This was reflected in the finding that the cumulative food intake for the 21 days was 329 ± 0.53 g for the gastric banded rats and 380 ± 15.22 g for the sham-operated animals, also a significant difference (P=0.025) (Figure 3).

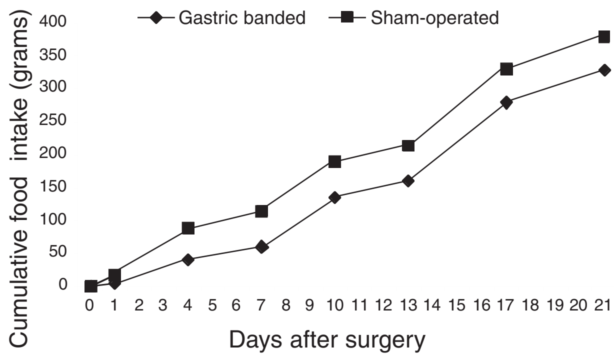

Figure 3. Comparison of cumulative food intake between gastric banded Wistar rats and sham-operated control during the 21 days that followed surgery. Gastric banding resulted in a statistically significant decrease in cumulative food intake.

Discussion

This investigation documents that weight loss can be reproduced in a rat model using a procedure similar to human bariatric surgery with gastric banding that is frequently employed in humans to treat morbid obesity. The rat was selected as the experimental model of bariatric surgery because it is the animal in which the pathways involved in appetite and the gut-brain cross-talk are better defined.[8,9] The development of gastric banding in the rat required several stages involving the surgical skills learning curve and experimentation of different techniques, due to anatomical differences between the human and rat stomach. To acquire these expertise was necessary before satisfactory results were reached concerning survival and effectiveness of the described method.

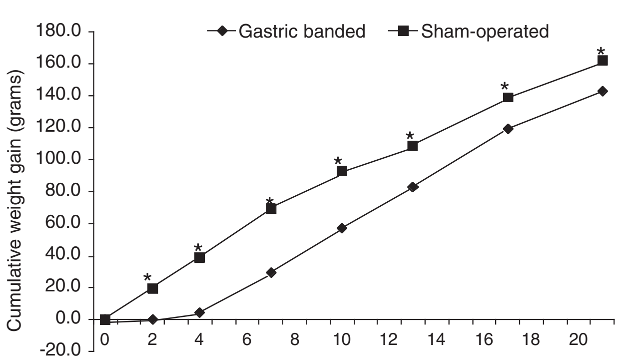

Figure 2. Comparison of the mean cumulative body weight gain between the two groups of Wistar rats: gastric banded (black diamonds) and sham-operated controls (black squares). Values are statistically significant (*P<0.05) between the two experimental groups.

Because of the existence in the rat stomach of a rumen, which has no correlate in the human stomach, and also to the proximity between esophagus and duodenum in the rat because the length of the lesser curvature is very short, it was necessary to adapt the surgical technique by placing the silicone band just below the rumen, passing it through the middle of the lesser curvature. This positioning of the band is somewhat lower than the usual placement in humans. Because of the anatomical and dietetic differences between the two species, this surgical strategy was elected as the one that better corresponded to the human banded stomach.

Because this was a pioneering attempt to establish a new animal model, we have used a small number of rats. Nevertheless, the numerical data revealed significant differences both in body weight and in cumulative food intake between rats submitted to bariatric surgery and sham-operated controls. It should be emphasized that in contrast to gastric banding in humans, we have used animals with normal weight. Furthermore, because these were normal weight and growing rats, it was not expected to observe a decrease in absolute weight but rather a decrease in weight gain and food intake.

Clearly, two goals are to be pursued in experiments in the near future: to reproduce these data in a larger number of Wistar rats and to apply this model in obese Zucker rats. These rodents, would be a better model than the normal weight Wistar rat, because that model could better replicate the common human obesity, with respect to weight loss and improvement in co-morbities that are observed after bariatric surgery.

In Zucker rats, obesity is due to a missense mutation of the gene coding for the leptin receptor, diminishing the leptin signalling in the brain, causing hyperphagia and positive energy balance.[10-12] Leptin resistance is also found in the most common cases of human obesity, for unknown reasons although considered to be multi-factorial and polygenic in nature.[13-15]

In conclusion, this is the first evidence for an animal model that reproduces changes in body weight that occur in obese humans after bariatric surgery with gastric banding. Thus, further investigation of endocrine and metabolic alterations associated with surgical treatment of human obesity can be researched using this proposed experimental model.

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