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An Obese Rat Model of Bariatric Surgery with Gastric Banding

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Background: Bariatric surgery is the only treatment that can provide effective long-term weight loss for morbid obesity. However, animal models of bariatric surgery have not yet been well established. The aims of this study were to establish an obese rat model of gastric banding and to determine whether the model would replicate the procedure of human gastric banding in terms of weight loss and metabolic parameters.

Methods: 27 male Zucker fatty rats were divided into 3 groups: the sham-operated control, gastric banding, and diet treatment groups. They were followed for 8 weeks after surgery, and their body weight change, cumulative food intake and metabolic parameters were examined.

Results: For the sham-operated control, gastric banding, and diet treatment groups, the mean body weights were 644±28 g, 511±77 g, and 339±15 g; % change of weight at 8 weeks after operaion were +63.7±8.3%, +33.2±20%, -12.0±2.0%, respectively. Absolute weekly food intake amounts were 233.8±38.1 g, 157.3±64 g, 80 g, and cumulative food intakes were 1862±111 g, 1258±375 g and 640 g, respectively. The gastric banding rats showed significant decreases in weight gain, % change of weight, absolute weekly food intake, and cumulative food intake compared to sham-operated control rats (*P*<0.05). The banding group also had lower levels of all metabolic parameters compared with controls (*P*<0.01), and these levels were equal to those of the diet-treated group.

Conclusion: The present study provides a new animal model of gastric banding using obese rats. This model may be useful in research on the biochemical and molecular mechanisms of morbid obesity.

Key words: Obesity, bariatric surgery, gastric banding, rat, Zucker fatty rat

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Introduction

The number of obese patients has been increasing worldwide, and the World Health Organization has declared that obesity is a disease of pandemic significance.[1] Obesity is associated with an increased prevalence of hypertension, type 2 diabetes, dyslipidemia, cardiovascular disease, non-alcoholic steatohepatitis, sleep apnea, osteoarthritis and depression,[2] and weight loss can improve or resolve these co-morbidities.[3,4] There are some medical therapeutic strategies for morbid obesity, but there has been very limited success in maintaining clinically significant weight loss.[5] Surgery is the only treatment that can provide effective long-term weight loss for the morbidly obese.[6,7] Gastric banding, a popular bariatric operation,[7,8] induces substantial weight loss due to a decrease in fat mass with relatively less reduction in the components of fat-free mass, and without significant harmful effects on body composition.[9,10]

Recently, rat models of bariatric surgery with gastric banding have been reported,[11,12] but such models have not been well established until quite recently. The aims of the present study were to establish an obese rat model of gastric banding and to examine whether the model would replicate the procedure of human gastric banding in morbidly obese patients.

Materials and Methods

Animals

Twenty-seven male ZUC-Lepr ^{fa}/Lepr ^{fa} rats (Zucker fatty rats) (8 weeks of age, 280-300 g) purchased from a local breeder (Charles River, Kanagawa, Japan) were maintained in individual cages under controlled temperature (24 ± 2°C), humidity and light cycle (12 h light, 12 h dark; lights on at 07:00) conditions, with *ad libitum* access to standard rat chow (CE-2, Clea Japan, Inc., Tokyo, Japan) and tap water. Zucker fatty rats are widely used as an animal model of obesity, and they are characterized by leptin resistance, insulin resistance, and hyperphagia.[13-15] The animals were acclimatized to the local facilities for 14 days before surgery. All studies were conducted in accordance with the Oita Medical University Guidelines, which are based on the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Surgical Procedure

After a 48-h fast, the rats were anesthetized with diethyl ether (Ethyl Ether; Wako Pure Chemical Industries, Ltd., Osaka, Japan) and intraperitoneal injection of 0.04-0.08 mg/g pentobarbital sodium (Nembutal; Abbott, Osaka, Japan). Since Zucker fatty rats are very hyperphagic, 48 h fasting is necessary to empty the stomach.[16] The rats were placed in the dorsal decubitus position with the 4 limbs fixed to the surgical table, and preoperative epilation of the abdomen was performed using a hair trimmer. The rat stomach consists of 2 anatomically different parts and is significantly different from the human stomach. The upper part (forestomach) serves as a reservoir and has a squamous epithelium. The lower part, which is similar to the human stomach (glandular stomach) is the pyloric or glandular region.[17,18] Because of these differences, it is very difficult to perform a gastric banding operation equivalent to that in humans. In order to establish a rat model of gastric banding which approximates the human procedure, unlike in previous models,[11,19] we developed a new model of gastric banding, as described below.

An upper abdominal midline incision (4-5 cm) was made in Zucker fatty rats. First, an incision 5 mm in length was made at the borderline between the upper and lower parts of the stomach and the incision lines were then sutured with 5-0 PDS® (Ethicon, Tokyo, Japan) (Figure 1-A). Next, a gastric band made of nylon (Insulok; Hellermann, Tyton, Tokyo, Japan; Figure 2) was placed around the lower part of stomach below the gastroesophageal junction. Bands of this type are often sold for use with electrical cords. In a different rat model recently published, a similar band was used.[19] To prevent band slippage, the separated stomach was fixed just above the band with 5-0 PDS® (Ethicon) (Figure 1-B). The length of the tied band was 18 mm in order to standardize the degree of gastric restriction. The abdominal wall was closed with 3-0 Vicryl (Ethicon).

We included two control groups: a sham-operated group; and a diet-treatment group which received meals 1/3 the size of those of the other groups. All operated rats were given 5 ml of sterile warmed saline subcutaneously to avoid dehydration and to aid in spontaneous recovery from anesthesia and surgery.

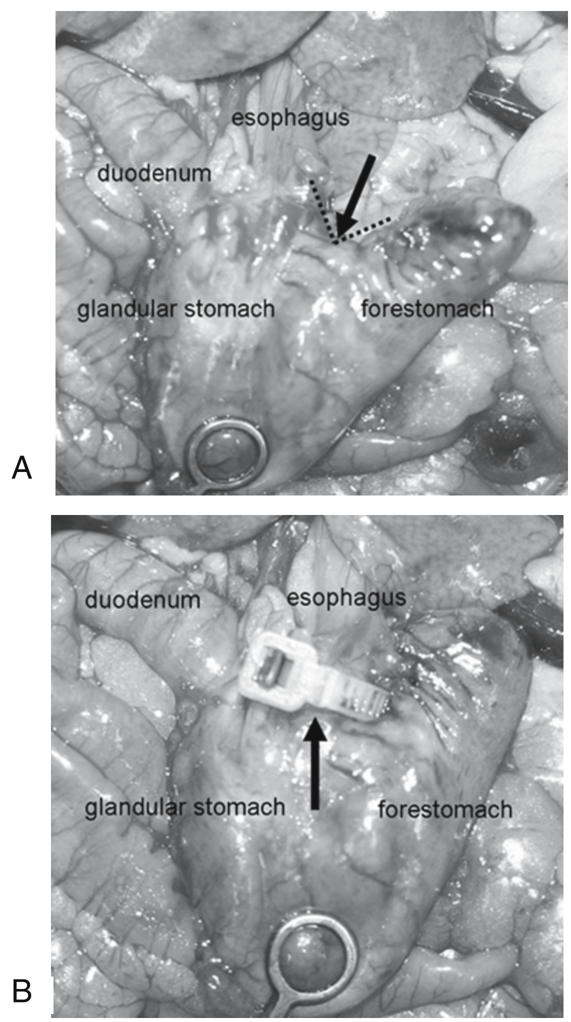

Figure 1. Surgical gastric banding procedure. **A.** An incision 5-mm long was made in the stomach at the borderline between the upper and lower parts (arrow), and sutured. **B.** The gastric band was placed around the lower part of stomach below the gastroesophageal junction (arrow).

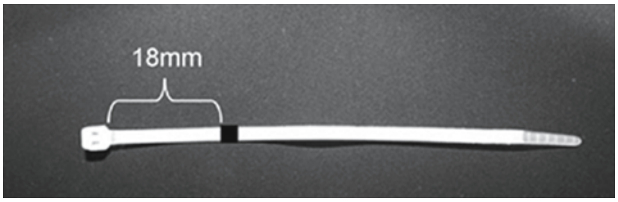

Figure 2. Gastric band. The length of the tied nylon band was 18 mm to standardize the degree of gastric restriction.

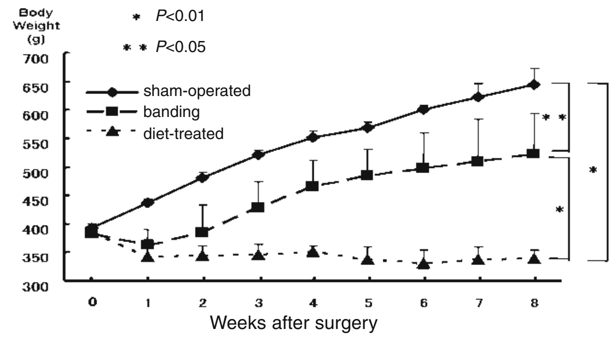

Figure 3. Changes in body weight after operation.

Measurement Protocol of Body Weight and Food Intake Amount, and Blood Sampling Protocol

Body weight and food intake were measured weekly at 10:00 using a scale (Animal Scale; Clare, Tokyo, Japan).

All blood sampling tests were performed at 8 weeks after operation. The rats were deprived of food but not of water for 24 h before sampling. The blood samples were obtained, immediately placed on ice and centrifuged. Plasma was removed and the samples were stored at -20° until assay. Blood glucose (Accu-Chek; Sanko Junyaku Co., Ltd., Tokyo, Japan), total cholesterol (L-type Wako CHO-H; Wako) and triglyceride (L-type Wako TG-H; Wako) were measured using commercial enzyme immunoassays.

Statistical Analysis

Results are shown as mean±SE. The body weight, food intake and metabolic parameters were compared between the three groups using repeated or non-repeated analysis of variance (ANOVA) with Bonferroni correction. $P<0.05$ was considered to be statistically significant.

Results

Changes in Body Weight

At 8 weeks after operation, the mean body weights were 644±28 g in the sham-operated rats, 511±77 g in the banding rats, and 339±15 g in the diet-treated rats (Figure 3). The gastric banding rats showed a decrease in weight gain 8 weeks after operation compared to sham-operated controls ($P<0.05$). Additionally, there were significant differences in the final weight between the banding rats and diet-treatment group ($P<0.01$). When these data were calculated as % changes of weight at 8 weeks after operation, we obtained increases of 63.7±8.3% in the sham-operated rats, 33.2±20% in the banding rats and -12.0±2.0% in the diet-treated rats (Figure 4). There were also significant differences between the banding and sham-operated groups ($P<0.05$).

Food Intake

Food consumption was measured weekly from operation day to 8 weeks after operation. The gastric banding rats showed a significant decrease in weekly food intake compared to sham-operated rats during the 8 weeks after operation ($P<0.05$; Figure 5). The decreased weekly food intake in the banding rats was sustained for the full 8-week follow-up period. When the banding rats were sacrificed at 8 weeks, no band slippages were recognized.

Total food intake was 1862±111 g in the sham-operated controls, 1258±375 g in the gastric banding rats, and 640 g in the diet-treated rats (Figure 6). The gastric banding rats showed a decrease in their total food intake compared to sham-operated rats ($P<0.05$). There were also significant differences in the total food intake between the banding and diet-

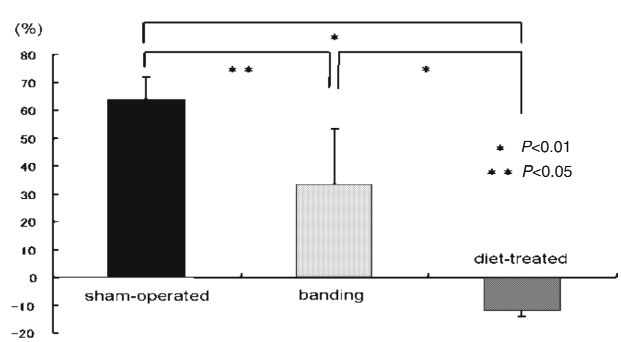

Figure 4. Percent changes in weight at 8 weeks after operation.

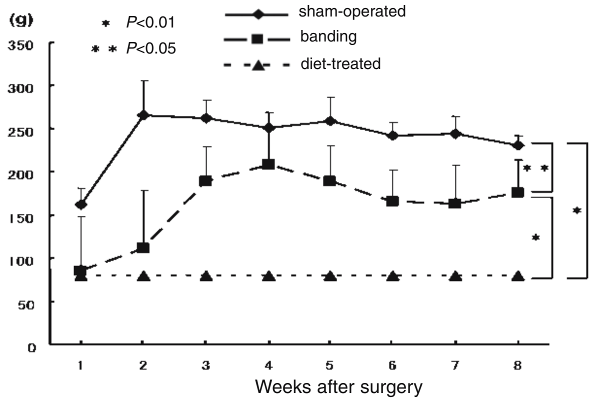

Figure 5. Absolute weekly food intake amounts after operation.

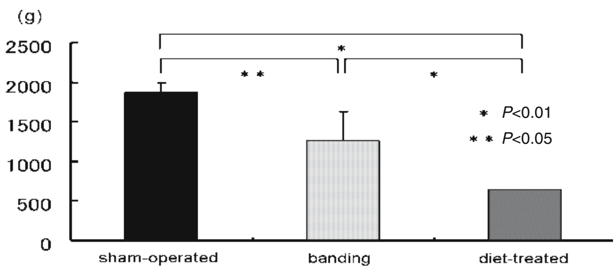

Figure 6. Total food intake for 8 weeks.

treated rats (P<0.01).

Changes in Metabolic Parameters

The data of mean blood glucose, total cholesterol and triglyceride at 8 weeks after operation are shown in Table 1. The banding group showed lower levels of all metabolic parameters compared to the sham-operated controls (P<0.01). However, there were no significant differences in the parameters between the banding and diet-treated groups.

Table 1. Metabolic parameters at 8 weeks after operation

	Sham-operated (n=10)	Banding (n=10)	Diet-treated (n=7)
Metabolic Parameters			
Glucose (mg/dl)	226±22	161±10*	147±12
Total cholesterol (mg/dl)	170±50	107±24*	97±7*
Triglyceride (mg/dl)	155±33	70±13*	50±2*

*P<0.05 vs sham-operated controls.

Discussion

The most popular bariatric surgical procedures for obesity worldwide are laparoscopic Roux-en-Y gastric bypass (RYGBP) and laparoscopic adjustable gastric banding (LAGB).[7] Recent studies have demonstrated that LAGB is equivalent to RYGBP in long-term weight loss, and superior to RYGBP in terms of perioperative safety.[8,20] Although percent excess weight loss (%EWL) in patients who undergo RYGBP increases rapidly during the first postoperative year, it then remains nearly unchanged until the third year. In contrast, in patients who undergo LAGB, weight loss has been found to be slower but steady over a 3-year follow-up period.[21] Both treatments offer sustained weight loss and improve co-morbidities associated with obesity. Since the goal of surgical treatment for obesity is to give obese patients long-lasting weight loss and resolution of co-morbidities,[5] both procedures are considered to be acceptable. In Japan, the criteria for metabolic syndrome were established in 2005, because the number of obese patients with co-morbidities requiring treatment has been gradually increasing.[22] In addition, we introduced LAGB to Japan in 2005.[23]

Although considerable basic research on RYGBP using animal models has been conducted,[16,24-26] animal models of gastric banding are very limited.[11,19] Bozbora et al[12] estimated the materials of gastric banding for gastric and esophageal mucosa of Wistar rats. De Monteiro et al[11] established an animal model of gastric banding using Wistar rats, and showed a decrease in both cumulative weight gain and food intake. Additionally, de Menze Ettinger et al[19] performed laparoscopic gastric banding in Wistar rats as a means of video-laparoscopic training. Reports on gastric banding rat models are increasing, but to the best of our knowledge, there have been no reports on improvements in metabolic parameters or on the detailed procedures of the gastric banding. It has thus been very difficult to standardize banding procedures in animal models.

The present study is the first report of a rat banding model using Zucker fatty rats. Rats with hyperphagia and obesity are frequently used in basic research on obesity.[13] In the present study, the rats with gastric banding showed significant decreases in both weight gain and food intake, and showed improvement in their metabolic parameters compared to those of sham-operated controls. Gastric banding in Zucker fatty rats thus suggests the possibility of ameliorating metabolic parameters. The gastric banding restricted two-thirds of food intake compared to sham-operated controls, but permitted about two-fold intake compared to the diet-treated group. As a result, the banded rats could gain weight and grow, but their metabolic parameters did not deteriorate. The decreased weekly food intake in the banded rats was sustained throughout the 8-week follow-up period. These results are different from those obtained by de Monteiro et al,[27] who found a similar daily food intake in banded and sham-operated rats after postoperative day 10. In the present model, there was no slippage of the gastric band and the band was maintained in a good position on the stomach. The present model may be useful in researching gastric banding and metabolic syndrome, because the model does not induce too much weight loss and there is no slippage of the gastric band.

In conclusion, we have developed a new obese animal model of gastric banding using Zucker fatty rats. This model may be beneficial in investigations on morbid obesity and bariatric surgery with gastric banding.

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