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Portal 5-hydroxytryptophan infusion enhances glucose disposal in conscious dogs

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Abstract

Intraportal serotonin infusion enhances net hepatic glucose uptake (NHGU) during glucose infusion but blunts nonhepatic glucose uptake and can cause gastrointestinal discomfort and diarrhea at high doses. Whether the serotonin precursor 5-hydroxytryptophan (5-HTP) could enhance NHGU without gastrointestinal side effects during glucose infusion was examined in conscious 42-h-fasted dogs, using arteriovenous difference and tracer ([3-^{3}H]glucose) techniques. Experiments consisted of equilibration (−120 to −30 min), basal (−30 to 0 min), and experimental (EXP; 0–270 min) periods. During EXP, somatostatin, fourfold basal intraportal insulin, basal intraportal glucagon, and peripheral glucose (to double the hepatic glucose load) were infused. In one group of dogs (HTP, n = 6), saline was infused intraportally from 0 to 90 min (P1), and 5-HTP was infused intraportally at 10, 20, and 40 μg·kg^{-1}·min^{-1} from 90 to 150 (P2), 150 to 210 (P3), and 210 to 270 (P4) min, respectively. In the other group (SAL, n = 7), saline was infused intraportally from 0 to 270 min. NHGU in SAL was 14.8 ± 1.9, 18.5 ± 2.3, 16.3 ± 1.4, and 19.7 ± 1.6 μmol·kg^{-1}·min^{-1} in P1–P4, whereas NHGU in 5-HTP averaged 16.4 ± 2.6, 18.5 ± 1.4, 20.8 ± 2.0, and 27.6 ± 2.6 μmol·kg^{-1}·min^{-1} (P < 0.05 vs. SAL). Nonhepatic glucose uptake (μmol·kg^{-1}·min^{-1}) in SAL was 30.2 ± 4.3, 36.8 ± 5.8, 44.3 ± 5.8, and 54.6 ± 11.8 during P1–P4, respectively, whereas in HTP the corresponding values were 26.3 ± 6.8, 44.9 ± 10.1, 47.5 ± 11.7, and 51.4 ± 13.2 (not significant between groups). Intraportal 5-HTP enhances NHGU without significantly altering nonhepatic glucose uptake or causing gastrointestinal side effects, raising the possibility that a related agent might have a role in reducing postprandial hyperglycemia.

Keywords

glycemia; liver; portal vein; leptin; adiponectin

Poor postprandial glycemic control is associated with elevated rates of all-cause mortality in individuals with type 2 diabetes (45), and thus control of postprandial hyperglycemia is an attractive pharmaceutical target. Intraportal infusion of serotonin (5-hydroxytryptamine or 5-HT) enhances net hepatic glucose uptake (NHGU) in the hyperinsulinemic, hyperglycemic conscious dog (28), indicating that 5-HT might be effective in reducing postprandial

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hyperglycemia. However, elevated circulating 5-HT is associated with intestinal cramping and diarrhea (3). Thus, for potential therapeutic use, agents that raise tissue levels of 5-HT without elevating blood 5-HT excessively are desirable.

Intraperitoneal administration of 5-hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, has a hypoglycemic effect in mice that is apparently related to intrahepatic accumulation of 5-HT (8). We have demonstrated that intraportal infusion of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, which prolongs the action of endogenous 5-HT, stimulates NHGU (27). One multicenter study comparing fluvoxamine and 5-HTP in treatment of depression determined that 5-HTP was more effective (37), suggesting that serotonin deficiency (which can be corrected by administration of 5-HTP but not an SSRI) may exist in some individuals. Similarly, experimental models of diabetes are reported to have reduced levels of 5-HT (26). Thus we hypothesized that 5-HTP would enhance NHGU, thereby directing increased amounts of glucose in the liver as opposed to the peripheral circulation, without elevating circulating 5-HT sufficiently to cause adverse symptoms. We therefore examined the ability of 5-HTP given intraportally to conscious dogs in which the pancreatic hormones and hepatic glucose load were fixed at postprandial levels.

RESEARCH DESIGN AND METHODS

Animals and surgical procedures

Studies were carried out on 13 conscious 42-h-fasted mongrel dogs of either sex with a mean weight of 23.1 ± 0.6 kg. Diet was as previously described (36), the animals were housed in a facility approved by the United States Department of Agriculture, and the protocol was approved by the Vanderbilt University Medical Center Institutional Animal Care and Use Committee. The 42-h fast was used to reduce hepatic glycogen concentrations to a stable minimum, which reduces variability in the animals' response to hyperglycemia and hyperinsulinemia. Dogs tolerate a fast of this duration well, with only a slight decline in blood glucose (~0.2–0.3 mM change) and little change in glucagon (~10%) between 18 and 42 h of fasting (30).

Approximately 16 days before study, each dog underwent a laparotomy for placement of ultrasonic flow probes (Transonic Systems, Ithaca, NY) around the portal vein and the hepatic artery, as well as for insertion of silicone rubber catheters for sampling in a hepatic vein, the portal vein, and a femoral artery and for infusion in a splenic and a jejunal vein as described elsewhere (36,42). Criteria for study were as previously described (36).

On the morning of the study, catheters and flow probe leads were exteriorized from their subcutaneous pockets (36). The splenic and jejunal catheters were used for intraportal infusion of insulin (Eli Lilly, Indianapolis, IN), glucagon (GlucaGen; Bedford Laboratories, Bedford, OH), and 5-HTP (Sigma-Aldrich, St. Louis, MO). Angiocaths (Deseret Medical, Sandy, UT) were inserted in three peripheral veins.

Experimental design

Each experiment consisted of a 90-min equilibration period (−120 to −30 min), a 30-min basal period (−30 to 0 min), and a 270-min experimental period (0–270 min) divided into four subperiods (P1, 0–90 min; P2, 90–150 min; P3, 150–210 min, and P4, 210–270 min). At −120 min, a primed (38 μCi), continuous (0.35 μCi/min) infusion of [3-^{3}H]glucose (NEN, Cambridge, MA) and a continuous infusion of indocyanine green dye (Sigma; 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were begun in all dogs, with the exception of one that did not receive [3-^{3}H] glucose. At 0 min, a constant peripheral infusion of somatostatin (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$; Bachem, Torrance, CA) was begun to suppress endogenous insulin and glucagon secretion. Insulin was

infused intraportally at 1.2 mU·kg^{-1}·min^{-1} (4-fold basal), and glucagon (0.55 ng·kg^{-1}·min^{-1}) was replaced intraportally in basal amounts. In addition, a primed, continuous variable-rate infusion of 50% dextrose was begun through a peripheral vein to maintain the hepatic glucose load twofold basal. During P1, all dogs received intraportal normal saline infusion. At the end of P1, the dogs were divided into two groups. In the saline (SAL) group (n = 7), the intraportal saline infusion continued for the remainder of the study. In the HTP group (n = 6), 5-HTP was infused in the portal vein at 10, 20, and 40 μg·kg^{-1}·min^{-1} during P2, P3, and P4, respectively. The infusion rates were the same as the infusion rates for 5-HT in our previous study (28). The portal route of infusion was chosen to target the 5-HTP at the liver as much as possible. In addition, we did not administer an inhibitor of peripheral aromatic L-amino acid decarboxylase (AADC). An AADC inhibitor would have reduced the conversion of 5-HTP to 5-HT in peripheral tissues, making more 5-HTP available to cross the blood-brain barrier (10). The liver has relatively high levels of AADC (21,44) and thus should synthesize substantial amounts of 5-HT from the substrate.

Femoral artery, portal vein, and hepatic vein blood samples were taken every 15–30 min throughout the study, as previously described (36). Arterial blood samples were also taken every 5 min throughout the experimental period to monitor the glucose level (36). After completion of each experiment, the animal was killed with an overdose of pentobarbital sodium.

Processing and analysis of samples

Hematocrit, blood glucose, lactate, glycerol, plasma glucose, nonesterified fatty acids (NEFA), insulin, glucagon, cortisol, catecholamines, and [^{3}H]glucose were measured as described previously (36,42). 5-HT concentrations were determined on whole blood by an HPLC-amperometric assay (38) with a coefficient of variation (CV) of 4%, as previously reported (28). Plasma leptin concentrations were analyzed by a sandwich ELISA assay using an anti-canine leptin antibody as previously described (20) with inter- and intra-assay CV <4%. Plasma adiponectin was measured using a commercial mouse/rat ELISA kit (Otsuka Pharmaceuticals, Tokushima, Japan) optimized for analysis of canine samples, with intra-assay CV of 6.7–8.5% and interassay CV of 3.4–7.5% (35).

Calculations and data analysis

Hepatic blood flow was measured using ultrasonic flow probes and by use of indocyanine green extraction. The two methods yielded similar results, but the data reported here were calculated with the ultrasonic-determined flows because their measurement did not require an assumption regarding the relative contribution of arterial and portal flow to total hepatic blood flow.

The rate of glucose delivery to the liver (or hepatic glucose load), net hepatic substrate balance, net hepatic fractional substrate extraction, net hepatic carbon retention, hepatic sinusoidal insulin and glucagon concentrations, and nonhepatic glucose uptake (non-HGU) were calculated as described previously (33). During the 1st h of glucose infusion, the non-HGU was corrected for the glucose required to fill the pool, using a pool fraction of 0.65 (6) and assuming that the volume of distribution for glucose equaled the volume of the extracellular fluid, or ~22% of the dog's weight (43). For all glucose balance calculations, glucose concentrations were converted from plasma to blood values by using correction factors (ratio of the blood to the plasma concentration), as previously established in our laboratory (18). Hepatic glucose uptake (in dpm·kg^{-1}·min^{-1}) was calculated as was NHGU, except that tritiated glucose measurements were used. The results were divided by the inflowing glucose specific activity (dpm/μmol glucose). Glucose rates of appearance (R_a) and disappearance (R_d) were calculated with a two compartment model using dog parameters previously described (7,25).

Statistical analysis

All data are presented as means ± SE. Time course data were analyzed with repeated-measures ANOVA, with Tukey's test for post hoc comparisons (SigmaStat; Jandel Scientific). Statistical significance was accepted at $P < 0.05$. Results for P1–P4 are the means of the three samples taken during the last 30 min of each period, when steady-state conditions prevailed.

RESULTS

5-HT, hormone, and catecholamine concentrations

Arterial blood 5-HT concentrations remained basal throughout the experiments in SAL and during P1–P3 in HTP, but the concentration increased significantly during P4 (Table 1). The arterial 5-HT concentration in HTP during P4 was similar to those evident in four dogs during the first 2 h after an oral glucose tolerance test consisting of 1.5 mg glucose/kg (M. C. Moore and A. D. Cherrington, unpublished observations). Net hepatic 5-HT balance remained basal in SAL throughout the experiments. In the HTP group, net hepatic 5-HT balance did not change from basal during P1–P3, but net hepatic 5-HT uptake increased significantly during P4.

The plasma insulin levels increased approximately three- to fourfold and remained stable during P1–P4 in both groups (Table 1). Arterial and hepatic sinusoidal plasma glucagon concentrations were basal and indistinguishable in both groups throughout the experiments (Table 1).

Arterial plasma cortisol concentrations remained basal in SAL throughout P1–P4. In HTP, the mean cortisol concentrations remained statistically unchanged from basal during P1–P4, but one animal did demonstrate a substantial increase from basal (84–271 nmol/l) during P4. This dog also exhibited a rise in arterial 5-HT concentrations to nearly threefold basal compared with the 40% increase observed in the other five dogs in the HTP group. Arterial plasma concentrations of epinephrine and norepinephrine did not change significantly during P1–P4 in either group (Table 1).

Plasma leptin and adiponectin concentrations were available on four animals in each group. The concentrations of both hormones were similar during the basal period in the two groups, and they did not change significantly during the study in either group (Table 2).

Hepatic blood flow, blood glucose concentrations, and hepatic glucose load

Portal vein blood flow decreased modestly in both groups during P1 as a response to somatostatin infusion (Table 3) and did not change significantly thereafter. There was a concomitant increase in hepatic artery flow. As a consequence, total hepatic blood flow was relatively stable throughout the experiments, with no differences between groups at any time.

Arterial blood glucose levels in SAL increased from a basal value of 4.6 ± 0.1 to 9.3 ± 0.1 mmol/l during all experimental periods (Fig. 1). In HTP, the arterial glucose concentration increased from 4.3 ± 0.2 to 9.0 ± 0.1 mmol/l. There were no significant differences between groups. In addition, the hepatic glucose loads were not significantly different between groups at any time (Fig. 1), increasing from 145 ± 9 (basal) to 271 ± 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during P1–P4 in SAL and from 137 ± 16 to 257 ± 18 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ in HTP.

Net hepatic glucose balance, net hepatic fractional glucose extraction, and endogenous glucose R_a

The groups exhibited a similar rate of net hepatic glucose output during the basal period. Coincident with the start of the experimental period, they switched from net production to net uptake, with the rates being no different between groups during P1 and P2 (Fig. 2). In both

groups, NHGU during P2 averaged 18.5 μmol·kg^{-1}·min^{-1}. Subsequently, the rate of NHGU remained relatively stable in SAL (mean rate 19.7 ± 1.6 μmol·kg^{-1}·min^{-1} in P4), whereas in HTP it increased to 27.6 ± 2.6 μmol·kg^{-1}·min^{-1} ($P < 0.05$ vs. SAL). Similarly, the net hepatic fractional extraction (FE) of glucose did not differ significantly between groups during P1 and P2, averaging 0.065 ± 0.007 and 0.074 ± 0.013 during P2 in SAL and HTP, respectively. Subsequently, FE changed little in SAL (0.060 ± 0.007 and 0.073 ± 0.006 during P3 and P4, respectively), but it increased in HTP (0.084 ± 0.014 and 0.110 ± 0.014 during P3 and P4, respectively; $P < 0.05$ vs. SAL during P4). The rate of unidirectional (tracer-determined) hepatic glucose uptake did not differ significantly between groups during any period, although there was a tendency ($P = 0.07$) for it to be greater in HTP vs. SAL during P4 (Table 4). However, compared with SAL, HTP demonstrated significant enhancement of hepatic glucose uptake between P1 and each of the last two periods (Δ between P1 and P3: 2.2 ± 2.1 vs. 11.3 ± 2.7 μmol·kg^{-1}·min^{-1} in SAL vs. HTP, respectively, $P < 0.05$; Δ between P1 and P4: 5.3 ± 1.4 vs. 17.6 ± 3.0 μmol·kg^{-1}·min^{-1}, $P < 0.005$; Table 4).

Endogenous glucose R_a decreased similarly in response to hyperglycemia and hyperinsulinemia in both groups (from 14.8 ± 1.0 to 3.4 ± 1.3 μmol·kg^{-1}·min^{-1} in SAL and from 15.6 ± 3.5 to 3.6 ± 2.4 μmol·kg^{-1}·min^{-1} in HTP), remained suppressed throughout the experimental periods and did not differ significantly between groups at any time (data not shown).

Total and nonhepatic glucose disposal

The glucose infusion rate in both groups increased steadily in a time-dependent manner during P1–P4, with no differences between groups (45.0 ± 5.3, 55.2 ± 7.4, 60.6 ± 6.9, and 73.7 ± 11.6 μmol·kg^{-1}·min^{-1} in SAL and 42.7 ± 7.9, 63.4 ± 10.4, 68.3 ± 10.4, and 79.0 ± 11.4 μmol·kg^{-1}·min^{-1} in HTP; Fig. 3). Similarly, both glucose R_d (Table 4) and non-HGU (Fig. 3) increased with time and did not differ between groups during any period. Non-HGU averaged 30.2 ± 4.3, 36.8 ± 5.8, 44.3 ± 5.8, and 54.6 ± 11.8 μmol·kg^{-1}·min^{-1} during P1–P4 in SAL and 26.3 ± 6.8, 44.9 ± 10.8, 47.4 ± 11.8, and 51.4 ± 13.2 μmol·kg^{-1}·min^{-1} in HTP.

Lactate metabolism and net hepatic carbon retention

Basal arterial blood lactate concentrations were significantly higher in SAL than HTP, but both groups demonstrated a significant increase in lactate levels in response to hyperglycemia and hyperinsulinemia (Table 5). The lactate concentrations continued to be lower in HTP than SAL throughout the study, but this did not reach statistical significance during P1 and P4. Both groups demonstrated a switch from net hepatic lactate uptake to output at the onset of the experimental period, and the rates in the two groups did not differ significantly at any time.

The rates of net hepatic carbon retention in SAL and HTP were similar during P1 and P2 (11.6 ± 1.9 and 17.0 ± 2.7 μmol·kg^{-1}·min^{-1} in SAL and 13.1 ± 2.6 and 16.7 ± 0.9 μmol·kg^{-1}·min^{-1} in HTP; Fig. 4). However, during P3 and P4, the rates in HTP (20.1 ± 2.4 and 26.2 ± 2.3 μmol·kg^{-1}·min^{-1}) were greater ($P < 0.05$) than those in SAL (15.4 ± 2.0 and 17.5 ± 1.8 μmol·kg^{-1}·min^{-1}).

Glycerol and NEFA metabolism

Arterial glycerol concentrations were reduced ~55–65% by hyperglycemia and hyperinsulinemia in both groups, and net hepatic glycerol uptake fell in parallel with the glycerol levels, remaining suppressed throughout the experimental period (Table 5). Arterial NEFA concentrations and net hepatic NEFA uptake changed in a manner similar to glycerol, decreasing ~80–90% during P1 in both groups and then remaining low throughout the remainder of the experimental period.

DISCUSSION

A twofold increase in the hepatic glucose load in the presence of fourfold basal insulin and basal glucagon concentrations resulted in NHGU of ~15.5 μmol·kg^{-1}·min^{-1} in the two groups. Between P1 and P4, the rate of NHGU increased ~33% in SAL. During infusion of 5-HTP at 10 μg·kg^{-1}·min^{-1}, there was no enhancement in NHGU compared with SAL. However, during 5-HTP infusion at 20 and 40 μg·kg^{-1}·min^{-1}, NHGU increased 29 and 40%, respectively, over the corresponding rates in SAL ($P < 0.05$ for both increments). By the end of the experimental period, NHGU in HTP had increased 68% over the rate during P1 ($P < 0.05$ vs. the increase in SAL). Tracer measurements confirmed that there was a significant enhancement of hepatic glucose uptake over the rate during P1 associated with 5-HTP delivery, and there was a strong tendency for hepatic glucose uptake to differ between groups during P4. Similar to NHGU, net hepatic carbon retention was virtually identical between the groups during P1 and P2. During P3 and P4, net hepatic carbon retention was 31 and 50% greater, respectively, in HTP than in SAL ($P < 0.05$ for both). In this initial study, we merely wanted to determine whether 5-HTP, given at any rate that would bring about 5-HT concentrations in the physiological range, would induce NHGU. Therefore, we administered 5-HTP in three increasing steps during P2–P4. As a result, it is not possible to separate the effects of time from those of dosage. Nevertheless, it is possible to conclude definitively that 5-HTP impacted NHGU, hepatic glucose uptake, and hepatic carbon retention.

The effects of 5-HTP on the liver could have resulted either from a direct effect of 5-HT or from a secondary signal initiated elsewhere. In regard to a potential direct effect of 5-HT on hepatocytes, the liver contains AADC enzyme for conversion of 5-HTP to 5-HT, and this is enzyme is reported to have high efficiency at physiological substrate concentrations (13). Moreover, the 5-HT$_{2B}$ receptor is known to be expressed in greatest abundance in the liver and kidney in humans (4), and isoforms of the 5-HT$_3$ receptor are also expressed in the human liver (23,31). The actions of 5-HT within the liver have not been well studied. However, in the kidney and intestinal tract (nonneural tissues where 5-HT is synthesized and its actions have been more fully explored), 5-HT acts via autocrine/paracrine mechanisms (13,24). Thus the potential exists for a direct hepatic action of 5-HT or an intrahepatic reflex elicited by 5-HT.

In regard to the possibility of indirect effects of 5-HT on the liver, 5-HT is commonly involved in afferent vagal signaling (e.g., see Ref. 16). The paracrine effects of 5-HT in the intestine involve stimulation of vagal afferents, with a reflex stimulation of pancreatic secretion (24). Niijima (32) determined that intraportal injection of 5-HT resulted in a decrease in the afferent firing rate in the hepatic branch of the vagus nerve and a stimulation of efferent firing in the pancreatic branch of the vagus, similar to the effect of intraportal glucose injection, suggesting a mechanism by which 5-HT could elicit a neural signal enhancing NHGU. Conversion of 5-HTP to 5-HT occurs in serum and many tissues, including the intestines, kidney, adrenals, and certain blood vessel walls (34,39,40,50). Although we have not compared NHGU during peripheral venous vs. intraportal infusion of 5-HT, 5-HT elicited a greater change in afferent firing in the common hepatic branch of the vagus (which innervates the liver but also portions of the gastrointestinal tract), or a shorter period of latency, when injected in the jugular rather than the hepatic portal vein of rats, suggesting that 5-HT was acting primarily on nerve fibers outside the hepatoportal region (17). Additionally, rather than acting via a peripheral afferent neural signal, 5-HTP could have reached the central nervous system. 5-HTP crosses the blood-brain barrier, and the brain is rich in AADC (39). An increase in the brain 5-HT level could have resulted in a centrally mediated neural signal to the liver.

Another possible mechanism for the action of 5-HTP is via stimulation of the release of other hormones such as leptin (46,47), which impacts upon insulin signaling and sensitivity in the liver (19,22), or adiponectin (48), a hormone with insulin-sensitizing actions (49). Therefore,

we measured these hormones in a subset of animals from each group. We were unable to identify any consistent changes related to 5-HTP administration, although we cannot rule out the possibility that 5-HTP increases the binding of leptin to its soluble receptor, thereby modulating its actions (5).

Because 5-HTP infusion was associated with a similar rate of non-HGU between groups but an enhancement of liver glucose uptake during P3 and P4, there was a tendency for whole body glucose disposal to be increased in the HTP group during those two periods. This tendency was evidenced in both the glucose infusion rate (~6–8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ greater in HTP than SAL during P3 and P4) and the glucose R_d (~4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ greater in HTP than SAL during P3 and P4), but neither parameter was statistically different between the groups (P = 0.4 for both). We have previously observed under a variety of conditions (e.g., Refs. 1,9,27, and 29) that, when NHGU is enhanced, there is a reciprocal reduction in nonhepatic (primarily skeletal muscle) glucose uptake such that there is little impact on whole body glucose disposal. Although the lack of reciprocity in the current study may simply have resulted from difficulty in observing a small change against the background of a high rate of non-HGU, it deserves further examination in the future. Impaired splanchnic (primarily liver) glucose uptake in response to glucose feeding is one of the defects associated with type 2 diabetes (2). We studied 5-HTP with the goal of determining whether it would be effective in increasing the proportion of a carbohydrate load extracted by the liver, thereby reducing the load to be disposed of in the peripheral tissues. Thus we did not expect 5-HTP to alter total body uptake. Nevertheless, the current data suggest that an optimal dosage or form of 5-HTP, or a related agent, might increase total glucose disposal.

This reciprocity of tissue glucose uptake (liver vs. muscle) was evident during 5-HT infusion at 20 and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (28), suggesting that 5-HT itself does not block the effect. However, differences in the circulating 5-HT concentrations are a possible explanation for differences in non-HGU with 5-HT and 5-HTP infusion. Circulating 5-HT rose substantially more during 5-HT infusion (28) than during 5-HTP infusion (~4-fold basal at the highest 5-HT infusion rate in contrast to the maximum 2-fold basal rise with 5-HTP). A direct effect of 5-HT to reduce peripheral glucose uptake is unlikely because 5-HT has either no effect (41) or a stimulatory effect (14) on glucose uptake in isolated skeletal muscle. The reduction of non-HGU with the higher concentrations of 5-HT infusion could have resulted from a change in muscle perfusion (41). In addition, at the higher rates of 5-HT infusion, we observed significant increases in cortisol and catecholamines (28), and this likely brought about a relative peripheral insulin resistance. The association of elevated 5-HT with increased levels of catecholamines and cortisol has been described in the clinical literature (15). No such elevation of stress hormones was observed in the HTP group, probably because of the more modest rise in circulating 5-HT. In the one dog with a threefold basal increase in 5-HT during 5-HTP infusion, there was a significant increase in cortisol and catecholamines during P4. However, that dog's NHGU and non-HGU during P4 did not differ from the others in the group (NHGU 18.8 vs. a group mean of 27.6 ± 2.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$; non-HGU 60.8 vs. the group mean of 51.4 ± 13.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). This agrees with previous data demonstrating that chronic elevation of cortisol brings about peripheral insulin resistance and markedly enhances NHGU (12), but acute elevations of cortisol have no such effect (11).

In conclusion, intraportal infusion of 5-HTP enhanced NHGU without blunting nonhepatic glucose disposal under hyperglycemic hyperinsulinemic conditions. We did not examine the effects of peripheral 5-HTP infusion, and thus it is not possible to speculate whether the effects observed were specific to the intraportal route of delivery. There were no significant increases in cortisol or catecholamines during 5-HTP delivery, and the dogs evidenced no diarrhea or signs of distress. Thus 5-HTP or related agents may provide a tool for reducing the proportion

of the glucose load that must be disposed of in the peripheral tissues postprandially in individuals with type 2 diabetes or impaired glucose tolerance.

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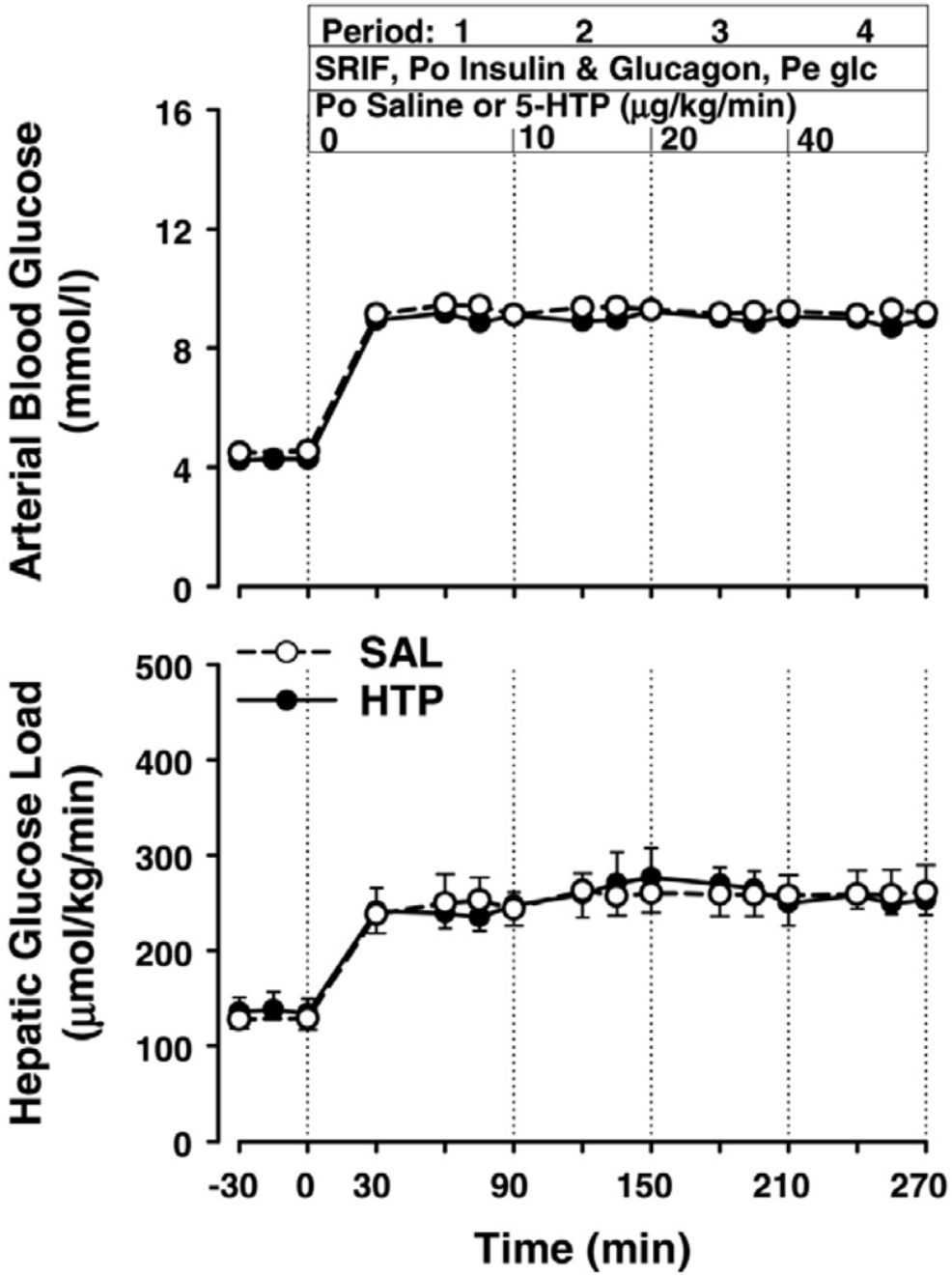

Fig. 1.

Arterial blood glucose and hepatic glucose load in dogs receiving somatostatin (SRIF), intraportal (Po) infusions of insulin (4-fold basal) and glucagon (basal), peripheral (Pe) glucose (Glc) infusion to double the hepatic glucose load, and intraportal infusion of 5-hydroxytryptophan [5-HTP (HTP) group; $n = 6$ dogs] at the rates shown or saline (SAL; $n = 7$). There were no significant differences between groups.

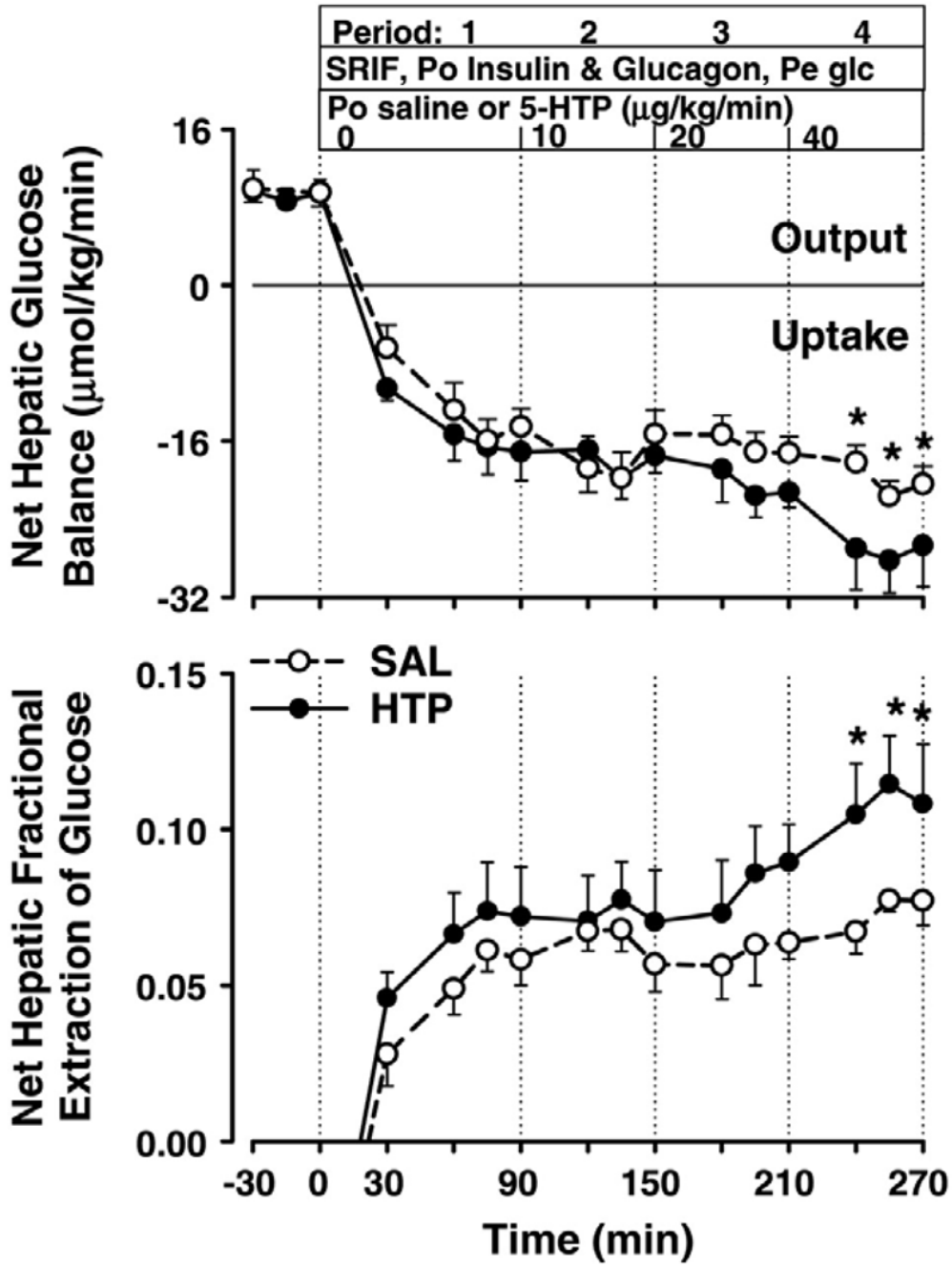

Fig. 2.
Net hepatic glucose uptake and fractional extraction of glucose. See legend to Fig. 1 for description of study conditions. *$P < 0.05$ between groups.

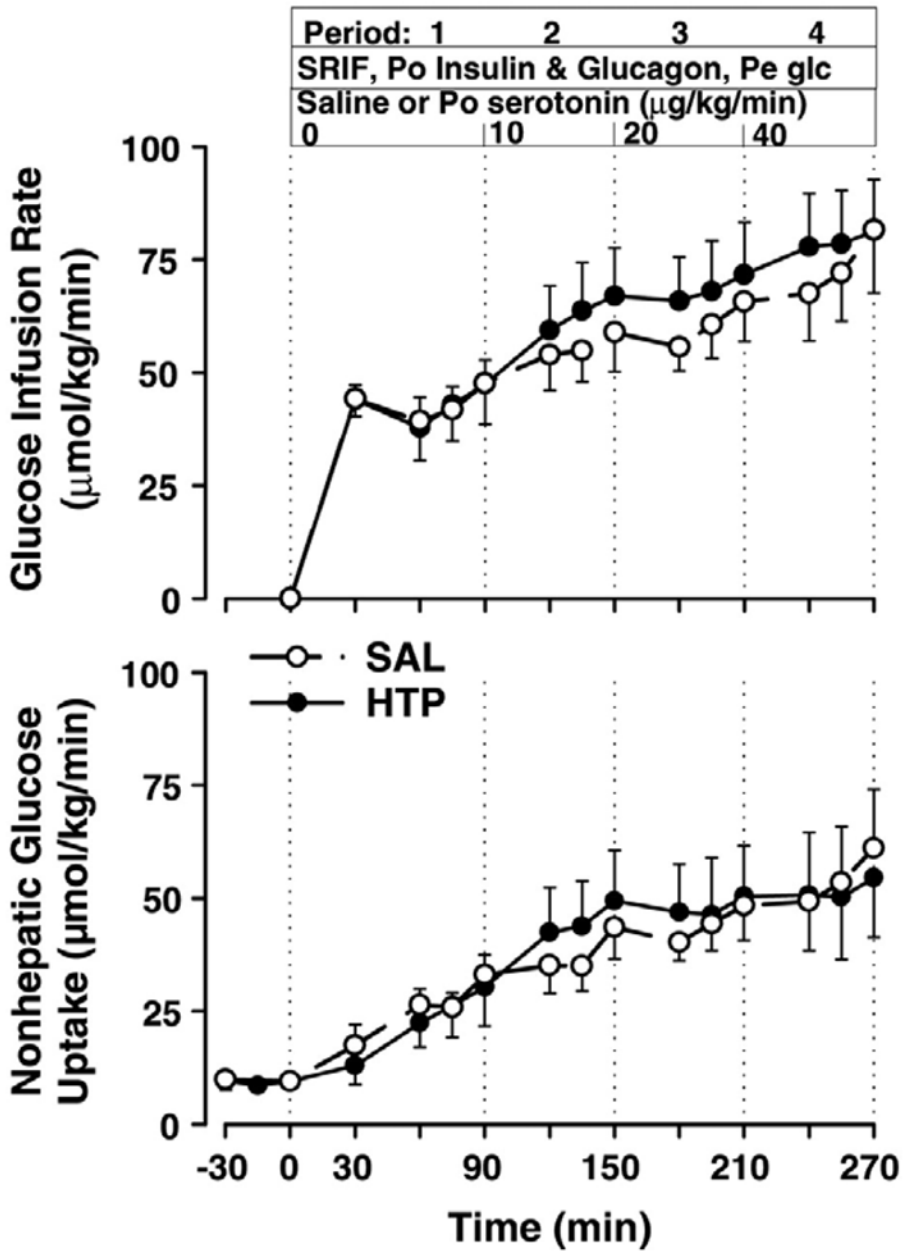

Fig. 3.

Glucose infusion rate and nonhepatic glucose uptake. See legend to Fig. 1 for description of study conditions. There were no significant differences between groups.

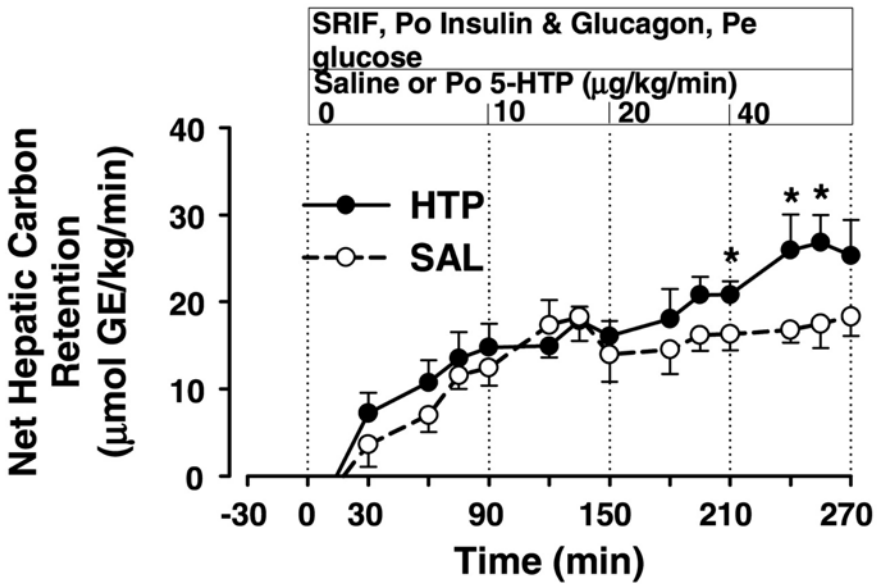

Fig. 4.

Net hepatic carbon retention. See legend to Fig. 1 for description of study conditions. GE, glucose equivalents. *$P < 0.05$ between groups.

Table 1

Serotonin and hormone data

Parameter and Group	Basal Period	Experimental Period			
		P1	P2	P3	P4
Arterial blood 5-HT, mg/l					
SAL	0.9±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.7±0.2
HTP	1.0±0.2	1.0±0.2	1.1±0.2	1.3±0.3	2.0±0.6*
Net hepatic 5-HT balance, $\mu g \cdot kg^{-1} \cdot min^{-1}$					
SAL	2.2±0.5	1.7±1.0	0.4±1.5	−0.1±2.2	1.2±1.4
HTP	−2.8±2.9	−3.3±1.9	−4.0±1.8	−2.8±3.1	−7.4±3.4*
Arterial plasma insulin, pmol/l					
SAL	46±8	108±18	110±11	129±13	135±17
HTP	27±3	120±9	123±11	143±11	155±6
Hepatic sinusoidal insulin, pmol/l					
SAL	128±21	417±67	425±45	399±47	414±37
HTP	181±15	411±34	359±39	383±44	386±40
Arterial plasma glucagon, ng/l					
SAL	46±7	41±5	38±5	38±4	35±8
HTP	33±4	39±4	28±3	32±3	34±2
Hepatic sinusoidal glucagon, ng/l					
SAL	54±8	58±8	56±5	52±5	48±4
HTP	45±7	44±4	42±4	47±4	42±5
Arterial plasma cortisol, nmol/l					
SAL	74±24	64±18	55±14	43±10	62±10
HTP	82±21	66±12	51±12	72±33	116±43
Arterial plasma norepinephrine, pg/ml					
SAL	185±39	154±33	152±52	177±39	173±44
HTP	114±38	139±59	115±57	140±65	142±49
Arterial plasma epinephrine, pg/ml					
SAL	149±55	78±33	55±14	74±33	75±39
HTP	102±43	93±39	79±43	112±55	61±38

Values are means ± SE. 5-HT, 5-hydroxytryptamine. SAL dogs (n = 7) received intraportal saline infusion during periods 1–4 (P1–P4); HTP dogs (n = 6) received saline during P1 and intraportal 5-hydroxytryptophan (5-HTP) at 10, 20, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, during P2–P4. Negative values indicate net hepatic uptake.

* $P < 0.05$ vs. SAL.

Am J Physiol Endocrinol Metab. Author manuscript; available in PMC 2008 June 16.

Table 2

Plasma leptin and adiponectin concentrations

Blood Vessel and Group	Leptin, ng/ml			Adiponectin, μg/ml		
		Experimental period			Experimental period	
	Basal period	P3	P4	Basal period	P3	P4
Artery						
SAL	13.1±0.9	13.6±1.3	13.9±1.0	15.2±2.2	12.8±1.9	13.5±2.7
HTP	12.1±1.3	13.5±1.8	13.9±1.7	13.3±2.5	12.6±1.6	12.6±3.4
Portal vein						
SAL	12.8±0.6	14.3±1.3	14.5±1.2	19.2±8.0	16.2±4.0	16.0±2.8
HTP	11.9±1.5	13.6±1.6	13.7±2.0	16.9±3.4	14.2±2.9	12.2±1.3
Hepatic vein						
SAL	12.8±0.5	14.2±1.2	14.3±1.2	18.4±2.9	20.7±5.4	20.1±5.8
HTP	11.8±1.3	13.0±1.5	13.4±1.6	17.3±2.6	14.6±2.5	12.9±1.6

Values are means ± SE. Samples were available from only 4 dogs/group and were collected only during the basal period, P3, and P4. SAL dogs received intraportal saline infusion during P1–P4; HTP dogs received saline during P1 and intraportal 5-HTP at 20 and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, during P3 and P4. There were no significant differences between groups.

Table 3

Hepatic blood flows

Group and Blood Vessel	Basal Period	Experimental Period			
		P1	P2	P3	P4
Hepatic artery					
SAL	6.1±0.6	7.7±0.6	8.6±0.8	9.2±1.1	9.7±1.4
HTP	5.7±0.9	6.0±1.2	7.3±2.1	7.8±2.0	7.9±1.9
Portal vein					
SAL	24.2±2.1	20.3±2.1	21.0±2.1	20.6±2.2	20.4±2.1
HTP	26.6±2.4	21.2±1.2	22.9±1.6	21.9±1.5	21.2±1.3

Values are means ± SE. (Units are $ml \cdot kg^{-1} \cdot min^{-1}$). SAL dogs ($n = 7$) received intraportal saline infusion during P1–P4; HTP dogs ($n = 6$) received saline during P1 and intraportal 5-HTP at 10, 20, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, during P2–P4. There were no significant differences between groups.

Table 4

Tracer-determined unidirectional HGU and glucose R_d

Group and parameter	Basal Period	Experimental Period			
		P1	P2	P3	P4
HGU					
SAL	0.7±0.6	14.3±3.1	17.0±4.0	16.5±3.9	19.6±3.0
HTP	0.1±0.9	10.2±3.3	13.2±1.5	21.5±2.2	27.9±5.3
Glucose R_d					
SAL	13.6±0.7	51.3±7.7	59.8±8.0	66.7±8.7	80.8±12.5
HTP	12.9±0.6	53.4±12.4	65.3±14.5	71.2±13.4	84.2±11.8

Values are means ± SE; n = 7 for SAL group, and n = 5 for HTP group. Units are $\mu mol \cdot kg^{-1} \cdot min^{-1}$. HGU, hepatic glucose uptake; R_d, rate of disappearance. SAL dogs received intraportal saline infusion during P1–P4; HTP dogs received saline during P1 and intraportal 5-HTP at 10, 20, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, during P2–P4. P = 0.07 between groups for HGU during P4.

Table 5

Arterial lactate, glycerol, and NEFA concentrations and net hepatic balances

Group	Basal Period	Experimental Period			
		P1	P2	P3	P4
Arterial blood lactate, μmol/l					
SAL	536±74	1,060±49	975±72	981±75	1,028±91
HTP	298±52*	802±148	665±92*	685±90*	816±135
Net hepatic lactate balance, μmol·kg^{-1}·min^{-1}					
SAL	−9.6±2.2	6.1±3.1	2.5±2.3	1.4±2.5	2.8±2.3
HTP	−6.1±0.8	6.6±1.8	4.6±0.9	2.0±0.9	2.2±0.5
Arterial blood glycerol, μmol/l					
SAL	86±16	29±3	28±5	28±6	30±7
HTP	64±7	25±4	19±4	22±5	26±6
Net hepatic glycerol uptake, μmol·kg^{-1}·min^{-1}					
SAL	1.7±0.4	0.4±0.0	0.4±0.1	0.4±0.1	0.4±0.1
HTP	1.5±0.2	0.4±0.1	0.2±0.1	0.3±0.2	0.5±0.2
Arterial plasma NEFA, μmol/l					
SAL	789±103	132±23	96±20	86±27	83±28
HTP	938±66	122±29	71±12	60±16	68±19
Net hepatic NEFA uptake, μmol·kg^{-1}·min^{-1}					
SAL	2.4±0.6	0.2±0.1	0.1±0.1	0.2±0.1	0.2±0.1
HTP	3.3±0.2	0.6±0.3	0.0±0.0	0.3±0.2	0.0±0.1

Values are means ± SE. NEFA, nonesterified fatty acid. SAL dogs (n = 7) received intraportal saline infusion during P1–P4; HTP dogs (n = 6) received saline during P1 and intraportal 5-HTP at 10, 20, and 40 μg·kg^{-1}·min^{-1}, respectively, during P2–P4. Negative values for balance indicate net hepatic lactate uptake; rates of net hepatic uptake are shown as positive values for substrates for which there was no net release by the liver.

*P < 0.05 vs. SAL.