Intraportal administration of neuropeptide Y and hepatic glucose metabolism

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Intraportal administration of neuropeptide Y (NPY) affects glucose metabolism in 42-h-fasted conscious dogs using arteriovenous difference methodology. The experimental period was divided into three subperiods (P1, P2, and P3). During all subperiods, the dogs received infusions of somatostatin, intraportal insulin (threefold basal), intraportal glucagon (basal), and peripheral intravenous glucose to increase the hepatic glucose load twofold basal. Following P1, in the NPY group (n = 7), NPY was infused intraportally at 0.2 and 5.1 pmol·kg⁻¹·min⁻¹ during P2 and P3, respectively. The control group (n = 7) received intraportal saline infusion without NPY. There were no significant changes in hepatic blood flow in NPY vs. control. The lower infusion rate of NPY (P2) did not enhance net hepatic glucose uptake. During P3, the increment in net hepatic glucose uptake (compared with P1) was 4 ± 1 and 10 ± 2 pmol·kg⁻¹·min⁻¹ in control and NPY, respectively (P < 0.05). The increment in net hepatic fractional glucose extraction during P3 was 0.015 ± 0.005 and 0.039 ± 0.008 in control and NPY, respectively (P < 0.05). Net hepatic carbon retention was enhanced in NPY vs. control (22 ± 2 vs. 14 ± 2 pmol·kg⁻¹·min⁻¹, P < 0.05). There were no significant differences between groups in the total glucose infusion rate. Thus, intraportal NPY stimulates net hepatic glucose uptake without significantly altering whole body glucose disposal in dogs.

dog; liver; nerves

NEUROPEPTIDE Y (NPY), a 36-amino-acid peptide discovered originally in the brain (45), is now known to have an important role in fuel homeostasis. The highest concentration of NPY in the central nervous system is in the hypothalamus, and NPY’s prominent action of stimulating food intake through Y1 and Y5 receptors has been established in many species (48). Besides its effect on the feeding behavior, NPY administered in the central nervous system has been shown to stimulate insulin secretion (24), increase hepatic glucose production (47), reduce thermogenesis in brown adipose tissue, and increase lipoprotein lipase activity (7). Animals injected chronically with NPY exhibit weight gain (43, 49).

On the other hand, NPY is well known to be widely distributed in the peripheral tissues, particularly in the sympathetic, mainly perivascular, nerves (12, 20). In those nerve fibers, NPY is usually colocalized with norepinephrine, and the canine liver releases both norepinephrine and NPY during sympathetic nerve stimulation (44). NPY is also found in postganglionic fibers of the parasympathetic nervous system in many organs, including the liver (42). Moreover, intrinsic neurons in the gastrointestinal tract are associated with dense accumulations of NPY, and these neurons are thought to be involved in the inhibition of gastric and intestinal motility and attenuation of gastrointestinal secretions (41).

The peripheral actions of NPY have been less well explored than its central actions. NPY infused intravenously evokes hypoglycemia without stimulating insulin secretion in the postabsorptive state in humans (2) and rats (8), suggesting that it increases peripheral glucose uptake and/or decreases glucose production. In agreement with the latter possibility, NPY antagonized glucagon- and norepinephrine-stimulated glucose production in the perfused rat liver (19). The physiological significance of these effects, however, is not clearly understood. Moreover, substantial increases of NPY in the circulation are observed during the postprandial period in humans (29) and dogs (6, 38). The postprandial NPY increment is not accompanied by an increase in splanchic norepinephrine spillover (29), but in dogs it can be ablated by cooling the vagus nerve to induce vagal blockade (39). Thus, NPY secretion following a meal might be brought about by a parasympathetic mechanism. Although the source of NPY released into the circulation upon food ingestion has not been pinpointed, the gastrointestinal tract and/or the pancreas could be the responsible organs because a significant increase of NPY levels was observed in the portal vein following a meal in dogs (6, 38). Moreover, NPY is known to distribute in the nerve fibers around the portal venous tract and the sinusoids in human liver (22). Therefore, NPY could be released from both the gut and the hepatoporal region or liver. Therefore, we designed this study to clarify the effect of NPY infused into the portal vein on glucose metabolism under hyperglycemic hyperinsulinemic clamp conditions to recreate insulin and glucose concentrations observed in the postprandial state in conscious dogs.

In these studies, glucose was infused via a peripheral vein rather than into the portal circulation because portal glucose delivery enhances net hepatic glucose uptake (NHGU), a phenomenon termed the “portal signal” (1). If the effects of NPY are not additive or synergistic with those of the portal signal, then the presence of the portal signal could obscure any potential effects of NPY. Therefore, peripheral glucose delivery was chosen to maximize the chance of observing an effect of NPY. NPY was delivered at a low rate (0.2 pmol·kg⁻¹·min⁻¹) to replicate the circulating concentrations after a meal and a higher rate (5.1 pmol·kg⁻¹·min⁻¹) to simulate concentrations that might be achieved locally in the...
liver following neural stimulation (6, 38). The duration of each infusion was 90 min, similar to the duration of the period of elevated circulating NPY after meal ingestion in the conscious dog (38).

METHODS

Animals and surgical procedures. Experiments were performed on 13 fasting (for 42 h) conscious mongrel dogs (23.6 ± 0.5 kg) of either sex that had been fed a standard meat and chow diet (31% protein, 52% carbohydrate, 11% fat, and 6% fiber based on dry weight; Kal Kan, Vernon, CA, and Purina Lab Canine Diet 5906; Purina Mills, St. Louis, MO) once daily. The dogs were housed in a facility that met American Association for the Accreditation of Laboratory Animal Care guidelines, and the protocols were approved by the Vanderbilt University Medical Center Animal Care Committee. A 42-h fast was chosen because it reduces hepatic glycogen concentrations to a stable minimum in the dog; prior to that time, liver glycogen content is on a steeply declining trajectory (13). It is not clear whether differing liver glycogen concentrations might have a differential impact upon NHGU, but elevated muscle glycogen concentrations have been shown to decrease muscle glucose uptake (15, 18). Thus, stable hepatic glycogen concentrations were desirable to maximize the chance of observing an effect on NHGU. NPY is normally released in the postprandial period, so this is not the time of physiological NPY elevation.

At least 16 days before an experiment, a laparotomy was performed under general anesthesia (15 mg/kg pentobarbital sodium presurgery and 1.0% isoflurane as an inhalation anesthetic during surgery). Silastic catheters (Dow Corning, Midland, MI) for blood sampling were placed into the portal vein, a hepatic vein, and a femoral artery as previously described (35). Catheters for intraportal infusions were inserted into a jejunal vein and a splenic vein. Ultrasonic flow probes (Transonic Systems, Ithaca, NY) were placed around the portal vein and the hepatic artery. On the day of the experiment, the proximal ends of the catheters, which had been embedded in the subcutaneous tissue, were exteriorized under local anesthesia. Peripheral venous access was established in three peripheral veins. Criteria for use of an animal in experimentation were as previously established (35).

Experimental design. Each experiment consisted of an equilibration period (−120 to −20 min), a basal period (−20 to 0 min), and a hyperglycemic-hyperinsulinemic experimental period. The experimental period was divided into three subperiods (0 to 120 min, P1; 120 to 210 min, P2; 210 to 300 min, P3). At −120 min, a primed (33 μCi), continuous (0.34 μCi/min) infusion of [3-3H]glucose (PerkinElmer, Waltham, MA) and a continuous infusion of indocyanine green dye (0.08 mg/min; Sigma, St. Louis, MO) were started. At time 0, a peripheral infusion of somatostatin (0.8 μg·kg⁻¹·min⁻¹; Bachem, Torrance, CA) was begun to inhibit endogenous pancreatic insulin and glucagon secretion (0 to 300 min). Intraportal infusions of regular insulin (1.2 mU·kg⁻¹·min⁻¹; Eli Lilly, Indianapolis, IN) to achieve hyperinsulinemia and glucagon at a basal rate (0.5 ng·kg⁻¹·min⁻¹; Bedford Lab, Bedford, OH) were also started at 0 min. A 50% dextrose solution was infused via peripheral vein at variable rates starting at 0 min to clamp the hepatic glucose load two- to fourfold basal (arterial plasma glucose ≤12 mmol/l). The glucose infusion rate was adjusted on the basis of a plasma glucose measurement every 5 min. In P2 and P3 in one protocol, human NPY (Sigma) was infused into the portal vein at doses of 0.2 and 5.1 pmol·kg⁻¹·min⁻¹, respectively (NPY group, n = 7). In a second group (control, n = 7), the animals received intraportal 0.9% saline infusion instead of NPY.

Analytical procedures. Plasma glucose, [3-3H] glucose, free fatty acids, insulin, glucagon, cortisol, epinephrine, and norepinephrine, blood lactate, glycerol, and alanine were analyzed as previously described (14, 35).

Calculations. Net hepatic substrate balance (NHB) was calculated using the formula \([H-F_1 - (A\cdot F_2 + P\cdot F_p)]\), where A, P, and H are substrate concentrations in the arterial, portal vein, and hepatic vein and F_1, F_2, and F_p are hepatic arterial, portal vein, and total hepatic blood or plasma flows, respectively. Hepatic substrate load was
calculated as A·Fa + P·Fp. Net hepatic fractional extraction was calculated as NHB divided by hepatic load. For all calculated data, plasma glucose concentrations were converted to blood concentrations with factors compiled in our laboratory from extensive data in which plasma and blood glucose values were compared (e.g., see Ref. 14). Sinusoidal hormone concentrations were calculated as for hepatic load and divided by the total hepatic plasma flow (14, 35). Nonhepatic glucose uptake represents the difference between the glucose infusion rate and NHGU. Net hepatic carbon retention, an index of the substrate available for glycogen deposition, was calculated as NHGU minus net hepatic lactate output. Glucose turnover was calculated with a two-compartment model (21) using dog parameters (11). Endogenous glucose rate of appearance (Ra) was calculated as total Ra minus the glucose infusion rate. The data in the text are reported as means of values during the last 30 min of the relevant experimental period, and changes in data are calculated as differences between the mean value of the last two time points in P1 and the values during the last 30 min of the other periods. The mean change in the data was calculated as the difference between the mean value of the last two time points in P1 and that in P2 or P3.

**RESULTS**

**Hormone concentrations.** The mean arterial and hepatic sinusoidal plasma insulin concentrations in the NPY group were not different from those in the control group during the basal period. In both groups they increased three- to four-fold during the experimental period (Fig. 1). The hepatic sinusoidal plasma glucagon concentrations during the experimental period were basal in both groups and not significantly different between groups. Plasma cortisol concentrations were not significantly different between groups at any time (Table 1).

**Hepatic blood flow and cardiovascular parameters.** There were no significant differences in hepatic arterial or portal vein blood flows between groups at any time (Fig. 2). Portal blood flow fell by ~15–20% in both groups in response to somato-

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal Period</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>55±10</td>
<td>56±7</td>
<td>46±5</td>
<td>38±5</td>
</tr>
<tr>
<td>NPY</td>
<td>50±4</td>
<td>68±9</td>
<td>49±5</td>
<td>53±7</td>
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</table>

Values are means ± SE. Both groups received intraportal saline infusion during period 1. The control group received intraportal saline during test periods 2 and 3; the NPY group received intraportal infusion of neuropeptide Y (NPY) at 0.2 and 5.1 pmol·kg⁻¹·min⁻¹ during test periods 2 and 3, respectively. There are no significant differences between groups.

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**Statistical analysis.** Data are expressed as means ± SE and statistically analyzed by SigmaStat (SPSS, Pt. Richmond, CA). Two-way repeated-measures ANOVA was used to compare the time course data of the groups. Classification factors were treatment group and time period. For significant F values, the Student-Newman-Keuls multi-range test was employed as a post hoc analysis. The unpaired t-tests were used for statistical analysis to compare the mean values between groups in each period. Differences were considered significant when P values were <0.05.
tostatin infusion. The heart rate and blood pressure did not change significantly from basal in either group during P1, P2, or P3 (data not shown).

Blood glucose levels and hepatic glucose balance. In the basal period, the arterial plasma glucose concentrations and hepatic glucose loads were not different between groups (Fig. 3). Peripheral glucose infusion increased the arterial plasma glucose from ≈5.9 to 11.8 mmol/l in both groups, and the hepatic glucose load during the experimental periods was approximately twofold basal in all dogs. Both groups displayed net hepatic glucose output during the basal period (≈9.5 μmol·kg⁻¹·min⁻¹) (Fig. 4). During P1, both groups switched to NHGU, and the rates did not differ significantly between the groups (≈11 μmol·kg⁻¹·min⁻¹). Low dose NPY had no effect on NHGU, but, in response to high-dose NPY, the increment in NHGU (rate during the last 30 min of P3 minus the rate in P1) was 10 ± 2 μmol·kg⁻¹·min⁻¹, compared with 4 ± 1 μmol·kg⁻¹·min⁻¹ in the control group (P < 0.01).

Net hepatic fractional extraction of glucose was not significantly different between groups during P1 or P2, but it was enhanced in NPY vs. control during P3 (P < 0.05) (Fig. 4). Between P1 and P3, the net hepatic fractional extraction of glucose in the NPY group increased by 0.039 ± 0.008, significantly more than the change in the control group (0.015 ± 0.005, P < 0.05). Net hepatic carbon retention was also significantly stimulated by intraportal NPY infusion during P3 (Fig. 4).

There were no significant differences in the glucose infusion rates between groups during any of the experimental subperiods, although there was a tendency for the rate to be higher with the high

![Net Hepatic Balance Measurements](image-url)

Fig. 4. Time course of net hepatic glucose balance, fractional extraction of glucose, and carbon balance (left) and increment over P1 in net hepatic glucose uptake, fractional extraction of glucose, and carbon retention (right). Study conditions were as described in the legend of Fig. 1. *P < 0.05 vs. control.
rate of NPY infusion [P1: 50 ± 8 and 53 ± 7 μmol·kg⁻¹·min⁻¹ (P = 0.8); P2: 60 ± 8 and 71 ± 8 μmol·kg⁻¹·min⁻¹ (P = 0.4); P3, 70 ± 10 and 82 ± 6 μmol·kg⁻¹·min⁻¹ (P = 0.27) in control and NPY, respectively] (Fig. 5). Similarly, there were no significant differences between groups in nonhepatic glucose uptake (Fig. 5). During P3, the rates of nonhepatic glucose uptake were 55 ± 10 and 61 ± 6 μmol·kg⁻¹·min⁻¹ in control and NPY, respectively. Both endogenous glucose Ra (P = 0.6) and Rd (P = 0.7) were similar between groups at all times (Fig. 6).

NEFA, glycerol, lactate, and alanine concentrations and balance data. The combination of hyperinsulinemia and hyperglycemia significantly increased the mean arterial blood lactate levels and switched hepatic lactate balance from uptake to output in both groups (Table 2). Although net hepatic lactate balance in the control group subsequently reverted to a low rate of net hepatic uptake while the NPY group exhibited net hepatic output of lactate throughout, there were no significant differences between groups. The arterial blood alanine levels and net hepatic alanine balances in each group were stable during the study. No significant differences between groups were observed (data not shown).

Hyperinsulinemia and hyperglycemia reduced the mean arterial plasma NEFA level and net hepatic NEFA uptake ~90% in both groups (Table 2). The arterial blood glycerol levels and net hepatic glycerol uptakes decreased in parallel in both groups, falling by ~60%.

DISCUSSION

NPY infused into the hepatic portal circulation stimulated NHGU in conscious dogs, raising the possibility of a role for NPY in the regulation of glucose homeostasis. At the lower rate of NPY infusion (0.2 pmol·kg⁻¹·min⁻¹), there was no evidence of an enhancement of NHGU, but during infusion at 5.1 pmol·kg⁻¹·min⁻¹, both NHGU and net hepatic fractional glucose extraction were enhanced >30%. Because all dogs in the NPY group received the low infusion rate during P2, followed by the 5.1 pmol·kg⁻¹·min⁻¹ rate, it is not possible to say definitively whether NHGU responded to the higher infusion rate or to more prolonged administration of NPY. The acute inflection of the rate of NHGU in the NPY group with the increase in the NPY infusion rate suggests, however, that it was probably dose dependent.

In conscious dogs, peripheral venous NPY concentrations were significantly elevated for at least 60 min after ingestion of a protein-containing mixed meal, but ingestion of pure fat or carbohydrate had no effect on plasma NPY concentrations (38). Following a standard mixed meal, portal vein NPY concentrations in dogs increased from a basal value of 89 pmol/l to 115 pmol/l (6). In the current study, during the intraportal infusion of NPY 0.2 pmol·kg⁻¹·min⁻¹, the sinusoidal plasma NPY concentration could be calculated to rise ~18 pmol/l, a physiologic postprandial increment. We analyzed plasma NPY concentrations in a single dog in the NPY group using a human/rat enzyme immunoassay kit with an antibody to total NPY (Peninsula Laboratories/Bachem, San Carlos, CA). In that animal, basal hepatic sinusoidal NPY concentrations were 96 pmol/l, and concentrations during P1, P2, and P3 were 83, 96, and 373 pmol/l, respectively (mean of 3 determinations per period). Thus during P2, the measured increment over P1 was 13 pmol/l, close to the anticipated value. At the high NPY infusion rate, the sinusoidal NPY...
NPY and liver glucose metabolism

Table 2. Arterial concentrations and net hepatic balances of lactate, nonesterified fatty acids (NEFA) and glycerol

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal Period</th>
<th>Period 1, min</th>
<th>Period 2, min</th>
<th>Period 3, min</th>
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<tr>
<td></td>
<td>90</td>
<td>120</td>
<td>130</td>
<td>150</td>
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<td></td>
<td>Arterial blood lactate (µmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>393 ± 102</td>
<td>678 ± 131</td>
<td>669 ± 118</td>
<td>730 ± 137</td>
</tr>
<tr>
<td>NPY</td>
<td>298 ± 64</td>
<td>704 ± 69</td>
<td>663 ± 114</td>
<td>721 ± 106</td>
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<tr>
<td></td>
<td>Net hepatic lactate balance (µmol·kg⁻¹·min⁻¹)</td>
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<tr>
<td>Control</td>
<td>-0.2 ± 2.1</td>
<td>0.9 ± 2.6</td>
<td>0.2 ± 2.4</td>
<td>-1.2 ± 2.1</td>
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<tr>
<td>NPY</td>
<td>-5.3 ± 0.4</td>
<td>3.6 ± 1.0</td>
<td>2.7 ± 0.8</td>
<td>1.7 ± 1.0</td>
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<td></td>
<td>Arterial plasma NEFA (µmol/l)</td>
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<tr>
<td>Control</td>
<td>862 ± 144</td>
<td>130 ± 49</td>
<td>106 ± 32</td>
<td>108 ± 31</td>
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<tr>
<td>NPY</td>
<td>1012 ± 58</td>
<td>129 ± 19</td>
<td>119 ± 33</td>
<td>100 ± 13</td>
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<td></td>
<td>Net hepatic NEFA uptake (µmol·kg⁻¹·min⁻¹)</td>
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<tr>
<td>Control</td>
<td>3.1 ± 0.8</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.2</td>
<td>0.3 ± 0.2</td>
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<tr>
<td>NPY</td>
<td>4.7 ± 0.9</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
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<td></td>
<td>Arterial blood glycerol (µmol/l)</td>
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<td></td>
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<tr>
<td>Control</td>
<td>91 ± 15</td>
<td>29 ± 3</td>
<td>32 ± 6</td>
<td>31 ± 4</td>
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<tr>
<td>NPY</td>
<td>87 ± 5</td>
<td>36 ± 4</td>
<td>34 ± 5</td>
<td>32 ± 4</td>
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<tr>
<td></td>
<td>Net hepatic glycerol uptake (µmol·kg⁻¹·min⁻¹)</td>
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<td></td>
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<tr>
<td>Control</td>
<td>1.7 ± 0.3</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>NPY</td>
<td>1.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
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</table>

Values are means ± SE; n = 7 per group. Both groups received intraportal saline infusion during period 1. The control group received intraportal saline during test periods 2 and 3; the NPY group received intraportal infusion of NPY at 0.2 and 5.1 pmol·kg⁻¹·min⁻¹ during test periods 2 and 3, respectively. Negative values for balance indicate net uptake. There were no significant differences between groups.

NPY concentration increased to fourfold the value during P2. This was less than would be expected with a 25-fold increase in the infusion rate, suggesting that clearance might increase at higher delivery rates, but sufficient to demonstrate the effects of a supraphysiological concentration of the peptide. Although the ileum is likely to be the source of some of the NPY in the splanchic circulation (38), NPY is also found in aminergic nerves supplying all portions of the hepatic portal venous system, the hepatic artery, and the bile ducts (22). Thus, NPY-containing fibers have a wide distribution and lie in close proximity to both parenchymal and stellate cells in the guinea pig, dog, and human liver (22), likely resulting in a considerably higher local NPY concentrations in the hepatic parenchyma than in the portal venous blood. Sympathetic stimulation of the canine liver significantly increased both hepatic NPY spillover and arterial NPY concentrations but not gut NPY spillover (44). In addition, NPY protein has been found in human adipocytes, with the abdominal subcutaneous adipocytes displaying the highest concentrations but with substantial amounts evident in visceral fat (16). It is not known whether NPY from the adipose depots enters the circulation, but this provides a potential source of NPY reaching the liver, in addition to the NPY-containing fibers observed in the hepatic innervation (22). Therefore, we examined the effect of NPY infused at a higher rate (5.1 pmol·kg⁻¹·min⁻¹) in an attempt to reproduce higher local concentrations within the liver. NPY at the higher infusion rate clearly stimulated NHGU and net hepatic fractional extraction in the presence of stable insulin and glucagon levels.

It is possible that NPY can act directly upon the liver to stimulate NHGU. The presence of a common receptor for the pancreatic polypeptide family, which includes NPY, has been reported on the surface of isolated hepatocytes in rats (33). In the ex vivo perfused rat liver, NPY had no effect on basal glucose metabolism, but it antagonized norepinephrine- and glucagon-stimulated glucogenesis (19). Insulin (100 nM) added to the perfusate did not suppress glucose production (virtually all from gluconeogenesis under the conditions of study), and the combination of insulin and NPY was also found to have no effect (19). On the other hand, NPY infused via peripheral vein suppressed splanchic glycogenolysis in postabsorptive humans (2). Thus, taken together, the rat and human data are consistent with a direct effect of NPY at the liver to suppress glycogenolysis but not gluconeogenesis. Alternatively, the effect of NPY on the liver may have been centrally mediated, either as part of reflex arc or via action of the circulating NPY in the brain. Afferent signaling in the hepatic branch of the vagus is responsive to substrates such as glucose (34) and intraportal appearance of some gastroenteropancreatic peptide hormones, e.g., glucagon-like peptide-1 and somatostatin-14 (31, 32, 36), but there are no data regarding possible NPY stimulation of afferent hepatic vagal activity. On the other hand, central levels of NPY apparently respond to signals induced by substrates in the liver or hepatoportal region. NPY concentrations in the arcuate nucleus of normal rats were significantly reduced by high-fat feeding (17). Compared with normal rats, streptozotocin-diabetic rats exhibited elevated arcuate nucleus NPY concentrations, and NPY could be reduced to levels no different from those in nondiabetic rats by a high-fat diet (17). In both normal and diabetic rats, the effect of the high-fat diet on NPY was ablated by hepatic vagotomy, while gastroduodenal vagotomy had no effect on NPY concentrations (17).
Consistent with the data showing that NPY can suppress glycogenolysis (2), we determined that the rate of net hepatic carbon retention, an index of the carbon available for glycogen synthesis, was ~50% greater during the high-dose NPY infusion vs. control. This calculation (see Calculations) ignores the glucose oxidized by the liver, as well as the contribution of glycerol and amino acids to glycogen synthesis. These processes are normally approximately equivalent in magnitude and thus are offsetting omissions in the calculation (40). We have not measured glucose oxidation in the presence of NPY, but we have found that the process remains relatively constant under a number of physiologic conditions (9, 26–28, 40). To the extent that this calculation is valid under the conditions of study, it suggests that hepatic glycogen synthesis was stimulated in parallel with NHGU.

A vasoconstrictive effect of NPY on splanchnic organs has been reported in several mammals including humans. NPY infused intravenously at 3 pmol·kg⁻¹·min⁻¹ induced an 18% reduction of splanchnic blood flow and concomitant reduction of plasma glucose levels in the postabsorptive state in humans (3). Thus, it is conceivable that NPY could regulate glucose metabolism by modifying the blood supply to splanchnic organs. Mundinger et al. (30) found that infusion of NPY directly into the canine hepatic artery at a high rate (500 pmol/min, greater than the hepatic NPY spillover during hepatic nerve stimulation) under basal, euglycemic conditions caused a slight constriction of the hepatic artery (~15% decrease in hepatic artery conductance), along with a modest (22%) decrease in hepatic glucose output. However, the hepatic artery infusion studies were not carried out under clamp conditions, and the insulin and glucagon concentrations during NPY infusion were not reported (30). In the current studies, using NPY infusion rates equivalent to ~1% to 30% of the rate employed by Mundinger et al. (30), there were no differences in hepatic blood flow between the NPY and control groups. Thus, there was no evidence of a vasoconstrictive effect of NPY in our studies. Moreover, if significant vasoconstriction had occurred, it would likely have blunted, rather than enhanced, NHGU (4, 25).

Despite the enhancement of NHGU in the NPY group, total body glucose disposal, as evidenced by both the glucose infusion rate and the glucose Ra, was not significantly stimulated. There was a tendency for the glucose infusion rate to be higher during infusion of NPY than saline (Fig. 3). However, the lack of an inflection in the rate of glucose infusion at the beginning of P3, when the high-dose NPY infusion was initiated, suggests that the tendency can be attributed to random differences between groups. We cannot rule out a possible stimulatory effect on nonhepatic glucose uptake at the lower NPY infusion rate, but because of the variability in the measurement, statistical significance between groups was not achieved. We have previously demonstrated that enhancement of NHGU by portal glucose infusion is accompanied by an offsetting reduction in nonhepatic glucose uptake, such that whole body glucose disposal is unaltered (1). Conversely, intraportal infusion of a nitric oxide donor blunts NHGU during intraportal glucose delivery under clamp conditions, but a concomitant enhancement of nonhepatic glucose uptake results in an unimpaired whole body glucose disposal (5). The arterial plasma glucagon concentrations were significantly lower in the NPY group than in the control group during both the basal and the experimental periods. However, virtually all of the effects of glucagon in regulation of glucose metabolism occur at the liver, and the hepatic sinusoidal concentrations were not different between groups during the experimental period. Thus, the difference in arterial glucagon concentrations should not have had an impact on the results.

It is not clear whether NPY would be as effective in stimulating NHGU in the presence of portal glucose infusion as it proved to be during peripheral glucose infusion. The enhancement of NHGU in response to portal glucose delivery appears to be mediated largely by a fall in sympathetic tone at the liver (10), and NPY is released during sympathetic signaling to the liver in the dog (44). Thus, it seems unlikely that NPY is involved in bringing about the portal signal. However, the effect of exogenous NPY or an NPY receptor agonist during oral or portal glucose delivery remains unknown, since NPY has been reported to inhibit glucagon- and norepinephrine-stimulated glucose output in perfused rat liver (19). It might, therefore, be expected to complement the effect of the portal signal, which primarily increases NHGU by stimulating hepatic glucose uptake (37).

Perspectives and Significance

The current findings indicate that intraportal NPY has the potential to play a role in regulation of hepatic glucose metabolism, particularly in the postprandial period. Postprandial hyperglycemia is associated with increased all-cause and cardiovascular mortality (23, 46). Additional pharmaceutical agents that control postprandial glycemia effectively are needed. It remains to be seen whether NPY or NPY receptor agonists might have a beneficial effect.

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