Original Articles

Augmentation of Hepatic Glucose Uptake by a Positive Glucose Gradient Between Hepatoportal and Central Nervous Systems

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To determine the role of the glucose gradient between the hepatoportal system (HPS) and the central nervous system (CNS) in regulating hepatic glucose uptake, experiments were conducted with seven conscious dogs using a hepatic venous catheterization technique. With the infusion of somatostatin (0.8 μg · kg^{-1} · min^{-1}), glucagon (0.65 ng · kg^{-1} · min^{-1}), and insulin (27 pmol · kg^{-1} · min^{-1}), arterial glucose levels could be maintained at 8 mmol/l by adjusting the intravenous glucose infusion (G_{inf}) according to the following three periods: *1*) peripheral glucose infusion period (PE), G_{inf} alone; *2*) portal glucose infusion period (PO), G_{inf} plus constant glucose infusion into the portal vein (GIR_{PV}, 55.6 μmol · kg^{-1} · min^{-1}); *3*) portal and brain glucose infusion period (PO+CNS), G_{inf} and GIR_{PV} plus additional glucose infusion into the unilateral carotid and vertebral arteries to abolish the positive glucose gradient between HPS and CNS. Arterial plasma glucose levels were clamped during the three periods (8.1 ± 0.1, PE; 8.2 ± 0.1, PO; 8.2 ± 0.1 mmol/l, PO+CNS). During PO, when a positive glucose gradient was promoted between HPS and CNS, the net hepatic glucose balance (NHGB) determined by the difference between hepatic glucose inflow and outflow was significantly lower than that of PE (−41.5 ± 5.3, PO vs. −7.5 ± 3.4 μmol · kg^{-1} · min^{-1}, PE; $P < 0.01$). However, this decrease in the NHGB significantly increased during PO+CNS, when the glucose gradient between HPS and CNS was minimized, compared with PO (−21.7 ± 3.2 μmol · kg^{-1} · min^{-1}, $P < 0.05$). We conclude that a positive glucose gradient between HPS and CNS is an important regulatory factor of hepatic glucose uptake, but other factors also play important roles because minimizing the glucose gradient between HPS and CNS diminished the net hepatic glucose uptake by 50%. *Diabetes* 46:1101–1105, 1997

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CNS, central nervous system; GIR_{CA}, glucose infusion into the carotid artery; G_{inf}, glucose infusion; HERG, hepatic extraction rate of glucose; HPS, the hepatoportal system; LH, lateral hypothalamus; NHGB, net hepatic glucose balance; NHGU, net hepatic glucose uptake; PE, peripheral glucose infusion period; PGU, peripheral glucose uptake; PO, portal glucose infusion period; PO+CNS, carotid and vertebral artery glucose infusion period; TGI, total glucose infusion rate; VMH, ventromedial hypothalamus.

The liver plays a central role in maintaining optimal glucose levels by balancing glucose entry into and removal from circulation. In the postabsorptive state, the liver releases a comparable amount of glucose to satisfy the glucose requirement of the brain and peripheral tissues. In the postprandial state, the liver switches from output to uptake of glucose, storing it as glycogen. Although the precise mechanism of glucose uptake acceleration by the liver in the postprandial condition is not fully understood, hepatic glucose uptake is known to be regulated by several factors, such as the hormonal factor (1–3), the glucose load to the liver (4), and the route of glucose delivery (5–7). Among these factors, portal glucose delivery may be a key regulator (8). Several reports have suggested that the nature of the portal signal may be the arterial-portal glucose gradient, which develops during intraportal or oral glucose loading (9).

The liver is richly innervated by sympathetic and parasympathetic nerves. Nerve terminals have been found in the liver on the spaces of Disse, the hepatocyte cell membrane, and portal vein (10,11). The afferent nerve in the hepatic branch of the vagus nerve (12) and neurons in the lateral hypothalamus (LH), the center of the parasympathetic nerve (13), can respond to the presence of glucose in the portal vein. On the other hand, two types of glucose sensors exist in the brain. One is a glucose-sensitive neuron in LH, the activity of which is suppressed by glucose (14). The other is a glucoreceptor neuron in the ventromedial hypothalamus (VMH), the center of the sympathetic nerve, which is stimulated by glucose (14). Moreover, recent studies have demonstrated that an intact nerve supply to the liver appears to be vital for its normal response of the liver to intraduodenal and intraportal glucose delivery (15,16). These findings suggest that both the hepatoportal and central nervous systems can independently detect ambient glucose levels, which can be integrated in the brain and then influence glucose metabolism in the liver.

In the present study, we tried to clarify the significance of the glucose gradient between the hepatoportal and central nervous systems on hepatic glucose uptake in conscious dogs under physiological hyperglycemic hyperinsulinemic conditions, which were equivalent to those observed after oral glucose administration. (7)

RESEARCH DESIGN AND METHODS

Animals and surgical procedures. Experiments were conducted on nine 18-h-fasted beagle dogs of both sexes weighing 9.7 ± 0.7 kg in the conscious condi-

tion. This study was approved by the Institutional Animal Experiments Committee of the Osaka University School of Medicine. These dogs were housed in metabolic cages and fed once daily in the morning with a diet of 350 g dry food (15% protein, 10% fat, 50% carbohydrate, and 5% fiber; Pedigree, Australia) and 200 g meat (Pedigree).

Fourteen days before the experiments, laparotomy was performed under general anesthesia induced with 25 mg/kg sodium pentobarbital. Silastic catheters were inserted into the left common hepatic and portal veins for sampling and into the jejunal and splenic veins for intraportal infusion. The tip of the portal vein catheter was placed 2 cm from the point at which the portal vein enters the liver, and the tip of the hepatic venous catheter was placed 1 cm inside the left common hepatic vein (5). The catheters were filled with saline containing heparin (500 U/ml, Novo, Japan) to prevent thrombosis, and their free ends were knotted. After the gastroduodenal artery was ligated, pulsed Doppler flow probes (Triton Tech) were positioned around the hepatic artery and the portal vein. The flow probe on the hepatic artery was located at a site distal from the ligated gastroduodenal artery. The flow probe in the portal vein was located at a site proximal to the branch of the splenic vein and the gastroduodenal vein. The free ends of the catheters and the wires of the flow probes were placed in subcutaneous pockets in the abdominal wall until the experiment. During the surgery, we verified that the female dogs were not pregnant.

Approximately 10 days after the laparotomy, catheters were inserted into the unilateral carotid and vertebral arteries to infuse glucose into the central nervous system (CNS), and pulsed Doppler flow probes were positioned around the bilateral carotid arteries and the contralateral vertebral artery. The vertebral artery was ligated at a site proximal to the cannulation. These catheters were filled with heparinized saline and placed in subcutaneous pockets in the neck. A small incision was made in the inguinal area, and a sampling catheter was inserted into the femoral artery and advanced into the abdominal aorta. These catheters were treated as described above and placed in subcutaneous pockets in the neck and inguinal area.

The dogs were used in the experiments only if they had a good appetite, normal stool, and no decrease of body weight after surgery. Their leukocyte count was <20,000/mm^3 and hematocrit was higher than 33% on the day of the experiment. The subcutaneous ends of the catheters were freed through small skin incisions in the abdominal, cervical, and inguinal regions under local anesthesia (1%, lidocaine). The content of each catheter was aspirated, and the catheters were flushed with saline. The catheters in the jejunal and splenic veins were used for intraportal infusion of insulin, glucagon and glucose, and those in the portal vein, common hepatic vein, and the femoral artery were used for blood sampling. The carotid artery and the vertebral artery were used for glucose infusion into the brain. A catheter was inserted into the inferior vena cava via the saphenous vein to infuse glucose peripherally. Each dog was kept in a Pavlov harness in the conscious condition.

Experimental protocols. Each experiment consisted of a 90-min pretest period and three 90-min test periods (Fig. 1). Somatostatin (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused peripherally throughout the experiment to inhibit endogenous insulin and glucagon secretion. Concurrently, intraportal replacement of insulin (27 $pmol \cdot kg^{-1} \cdot min^{-1}$) and glucagon (0.65 $ng \cdot kg^{-1} \cdot min^{-1}$) was continued during the experiments. The plasma glucose level was monitored every 5 min, and the rate of peripheral glucose infusion was adjusted to maintain moderate hyperglycemia (8 mmol/l). After the first 90-min test period (PE), portal glucose infusion (GIR_{PV}: 55.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) was administered for 90 min (PO). To diminish the glucose gradient between the hepatoportal and central nervous systems (HPS-CNS glucose gradient), glucose was administered simultaneously into the carotid and vertebral arteries during the third period (PO+CNS). The rates of glucose infusion into the carotid artery (GIR_{CA}) and the vertebral artery (GIR_{VA}) were calculated based on the ratio of plasma flow in the portal vein (PF_{PV}) to those in the carotid artery (PF_{CA} = plasma flow of right carotid artery [PF_{RCA}] + plasma flow of left carotid artery [PF_{LCA}]) and the vertebral artery (PF_{VA}).

$$GIR_{CA} = GIR_{PV} \times PF_{CA}/PF_{PV}$$
$$GIR_{VA} = GIR_{PV} \times PF_{VA}/PF_{PV}$$

Analytical procedures and calculations. Blood sampling and measurement of blood flow were done every 15 min in each period in the protocols. The arterial and portal blood samples were collected simultaneously, and a hepatic vein sample was taken after a 30-s delay to compensate for transit time through the liver (5).

Plasma glucose concentrations were measured by the glucose oxidase method using a Glucose Analyzer II (Beckman, Fullerton, CA). Arterial plasma insulin and glucagon levels were analyzed by radioimmunoassays (Amersham International, Buckinghamshire, England, and Daiichi Radioisotope Labs, Japan, respectively). Blood flow in the portal vein and the hepatic vein was measured directly using a Doppler flow meter (Valpey-Fisher) (17).

The load of glucose entering the liver ($Load_{in}$) was calculated as in the following:

$$Load_{in} = [G]_{HA} \times PF_{HA} + [G]_{PV} \times PF_{PV}$$

in which $[G]_{HA}$ and $[G]_{PV}$ represent plasma glucose concentration in the hepatic artery and portal vein, and PF_{HA} represents plasma flow in the hepatic artery. Plasma flow was calculated as in the following:

$$PF = BF \times (1 - Ht)$$

in which Ht represents the hematocrit and BF is the blood flow determined by a Doppler flow meter. The load of glucose exiting the liver ($Load_{out}$) was calculated using the following equation:

$$Load_{out} = [G]_{HV} \times PF_{HV}$$

where $[G]_{HV}$ and PF_{HV} represent plasma glucose concentration and plasma flow in the hepatic vein.

Net hepatic glucose balance (NHGB) was calculated as in the following:

$$NHGB = Load_{out} - Load_{in}$$

Positive values of NHGB mean a net glucose output by the liver, while negative values mean a net hepatic glucose uptake. To eliminate the effect of the hepatic glucose load, the hepatic extraction rate of glucose (HERG) was determined as in the following:

$$HERG = NHGB / Load_{in}$$

Hepatic extraction of insulin was determined from the same calculation of HERG.

Under hyperglycemic hyperinsulinemic conditions, net hepatic glucose production was assumed to be completely suppressed. Therefore, peripheral glucose uptake (PGU) was calculated from the summation of total glucose infusion rate (TGI) and net hepatic glucose uptake (NHGB).

$$PGU = TGI + NHGB$$

To determine the glucose mixing in the portal vein, we compared portal glucose levels with the estimated portal glucose levels (estimated $[G]_{PV}$) determined with the following formula:

$$\text{Estimated } [G]_{PV} = [G]_{HA} + GIR_{PV}/PF_{PV} - \Delta[G]_{GI},$$

where $\Delta[G]_{GI}$ shows glucose extracted by the intestine and is determined by the difference of glucose levels between the arterial and portal samples during PE. The results were from the experiment in which the difference between portal glucose and the estimated value was within 20%. Two dogs were excluded from the original group of nine because of poor portal mixing.

Arterial plasma glucose levels were stable in the last 30 min of each experimental period, and the data in the figures and tables are averages under the steady state. All data are represented as means ± SE. Data within each protocol were evaluated by Wilcoxon's single-rank test. Statistical significance was accepted at $P < 0.05$.

RESULTS

Plasma glucose, plasma insulin, and glucagon levels. Hyperglycemic hyperinsulinemic clamp produced stable and comparable arterial plasma glucose levels in each period (8.1 ± 0.1, PE; 8.2 ± 0.1, PO; 8.2 ± 0.1 mmol/l, PO+CNS) (Table 1). Average plasma glucose levels in the portal and hepatic veins were 7.5 ± 0.1 and 7.4 ± 0.1 in PE and increased significantly to 10.3 ± 0.2 and 8.1 ± 0.2 in PO and increased to 10.0 ± 0.2 and 8.5 ± 0.2 mmol/l in PO+CNS, respectively ($P < 0.05$). Arterial plasma insulin levels were 543 ± 83 in PE and increased significantly to 601 ± 91 and 655 ± 87 pmol/l in PO and PO+CNS, respectively ($P < 0.05$). Hepatic extraction of insulin and arterial plasma glucagon levels were comparable among the three periods (Table 1).

Glucose infusion rate and HPS-CNS glucose gradient. In PE, the mean peripheral glucose infusion rate was 121 ± 12 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, which maintained arterial plasma glu-

TABLE 1
Plasma glucose concentrations in the artery, portal vein, and hepatic vein, and arterial plasma insulin and glucagon levels.

	PE	PO	PO+CNS
Plasma glucose levels (mmol/l)			
Artery	8.1 ± 0.1	8.2 ± 0.1†	8.2 ± 0.1†
Portal vein	7.5 ± 0.1	10.3 ± 0.2*	10.0 ± 0.2*
Hepatic vein	7.4 ± 0.1	8.1 ± 0.2*†	8.5 ± 0.2*†
Insulin (pmol/l)	543 ± 83	601 ± 92*	655 ± 87*
Hepatic extraction of insulin (%)	54 ± 9.5	62 ± 5.2	48 ± 8.1
Glucagon (ng/l)	60 ± 5.5	60 ± 8.8	57 ± 3.3

Data are means ± SE for seven dogs with hyperglycemic hyperinsulinemic clamp during variable glucose infusion into the peripheral vein (PE), variable and constant glucose infusion into the peripheral and portal veins, respectively, (PO), and additional glucose infusion into the carotid and vertebral arteries with peripheral and portal glucose delivery (PO+CNS). *P < 0.05 vs. PE. †P < 0.05 vs. portal vein in each period.

cose levels at 8 mmol/l. The peripheral glucose infusion rate decreased to 83 ± 13 μmol · kg^{-1} · min^{-1} in PO. In PO+CNS, the peripheral glucose infusion rate decreased to 60 ± 13 μmol · kg^{-1} · min^{-1}, and the glucose infusion rates into the carotid and vertebral arteries were 20 ± 2 and 8 ± 1 μmol · kg^{-1} · min^{-1}, respectively.

In PO, HPS-CNS glucose gradients were identical with the glucose gradient between portal and arterial samples (2.1 ± 0.2 mmol/l) and significantly higher than that in PE (–0.5 ± 0.1 mmol/l, P < 0.05). In PO+CNS, the arterial-portal glucose gradient was comparable with that in PO (1.8 ± 0.2 mmol/l), but the HPS-CNS glucose gradient was assumed to be equal to that observed in PE with glucose infusion into the carotid and vertebral arteries.

Hepatic plasma flow and hepatic glucose load. There was no significant difference in the plasma flow of the hepatic artery and portal vein among the three periods (Fig. 2). The hepatic glucose load was 187 ± 25 in PE and increased significantly to 259 ± 30 and 244 ± 34 μmol · kg^{-1} · min^{-1} in PO and PO+CNS, respectively (Fig. 2).

Net hepatic glucose balance (NHGB) and hepatic extraction ratio of glucose (HERG). In PE, NHGB was –7.4 ± 3.4 μmol · kg^{-1} · min^{-1} under the hyperglycemic hyperinsulinemic condition. In PO, NHGB decreased immediately and reached a plateau at –41.5 ± 5.3 μmol · kg^{-1} · min^{-1}, 5.5 times the rate of the hepatic glucose uptake seen in PE (P < 0.05, Fig. 3). In PO+CNS, NHGB was significantly lower than that in PE (–21.7 ± 3.2 μmol · kg^{-1} · min^{-1}, P < 0.05) and 50% of that observed in PO (P < 0.05). HERG was 3.2 ± 1.4 in PE and increased to 17.4 ± 2.7% (P < 0.05) in PO. HERG

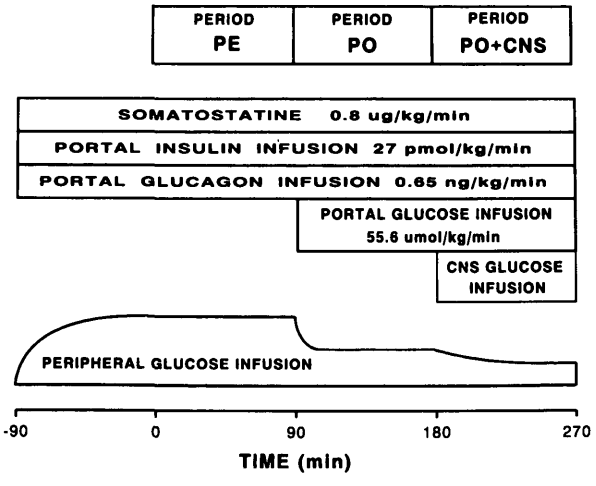

FIG. 1. Experimental design.

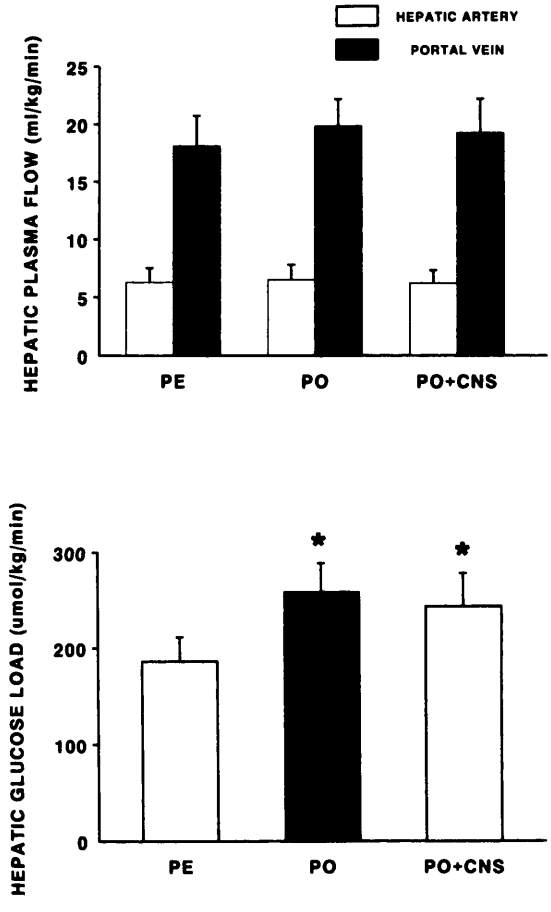

FIG. 2. Hepatic plasma flow and hepatic glucose load in seven dogs with hyperglycemic hyperinsulinemic clamp during variable glucose infusion into the peripheral vein (PE), variable and constant glucose infusion into the peripheral and portal veins, respectively (PO), and additional glucose infusion into the carotid and vertebral arteries with peripheral and portal glucose delivery (PO+CNS). *P < 0.05 vs. PE.

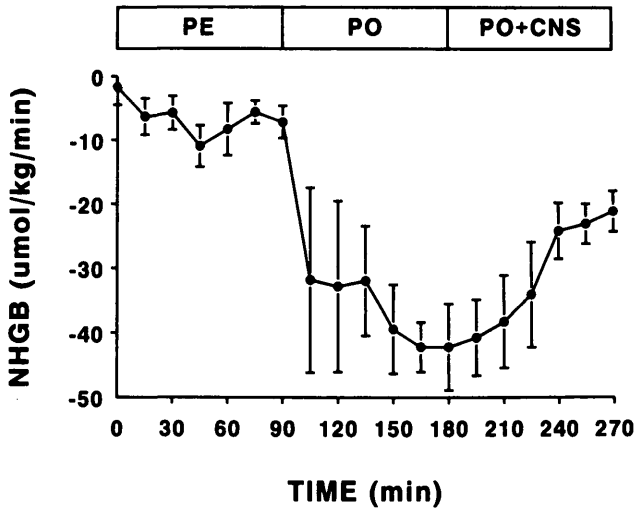

FIG. 3. Net hepatic glucose balance in seven dogs with hyperglycemic hyperinsulinemic clamp during variable glucose infusion into the peripheral vein (PE), variable and constant glucose infusion into the peripheral and portal veins (PO), respectively, and additional glucose infusion into the carotid and vertebral arteries with peripheral and portal glucose delivery (PO+CNS).

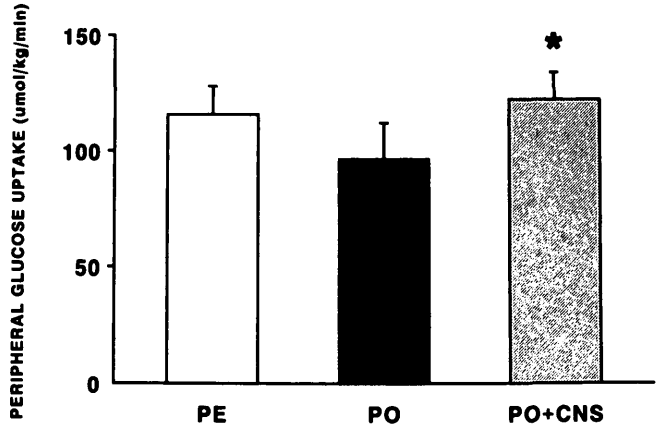

FIG. 4. Peripheral glucose uptake in seven dogs with hyperglycemic hyperinsulinemic clamp during variable glucose infusion into the peripheral vein (PE), variable and constant glucose infusion into the peripheral and portal veins (PO), respectively, and additional glucose infusion into the carotid and vertebral arteries with peripheral and portal glucose delivery (PO+CNS). *P < 0.05 vs. PO.

decreased significantly to 10.2 ± 2.3% in PO+CNS compared with PO (P < 0.05), but was higher than that observed in PE (P < 0.05).

Peripheral glucose uptake. There were no significance differences in peripheral glucose uptake during PE (116 ± 12) and PO (97 ± 15 μmol · kg^{-1} · min^{-1}) (Fig. 4). In PO+CNS, peripheral glucose uptake increased to significantly more than that observed in PO (122 ± 12 μmol · kg^{-1} · min^{-1}, P < 0.05).

DISCUSSION

Hepatic glucose uptake is well known to be markedly enhanced when glucose is administered intraportally rather than peripherally in humans (18) and dogs (2,4,5,8,9). The present study confirms this in conscious dogs under hyperglycemic hyperinsulinemic conditions. Furthermore, we found that diminution of a positive glucose gradient between the portal vein and the brain suppressed the hepatic glucose uptake enhanced by portal glucose delivery.

A number of studies have demonstrated that a neural factor can regulate the hepatic glucose metabolism. Lautt et al. (19) showed that electrical stimulation of the hepatic parasympathetic nerve decreases hepatic glucose production in perfused rat liver. Shimazu et al. reported that electrical stimulation of LH increased the activity of glycogen synthetase (20) and decreased the activity of phosphoenolpyruvate carboxykinase (a key enzyme in gluconeogenesis) in the liver (21). Thus, the efferent signal of the autonomic nervous system influences glucose metabolism in the liver by regulating hepatic enzyme activities. Therefore, such a neural network between CNS and the liver can enhance hepatic glucose uptake, probably by mediating hepatic enzyme activity.

A recent study by Pagliassotti et al. (22) demonstrated that enhanced net hepatic glucose uptake persisted for at least 240 min. Therefore, it is unlikely for the decrease of net hepatic glucose uptake in PO+CNS not to be the natural course of hepatic glucose uptake during prolonged intraportal glucose infusion under hyperglycemic hyperinsulinemic conditions. Net hepatic glucose uptake increased immediately within 15 min in PO and decreased gradually for 60 min in PO+CNS. Such a quick response of the net hepatic glucose uptake also suggests that the portal signal involves a neural factor. However, once the portal signal activates the liver, accelerated activity of hepatic enzymes, such as glycogen synthase and glucokinase, persists under the hyperinsulinemic condition after removal of the portal signal. The same findings were observed after discontinuation of portal glucose delivery under euglycemic hyperinsulinemic conditions (23).

There are several reasons why abolishment of the HPS-CNS glucose gradient could not completely suppress enhanced hepatic glucose uptake by intraportal glucose delivery. First, the glucose load to the liver and the insulin concentrations increased by 35 and 25%, respectively, during PO and PO+CNS. These increases enhanced net hepatic glucose uptake in PO and PO+CNS compared with PE. Second, since glucose was infused into the unilateral carotid and vertebral artery, abolishment of the HPS-CNS glucose gradient might have been incomplete. Third, there is a local effect of portal glucose delivery on hepatic glucose uptake, which has been demonstrated by Gardemann et al. (24) in isolated perfused liver. Hepatic glucose uptake in the isolated perfused liver increased insulin dependently when a glucose gradient was established between the portal vein and the hepatic artery. Since there was no neural network between the central nervous system and the liver in the perfused liver, it may have used a glucose gradient between the portal vein and hepatic artery as a local regulatory mechanism of glucose handling. Moreover, we could not exclude the effects of still unknown factors on hepatic glucose uptake.

It might be argued that cerebral glucose infusion itself affects hepatic glucose handling directly by altering hormonal or hemodynamic factors. In a preliminary study, to determine the effect of glucose infusion on glucose sensors in the brain, glucose was infused at a total rate of 38.9 μmol · kg^{-1} · min^{-1} into the peripheral vein or the carotid and vertebral arteries in seven mongrel dogs. Glucose infusion rates into the carotid and vertebral arteries were calculated based on the ratio of blood flow in those arteries. Net hepatic

glucose balance was –7.8 ± 3.3 μmol · kg^{-1} · min^{-1} during peripheral glucose infusion and was –9.4 ± 3.3 μmol · kg^{-1} · min^{-1} during glucose infusion into carotid and vertebral arteries. Therefore, it is unlikely that glucose infusion into unilateral carotid and vertebral arteries can directly suppress hepatic glucose uptake.

We could not verify glucose mixing in the brain because no sample could be obtained from downstream of the carotid and vertebral arteries during the experiments. Blood to the hypothalamus, regarded as an important integrative center for neural and hormonal regulation, is supplied by the arterial circle of the brain which is formed by the right and left carotid arteries and the basilar artery (25). The right and left vertebral arteries anastomose to form the basilar artery. Therefore, it is expected that glucose is mixed well in the arterial circle and delivered into the hypothalamus. Even if complete mixing of glucose did not occur in PO+CNS, the glucose gradient between the hepatoportal and central nervous systems should have been considerably decreased.

In the present study, arterial plasma insulin levels in PO and PO+CNS were significantly higher than that in PE, but insulin infusion rates were constant, and hepatic extraction of insulin was comparable among the three periods. Therefore, insulin clearance in the extrahepatic tissues might be affected by portal glucose delivery.

Adkins et al. (8) and Myers et al. (4) demonstrated that peripheral glucose disposal was decreased by intraportal glucose delivery at low insulin concentrations, but not at high physiological insulin concentrations. In the present study, portal glucose delivery did not affect peripheral glucose disposal because of a high concentration and increase of arterial plasma insulin. However, decrease of the glucose gradient between HPS and CNS significantly increased peripheral glucose uptake during portal glucose infusion even at high insulin concentrations. Recently, Minokoshi et al. (26) demonstrated that VMH stimulation enhanced glucose disposal in the peripheral tissues through intermediation by the autonomic nervous system. Thus, the glucose gradient between the hepatoportal and central nervous systems may regulate the peripheral glucose uptake through the autonomic nervous system.

In conclusion, a positive glucose gradient between the hepatoportal system and central nervous system plays the most important role in accelerated hepatic glucose uptake during portal glucose load under hyperglycemic hyperinsulinemic conditions in conscious dogs. However, other factors, such as hepatic glucose load and insulin level, and local regulatory factors may also have important roles in hepatic glucose uptake.

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