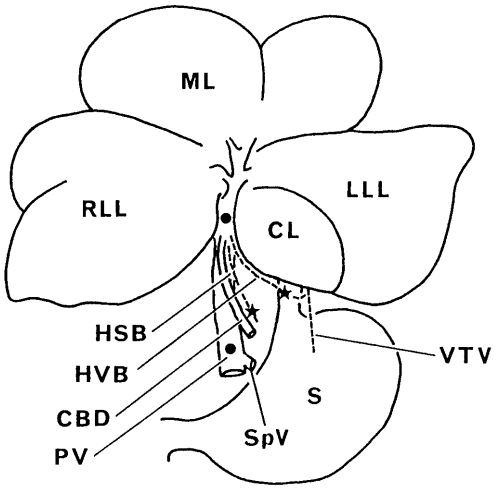

Fig. 1. Schematic representation of the portal and neural pathways. The filled circle (●) indicates the tip position of the portal catheter, and the asterisk (★) the sectioned site.
RLL, right lateral lobe; ML, median lobe; LLL, left lateral lobe; CL, caudal lobe; VTV, ventral trunk of the vagal nerve; HSB, hepatic splanchnic branch; HVB, hepatic vagal branch; CBD, common bile duct; PV, portal vein; SpV, splenic vein; S, stomach.

taken by the method described previously.[1] Briefly, a polyethylene tube was introduced into the stomach through the esophagus and was tied in position with a ligature around the esophagus in the neck. Another cannula was then inserted into the pyloroduodenal junction and passed up into the stomach. Physiological saline warmed to 36.0°C was perfused through the stomach at the rate of 2.0 ml/min, and titratable acidity (end point pH 6.0) was determined with 0.1 mM NaOH using a pH controller (FC-1, Tokyo Rikakikai Co., Ltd., Tokyo). Acid output was calculated every 3 min. Regular insulin (42 μg/kg/h, Novo Nordisk, Copenhagen) was administered by a pump through a catheter inserted in the right jugular vein, and portal injection experiments were conducted 40–120 min after insulin administration.

Under a microscope (×20) visible fibers of the hepatic vagal and splanchnic branches were coated with vaseline; it was preliminarily confirmed that the coating of these neural branches did not influence the neural function. A thread was then looped around the hepatic vagal branch and the hepatic splanchnic branch at the required position (Fig. 1), and then both ends were led through a plastic tube so that the nerve could be cut by pulling the ends of the loop.[1] The rectal temperature was maintained at 36.0 ± 0.5°C with a heating lamp.

Partial hepatectomy was performed during gastric perfusion at the required time by the methods previously described.[7,8] Either the median lobe, being about 40%, or the median and left lateral lobes, being about 66%, and forming a unit, was ligated and removed.

Glucose (D-glucose) dissolved in physiological saline kept at 36.5°C was injected into the portal vein. Physiological saline was used as the control. Each test injection was 20 μl, and was completed in 10 sec with an infusion pump through a catheter placed in the intrahepatic portal portion (about 1 mm before the liver lobes) or in the extrahepatic portal portion adjacent to the splenic vein (Fig. 1). The distance between the two portal catheters was 8.9 ± 0.1 mm (mean ± SEM, n=6). Lidocaine, an anesthetic agent, (Fujisawa Pharmaceutical Co., Ltd., Osaka) in jelly, was utilized through a 26-gauze stainless steel tube.

Blood for chemical analysis (120 μl) was drawn off through the extrahepatic portal catheter, cooled immediately with iced water, and then centrifuged at 2,200 rpm for 20 min. The separated serum was stored at −20°C until measurement of the following parameters with an auto-analyzer (Hitachi-7070, Hitachi, Tokyo).[9]: glucose (Glu, glucose oxidase method). glutamic pyruvic transaminase (GPT, ultraviolet method), alkaline phosphatase (Alp, Bessy-Lowry method), and total bilirubin (TB, azobilirubin method).

Data were ANOVA analyzed, and specific values were evaluated by Duncan's multiple range test.

RESULTS

Changes in gastric acid outputs after extrahepatic portal injections of 20 mM glucose or saline in the intact liver are shown in Fig. 2A. Portal injection of glucose decreased the acid output: the response reached its nadir 3 min after injection, and then returned to the control level within another 3 min. On the basis of this finding, the acid output 3 min after glucose injection was analyzed.

With the injection of three different concentrations of glucose (5, 10 and 20 mM) and saline into the extrahepatic portal vein, the inhibitory acid response was found to be dose-dependent, and the acid decrease with 20 mM glucose was blocked by hepatic branch vagotomy (Fig. 2B). The acid response with 20 mM glucose was not affected by lidocaine anesthesia of the extrahepatic portal wall. Hepatic branch splanchnicotomy failed to modify the acid response with 20 mM glucose (Fig. 2B).

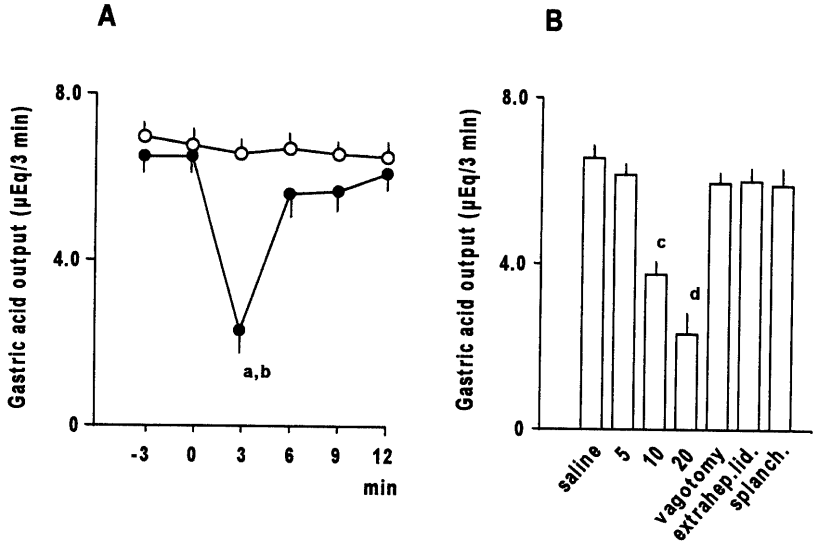

Fig. 2. **A.** Changes in gastric acid output after an extrahepatic portal injection of glucose. Twenty mM glucose (●) or saline (○) was injected. Zero indicates the time of injection. Values are the mean ± SEM (n=6). $^{a}p<0.01$ vs the value before injection. $^{b}p<0.01$ vs saline. **B.** Gastric acid outputs 3 min after an extrahepatic portal injection of glucose. Different injections of glucose (5, 5 mM glucose; 10, 10 mM glucose; 20, 20 mM glucose; vagotomy, 20 mM glucose with hepatic branch vagotomy; extrahep. lid., 20 mM glucose with lidocaine anesthesia of the extrahepatic portal wall; splanch., 20 mM glucose with hepatic branch splanchnicotomy) are shown. Saline was used as the control. Values are the mean ± SEM (n=6). $^{c}p<0.01$ vs saline and 5. $^{d}p<0.05$ vs 10.

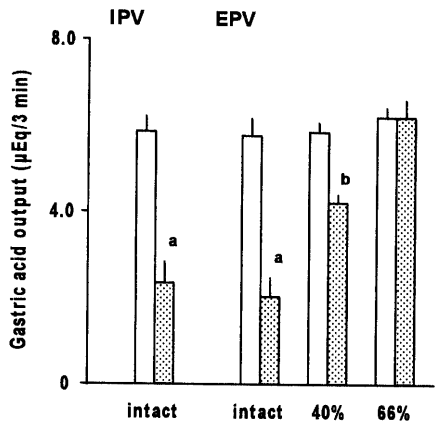

Fig. 3. Gastric acid outputs after injections of different portions of glucose and hepatectomy. Twenty mM glucose was injected into the intrahepatic portal vein (IPV) or into the extrahepatic portal vein (EPV). The injections were conducted in the intact liver, 40% and 66% hepatectomized rats. The acid outputs before (open bars) and 3 min after (shaded bars) injection are shown. Values are the mean ± SEM (n=6). $^{a}p<0.01$ vs before. $^{b}p<0.05$ vs before 40% and after, intact and 66%.

An acid decrease due to 20 mM glucose was obtained when glucose was injected into the intrahepatic portal portion of the intact liver (Fig. 3). The inhibition of acid output caused by an extrahepatic portal injection of 20 mM glucose was diminished by a 40% hepatectomy, and completely blocked by a 66% hepatectomy (Fig. 3).

Plasma glucose levels in the portal area were unchanged before and 3 min after a portal injection of 20 mM glucose. The levels of GPT, Alp, and TB during injection experiments were unchanged (Table 1).

DISCUSSION

We found that vagal glucose signals from a specific field of the hepatic portal vein control gastric acid secretion; a portal injection of glucose vagally decreased gastric acid output in a dose-dependent manner without any change in the glucose concentration or hepatic function scores in the blood, and the response originated in the intrahepatic portal innervation. This is partially in keeping with the view that hepatic portal signals related to glucose vagally

Table 1. Blood chemical parameters during experiments

A. Before (I) and 3 min after (II) portal injection of 20 mM glucose		
	(I)	(II)
Glu (mmol/L)	3.88 ± 0.07	3.90 ± 0.06
B. Immediately after 66% hepatectomy (I) and 40 min later (II)		
	(I)	(II)
GPT (U/L)	25 ± 3	27 ± 4
Alp (U/L)	336 ± 41	324 ± 39
TB (mg/dl)	0.1 ± 0.0	0.1 ± 0.0

Values are the mean ± SEM (n=6).

regulate gastric acid secretion via a change in central nervous activity.[1,2,10]

A glucose receptive field has been considered to exist in the extrahepatic portion of the portal vasculature ever since an electrophysiological study,[3,11] but histological findings have revealed that hepatic vagal fibers terminate in both the extra- and intrahepatic walls of the portal vein, and not in the parenchyma of the liver.[4-6] In the present study, intra- and extrahepatic portal glucose vagally decreased acid secretion, but the acid response caused by extrahepatic portal glucose was not influenced by anesthesia of the extrahepatic portal innervation, and was not reproduced in the 66% hepatectomized rats. This could be interpreted to mean that hepatic vagal fibers responsible for gastric acid secretion are predominantly derived from the intrahepatic portal areas.

Glucose solution injected into the portal vein area has been shown to inhibit eating[12,13], and hepatic branch vagotomy resulted in a decrease in food intake[14]. Accordingly, glucose signals in the hepatic vagal nerve contribute to feeding behavior. It has also been demonstrated that, in 66% hepatectomized rats, hepatic branch vagotomy induced further suppression of food intake compared with the hepatectomized control[8], and the possibility has arisen that feeding behavior is modulated by neural signals of the vagal fibers distributing along the extrahepatic portal wall. Considering these reports together with the present finding that gastric acid response due to glucose was derived from the intrahepatic portal wall, it is suggested that the hepatic vagal fibers receptive to glucose differentially regulate physiological function according to the terminating areas.

This speculation is supported by our preliminary electrophysiological data indicating that efferent activity obtained from the gastric vagal nerve showed no response to glucose injection into the extrahepatic portal vein in 66% hepatectomized rats (Sakaguchi, unpublished data), although it was reduced in the intact liver.[15]

There is a reciprocal action on gastric acid secretion between the efferent vagal nerve and the efferent splanchnic nerve at the stomach.[10] However, a portal injection of glucose with hepatic branch splanchnicotomy failed to modify the vagally induced acid response. It is likely that the afferent or efferent splanchnic function of the liver does not interfere with the reciprocal neural action on acid secretion.

These observations lead us to the conclusion that the vagal receptive field of glucose signals responsible for gastric acid secretion is mainly distributed in the intrahepatic portal structures.

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