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Original article

Preservation of the gut by preoperative carbohydrate loading improves postoperative food intake☆

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SUMMARY

Background & aims: A carbohydrate (CHO) drink given preoperatively changes the fasted state into a fed state. The ESPEN guidelines for perioperative care include preoperative CHO loading and re-establishment of oral feeding as early as possible after surgery. An intestinal ischaemia reperfusion (IR) animal model was used to investigate whether preoperative CHO loading increases spontaneous postoperative food intake, intestinal barrier function and the catabolic response.
Methods: Male Wistar rats ($n = 65$) were subjected to 16 h fasting with ad libitum water and: A) sham laparotomy (Sham fasted, $n = 24$); B) intestinal ischaemia (IR fasted, $n = 27$); and C) intestinal ischaemia with preoperatively access to a CHO drink (IR CHO, $n = 14$). Spontaneous food intake, intestinal barrier function, insulin sensitivity, intestinal motility and plasma amino acids were measured after surgery.
Results: The IR CHO animals started eating significantly earlier and also ate significantly more than the IR fasted animals. Furthermore, preoperative CHO loading improved the intestinal barrier function, functional enterocyte metabolic mass measured by citrulline and reduced muscle protein catabolism, as indicated by normalization of the biomarker 3-methylhistidine.
Conclusions: Preoperative CHO loading improves food intake, preserves the GI function and reduces the catabolic response in an IR animal model. These findings suggest that preoperative CHO loading preserves the intestinal function in order to accelerate recovery and food intake. If this effect is caused by overcoming the fasted state or CHO loading remains unclear.

1. Introduction

Fasting before surgery has serious consequences for organs such as the gastrointestinal (GI) tract, liver, kidney, heart, and lungs, probably because it exhausts the energy reserves of the body.[1] Fasting further increases the effects of surgical stress, it results in depletion of glycogen stores, dehydration, muscle wasting, a weakened immune response and production of inflammatory mediators.[2] Furthermore, overnight fasting has been reported to induce postoperative insulin resistance, resulting in decreased cellular uptake of glucose, despite high levels of glucose and adequate levels of insulin in the blood. Insulin resistance is an unwanted phenomenon in modern surgical practice because it may lead to an increased infectious complication rate and prolonged length of hospital stay.[3]

A carbohydrate (CHO) drink containing at least 48 g of CHO's given preoperatively changes the fasted state into a fed state and

Abbreviations used: CHO, carbohydrate; GI, gastrointestinal; HOMA-IR, homeostasis model assessment insulin resistance; HRP, horseradish peroxidase; IR, ischaemia reperfusion; 3-MeHis, 3-Methylhistidine; TER, transepithelial electrical resistance.

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counteracts the disadvantageous effects of fasting on patients' well-being. In addition, it is safe and empties rapidly from the stomach to decrease the risk of gastric aspiration.[4] CHO loading reduces postoperative insulin resistance, improves muscle strength, and has a positive effect well-being and shortens length of hospital stay.[5-8] Therefore the use of preoperative CHO loading has been incorporated in the ESPEN guidelines (European Society for Parenteral and Enteral Nutrition).[9] These guidelines for perioperative care include avoidance of long periods of preoperative fasting and re-establishment of oral feeding as early as possible after surgery.

Previously, we have shown in an intestinal ischaemia reperfusion (IR) rat model, that preoperative CHO loading preserves the intestinal barrier function and reduces bacterial translocation.[10] In this model, the animals were allowed to recover for 3 h after surgery under complete narcosis. The results suggest a preservation of the function of the GI tract. Based on this, we hypothesise that preoperative CHO loading may lead to earlier postoperative food intake. To test this hypothesis, ad libitum food intake was measured in an IR rat model, comparing preoperative CHO loading versus fasting. GI function, intestinal barrier function and the catabolic response were also measured 24 h after intestinal ischaemia. We used a well established experimental setup in which we extended the recovery time to at least 24 h.

2. Materials and methods

2.1. Animals

All experimental procedures were approved by an independent animal experiments committee (DEC Consult, Bilthoven, The Netherlands) and complied with the principles of laboratory animal care. Male Wistar rats (Harlan Laboratories, Horst, The Netherlands; 225–250 g on arrival) were pair-housed under a light–dark schedule of 12:12 (lights on at 11 PM) in a temperature and humidity controlled room (21 ± 2 °C and 50 ± 5%, respectively). All animals were allowed to acclimate for 2 weeks and had free access to standard rodent diet and tap water unless stated otherwise.

2.2. Canulation of the jugular vein

All animals were equipped with a jugular vein catheter for stress-free blood sampling according to the Steffens method.[11] The animals were allowed to recover, until they all had regained the weight they had prior to this procedure.

2.3. Study design

Animals ($n = 65$) were divided into 3 groups. A fasted sham-operated group (Sham fasted: $n = 24$) was subjected to 16 h of fasting and laparotomy. The second group (IR fasted: $n = 27$) was also fasted for 16 h followed by laparotomy and intestinal ischaemia by clamping the superior mesenteric artery for 70 min. The remaining group was subjected to laparotomy and intestinal ischaemia, and had ad libitum access to a clear CHO drink (IR CHO: $n = 14$; 12.6% carbohydrates, Nutricia preOp, Nutricia N.V., Zoetermeer, The Netherlands). Water remained ad libitum for all animals and all animals in the IR CHO group voluntarily ingested 35 ml of the provided CHO drink prior to surgery. Surgery was performed under O_2/N_2O/isoflurane anaesthesia (Forene Abbott, Hoofddorp, The Netherlands) and body temperature of the animals was maintained at 37 °C. Peritoneal fluid resuscitation was given during the intestinal ischaemia. Buprenorfine was injected subcutaneously once (3 mg/ml, 1 mg/kg) immediately after surgery. Animals were housed individually in food registration cages with free access to food and water. Spontaneous food intake was automatically recorded every 5 min (Food Intake Monitor for Rat, MED Associates Inc., Georgia, Vermont, USA). Animals were dissected 24 or 48 h after surgery. Blood was drawn via heart puncture. The distal ileum was removed for determination of *ex vivo* intestinal barrier function and the jejunum was removed for *ex vivo* measurements of the motility.

2.4. Ex vivo analysis of intestinal barrier function

After removal of the distal ileum, the epithelium was stripped from the external muscle layer and mounted in Ussing chambers. This procedure was repeated five more times per animal. Horseradish peroxidase, a 40 kD protein (HRP, UKO protein, 15 μL, $1^{*}10^{-3}$ M) was added to the mucosal compartment, and the mucosal to serosal flux of HRP was determined after 150 min. The serosal concentration of enzymatically active HRP was measured using a method based on Gallati and Pracht.[12] The transepithelial electrical resistance (TER) was determined after 150 min, using an epithelial voltohmmeter (WPI, Sarasota, Florida, USA).[13] TER mainly represents paracellular barrier function, whereas the barrier function for HRP is mainly related to endocytosis and represents transcellular barrier function. Both HRP-flux and TER are well established methods for analysis of *ex vivo* measurement of intestinal barrier function.[10]

This model, in which the superior mesenteric artery is clamped for 70 min, is considered to have a great impact on the intestine. To validate this intestinal IR model we wanted to find out whether the damage to the intestine was transient and reversible; 15 animals (Sham fasted: $n = 7$, IR fasted: $n = 8$) were allowed to recover for 48 h after which HRP-flux and TER was measured.

2.5. Determination of intestinal motility

Per animal, four approximately 1 cm sections of the jejunum were placed into organbaths of a myograph (Schuler organbath, Hugo Sachs Elektronik, March, Germany), which measured the contractions of the jejunum. In this experiment we used 8 section of Sham fasted, 8 sections of IR fasted and 4 section of IR CHO jejunum. The sections were incubated with Carbachol (CCh, Sigma, Steinheim, Germany) in increasing concentrations in a range of 0.01, 0.05, 0.1, 0.5, 1, 5, 10 μM for approximately 5 min per concentration. Contractions of the jejunum were recorded and the strength of the contraction was calculated by comparing the tension caused by CCh incubation to the preload tension (gr).

2.6. Plasma analyses

Plasma glucose was determined colorimetrically (GOD-PAP, Roche Diagnostics, Mannheim, Germany). Plasma insulin was analysed in triplicate using serially diluted samples with a specific rat ELISA kit (DRG Diagnostics, Diagnostic System Laboratories, Benelux) with a detection limit of 22.6 pmol/L. The insulin resistance index was assessed by homeostasis model assessment (HOMA-IR = 0.403 * [Glucose $_{t=0}$ (mmol/L) * Insulin $_{t=0}$ (pmol/L)/405]).[14,15] Plasma citrulline, glutamine and 3-methylhistidine (3-MeHis) were determined by high-pressure liquid chromatography (HPLC) as previously described by Hoorn et al.[16]

2.7. Statistics

Statistical analyses were performed using SPSS 15.0.1 software (SPSS Benelux, Gorinchem, The Netherlands). Variables were checked for Gaussian distribution with the Shapiro-Wilkes and Kolmogorov–Smirnov test. Levene's test for equality of variance was used to assess the probability of different variances among