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Salt and water handling after gastric bypass surgery in rats

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Abstract

Background—The interaction between the gastrointestinal tract and the renal excretion of sodium and water is poorly understood. The observation that beneficial effects on blood pressure are seen in bariatric surgery patients before significant weight loss, led us to hypothesise that the Roux-en-Y gastric bypass (gastric bypass) would alter renal salt and water handling.

Material and Methods—21 male wistar rats (Body weight (BW) 348±19g) underwent either gastric bypass (n=14) or sham operation (n=7). Animals were kept on a low sodium diet (DO2051701, Research Diets, Inc., New Brunswick, USA) and deionized water *ad libitum*. Before and after surgery rats received oral hypertonic sodium solution (1.5 mmol/kg BW) and were placed individually in metabolic cages to measure urine production and water intake for 8 h. Urine sodium concentration was measured by Integrated Chip Technology (ICT) using the Architect ci16200 (Abbott, Illinois, USA).

Results—Rats that underwent gastric bypass had a significantly lower body weight than sham-operated controls over the entire follow-up period. (387.5 ± 18.3g vs. 501.3 ± 8.0g, p=0.0004). An oral sodium load following gastric bypass operation led to increase in water intake (0.065±0.012 ml/g BW vs. 0.033±0.006 ml/g BW, p= 0.023), urine output (0.034±0.007 ml/g BW vs. 0.015±0.002 ml/g BW, p= 0.027) and natriuresis (65.99±10.7 mol vs. 31.71±8.7 mol, p=0.020). These differences were greater in bypass operated animals that lost weight (“Responders”) compared to those that did not (“Non-Responders”). There was no change in water intake, urine production or sodium excretion after surgery in the sham-operated group.

Conclusions—Urine production, water intake and sodium excretion are increased after gastric bypass in rats following oral salt loading. The magnitude of this effect correlates with the amount of weight loss after surgery. These observations may explain part of the mechanism underlying the effects of bariatric surgery on blood pressure.

Keywords

Gastro-intestinal tract; hypertension; sodium; water

Background

Gastric bypass surgery is currently the most effective treatment for obesity and the beneficial effects on obesity-related comorbidities such as diabetes and hypertension are well documented [1]. The research focus in this field to date has been on the effects of bariatric surgery on gut hormone release and the improvement in glucose homeostasis as a result [2,3]. Less attention has been given to the mechanisms underlying the resolution of hypertension after bariatric surgery. In the Swedish obese subjects (SOS) study, systolic blood pressure decreased by approximately 11 mmHg and diastolic by approximately 7 mmHg in the first 6 months after bariatric surgery [4,5], although this effect was not sustained in the longer term. Several other studies have shown similar observations [1,6-8]. The improvement in blood pressure seen after bypass surgery was initially thought to be a medium-term effect, with the first documented reductions seen at eight weeks. However, Ahmed et al. observed significant reductions in systolic (9 mmHg) and diastolic (7 mmHg) blood pressures as early as one week after gastric bypass surgery [9]. Furthermore, the beneficial effect was maintained for at least one year, and the postoperative usage of antihypertensive medication was reduced by a third [9].

Hypertension is associated with central adiposity and insulin resistance [10,11], but the pathophysiological mechanism remains unclear. There are several plausible hypotheses including insulin resistance [12,13], aldosterone and aldosterone releasing factors (ARF) [14,15], as well as hyperleptinemia [16,17]. The reduction of visceral fat mass and subsequent decrease of sympathetic activation and sodium retention is not immediate and does not explain the early reductions in blood pressure after RYGB described by Ahmed et al [9]. Thus, we hypothesized that salt and water handling of the kidney might be altered after bypass surgery and this modification potentially contributes to the early resolution of hypertension after gastric bypass.

Our aim was to evaluate water intake, urine production and urinary sodium excretion in rats before and shortly after gastric bypass surgery.

Methods

Animals

21 male wistar rats (BW 348±19g) were randomized to have either a gastric bypass (n=14) or sham operation (n=7). The work was performed under UK Home Office licence (PL 70-5569). All animals were kept in identical environmental conditions (temperature 24°C, humidity 60%, light cycle 7.00 – 19.00) with normal chow (RM1 diet, Special Diet Services Ltd, UK) and tap water *ad libitum* unless otherwise stated. Body weight was measured daily.

Metabolic cage experiments

Metabolic cage experiments were performed one week preoperatively and on postoperative day 30 and 60. Prior to each experiment animals were on low sodium diet and deionized water *ad libitum* for one week to establish a constant urinary sodium excretion for all animals [18]. The low sodium diet was identical to normal chow except for its salt content (D02051701, Research Diets Inc., New Brunswick, NJ, USA; sodium content 102.6 ppm). For measurements before surgery and on postoperative day 30, salt (1.5 mmol Na/kg BW) was given intragastrically via an oral gavage over 10s in the form of an hypertonic NaCl

solution (616 mM) at the beginning of the light phase (7.00 am). Animals were then placed individually into a metabolic cage designed for urine collection and measurement of water intake for eight hours. For baseline measurements on postoperative day 60, animals were placed into the metabolic cage without an oral sodium load. In all experiments urine was collected in pre-weighed plastic tubes. Water was given in pre-weighed plastic bottles which were also re-weighed at the end of the experiment. The cages were cleaned and rinsed with deionized water after each experiment.

Surgery

Surgery was performed according to an established and standardized protocol under isoflurane anaesthesia [2]. All operations were carried out by one investigator (M.B.). The rats were fasted overnight, but had access to tap water ad libitum. Briefly, the stomach was transected close to the gastro-oesophageal junction, which was subsequently anastomosed to a loop of jejunum 7 cm distal to the ligament of Treitz in an end-to side fashion. A 7 mm side-to-side small bowel anastomosis was performed between the biliopancreatic and the alimentary limbs to create a common channel of 25 cm, and the omega loop of small bowel was then divided. Figure 1 shows a diagrammatic representation of the RYGB rodent model. The sham operation consisted of a laparotomy, a 7mm gastrotomy on the anterior wall of the stomach with subsequent closure, and a 7 mm jejunotomy with subsequent closure. Preoperatively, gentamicin 8 mg/kg and carprofen 0.01 mL were administered intraperitoneally (ip) as prophylaxis for postoperative pain and infection.

Measurement of urinary sodium

Urine sodium concentration was measured by Integrated Chip Technology (ICT) using the Architect ci16200 (Abbott, Illinois, USA). It obtains millivolt readings, and then converts them to assay-specific analyte conversion units. The measurement of ICT reference solution and ICT samples are used to calculate the assay results.

Statistical analysis

Data is presented as mean $\pm$ SEM unless otherwise indicated. Data were compared with the use of 2-tailed, paired Student t tests (Graphpad Prism, USA). $P < 0.05$ was considered significant.

Results

Weight loss

Body weight (BW) was significantly lower in the group of rats that underwent gastric bypass compared with the sham-operated group (Day 60: 388 ± 18 g vs. 501 ± 8 g, $p = 0.0004$). Figure 2 shows the percentage of initial BW for all bypass ($n = 14$) and sham operated rats ($n = 7$). However, it was clear that not all rats lost weight after the bypass procedure. Those animals that lost weight compared to baseline were defined as 'responders' ($n = 8$) while all others were defined as 'non-responders' ($n = 6$). The mean BW of these two groups were significantly different from day 8 for the rest of the study (Day 8: 316.6 ± 5.3 g vs. 336.5 ± 4.5 g, $p = 0.02$). Representative data for postoperative day 30 (311 ± 12 g vs. 379 ± 8 g, $p = 0.0011$) and day 60 (346 ± 21 g vs. 443 ± 10 g, $p = 0.0029$) are shown in Figure 3. However, after 60 days the "non-responders" still weighed significantly less than the sham-operated animals (443.3 ± 10.3 g vs. 501.3 ± 8 g, $p = 0.0009$).

Urine production

In gastric bypass rats, oral salt loading on postoperative day 30 led to a greater increase in urine output when compared to urine production following oral salt loading prior to surgery

(0.034 ± 0.007 ml/g BW vs. 0.015 ± 0.002 ml/g BW, $p = 0.027$). There was no post-operative change in urine production seen in the sham-operated group (0.010 ± 0.002 ml/g BW vs. 0.011 ± 0.001 ml/g BW, $p = 0.44$). Furthermore, bypass rats produced significantly more urine than sham-operated rats after oral salt loading (0.034 ± 0.007 ml/g BW vs. 0.010 ± 0.002 , $p = 0.038$). There was no difference between urine production on day 60 without oral salt loading and preoperative data (Bypass: 0.017 ± 0.003 ml/g BW vs. 0.015 ± 0.002 ml/g BW, $p = 0.66$ and Sham: 0.012 ± 0.001 ml/g BW vs. 0.011 ± 0.001 ml/g BW, $p = 0.93$). Figure 4 summarizes data for urine output. There appeared to be a relationship between BW loss and urine production as “Responders” produced significantly more urine than “Non-Responders” (0.051 ± 0.009 ml/g BW vs. 0.014 ± 0.003 , $p = 0.006$).

Water intake

Data for water consumption are summarized in Figure 5. Gastric bypass rats consumed significantly more water after the oral salt challenge (1.5 mmol Na/kg BW of a 616 mM NaCl solution) when compared with their water consumption after oral salt loading before surgery (0.065 ± 0.012 ml/g BW vs. 0.033 ± 0.006 ml/g BW, $p = 0.023$). No changes were observed for water intake in the sham operated animals (0.029 ± 0.006 ml/g BW vs. 0.021 ± 0.002 ml/g BW, $p = 0.30$). Moreover, bypass rats drank significantly more water than sham-operated rats (0.065 ± 0.012 ml/g BW vs. 0.02137 ± 0.002 ml/g BW, $p = 0.019$) after oral salt loading. There was no difference between water intake on day 60 without oral salt challenge and preoperative data (Bypass: 0.018 ± 0.005 ml/g BW vs. 0.033 ± 0.006 ml/g BW, $p = 0.10$ and Sham: 0.018 ± 0.005 ml/g BW vs. 0.029 ± 0.006 ml/g BW, $p = 0.21$). Water intake after bypass surgery showed a positive correlation to the level of BW loss as “Responders” displayed significantly greater water intake than “Non-Responders” (0.090 ± 0.015 ml/g BW vs. 0.031 ± 0.006 ml/g BW, $p = 0.007$).

Sodium excretion

Data for sodium excretion are summarized in Figure 6 and 7. Oral salt loading on postoperative day 30 (1.5 mmol Na/kg BW of a 616 mM NaCl solution) led to an increase in cumulative sodium excretion after 8 hours in the gastric bypass rats compared to preoperatively (65.9 ± 10.7 μ mol vs. 31.7 ± 8.7 μ mol, $p = 0.02$). No changes in natriuresis after 8 hours were observed for the sham operated animals (36.2 ± 10.7 μ mol vs. 40.9 ± 16.0 μ mol, $p = 0.81$). There was a trend towards increased sodium excretion in bypass rats compared to their sham-operated counterparts, but this did not attain statistical significance (65.9 ± 10.7 μ mol vs. 36.2 ± 10.7 μ mol, $p = 0.09$). However, differences became significant when bypass rats were divided into “Responders” and “Non-Responders” (80.9 ± 14.4 μ mol vs. 36.2 ± 10.7 μ mol, $p = 0.03$) and cumulative sodium excretion after bypass surgery showed a correlation to postoperative BW ($r^2 = 0.45$ and $p = 0.017$, Figure 7). There was no significant difference between preoperative sodium excretion and sodium excretion on day 60 (Bypass: 35.1 ± 8.8 μ mol vs. 31.7 ± 8.7 μ mol, $p = 0.79$ and Sham: 45.4 ± 9.2 μ mol vs. 40.9 ± 16.0 μ mol, $p = 0.81$).

Discussion

Numerous central and peripheral abnormalities account for the development and maintenance of high arterial pressure in obesity [19]. To date, visceral obesity is considered the most important risk factor for hypertension and cardiovascular disease [20]. Visceral obesity is linked to hyperinsulinemia, hyperleptinemia and increased levels of aldosterone and aldosterone releasing factors (ARF) all of which lead to activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [21-23].

Gastric bypass surgery is currently the most effective treatment for obesity and the beneficial effects on obesity-related comorbidities such as hypertension are well documented [24,25]. However, the reduction of visceral fat mass and subsequent decrease of sympathetic activation and sodium retention is not immediate and does not explain the very early reduction in blood pressure after RYGB described by Ahmed et al [9]. Thus, we reasoned that other mechanisms might be involved in the early resolution of hypertension after gastric bypass and that alteration of renal salt and water handling might be one of them.

We have demonstrated a significant increase in urine production, water intake and sodium excretion after RYGB compared with pre-operative measurements. Sham operated animals show no changes in water intake, urine production or sodium excretion after surgery. Furthermore, we showed that those animals who lost weight after RYGB surgery ("Responders") demonstrated a greater urine production, water intake and natriuresis compared with animals that did not lose weight after RYGB ("Non-Responders"), suggesting a correlation between weight loss and renal sodium handling.

In many groups of patients, hypertension is related to sodium imbalance [26]. Only a few studies have focused on the possible role of the gastrointestinal tract in the control of sodium homeostasis and arterial hypertension. The idea that dietary intake and composition affects renal function is perhaps self-evident, but an exact definition of this relationship is still lacking. Several physiological mechanisms are involved in controlling sodium balance such as the hormones aldosterone, angiotensin [27] and atrial natriuretic peptide [28]. In addition, there is evidence to suggest the involvement of the gastrointestinal tract. Analogous to the "incretin effect", characterized by an exaggerated plasma insulin response to an oral glucose load compared with the same amount of glucose administered intravenously, oral ingestion of sodium chloride has a greater natriuretic effect than when given intravenously in subjects on a low sodium diet [29]. This effect has been shown to be independent of changes in aldosterone and atrial natriuretic peptide [29]. In the case of insulin release, the important incretin gut hormone has been shown to be GLP-1, which has since been developed into a successful treatment for type 2 diabetes [30]. The mechanism for the analogous effect on sodium excretion, and therefore potentially, blood pressure control, has yet to be identified.

Animal studies provide some evidence that the gastrointestinal tract may exert direct influence on renal function. Morgan et al observed that salt-sensitive Harlan Sprague Dawley (HSD) rats (SS/Jr) with transplanted kidneys from salt-resistant HSD rats (SR/Jr) developed a significant NaCl-induced hypertension, suggesting that extrarenal factors contribute to the salt-induced hypertension in salt sensitive rats [31]. These observations were not accounted for by any changes in established hormones known to control renal sodium excretion including aldosterone, renin and angiotensin [27] or atrial natriuretic peptide [28]. Hence, the presence of an intestinal natriuretic factor influencing electrolyte transport in renal tubular cells and causing diuresis was suggested [31]. Studies on other animal models for essential hypertension, such as Spontaneously Hypertensive Rats (SHR) and their genetically matched normotensive controls, Wistar-Kyoto (WKY) rats, have shown that WKY rats have greater difficulties than SHR in conserving sodium both via the gastrointestinal tract and via the kidneys [32,33].

A well-recognized problem associated with gastric bypass is weight re-gain after the operation in some patients [34,35]. This clinical observation is reflected by the fact that not all rats exhibited sustained weight loss following the bypass procedure. Our model closely reproduces the RYGB operation in humans. Thus, we defined animals that lost weight as 'responders' and all others as 'non-responders' [36]. As all operations were carried out by a single surgeon according to a standardized protocol [2], technical variations or inconsistencies are unlikely to account for these postoperative variations in body weight. We

previously postulated that poor weight loss or poor weight loss maintenance post RYGB might be correlated with lower levels of PYY and GLP-1 compared with patients with good sustained weight loss [35]. In this study, reduced urine output, less water intake and decreased sodium excretion were also correlated with lower levels of weight loss after RYGB. This correlation points to the altered salt and water homeostasis seen after bypass surgery being modulated by changes in circulating gut hormone concentrations. Potential mediators include Peptide YY (PYY) and glucagon-like peptide (GLP)-1. It is reasonable to speculate that GLP-1 and PYY may provide the missing link between the gastrointestinal tract and the kidney, as effects on renal salt and water handling have been demonstrated for both [37-39].

In conclusion, gastric bypass provides us with a valuable model to facilitate our understanding of the role that the gastrointestinal tract plays in sodium homeostasis and the development of salt-dependent hypertension. RYGB results in a greater urine output, water intake and sodium excretion in salt-restricted rats following an oral salt challenge. This observation may provide insight into the mechanism of the early improvement in arterial hypertension seen after gastric bypass.

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Figure 1.

Diagrammatic representation of the RYGB rodent model. A= Gastro-Jejunostomy, B=Jejuno-Jejunostomy, C=Alimentary limb, D=Biliopancreatic Limb (7 cm), E= Common channel (25 cm).

Figure 2. Percentage weight change for the RYGB (●) (n=14) and sham-operated rats (■) (n=7). Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

Figure 3.

a and b: Body weight (BW) [g] after sham operation (white columns, n=7), 'Non-Responders' (light grey, n=8) and 'Responders' (dark grey, n=6) after bypass operations on postoperative day 30 (a) and 60 (b). Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

Figure 4. Urine production of bypass operated (black columns, n=14) and Sham operated rats (white columns, n=7) after oral salt loading (1.5 mmol Na/kg BW of a 616 mM NaCl solution) preoperatively and on postoperative day 30. On day 60 urine production was measured without oral salt loading. Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

Figure 5. Water intake of bypass operated (black columns, n=14) and Sham operated rats (white columns, n=7) after oral salt loading (1.5 mmol Na/kg BW of a 616 mM NaCl solution) preoperatively and on postoperative day 30. On day 60 water intake was measured without oral salt loading. Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

a

Figure 6.

a: Cumulative Sodium excretion of bypass operated (black columns, n=14) and Sham operated rats (white columns, n=7) after oral salt loading (1.5 mmol Na/kg BW of a 616 mM NaCl solution) preoperatively and on postoperative day 30. On day 60 sodium excretion was measured without oral salt loading. Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

b: Cumulative Sodium excretion of “Responders” (dark grey columns, n=8) and “Non-Responders” (light grey columns, n=6) and Sham operated rats (white columns, n=7) after oral salt loading (1.5 mmol Na/kg BW of a 616 mM NaCl solution) on postoperative day 30. Data are shown as mean values $\pm$ SEM. $p < 0.05$ was considered significant (*).

Figure 7.

Linear regression analysis of cumulative sodium excretion against percentage weight change in RYGB rats after oral salt loading (1.5 mmol Na/kg BW of a 616 mM NaCl solution) on postoperative day 30 ($r^2=0.57$, $p=0.0067$).