

Ghrelin stimulates intestinal adaptation following massive small bowel resection in parenterally fed rats



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ABSTRACT

Background: Since short bowel syndrome (SBS) patients face life-threatening conditions, the development of therapeutic strategies to induce intestinal adaptation has been investigated. Ghrelin, a ligand of growth hormone (GH) secretagogue-receptor that stimulates the release of GH and insulin like growth factor-1 (IGF-1), has several pleiotropic effects. We investigated whether ghrelin induces intestinal adaptation in parenterally fed rats with SBS.

Methods: Sprague-Dawley rats underwent venous catheterization and were divided into 3 groups: those receiving 90% small bowel resection while leaving the proximal jejunum and distal ileum (90% SBR) with TPN (SBS/TPN group), those receiving 90% SBR with TPN + ghrelin (SBS/TPN/ghrelin group), and those receiving sham operation and fed chow (sham group). Ghrelin was administered intravenously at 10 µg/kg/day. On Day 13, the rats were euthanized and the small intestine harvested, and the histology and crypt cell proliferation rates (CCPR), apoptosis, and nutrient transporter protein levels were analyzed and the plasma hormones were measured.

Results: The villus height and crypt depth of the ileum in the SBS/TPN/ghrelin group were significantly higher than in the SBS/TPN group. The CCPR of the jejunum and the ileum significantly increased by the administration of ghrelin; however, the apoptosis rates did not significantly differ between the SBS/TPN and SBS/TPN/ghrelin groups. Significant differences did not exist in the plasma IGF-1 and nutrient transporter protein levels among three groups.

Conclusions: The intravenous administration of ghrelin stimulated the morphological intestinal adaptation of the ileum to a greater degree than the jejunum due to the direct effect of ghrelin.

1. Introduction

Short bowel syndrome (SBS) is a malabsorptive condition that occurs following extensive small intestinal resection [1]. The most common causes of SBS in children are necrotizing enterocolitis, intestinal atresia, and malrotation with midgut volvulus [2]. As the functional ability of the residual intestine is often inadequate to support growth and hydration, SBS patients require parenteral nutritional support for years. Hence, SBS patients are at risk for many life-

threatening complications such as sepsis due to catheter-related blood stream infections [3] and parenteral nutrition-associated liver disease [4]. The strategy of treatments for SBS patients is often based on trial-and-error. Therefore, we have attempted to develop therapies for restoring the function of the residual small intestine.

After massive bowel resection, the nutritional absorption of the residual small intestine is compensated gradually by increasing the mucosal surface area and absorptive enzymatic capacity, which is accompanied by increases in the villus height and crypt cell proliferation

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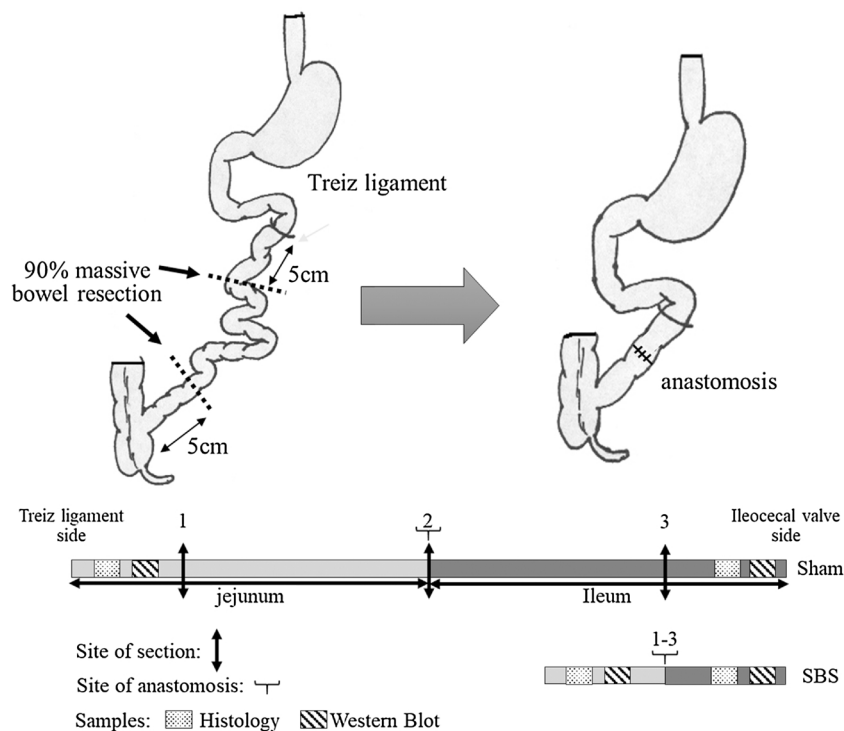


Fig. 1. Schematic illustrations of the surgeries and tissue collection on postoperative day 13.

rate [5]. This process of increasing the nutrient absorptive capacity is known as intestinal adaptation [6,7]. The regulation and augmentation of the function of the remaining intestine is induced through a complex interaction of many different factors, including luminal nutrients and gastrointestinal hormones [2,8,9]. Recent clinical studies have shown that several growth factors, including growth hormone (GH) [10], glucagon-like peptide-2 (GLP-2) [11], and its analogue [12], induce intestinal adaptation following extensive small intestinal resection. The effect of these hormones was strongly associated with the interaction of insulin-like growth factor 1 (IGF-1) [13]. Experimentally, total parenteral nutrition (TPN) with coinfusion of IGF-1 after massive bowel resection induced an increase in the body weight, and intestinal mucosal cellularity in a rat model [14]. These findings suggest that IGF-1 may be an important factor encouraging intestinal adaptation following massive bowel resection.

Ghrelin is a 28-amino-acid peptide with an n-octanoylation modification at serine 3 produced mainly by the X/A-like endocrine cells of the gastrointestinal tract [15]. Ghrelin has a vast range of physiological functions, including orexigenic, metabolic, and hormonal functions [16]. Ghrelin is presumed to be a ligand of the GH secretagogue receptors and is reported to stimulate the release of GH and IGF-1 [17]. Indeed, several animal studies have shown that the administration of ghrelin improved the intestinal mucosal damage induced by elemental diet [18], doxorubicin [19], and total parenteral nutrition [20]. Furthermore, experimental *in vitro* studies have suggested that ghrelin improved the gastrointestinal pathological conditions via the stimulation of intestinal mucosal proliferation [21,22].

We hypothesized that ghrelin might have a therapeutic potential in intestinal adaptation. The aim of this study was to investigate the effect of the administration of ghrelin in a parenterally fed rat model of SBS.

2. Materials and methods

2.1. Animals

Seven-week-old male Sprague-Dawley (SD) rats weighing 200 to 240 g (purchased from Kyudo Co., Ltd., Saga, Japan) were used in this

experiment. The animals were individually housed in metabolic cages with free access to standard rat chow and water and acclimatized to their environment for 6 days before experiments. The animals were maintained under standardized temperature ($23 \pm 1^\circ\text{C}$) and humidity ($50\% \pm 10\%$) and 12-h light-dark cycles (lights on at 7:00 a.m.). All experimental procedures were approved by the Laboratory Animal Committees of Kagoshima University Graduate School and were performed in accordance with the “Guidelines for the Care and Use of Laboratory Animals” (Approval number: MD15083).

2.2. Study design

The animals were fasted overnight, and after the placement of a central venous catheter, they were randomly assigned to 1 of the following 3 treatment groups ($n = 9$ per group): sham operation and oral feeding with normal chow plus vehicle (sham group), 90% small bowel resection (SBR) and TPN alone (SBS/TPN group), and 90% SBR and TPN plus ghrelin (SBS/TPN/ghrelin group). Ghrelin (Peptide Institute Inc., Osaka, Japan) was dissolved in distilled water and administered intravenously at $10 \mu\text{g}/\text{kg}/\text{day}$. On Day 13, the animals were anesthetized, weighed, and then sacrificed for the assessment of intestinal gross morphology and harvesting of tissue for the analysis. The morphological changes reached a plateau (equivalent to 30-postoperative-day levels) within 12 days in a 70% SBR rat model [23]. We therefore set the experimental period for this study as 13 days post-surgery.

2.3. Surgical procedure and maintenance methods

A schematic illustration of the position of bowel resection is shown in Fig. 1. For surgery, the animals were anesthetized with isoflurane (1.5% inhalation by mask), and an intravenous catheter was inserted into the right jugular vein. A silastic catheter with an outside diameter of 1.2 mm (NIPRO Co., Ltd., Osaka, Japan) was used, tunneled out of the back, and attached to a standard swivel device (LOMIR BIOMEDICAL INC., Quebec, Canada). For the SBR-operated rats, the intestinal length was measured in a standardized fashion, and 90% SBR operation was performed, leaving 5 cm of the ileum above the ileocecal valve

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