Important Role of the Hepatic Vagus Nerve in Glucose Uptake and Production by the Liver

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We examined the role of the hepatic vagus nerve in hepatic and peripheral glucose metabolism. To assess endogenous glucose production (EGP), hepatic uptake of first-pass glucose infused intraportally (HGU), and the metabolic clearance rate of glucose (MCR), rats were subjected to hepatic vagotomy (HV, n = 7) or sham operation (SH, n = 8), after 10 days, they were then subjected to a euglycemic-hyperinsulinemic clamp together with a portal glucose load in the 24-hour fasting state. Metabolic parameters were determined by the dual-tracer method using stable isotopes. During the experiment, [6,6-$^2H_2$]glucose was continuously infused into the peripheral vein. To maintain euglycemia (4.5 mmol/L), insulin (54 pmol · kg^{-1} · min^{-1}) and glucose were infused peripherally after the 90-minute tracer equilibration and 30-minute basal periods, and glucose containing 5% enriched [U-^{13}C]glucose was infused intraportally (50 μmol · kg^{-1} · min^{-1}) for 120 minutes (clamp period). EGP was significantly higher in HV rats versus SH rats during the basal period (64.3 ± 7.6 *v* 43.6 ± 5.3 μmol · kg^{-1} · min^{-1}, $P < .005$) and was comparable to EGP in SH rats during the clamp period (9.3 ± 21.5 *v* 1.1 ± 11.7 μmol · kg^{-1} · min^{-1}). HGU was reduced in HV rats compared with SH rats during portal glucose infusion (5.9 ± 2.4 *v* 10.1 ± 3.2 μmol · kg^{-1} · min^{-1}). The MCR in HV rats was significantly higher than in SH rats in the basal period (11.0 ± 2.0 *v* 7.9 ± 0.8 mL · kg^{-1} · min^{-1}, $P < .01$) and was comparable to the MCR in SH rats during the clamp period (41.9 ± 10.0 and 36.6 ± 5.7 mL · kg^{-1} · min^{-1}). We conclude that innervation of the hepatic vagus nerve is important for the regulation of hepatic glucose production in the postabsorptive state and HGU in the postprandial state.

THE LIVER plays a key role in maintaining optimal glucose levels by balancing glucose entry into and removal from the circulation. In the postabsorptive state, the liver releases sufficient glucose to satisfy the requirements of the brain and peripheral tissues. In the postprandial state, the liver switches immediately from output to uptake of glucose and stores glucose as glycogen. Although the precise mechanism of accelerated glucose uptake by the liver in the postprandial condition is not fully understood, it is known to be regulated by several factors including hormonal factor,[1-3] the glucose load to the liver,[4] the route of glucose delivery,[5-7] and a negative arterial-portal glucose gradient.[1,3,8,9] We have recently demonstrated that enhanced hepatic glucose uptake (HGU) by portal glucose delivery is mainly due to the establishment of a positive glucose gradient between the hepatoportal and central nervous systems.[10]

The liver is richly innervated by sympathetic and parasympathetic nerves, which regulate glucose metabolism in a reciprocal manner.[11] The afferent nerve in the hepatic branch of the vagus nerve[12] and neurons in the lateral hypothalamus, the center of the parasympathetic nervous system,[13] can respond to the presence of glucose in the portal vein. In the brain, there are 2 types of glucose sensors: one is a glucose-sensitive neuron in the lateral hypothalamus, and the other is a glucoreceptor neuron in the ventromedial hypothalamus, the sympathetic nerve center.[14] Recent studies have demonstrated that an intact nerve supply to the liver appears to be vital for its normal response to intraduodenal and intraportal glucose delivery in conscious dogs.[15,16] Therefore, both the hepatoportal and central nervous systems may independently detect ambient glucose levels, which are integrated in the brain, from which efferent signals are sent to the liver via the autonomic nervous system. Stümpel and Jungermann[17] demonstrated that in isolated perfused rat liver, the effect of an arterial-portal glucose gradient seemed to be mediated by the intrahepatic parasympathetic nervous system. Moreover, Chaps et al[18] found that pharmacological blockade of the parasympathetic nervous system with atropine reduced HGU after an oral glucose load in dogs, and suggested that the parasympathetic nervous system regulates HGU. However, systemic administration of atropine also affected glucose absorption from the gut and induced hemodynamic change in the liver.[18] Thus, the direct role of intact hepatic parasympathetic nerves in HGU remains uncertain.

In the present study to clarify the significance of the parasympathetic nerve in hepatic glucose metabolism, we determined endogenous glucose production (EGP), HGU, and glycogen synthesis in conscious rats subjected to hepatic vagotomy (HV) or sham operation (SH) under euglycemic-hyperinsulinemic conditions with portal glucose loading.

MATERIALS AND METHODS

Animals and Surgical Procedures

The study was approved by the Institute of Experimental Animal Science of Osaka University Medical School. Experiments were performed with 29 male Sprague-Dawley rats weighing 262 ± 14 g at 8 weeks of age. All rats were fed standard chow (Oriental Yeast, Tokyo, Japan) and housed in an environmentally controlled room with a 12-hour light/dark cycle. The rats were randomized into 2 groups, 15 HV and 14 SH. Five SH and 5 HV rats were used to determine hepatic glycogen content after 24-hour fasting. At 10 days before the experiment or liver sampling, a laparotomy was performed under general anesthesia induced with an intraperitoneal injection of pentobarbital (50 mg · kg^{-1}). A silastic catheter (Phicon Tube; Fuji-Systems, Tokyo, Japan) was inserted into the portal vein via the inferior mesenteric vein. The catheter was filled with saline containing heparin (200 U/mL) to prevent thrombosis, and the free end was knotted. The catheter was

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externalized through the back of the neck. HV was performed by resection of the hepatic branch of the vagus nerve in HV rats.[19,20] To ensure complete HV, no tissue was left between the liver and esophagus from the esophageal plexus to the cardia of the stomach. When there was any ambiguity concerning identification of the hepatic branch, the animal was excluded from the experiment. With SH rats, the hepatic branch of the vagus was exposed. At 3 days before the experiment, silastic and polyethylene (PE-50; Clay Adams, Sparks, MD) catheters were inserted into the right jugular vein and left carotid artery, respectively. The catheters, filled with heparin solution, were externalized through the back of the neck. Two rats were excluded from this study because of ambiguity about completion of HV. One rat each was excluded from the HV and SH groups due to loss of appetite and body weight after the laparotomy. Experiments to determine in vivo glucose turnover were performed with 7 HV and 8 SH rats.

HV Verification

To validate our surgical technique, a separate experiment was performed in which the stimulation of insulin secretion by acute HV in adrenalectomized rats was tested with anesthetized animals according to a previously described method.[21,22] At 30 minutes after sectioning of the hepatic vagus nerve, increases in peripheral insulin (0.6 ± 0.2 to 4.6 ± 2.9 ng/mL, $P < .05$, n = 5) and portal venous insulin (1.4 ± 0.6 to 9.1 ± 5.1 ng/mL, $P < .05$, n = 5) were observed. These results agree with those of previous reports,[21,22] thus confirming the validity of the HV procedure.

Experimental Protocol

To determine peripheral and hepatic glucose metabolism in conscious and unstressed rats, the animals were subjected to a euglycemic-hyperinsulinemic clamp combined with an intraportal glucose load after a 24-hour fast before the experiments. Observations were made by the dual-tracer method using stable isotopes. Each experiment consisted of a 90-minute tracer equilibration period (from −120 to −30 minutes), 30-minute basal period (−30 to 0 minutes), and 120-minute clamp period (0 to 120 minutes). To determine the glucose turnover rate, a 10-minute priming infusion (17 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) followed by continuous infusion (1.7 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) of [6,6-$^2H_2$]glucose (Cambridge Isotope, Andover, MA) was started at −120 minutes via the jugular vein. At 0 minutes, regular human insulin (Eli Lilly, Indianapolis, IN) was infused at a priming rate (540 $pmol \cdot kg^{-1} \cdot min^{-1}$, 0 to 5 minutes) and then at a constant rate (54 $pmol \cdot kg^{-1} \cdot min^{-1}$, 5 to 120 minutes), and the infusion rate of [6,6-$^2H_2$]glucose into the jugular vein was increased to 5.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to prevent the decrease of plasma enrichment, which could lead to errors in the calculation of metabolic parameters. Simultaneously, continuous infusion of 0.5 mol/L glucose containing 5% enriched [U-^{13}C]glucose (Cambridge Isotope) into the portal vein was started and continued until 120 minutes at a rate of 50 $\mu mol \cdot kg^{-1} \cdot min^{-1}$. During the clamp period, the plasma glucose level was monitored every 5 minutes, and the rate of exogenous glucose (20% dextrose) into the jugular vein was adjusted to maintain arterial euglycemia at 4.5 mmol/L. Blood samples of 200 μL were obtained from the carotid artery at −120, −30, −15, 0, 60, 75, 90, 105, and 120 minutes to determine the enrichment of [6,6-$^2H_2$]glucose and [U-^{13}C]glucose. A blood sample of 600 μL from the carotid artery was taken at −120 minutes to determine plasma insulin and free fatty acid (FFA) concentrations, and a sample of 300 μL was obtained at 120 minutes to determine the plasma insulin level. These blood samples were immediately placed on ice and centrifuged at 4°C, and the separated plasma was frozen at −20°C until assay. Blood samples for measuring glucose and insulin levels were collected in dry heparinized tubes containing sodium fluoride. To determine plasma glucose during the clamp period, 30-μL blood samples were collected at 5-minute intervals and replaced with isotonic saline. After removal of the plasma, the packed blood cells were resuspended in heparinized saline and reinfused after each blood sampling to prevent volume depletion and anemia. At the end of the experiment, the rats were anesthetized with pentobarbital (50 mg/kg intravenously), the abdomen was quickly opened, and the liver was freeze-clamped in situ with aluminum tongs precooled in liquid nitrogen. Tissue samples were stored at −80°C (Fig 1).

Analytical Procedures

Plasma glucose levels were measured by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman, Fullerton, CA). Insulin was analyzed by radioimmunoassay using a rat or human insulin standard as appropriate (Pharmacia & Upjohn, Tokyo, Japan). Blood samples for FFA measurement were collected in tubes containing a lipoprotein lipase inhibitor, diethyl *p*-nitrophenyl phosphate (Sigma, St Louis, MO). Plasma FFA levels were determined by an enzymatic calorimetric method. The enrichment of plasma [6,6-$^2H_2$]glucose and [U-^{13}C]glucose was simultaneously determined as previously reported.[23] In brief, 40 μL plasma was deproteinized with 120 μL 99.5% ethanol and the supernatant was evaporated. To derive the residue for analysis by gas chromatography–mass spectrometry (GCMS), 10 μL MBTFA (*N*-methyl-bis-trifluoroacetamide; Pierce, Rockford, IL) and 10 μL pyridine were added to the residue, and the mixture was heated for 1 hour at 60°C with occasional shaking. One microliter of the reaction product containing trifluoro-acetylated (TFA) glucose was taken for analysis by GCMS on a TSQ-700 (Finnigan MAT, San Jose, CA) with a silicon SE-30 capillary column (30 × 0.25 mm ID; Gasukuro Kogyo, Tokyo, Japan). The TFA derivative of glucose separated from the other compounds by gas chromatography was analyzed by 70-eV electron-impact mass spectrometry. The enrichment of [6,6-$^2H_2$]glucose and [U-^{13}C]glucose in plasma samples was determined by comparison to the standard curve of each labeled glucose.

Calculations

EGP and HGU were calculated using a method[23] modified from the dual-tracer method described by Radziuk et al.[24] In brief, the rate of appearance (Ra) in the systemic circulation of the infused glucose via the portal vein and total glucose was calculated using the equation, $Ra = (I - M_T \times dE/dt) \times (Ei/E - 1)$, where I is the infusion rate of the tracer, M_T is the total volume of glucose, Ei is the isotopic enrichment of infused tracer, and E is the isotopic enrichment of plasma glucose. From the enrichment of [6,6-$^2H_2$]glucose in plasma glucose, we can calculate the Ra of total glucose (RaTG), which includes both infused and endogenously produced glucose. During the basal period, RaTG is equal to the sum of EGP and I. During portal glucose infusion, the Ra of infused glucose in the circulatory system via the portal vein (RaPG) is

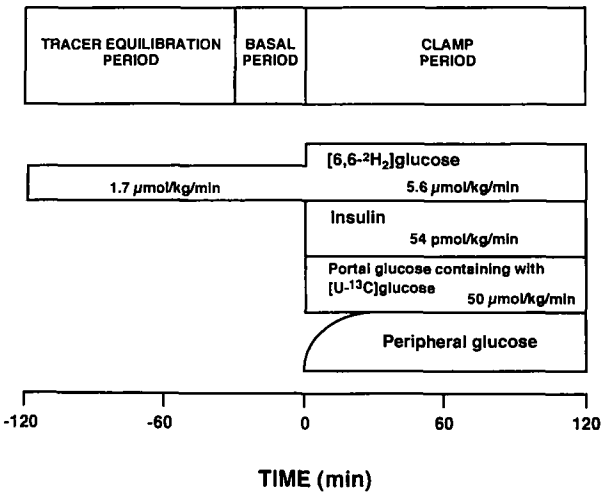

Fig 1. Experimental protocol.

calculated from the enrichment of plasma [U-^{13}C]glucose and RaTG. HGU, hepatic disposal of first-pass glucose via the portal vein, is obtained from the equation, HGU = GIR_{PV} − RaPG, where GIR_{PV} is the fixed rate of portal glucose infusion (50 μmol · kg^{-1} · min^{-1}). RaTG in the clamp period consists of RaPG, EGP, and the infusion rate of labeled and unlabeled glucose (GIR) and I via the jugular vein. EGP is therefore calculated from the equation, EGP = RaTG − (GIR + RaPG + I).

The rate of disappearance of glucose (Rd), which indicates total-body glucose uptake, can be determined from the equation, Rd = RaTG − dM_T/dt.

To exclude the influence of the mass-action of glucose per se on peripheral glucose uptake (PGU), PGU was determined as the metabolic clearance rate of glucose (MCR), which was calculated by dividing RaTG by the plasma glucose concentration. Results are presented as the mean values for RaTG, EGP, MCR, and HGU during the last 30 minutes in each period.

Liver Assays

Hepatic glucokinase activity was determined using a modification of a previously reported spectrophotometric method.[25,26] Small fragments sampled from different parts of the liver were homogenized in 50 mmol/L HEPES, 100 mmol/L EDTA, 5 mmol/L $MgCl_2$, and 2.5 mmol/L dithioerythritol. The homogenates were centrifuged at 100,000 × *g* for 45 minutes to sediment the microsomal fraction. The postmicrosomal fraction was assayed at 37°C in medium (pH 7.4) containing 50 mmol/L HEPES, 100 mmol/L KCl, 7.5 mmol/L $MgCl_2$, 5 mmol/L ATP, 2.5 mmol/L dithioerythritol, 10 mg/mL albumin, 0.5, 7, 10, 15, 18, and 50 mmol/L glucose, 0.5 mmol/L NAD^+, and 4 U G-6-P dehydrogenase (Sigma, St Louis, MO). The reaction was initiated by addition of ATP, and the rate of NAD^+ reduction was recorded at 340 nm. Glucose phosphorylation was determined as the absorbance. The glycogen content was extracted from the liver sample using the H_2SO_4 extraction and ethanol precipitation method described by Good et al.[27] The glucose hydrolyzed from glycogen was assayed by a glucose oxidase method.[28] To determine the direct incorporation of [U-^{13}C]glucose into hepatic glycogen, we measured the enrichment of [U-^{13}C]glucose in the glucose units converted from glycogen using GCMS.

Data Analysis

Data are expressed as the mean ± SD. The difference between 2 groups was assessed with the Mann-Whitney *U* test. Comparisons of repeated measurements within the same experimental group were assessed using the Friedman or Wilcoxon signed-ranks test where appropriate. Statistical significance was accepted at a *P* level less than .05.

RESULTS

Arterial Plasma Glucose, Insulin, FFA, Isotopic Enrichment, and GIR

At −120 minutes, fasting arterial plasma glucose (SH *v* HV, 5.5 ± 1.0, *v* 5.8 ± 0.9 mmol/L) and insulin (SH *v* HV, 155 ± 52 *v* 189 ± 69 pmol/L) levels were similar between HV and SH rats. Also, fasting FFA levels were not significantly different between the 2 groups (SH *v* HV, 0.56 ± 0.17 *v* 0.65 ± 0.19 mmol/L).

Arterial plasma glucose levels during the basal period were comparable to the fasting levels in both HV and SH rats, and there was no significant difference between the 2 groups (Fig 2). During the clamp period, the mean arterial plasma glucose level was 4.3 ± 0.4 and 4.4 ± 0.3 mmol/L in HV and SH rats, respectively, and was significantly lower versus the basal period in each group ($P < .05$). Arterial plasma insulin levels in HV and SH rats increased to 978 ± 198 and 1,062 ± 84 pmol/L during the clamp period, respectively. The GIR during the clamp period increased gradually and reached a similar level in HV and SH rats (133 ± 13 and 123 ± 25 μmol · kg^{-1} · min^{-1}, respectively). Plasma enrichment of [6,6-$^2H_2$]glucose was significantly higher in HV rats versus SH rats from −30 to 0 minutes during the basal period. During the clamp period, plasma enrichment of [6,6-$^2H_2$]glucose was comparable between the 2 groups. Plasma enrichment of [U-^{13}C]glucose reached comparable steady-state levels in HV and SH rats.

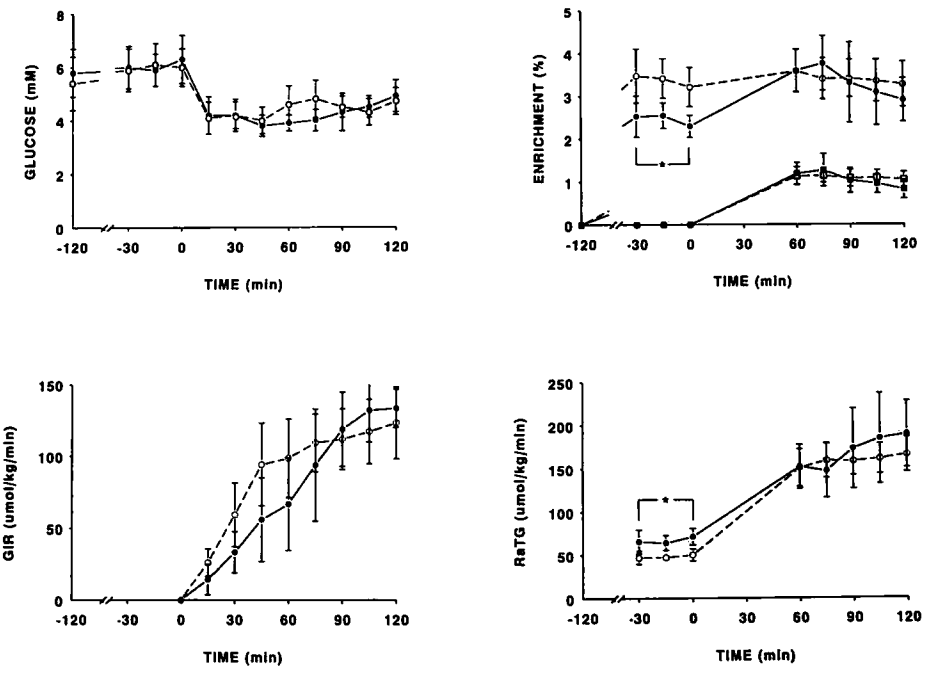

Fig 2. Plasma glucose level, GIR via the jugular vein, RaTG, and enrichment of [6,6-$^2H_2$] glucose (○, ●) and [U-^{13}C]glucose (□, ■) in SH (○, □) and HV (●, ■) rats during basal and clamp periods. Data are the mean ± SD. *$P < .05$ *v* SH.

RaTG, MCR, EGP, and HGU

RaTG was significantly higher in HV rats versus SH rats during the basal period (66.4 ± 8.6 *v* 47.3 ± 5.3 μmol · kg^{-1} · min^{-1}, $P < .005$) and increased to a level comparable to that in SH rats during the clamp period (170.9 ± 37.1 *v* 156.4 ± 16.4 μmol · kg^{-1} · min^{-1}, NS; Fig 2). The MCR was significantly higher during the basal period in HV rats versus SH rats (11.0 ± 2.0 *v* 7.9 ± 0.8 mL · kg^{-1} · min^{-1}, $P < .01$; Fig 3). During the clamp period, the MCR was significantly higher versus the basal period in both groups and was comparable between HV and SH rats (41.9 ± 10.0 and 36.6 ± 5.7 mL · kg^{-1} · min^{-1}, $P < .01$, respectively). EGP during the basal period was significantly higher in HV rats versus SH rats (64.3 ± 7.6 *v* 43.6 ± 5.3 μmol · kg^{-1} · min^{-1}, $P < .005$). During the clamp period, EGP was suppressed by 74% in HV and 97% in SH rats (9.3 ± 21.5 and 1.1 ± 11.7 μmol · kg^{-1} · min^{-1}, respectively). EGP did not differ significantly between the 2 groups. Hepatic uptake of first-pass glucose determined by the dual-tracer method was significantly lower in HV rats compared with SH rats during the clamp period (5.9 ± 2.4 *v* 10.1 ± 3.2 μmol · kg^{-1} · min^{-1}, $P < .05$).

Hepatic Glucokinase Activity, Glycogen Content, and Direct Incorporation of [U-^{13}C]Glucose Into Liver Glycogen

Fasting glycogen concentrations were similar between the SH and HV rats (Table 1). The hepatic glycogen concentration at the end of the experiment was significantly lower in HV rats versus SH rats. The ratio of [U-^{13}C]glucose incorporation into hepatic glycogen was significantly lower in HV versus SH rats. Glucokinase activity in the liver was similar between HV and SH rats.

DISCUSSION

Hepatic glucose disposal is markedly higher when glucose is delivered into the portal vein rather than the peripheral vein.[5-7] In the present study, we found that HV increased hepatic glucose production under basal conditions and decreased HGU by approximately 40% under euglycemic-hyperinsulinemic conditions with portal glucose infusion in conscious rats. In a prior study, we demonstrated that a positive glucose gradient between the hepatoportal and central nervous systems could contribute to approximately 50% of the accelerated HGU during portal glucose administration in conscious dogs.[10] Adkins et al[15] demonstrated that net HGU was similar whether glucose was administered via the peripheral or portal vein in conscious dogs with hepatic denervation of the sympathetic and parasympathetic nervous systems. In their study, net HGU during portal glucose infusion was approximately 40% of that observed in healthy conscious dogs. In the present study, intact innervation of the hepatic vagus nerve contributed to a similarly increased HGU during portal glucose infusion in conscious rats. These findings suggest that the regulation of HGU by the presence of higher glucose levels in the portal vein rather than the central nervous system may be modulated by the neural network between the hepatoportal and central nervous systems, mainly via the parasympathetic nervous system.

Pharmacological blockade of the parasympathetic nervous system, such as by systemic administration of atropine, does not affect basal blood flow in the liver but does suppress the

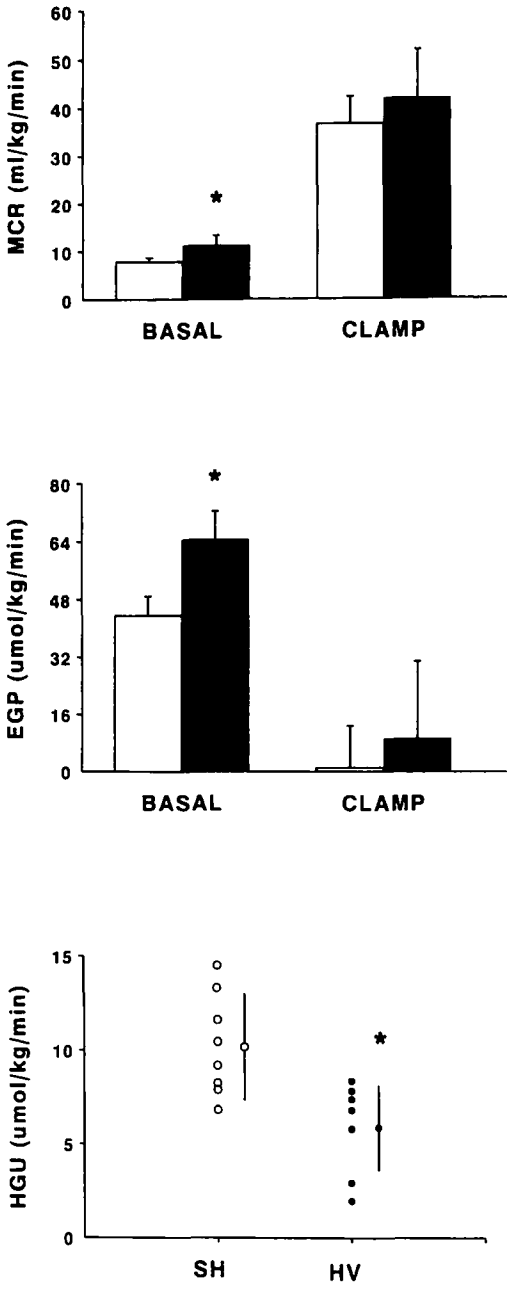

Fig 3. Glucose MCR, EGP, and HGU in SH (□, ○) and HV (■, ●) rats during basal and clamp periods. Data are the mean ± SD. *$P < .05$ *v* SH.

increase in portal blood flow after an oral glucose load.[18] An atropine-induced decrease of HGU after an oral glucose load was found to be associated with such an inhibition of the increase in portal blood flow, as well as glucose absorption from the intestine. Thus, a decrease of hepatic blood flow may impair the hepatic uptake of glucose infused intraportally in HV rats. However, portal glucose administration has been shown to enhance glucose uptake by the liver independently of an increase in portal blood flow.[10] In addition, hepatic denervation of both the sympathetic and parasympathetic nervous systems was shown to decrease net HGU without altering the portal and

Table 1. Hepatic Glycogen Content, Direct Incorporation of [U-^{13}C]Glucose Into Glycogen, and Glucokinase Activity in SH and HV Rats

Parameter	SH	HV
24-hour fasting glycogen content (mg/g dry tissue)	1.0 ± 0.8 (n = 5)	0.6 ± 0.5 (n = 5)
End of experiment		
Glycogen content (mg/g dry tissue)	12.0 ± 5	5.21 ± 2.5*
Direct incorporation of [U-^{13}C]glucose into glycogen (%)	58.8 ± 20.0	37.0 ± 15.6*
Glucokinase activity (mmol/min/mg protein)	13.2 ± 2.4 (n = 8)	10.4 ± 4.6 (n = 7)

NOTE. Data are the mean ± SD.

*$P < .05$ *v* SH. Hepatic glycogen content in the fasting state and at the end of the experiment was determined in different groups.

arterial blood flow in conscious dogs.[16] Therefore, in the present study, the hemodynamic changes in the liver might not have contributed to the attenuation of HGU in HV rats.

Although the molecular mechanisms of the acceleration in HGU during a portal glucose load have not been precisely clarified, glucose phosphorylation has been found to be rate-limiting for HGU and glucose utilization in rat hepatoma cells.[29] In the present study, hepatic glucokinase activity was similar between HV and SH rats, and this suggests that the parasympathetic nervous system enhances HGU without affecting hepatic glucokinase activity. However, since a recent study demonstrated that hepatic glucokinase activity can be regulated by intracellular translocation,[30] further experiments are needed to determine the significance of hepatic glucokinase for HGU.

We found that the basal hepatic glycogen concentration was almost depleted and similar between the SH and HV rats after a 24-hour fast, as described in a previous report by Lavoie et al.[31] After 2-hour portal glucose infusion under a euglycemic-hyperinsulinemic condition, HV attenuated the increase in hepatic glycogen deposition by direct formation of glycogen from glucose infused intraportally. Mondon and Burton[32] reported a similar result in a study with rats subjected to acute cervical vagotomy showing reduced hepatic glycogen deposition after an oral glucose load. Shimazu[33] reported that hepatic vagal stimulation directly enhances glycogen synthetase activity in the liver. Therefore, impaired stimulation of glycogen synthetase and a decrease of HGU reduced hepatic glycogen disposal in the vagotomized liver.

The possibility of the residual increment of HGU being due to incomplete section of the afferent innervation is difficult to rule out. Anatomic studies have demonstrated that the liver can be innervated by more than 1 branch from the anterior vagus.[34] However, great care was taken during the surgical procedures to ensure that no tissue remained between the liver and esophagus from the esophageal plexus to the cardia of the stomach. In addition, we observed a significant effect of acute surgical vagotomy of the hepatic branch on insulin secretion. During portal glucose infusion, the residual glucose uptake observed in HV rats could be mediated by a local factor in the liver, such as increased glucose and/or insulin in the liver.

We demonstrated that HV accelerated hepatic glucose production during the basal period. Since hepatic glycogen was almost depleted in SH rats and HV rats during the basal period, the increase in hepatic glucose production observed in HV rats was mainly due to an increase in gluconeogenesis in the liver. In cats with chemically sympathectomized liver, parasympathetic activation by electrical stimulation of the hepatic nerve was found to reduce hepatic glucose production.[35] These findings suggest that intact innervation of the hepatic vagus nervous system regulates EGP under the basal condition, possibly by suppressing gluconeogenesis.

In the present study, we found that peripheral glucose utilization in the basal period was elevated in HV rats. Electrical stimulation of the ventromedial hypothalamus, the center of the sympathetic nervous system, has been shown to enhance glucose uptake in the skeletal muscle.[36] Therefore, basal sympathetic nervous tone may enhance peripheral glucose utilization under the basal condition in HV rats. Since arterial plasma insulin levels were similar between SH and HV rats, HV affected peripheral glucose uptake in an insulin-independent manner. These results suggest that the neural network between the brain and peripheral tissues plays a compensatory role in the accelerated EGP in an insulin-independent manner to maintain glucose levels in the euglycemic range.

In summary, we conclude that innervation of the hepatic vagus nerve plays a role in regulating hepatic glucose production under the basal condition and enhances HGU during a portal glucose load. Thus, an intact parasympathetic neural system is important for maintaining normal glucose metabolism in the liver under postabsorptive and postprandial conditions.

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