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Intact neural system of the portal vein is important for maintaining normal glucose metabolism by regulating glucagon-like peptide-1 and insulin sensitivity

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ABSTRACT

The portal neural system may have an important role on the regulation of glucose homeostasis since activation of the gut–brain–liver neurocircuit by nutrient sensing in the proximal intestine reduces hepatic glucose production through enhanced liver insulin sensitivity. Although there have been many studies investigating the role of portal neural system, surgical denervation of the sole portal vein has not been reported to date. The aim of this study was to clarify the role of the portal neural system on the regulation of glucose homeostasis and food intake in the physiological condition. Surgical denervation of portal vein (DV) was performed in 10 male 12 week-old Wistar rats. The control was a sham operation (SO). One week after surgery, food intake and body weight were monitored; an oral glucose tolerance test (OGTT) was performed; and glucagon-like peptide-1 (GLP-1) and insulin levels during OGTT were assayed. In addition, insulinogenic index, homeostatic model assessment, and Matsuda index were calculated. All rats regained the preoperative body weight at one week after surgery. There was no significant difference in food intake between DV and SO rats. DV rats exhibited increased blood glucose levels associated with decreased insulin sensitivity but increased GLP-1 and insulin secretion during OGTT. In summary, in the physiological state, loss of the portal neural system leads to decreased insulin sensitivity and increased blood glucose levels but does not affect food intake. These data indicate that an intact portal neural system is important for maintaining normal glucose metabolism.

1. Introduction

Morbid obesity is a worldwide health problem because it promotes the development of various diseases such as cardiovascular disease and type 2 diabetes mellitus, which greatly increases mortality. Current therapies, including diet, exercise, lifestyle modification, and medication, are insufficient to treat morbid obesity. There is strong evidence that bariatric surgery can cure not only obesity but also type 2 diabetes mellitus [18]; however, the underlying mechanisms remain elusive.

Rerouting of nutrients and/or increasing nutrient delivery to the small intestine after bariatric surgery may have an important potential as a diabetes treatment modality [35]. Manipulation of gastrointestinal anatomy through surgery has been shown to profoundly affect the physiological and metabolic processes that control body weight and glycemia [26]. In fact, duodenal–jejunal bypass surgery enhances nutrients flow into the jejunum, which may affect the regulation of glucose metabolism and feeding behavior via jejunal nutrient sensing [20,34]. Duodenal nutrient sensing also reduces food intake and endogenous glucose production via gut–brain axis [8,48]. More recently, Breen et al. found that intrajejunal nutrient administration lowered endogenous glucose production in normal rats through a gut–brain–liver network in the presence of basal insulin concentration [5]. The vagus is a key signaling relay system between the gut and the brain and an

Abbreviations: DV, surgical denervation of portal vein; SO, sham operation; GLP-1, glucagon-like peptide-1; OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment; AUC, area under the curves.

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important regulator of food intake and body weight. Against the hypothesis that the vagus is important after gastric bypass surgery, a selective common hepatic vagotomy in rat models of gastric bypass surgery did not have any effect on food intake, weight loss, and metabolic control [42].

Energy and glucose homeostasis are regulated by food intake and liver glucose production, respectively [48]. The upper intestine has a critical role in nutrient digestion and absorption. However, several studies indicated that upper intestinal infusion of lipid inhibits food intake by the activation of an intestine–brain axis [2,30]. In parallel, a brain–liver axis has recently been proposed to detect blood lipids and subsequently inhibit glucose production in rodents [22]. However, these studies have not shown how important is the portal neural system including the afferent and efferent vagal nerve, to the glucose homeostasis. Although there have been many studies investigating the role of portal neural system through common hepatic vagotomy in the physiological condition or after Roux-en-Y gastric bypass, surgical denervation of the sole portal vein has not been reported to date. Moreover, for vagal afferent innervation, retrograde and anterograde tracing studies in the rat have clearly shown that only a minor portion of the common hepatic branch innervates the liver area, while the major portion descends in the gastroduodenal branch toward duodenum, pancreas, and pylorus [4,17]. Therefore, it is difficult to conclude that the effects of common hepatic vagotomy result solely from loss of portal innervation.

Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is released by enteroendocrine L cells in the intestine and plays a crucial role on regulation of food intake and glucose homeostasis [16]. Thus, we conducted this first pilot to investigate the role of the portal neural system on the regulation of glucose homeostasis, food intake, glucagon-like peptide-1 (GLP-1), and insulin in the physiological condition by surgical denervation of the portal vein. Our goal was to determine that the loss of the neural system of the portal vein would affect food intake and glucose homeostasis by regulating GLP-1 and insulin.

2. Materials and methods

2.1. Animals

Twenty male 10-week-old Wistar rats were housed in individual cages under constant ambient temperature and humidity and a 12-h light/dark cycle, and were fed with standard rat chow. When the rats were 12 weeks old, they were subjected to the surgical procedures described below.

The protocol was approved by the Committee on the Ethics of Animal Experiments of Shiga University of Medical Science, Shiga, Japan. All surgery was performed under sevoflurane anesthesia, and all efforts were made to minimize suffering.

2.2. Surgical procedures

The rats were randomly divided into two groups of 10 animals each: a denervation of whole portal vein (DV) group and a sham operation (SO) group. The rats were anesthetized with sevoflurane, Penicillin (20,000 units/kg, Nacalai Tesque, Inc., Kyoto, Japan) was administered intramuscularly 30 min before operation, and DV was performed by cutting all nerves terminating in the whole portal vein. We identified the anatomy and neural system of portal vein through previously published schematic representations of the portal vein and its neural system [4,11,42]. To assure successful denervation, we performed dissection along the portal vein and all the fat tissues surrounding the portal vein were eliminated (Fig. 1A–C).

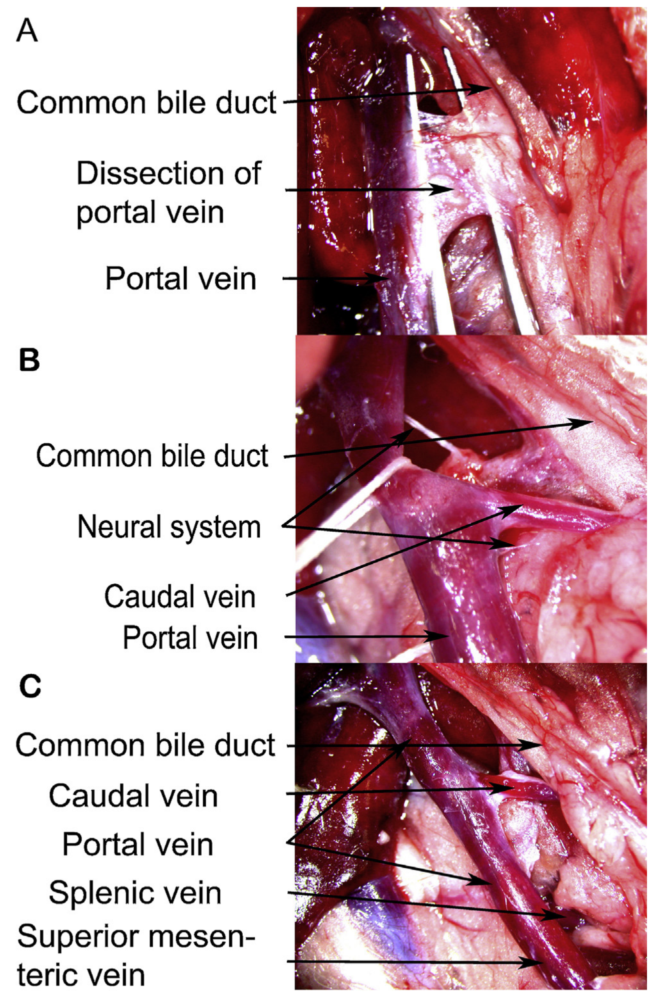

Fig. 1. Surgical denervation of the portal vein. (A) At the beginning of dissection of portal vein. (B) Some nerves of the portal vein. (C) Macroscopic aspect of portal vein after surgical denervation, neither vagal fiber nor tissue terminating in the portal vein was observed.

Sham surgery consisted of a laparotomy and manipulations applied to duodenum and liver in the DV group. To imitate surgical stress, the sham rats were submitted to an equal operation time. All procedures were performed under sterilized condition, antibiotics and analgesics were not used after surgery.

2.3. Postoperative care

The rats were fed ad libitum with normal chow after surgery. To reduce the effects of surgical stress, the rats were followed for one week after surgery before they were subjected to OGTT.

2.4. Outcome measures

2.4.1. Body weight

Body weight was tracked before and one week after surgery to make sure that all rats regained the preoperative body weight.

2.4.2. Food intake

Food intake per day was monitored before and one week after surgery.

2.4.3. OGTT

The rats were fasted overnight during 8 h. At 08:00 AM in the morning, glucose tolerance tests were performed in conscious rats