Glucagon’s actions are modified by the combination of epinephrine and gluconeogenic precursor infusion

Stephanie M. Gustavson,1 Chang An Chu,1 Makoto Nishizawa,1 Ben Farmer,1 Doss Neal,1,2 Ying Yang,2 Suzan Vaughan,2 E. Patrick Donahue,2 Paul Flakoll,2 and Alan D. Cherrington1,2

1Department of Molecular Physiology and Biophysics and 2Diabetes Research and Training Center, Vanderbilt University, Nashville, Tennessee 37232–6303

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Glucagon’s actions are modified by the combination of epinephrine and gluconeogenic precursor infusion. Am J Physiol Endocrinol Metab 285: E534–E544, 2003. First published May 7, 2003; 10.1152/ajpendo.00059.2003.—It was previously shown that glucagon and epinephrine have additive effects on both gluconeogenesis and glycogenolytic flux. However, the changes in gluconeogenic substrates may have been limiting and thus may have prevented a synergistic effect on gluconeogenesis and a reciprocal inhibitory effect on glycogenolysis. Thus the aim of the present study was to determine if glucagon has a greater gluconeogenic and a smaller glycogenolytic effect in the presence of both epinephrine and clampable gluconeogenic precursors. Two groups (Epi and G + Epi + P) of 18-h-fasted conscious dogs were studied. In Epi, epinephrine was increased, and in G + Epi + P, glucagon and epinephrine were increased. Gluconeogenic precursors (lactate and alanine) were infused in G + Epi + P to match the rise that occurred in Epi. Insulin and glucose levels were also controlled and were similar in the two groups. Epinephrine and precursor administration increased glucagon’s effect on gluconeogenesis (4.5-fold; P < 0.05) and decreased glucagon’s effect on glycogenolysis (85%; P = 0.08). Thus, in the presence of both hormones, and when the gluconeogenic precursor supply is maintained, gluconeogenic flux is potentiated and glycogenolytic flux is inhibited.

Address for reprint requests and other correspondence: S. M. Gustavson, Div. of Diabetes, Endocrinology, and Metabolism, Vanderbilt Univ. Medical Center, 715 Preston Research Bldg., Nashville, TN 37232–6303 (E-mail: stephanie.m.gustavson@vanderbilt.edu).

Glucagon has only a modest effect on gluconeogenesis in dogs (4) and humans (5, 30), which is surprising considering that the hormone is known to stimulate both transcription and activation of hepatic gluconeogenic (GNG) enzymes (16, 29, 36, 37). In fact, glucagon has been shown to increase hepatic GNG efficiency in vivo both acutely (45) and chronically (32), yet the contribution of the rise in gluconeogenesis to the increase in glucose production was small. This paradox may be explained by the fact that glucagon has little or no effect on GNG substrate mobilization from muscle or fat. Thus any enhancement of GNG flux would initially increase gluconeogenesis, but then the GNG substrate levels in blood would fall and GNG flux would return toward its basal rate.

In contrast, Chu and colleagues (7–9) showed that epinephrine stimulates gluconeogenesis indirectly by increasing peripheral substrate release, rather than by increasing hepatic GNG efficiency. Chu et al. (7) also observed that there appeared to be a reciprocal relationship between gluconeogenesis and glycogenolysis, such that when one process increased the other decreased. Further support for a reciprocal relationship or interregulation of gluconeogenesis and glycogenolysis can be found in several other previous studies in humans (24, 25, 51) and in dogs (11, 14). In those studies, increasing the GNG precursor supply to the liver increased gluconeogenesis and reciprocally decreased glycogenolysis. On the other hand, inhibiting glycogen breakdown has not been uniformly shown to stimulate gluconeogenesis (17, 18, 43), perhaps because GNG precursor supply became limiting.

Recently, we found that combined glucagon and epinephrine infusion in conscious dogs resulted in additive effects on both gluconeogenesis and glycogenolysis (21). Synergistic effects of the hormones on hepatic gluconeogenesis were anticipated because glucagon upregulates the GNG machinery of the liver while epinephrine provides increased GNG substrates. It is possible that the combination of the hormones caused a transient synergistic effect on GNG flux that resulted in a reduction in the plasma levels of the GNG precursors because of the stimulation of hepatic gluconeogenesis occurring in the absence of an effect of glucagon on the precursor supply reaching the liver. This reduction in GNG precursor availability would reset GNG flux to a rate similar to that seen with epinephrine alone. Although we had initially expected that epinephrine would increase precursor availability for a long enough time to observe a significant GNG effect of glucagon, this in fact was not the case. The present study was therefore designed to determine whether supplying GNG precursors in the presence of epinephrine and...
glucagon would alter the GNG and glycogenolytic (GLY) responses to glucagon.

RESEARCH DESIGN AND METHODS

Animals and surgical procedures. Studies were performed on 12 overnight-fasted conscious mongrel dogs of either sex (19.4–26.9 kg, mean = 23.1 kg). Animals were fed one food daily a diet of meat (Kal Kan, Vernon, CA) and chow (Purina Lab Canine Diet No. 5006; Purina Mills, St. Louis, MO) comprised of 46% carbohydrate, 34% protein, 14% fat, and 6% fiber based on dry weight. The animals 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.

Approximately 16 days before the study, a laparotomy was performed under general anesthesia (15 mg/kg body wt sodium pentothal presurgery; 1.0% isoflurane as an inhalation anesthetic during surgery). In all dogs, ultrasonic flow probes (Transonic Systems, Ithaca, NY) were positioned around the portal vein and a hepatic artery as previously described (7). A Silastic catheter (Dow Corning, Midline, MI) was inserted in a femoral artery, the portal vein, and the left common hepatic artery, the portal vein, and the left common hepatic vein for blood sampling and in the splenic and jejunal veins for intraportal hormone delivery, as previously described (35). A Silastic catheter was also inserted in the inferior vena cava (IVC) for the protocols involving GNG precursor infusion. The catheters were filled with heparinized saline (200 U/ml; Abbott Laboratories, North Chicago, IL), and the free ends were knotted. The free ends of the catheters and the flow probe leads were placed in subcutaneous pockets until the study day. Animals were studied only if the following criteria were met before the study: 1) leukocyte count <18,000/mm³, 2) hematocrit >35%, 3) good appetite, and 4) normal stools.

On the morning of a study, the Transonic leads and catheters were exteriorized under local anesthesia (2% lidocaine; Abbott Laboratories). The dog was placed in a Pavlov harness, and the catheters were cleared, flushed with saline, and subsequently used for blood sampling or infusion. Angiocaths (20 gauge; Becton-Dickinson, Sandy, UT) were inserted in the right and left cephalic veins for infusion of [3-3H]glucose (New England Nuclear, Boston, MA) and glucose (20% dextrose; Baxter Healthcare, Deerfield, IL), respectively. An angiocath was also placed in the left saphenous vein for indocyanine green dye (ICG; Sigma Chemical) and somatostatin (Bachem, Torrance, CA) infusion. Finally, an angiocath was placed in the right saphenous vein for peripheral epinephrine (Sigma Chemical) infusion.

Experimental design. Each experiment consisted of a 100-min tracer equilibration and hormone adjustment period (−140 to −40 min) followed by a 40-min control period (−40 to 0 min). During these periods, [3-3H]glucose (−50 μCi prime; ∼0.50 μCi/min) and ICG (0.07 mg/min) were infused. In addition, a pancreatic clamp was performed. This involved infusion of somatostatin (0.8 μg·kg⁻¹·min⁻¹) through a peripheral vein to inhibit endogenous insulin and glucagon secretion and replacement of insulin (−250 μU·kg⁻¹·min⁻¹; Eli Lilly, Indianapolis, IN) and glucagon (0.5 ng·kg⁻¹·min⁻¹; Bedford Laboratories, Bedford, OH) intraportally. The insulin infusion rate was varied as necessary during the equilibration period to maintain euglycemia. The control period was followed by a 4-h experimental period (0–240 min) during which basal insulin was maintained. Each dog underwent one of two different experimental protocols. In Epi (n = 6), basal glucagon was maintained (0.5 ng·kg⁻¹·min⁻¹; por- tally) and epinephrine (50 ng·kg⁻¹·min⁻¹; peripherally) was infused, whereas in G + Epi + P (n = 6) glucagon was elevated (1.5 ng·kg⁻¹·min⁻¹; portally) and epinephrine (50 ng·kg⁻¹·min⁻¹; peripherally) was infused. Additionally, in G + Epi + P, a “precursor clamp” was performed, whereby the GNG precursors lactate and alanine were infused at rates designed to create increases in their arterial levels similar to those seen previously in response to epinephrine alone, reaching lactate and alanine levels of −3,800 and −560 μmol/l, respectively (21). The data from the previously studied Epi group are reported in the current paper to facilitate comparisons with the results of the G + Epi + P protocol.

For precursor infusion, lactate and alanine ([L-(+)-lactate and l-alanine; Sigma Chemical] were dissolved in distilled water, and the pH was adjusted to 3.8 to eliminate the alkalinizing effects of lactate infused at pH 7.4 (20). The solution was then infused in the IVC to prevent the lysis of red blood cells that occurs when the solution is infused in a smaller peripheral vessel (11). Lactate and alanine were infused from 0 to 30 min at 10 and 0.53, from 30 to 60 min at 1.17 and 0.53, from 60 to 90 min at 1.9 and 1.82, from 90 to 120 min at 2.29 and 2.29, from 120 to 180 min at 3.84 and 3.84, and from 180 min to 240 min at 0.64 μmol·kg⁻¹·min⁻¹, respectively. To ensure that the lactate infusion did not alter the blood gases or pH, Pco₂, and Po₂ were measured periodically in five of the six dogs (Radiometer, Copenhagen, Denmark). None of the parameters changed significantly from the basal period as a result of lactate infusion (pH: 7.36 ± 0.01 to 7.37 ± 0.01; Pco₂: 40 ± 1 to 38 ± 1 mmHg; Po₂: 93 ± 3 to 97 ± 3 mmHg). In both Epi and G + Epi + P, glucose was infused peripherally at variable rates to match the plasma glucose level seen in our earlier studies (−250 mg/dl). The [3-3H]glucose infusion rate was varied in both groups throughout the experimental period to clamp the glucose specific activity and thereby minimize errors in glucose turnover calculation. Basically, for every increase of 2 μg·kg⁻¹·min⁻¹ in total glucose rate of appearance (Rg), the [3-3H]glucose infusion rate was increased by an amount equal to the basal infusion rate. This rate of increase was similar to that used in previous studies and was refined based on the results of the first few dogs of the present study. In addition, to prevent a slow decline in glucagon levels, the glucagon infusion was increased slightly each hour in both groups. Specifically, the glucagon infusion rate was increased from 1.5 to 1.62, 1.74, and 1.86 ng·kg⁻¹·min⁻¹ in G + Epi + P and from 0.50 to 0.54, 0.58, and 0.62 ng·kg⁻¹·min⁻¹ in Epi at 60, 120, and 180 min, respectively. In all dogs, mean arterial blood pressure and heart rate were determined throughout the experiment at each sampling time point by using either a chart recorder with blood pressure transducer (Gould BS3200; Gould) or a Digi-Med Blood Pressure Analyzer (Micro-Med, Louisvile, KY).

Analytical procedures. The immediate processing of the samples and the measurement of whole blood glucose, glutamine, glutamate, acetoacetate, individual amino acids (serine, threonine, glycine), and metabolites (lactate, alanine, glycerol, β-hydroxybutyrate) were described previously (7, 42). In addition, plasma levels of glucose, [3-3H]glucose, ICG, catecholamines, insulin, glucagon, cortisol, and nonesterified fatty acids (NEFA) were measured as previously described (7, 42). C-peptide (in plasma to which 500 kallikrein inhibitor [Trasylol had been added; FBA Pharmaceuticals, New York, NY] was determined via disequilibrium double-antibody RIA (Linco Research, St. Charles, MO) with an interassay coefficient of variation of 5%.

Calculations. Both ICG and Transonic flow probes were used to estimate total hepatic blood flow in these studies. The
net hepatic balances and net hepatic fractional extractions of blood glucose, lactate, alanine, glyceral, β-hydroxybutyrate, glutamine, glutamate, acetacetate, serine, threonine, glycine, and plasma NEFA were calculated using both Transonic-determined and ICG-determined flow. The data shown are those calculated using Transonic-determined flow, as this flow does not require an assumption about the distribution of arterial vs. portal flow. Note that the same conclusions were drawn when ICG-determined flow was used to calculate the data. Equations used were as follows:

net hepatic balance = H × HF − [A × AF + P × PF]
net hepatic fractional extraction =

H × HF − [A × AF + P × PF] / [A × AF + P × PF] × (PF/HF)

hepatic sinusoidal level = A × (AF/HF) + P × (PF/HF)

where A, P, H are arterial, portal vein, and hepatic vein concentrations (blood or plasma), respectively; AF and PF are the arterial and portal vein flow (blood or plasma) measured by the Transonic flow probes, respectively; and HF (total liver flow; blood or plasma) is equal to A + P + H. Positive numbers for net hepatic balance indicate net production, whereas negative numbers indicate net uptake. In some cases, uptake is presented rather than balance, and when such is the case positive values are used. Note that, because the liver is supplied by blood from both the hepatic artery and the portal vein, neither represents the true inflowing hepatic blood supply. For this reason, we calculated hepatic sinusoidal hormone levels, which provide an estimate of the average inflowing hormone concentration at the confluence of the two inputs, assuming it occurs early in the sinusoid.

Tracer-determined total RA and utilization (Ra d) were calculated according to the isotope dilution method outlined by Wall et al. (48), as simplified by DeBodo et al. (13), and using a two-compartment model described by Mari (31) and canine parameters established by Dobbins et al. (15). Endogenous Ra was then calculated by subtracting the glucose infusion rate from the total glucose production rate. Note that endogenous glucose production represents both hepatic and renal glucose production and thus slightly overestimates hepatic glucose production.

Gluconeogenesis, as classically defined, is the synthesis and subsequent release of glucose from noncarbohydrate precursors. Carbon produced from flux through the GNG pathway does not necessarily have to be released as glucose; it can also be stored as glycogen, oxidized, or released as lactate. Therefore, there is a distinction between GNG flux to glucose 6-phosphate (G-6-P; conversion of precursors to G-6-P), already called G-6-P neogenesis) and gluconeogenesis (release of glucose derived from GNG flux) in the present studies, we estimated hepatic GNG flux to G-6-P, net hepatic GNG flux, and net hepatic GLY flux.

Hepatic GNG flux to G-6-P was obtained by summing net hepatic uptake rates of the GNG precursors (alanine, serine, glycine, threonine, glutamine, glutamate, glyceral, lactate, pyruvate) and then dividing by two to transform the data into glucose equivalents (by accounting for incorporation of 3-carbon precursor molecules into 6-carbon glucose molecules). Net hepatic pyruvate uptake was assumed to be 10% of net hepatic lactate uptake (47). When net hepatic output of any precursor occurred, rather than uptake, the precursor was considered to be a product of the liver, and thus net uptake was set to zero. However, note that the net hepatic balance data of the precursors represents the entire database, regardless of net output or net uptake. Limitations of using net hepatic balance data rather than unidirectional hepatic uptake rates to calculate hepatic GNG flux to G-6-P were previously discussed (21). Additionally, the assumptions inherent in this approach to estimate GNG flux to G-6-P were discussed previously (21).

Net hepatic GNG flux was determined by subtracting the summed net hepatic output rates (when such occurred) of the substrates noted above (in glucose equivalents) and glucose oxidation (GO) from the GNG flux to G-6-P. A positive number represents net GNG flux to G-6-P, whereas a negative number indicates net GLY flux from G-6-P. GO was assumed to be 0.3 mg·kg⁻¹·min⁻¹ throughout each experiment, similar to the basal period of earlier studies in conscious dogs fasted for 18 h (22) and 24 h (0.3 ± 0.1 mg·kg⁻¹·min⁻¹; MC Moore, MJ Pagliassotti, LL Swift, J Asher, J Murrell, D Neal, and AD Cherrington, unpublished observations). In the previous studies, hepatic GO was determined by infusing [14C]glucose, measuring 14CO₂ in the blood (1), and then using the net hepatic balance calculation. Although assuming GO of 0.3 mg·kg⁻¹·min⁻¹ may slightly overestimate or underestimate the true GO rate, it is unlikely to differ by more than 0.1 mg·kg⁻¹·min−1. Our earlier studies showed that hyperglycemia (in the presence of euglycemia) did not appreciably change the hepatic GO rate (0.4 ± 0.2 mg·kg⁻¹·min⁻¹; see Ref. 41). It also seems unlikely that glucagon and epinephrine would change hepatic GO significantly. Although both have been shown to inhibit pyruvate dehydrogenase and thus pyruvate oxidation (19, 39, 40), the basal oxidation rate is so low that any effect would have been difficult, if not impossible, to detect.

Net hepatic GLY flux was determined by subtracting net hepatic GNG flux from net hepatic glucose balance. A positive number therefore represents net glycogen breakdown, whereas a negative number indicates net glycogen synthesis. The validity of this rate has been discussed previously (21).

The area under the curve (AUC) for hepatic GNG flux to G-6-P, net hepatic GNG flux, and net hepatic GLY flux in each group was calculated for the basal period, the first hour, and the last hour of the experimental period using the trapezoidal rule. The basal period AUC for each dog was multiplied by 3/2 to account for the fact that the period was only 40 min in length and was then subtracted from the AUC of the first hour and the AUC of the last hour to obtain the change from basal AUC. After this, the mean change from basal AUC of the hyperglycemic control group from a previous study (21) was subtracted from that of each of the individual dogs in the present study. This hyperglycemic control group had basal levels of glucagon and epinephrine and hyperglycemia similar to that seen in the present study (~250 mg/dl). These final results are presented as the change from basal AUC during the first or last hour (Fig. 5). Additionally, the mean change from basal AUC of the Epi group was subtracted from each individual dog in the G + Epi + P group (for both the first and last hour). This resulted in glucagon’s effect in the presence of epinephrine (Fig. 6), which was compared with glucagon’s effect in the absence of epinephrine as determined in our previous study (21).

Statistical analysis. Data are expressed as means ± SE. Statistical comparisons were made by two-way ANOVA with repeated-measures design run on SigmaStat (SPSS Science, Chicago, IL). Post hoc analysis was performed with the Bonferroni corrected t-test and the Tukey test. Analysis of AUC data between groups was done with one-way ANOVA. Analysis of AUC data within groups (first hour vs. last hour) was done with repeated-measures one-way ANOVA. Statistical significance was accepted at P < 0.05.
RESULTS

Glucose and hormone levels. In both groups, plasma glucose levels rose from ~110 to ~250 mg/dl (Table 1). To achieve similar glucose levels, significantly less glucose infusion was required in the G + Epi + P group (Table 1). Plasma insulin levels remained essentially unchanged and at the basal level in both groups (Table 1). In addition, arterial plasma C-peptide levels, measured as an index of endogenous insulin secretion, remained suppressed in both groups (data not shown). Arterial and hepatic sinusoidal plasma glucagon levels rose significantly when the glucagon infusion was increased (G + Epi + P) but remained basal when extra glucagon was not infused (Epi; Table 1 and Fig. 1). Arterial and sinusoidal plasma epinephrine levels rose significantly in both groups (Table 1 and Fig. 1), and the measurements were not significantly different. Arterial cortisol levels and arterial and sinusoidal norepinephrine levels remained basal in both groups (data not shown).

Arterial blood pressure and heart rate. Mean arterial blood pressure (mmHg) was normal and decreased modestly in both groups during the experimental period (Epi = 112 ± 9 to 96 ± 11; G + Epi + P = 108 ± 7 to 90 ± 6), with no significant difference between groups. Heart rate (beats/min) rose modestly in both groups, as a result of epinephrine administration (Epi = 104 ± 13 to 134 ± 8; G + Epi + P = 114 ± 8 to 139 ± 4), with no significant difference between groups.

Lactate and alanine: arterial levels and net hepatic balance. Arterial lactate levels rose similarly in both groups (P < 0.05; Fig. 2). Net hepatic lactate balance switched from production to uptake in both groups (P < 0.05), again with no overall significant difference between groups. By the end of the study, however, net hepatic lactate uptake was 10 ± 3 μmol·kg⁻¹·min⁻¹ in G + Epi + P and only 3 ± 5 μmol·kg⁻¹·min⁻¹ in Epi.

Arterial alanine levels also rose similarly in both groups (P < 0.05; Table 2). Net hepatic alanine uptake increased in both groups (P < 0.05), although to a significantly greater extent in G + Epi + P than in Epi (P < 0.05). Net hepatic alanine fractional extraction did not change in Epi but increased significantly in G + Epi + P (P < 0.05; Table 2).

Glycerol, NEFA, and ketones: arterial levels, net hepatic balance, and net hepatic fractional extraction. Epinephrine caused a transient rise in both the arterial glycerol level and net hepatic glycerol uptake (P < 0.05; Table 3). The combination of glucagon, epinephrine, and precursors resulted in little change in glycerol metabolism. There was no effect of either treat-
Both hormones and matched GNG precursors levels, with time (0.0 ± 0.3 at 240 min). Changes in tracer-determined whole body endogenous glucose production ($R_g$) paralleled the changes in NHGO (Table 4).

Tracer-determined whole body glucose utilization ($R_d$; mg·kg$^{-1}$·min$^{-1}$; Table 4) tended to increase more in Epi (2.9 ± 0.2 to 4.0 ± 0.9 at 240 min; $P < 0.05$) than in G + Epi + P (2.5 ± 0.4 to 3.3 ± 0.5 at 240 min; not significant).

Gluconeogenesis and glycogenolysis. In response to epinephrine, hepatic GNG flux to G-6-P almost tripled by 240 min (Fig. 4). Net hepatic GNG flux (mg·kg$^{-1}$·min$^{-1}$) went from being negative ($-0.8 ± 0.4$) to positive by 240 min (0.7 ± 0.6). In contrast, there was only a small rise in net hepatic GLY flux (2.6 ± 0.7 to 3.4 ± 1.1 mg·kg$^{-1}$·min$^{-1}$ at 15 min) that waned with time ($-0.6 ± 1.0$ mg·kg$^{-1}$·min$^{-1}$ at 240 min). When the hormones were combined in the presence of matched GNG precursors, GNG flux to G-6-P increased ($P < 0.05$), and net hepatic GNG flux tended to increase to a greater rate than with epinephrine alone. Net hepatic GLY flux (mg·kg$^{-1}$·min$^{-1}$) increased from being negative ($-0.5 ± 0.5$) to positive by 240 min ($0.05; n = 6$ for Epi and G + Epi + P. *Significant change from basal within a group. †Significantly different from Epi. For hepatic sinusoidal glucagon, there was no significant difference between the groups, and both Epi and G + Epi + P increased from basal.

Fig. 1. Hepatic sinusoidal plasma glucagon and epinephrine levels in the control (–40 to 0 min) and experimental (0–240 min) periods in Epi and G + Epi + P 18-h-fasted conscious dogs. Data are expressed as means ± SE. Statistical comparisons were made by two-way ANOVA with repeated-measures design, and significance was accepted at $P < 0.05$; $n = 6$ dogs for Epi and G + Epi + P. *Significant change from basal within a group. †Significantly different from Epi. For hepatic sinusoidal glucagon, there was no significant difference between the groups, and both Epi and G + Epi + P increased from basal.

Fig. 2. Arterial blood lactate levels and net hepatic lactate balance in the control (–40 to 0 min) and experimental (0–240 min) periods in Epi and G + Epi + P 18-h-fasted conscious dogs. Data are expressed as means ± SE. Statistical comparisons were made by two-way ANOVA with repeated-measures design, and significance was accepted at $P < 0.05$; $n = 6$ for Epi and G + Epi + P. *Significant change from basal within a group. For arterial lactate levels and net balance, there was no significant difference between groups. Arterial lactate levels in both groups increased significantly from basal.

NHGO rose to 7.2 ± 0.8 at 15 min and once again waned with time (1.2 ± 0.3 at 240 min). Changes in tracer-determined whole body endogenous glucose production ($R_g$) paralleled the changes in NHGO (Table 4).

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min\(^{-1}\)) also rose to a greater rate than with epinephrine alone (\(P < 0.05; 2.8 \pm 0.8\) to 8.0 \(\pm 1.3\) at 15 min) and then fell to a rate significantly below basal (\(P < 0.05; -0.5 \pm 0.3\) at 240 min).

Table 3. Arterial blood levels of glycerol and ketones and arterial plasma NEFA, in addition to NH glycerol U, NH NEFA U, and NH ketone \(P\) during the control (\(-40\) to 0 min) and experimental (0–240 min) periods in studies conducted on 18-h-fasted conscious dogs maintained on a pancreatic clamp and exposed to a rise in either Epi or \(G + Epi + P\)

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<td></td>
</tr>
<tr>
<td>Epi</td>
<td>381 (\pm 49)</td>
<td>377 (\pm 48)</td>
<td>379 (\pm 47)</td>
<td>412 (\pm 46)</td>
<td>461 (\pm 53^*)</td>
<td>510 (\pm 49^*)</td>
<td>534 (\pm 52^*)</td>
<td>549 (\pm 50^*)</td>
</tr>
<tr>
<td>G + Epi + P</td>
<td>478 (\pm 80)</td>
<td>484 (\pm 77)</td>
<td>518 (\pm 69)</td>
<td>552 (\pm 73)</td>
<td>607 (\pm 56^*)</td>
<td>626 (\pm 51^*)</td>
<td>622 (\pm 49^*)</td>
<td>622 (\pm 50^*)</td>
</tr>
</tbody>
</table>

Net hepatic alanine uptake, \(\mu mol-kg^{-1}\cdot min^{-1}\)

| Epi       | 2.21 \(\pm 0.18\) | 2.79 \(\pm 0.36\) | 3.07 \(\pm 0.54\) | 3.52 \(\pm 0.61\) | 3.10 \(\pm 0.63\) | 3.64 \(\pm 0.64\) | 4.34 \(\pm 0.63^*\) | 4.64 \(\pm 0.50^*\) | 4.27 \(\pm 0.42^*\) |
| G + Epi + P | 3.04 \(\pm 0.19\) | 2.89 \(\pm 0.39\) | 3.09 \(\pm 0.61\) | 4.62 \(\pm 0.42^*\) | 5.08 \(\pm 0.73^*\)^† | 6.27 \(\pm 0.46^*\)^† | 6.68 \(\pm 0.50^*\)^† | 7.64 \(\pm 0.50^*\)^† | 7.95 \(\pm 0.38^*\)^† |

Net hepatic alanine fractional extraction

| Epi       | 0.22 \(\pm 0.03\) | 0.27 \(\pm 0.03\) | 0.27 \(\pm 0.06\) | 0.29 \(\pm 0.06\) | 0.23 \(\pm 0.04\) | 0.24 \(\pm 0.04\) | 0.29 \(\pm 0.01\) | 0.25 \(\pm 0.02\) | 0.25 \(\pm 0.02\) |
| G + Epi + P | 0.20 \(\pm 0.02\) | 0.19 \(\pm 0.03\) | 0.19 \(\pm 0.04\) | 0.23 \(\pm 0.02\) | 0.23 \(\pm 0.02\) | 0.29 \(\pm 0.02\) | 0.30 \(\pm 0.03^*\) | 0.34 \(\pm 0.03^*\) | 0.35 \(\pm 0.02^*\) |

Table 2. Arterial blood levels, net hepatic uptake, and net hepatic fractional extraction of alanine during the control (\(-40\) to 0 min) and experimental (0–240 min) periods of studies conducted on 18-h-fasted conscious dogs maintained on a pancreatic clamp and exposed to a rise in either Epi or \(G + Epi + P\)

<table>
<thead>
<tr>
<th>Time, min</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Arterial alanine, (\mu mol/l)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td>622 (\pm 49^*)</td>
<td>622 (\pm 50^*)</td>
</tr>
</tbody>
</table>

Data are means \(\pm\) SE; \(n = 6\) for both groups. For arterial alanine, there was no significant difference between groups, and both groups increased significantly. For net hepatic alanine uptake, both groups increased significantly, and the increase in \(G + Epi + P\) was larger than that in Epi. There was no significant difference between groups for net hepatic alanine fractional extraction. However, \(G + Epi + P\) increased significantly from basal, whereas Epi did not. \(P < 0.05\), significant change from basal within a group (†) and \(G + Epi + P\) is significantly different from Epi (‡).

Figure 5 presents the results in a different manner. The changes from basal AUCs for the measurements are given for the first and last hour in each group [after subtracting the respective change from basal of our
in both groups compared with the first hour. Although the differences between Epi and G + Epi + P were not statistically significant, the increase in GNG flux to G-6-P was nearly two times larger in G + Epi + P \((P = 0.06)\), and the increase in net GNG flux was ~1.5 times larger in G + Epi + P \((P = 0.06)\) compared with Epi. Finally, in the last hour, the changes in net hepatic GLY flux were minimal in both groups.

Figure 6 was obtained by subtracting the Epi AUC from the G + Epi + P AUC. This difference depicts the effects of glucagon on GNG flux to G-6-P, net GNG flux, and net GLY flux in the presence of epinephrine and GNG precursors (denoted as +). For comparison, Fig. 6 also shows the difference in the AUC between the hyperglycemia control group and the glucagon group (21) from our previous study (in the absence of epinephrine and GNG precursors; denoted as −). In the first hour, there were no differences between groups with respect to GNG flux to G-6-P, net GNG flux, or net GLY flux. The AUCs of the last hour, however, revealed that glucagon’s effects on hepatic GNG flux to G-6-P, net hepatic GNG flux, and net hepatic GLY flux were modified by the combination of epinephrine and clamped GNG precursor supply. Specifically, the presence of epinephrine and GNG precursors resulted in an ~4.5-fold rise in glucagon’s effect on GNG flux to G-6-P \((P < 0.05)\) and an ~3.5-fold rise in glucagon’s effect on net GNG flux \((P = 0.07)\) as well as an ~85% inhibition of glucagon’s effect on net GLY flux \((P = 0.08)\).

**DISCUSSION**

Glucagon and epinephrine were previously found to have additive effects on overall glucose production, as well as on hepatic GNG flux to G-6-P and net hepatic GLY flux (21). However, it was hypothesized that the hormones would have a synergistic effect on gluconeogenesis and a less than additive effect on glycogenolysis. A proposed explanation for the lack of synergism was that GNG precursor levels did not rise as much as they did when epinephrine was given alone because glucagon enhanced hepatic GNG efficiency in the absence of an ability to increase GNG precursor supply from muscle and adipose tissue. As a result, the levels

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**Table 4.** Tracer-determined whole body glucose Ra and Rg during the control (−40 to 0 min) and experimental (0–240 min) periods in studies conducted on 18-h-fasted conscious dogs maintained on a pancreatic clamp and exposed to a rise in either Epi or G + Epi + P

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Epi</th>
<th>G + Epi + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>−40</td>
<td>3.1 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>0</td>
<td>2.7 ± 0.2</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>60</td>
<td>3.0 ± 0.6</td>
<td>6.6 ± 0.8**†</td>
</tr>
<tr>
<td>90</td>
<td>2.6 ± 0.3</td>
<td>4.8 ± 0.8**†</td>
</tr>
<tr>
<td>120</td>
<td>2.2 ± 0.4</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>180</td>
<td>2.5 ± 0.4</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>240</td>
<td>1.9 ± 0.6</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>1.6 ± 0.7</td>
<td>2.5 ± 0.3</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 6 for both groups. Ra, glucose production; Rg, glucose utilization. For endogenous Ra, \(P < 0.05\) for Epi vs. G + Epi + P. Epi did not change significantly, but G + Epi + P increased and then waned with time. For Rg, there was no significant difference between the groups. However, Epi increased significantly, whereas G + Epi + P did not. \(P < 0.05\), significant change from basal within a group (**). G + Epi + P is significantly different from Epi (†).
The results of the rise in epinephrine and/or GNG pre-
by 85%.

whereas its effect on glycogenolysis was inhibited

GLY
fl
would modify the action of glucagon on GNG
concentrations seen in the epinephrine-alone group
whether sustaining the GNG substrate levels at the

Thus the aim of the present study was to determine

reduction in the GNG substrate levels. This in turn
increase in GNG
fl
ux. It was found that, under such conditions,
glucagon’s effect on GNG
fl
ux, both
fl
ux to G-6-
P
and net GNG
fl
ux to glucose 6-phosphate
increased to a greater level in G + Epi + P than Epi; however, for net hepatic GNG
fl
ux, both
groups rose similarly. In contrast, net hepatic GLY
fl
ux in Epi fell significantly by the end of the study, and net hepatic GLY
fl
ux in G + Epi + P rose significantly and then fell to a level significantly
lower than basal. The differences between Epi and G + Epi + P on net hepatic GLY
fl
ux were significant.

The above changes in GNG and GLY
fl
ux could be
the result of the rise in epinephrine and/or GNG pre-
cursors that occurred in the present experiments. Pre-
vious data from Gustavson et al. (21) are useful in
distinguishing between the effects of epinephrine and
GNG precursors. When both hormones were infused
previously (in the absence of precursor infusion), the
change in AUC above control during the last hour for
hepatic GNG
fl
ux to G-6-P was 24 ± 9 mg/kg. The
addition of precursor infusion resulted in a change in
AUC of 88 ± 14 mg/kg, an ~3.5-fold increase (P <
0.05). The increase in hepatic GNG
fl
ux to G-6-P was
associated with a complete inhibition (P < 0.05) of
glucagon’s effect on net hepatic GLY
fl
ux in the last
hour (change in AUCs: 159 ± 18 mg/kg for both hor-
omones without precursors, −10 ± 48 mg/kg for both
hormones with precursors). Thus it is clear that pre-
cursor availability is a necessary factor for increased

of lactate and alanine in blood were lower than with
epinephrine alone, and this prevented a significant
increase in GNG
fl
ux. In other words, glucagon’s effect
on the liver to increase GNG efficiency was offset by a
reduction in the GNG substrate levels. This in turn
prevented a change in glycogenolysis from occurring.
Thus the aim of the present study was to determine
whether sustaining the GNG substrate levels at the
concentrations seen in the epinephrine-alone group
would modify the action of glucagon on GNG
fl
ux or
GLY
fl
ux. It was found that, under such conditions,
glucagon’s effect on GNG
fl
ux was increased 4.5-fold,
whereas its effect on glycogenolysis was inhibited by
85%.

The above changes in GNG and GLY
fl
ux could be
the result of the rise in epinephrine and/or GNG pre-

Fig. 4. Hepatic gluconeogenic (GNG)
fl
ux to glucose 6-phosphate
(G-6-P), net hepatic GNG
fl
ux and net hepatic glycogenolytic (GLY)
fl
ux in the control (−40 to 0 min) and experimental (0–240 min)
periods in Epi and G + Epi + P 18-h-fasted conscious dogs. Data are
expressed as means ± SE. Statistical comparisons were made by
two-way ANOVA with repeated-measures design, and significance
was accepted at P < 0.05; n = 6 for Epi and G + Epi + P. *Significant
change from basal within a group. †G + Epi + P is significantly
different from Epi. In Epi and G + Epi + P, GNG
fl
ux to G-6-P and net
hepatic GNG
fl
ux both rose. GNG
fl
ux to G-6-P increased to a greater
level in G + Epi + P than Epi; however, for net hepatic GNG
fl
ux, both
groups rose similarly. In contrast, net hepatic GLY
fl
ux in Epi fell significantly by the end of the study, and net hepatic GLY
fl
ux in G + Epi + P rose significantly and then fell to a level significantly
lower than basal. The differences between Epi and G + Epi + P on net hepatic GLY
fl
ux were significant.

Fig. 5. Areas under the curve (AUC) of hepatic GNG
fl
ux to G-6-P,
net hepatic GNG
fl
ux, and net hepatic GLY
fl
ux. All AUCs are shown
as change from basal of the first and last hours, after subtracting
change from basal of the previous hyperglycemic control (21). Data
are expressed as means ± SE. Statistical comparisons were made by
one-way ANOVA, with or without repeated measures, depending on
the comparison, and significance was accepted at P < 0.05; n = 6 for
Epi and G + Epi + P. *Significant change from the 1st h to the last
hour within a group. †G + Epi + P is significantly different from Epi.
The only significant difference between groups in the 1st h was for
net hepatic GLY. In the last hour, GNG
fl
ux to G-6-P and net hepatic GNG
fl
ux tended to be larger in G + Epi + P than in Epi (P = 0.06 and P =
0.06, respectively). By the last hour, net hepatic GLY
fl
ux was not
different in the two groups and was not significantly different from
the previous hyperglycemic control. Note that within each group for
each parameter, with the minor exception of Epi for hepatic GNG
fl
ux to G-6-P (P = 0.09), there was a significant change from the 1st
h to the last hour.
The increase in GNG flux to G-6-P in the presence of both glucagon and epinephrine compared with glucagon alone was proportional to the increase in the GNG precursor load to the liver caused by epinephrine (21). When precursors were infused in the present study in addition to both hormones, the increase in GNG flux that resulted was proportional to the even greater rise in the precursor load. This implies that glucagon increases the GNG efficiency of the liver and that, when more precursors are made available in the presence of glucagon (first by epinephrine administration and then by epinephrine and precursor administration), the liver reaches a higher steady-state GNG flux rate, thus making precursor availability the rate-determining factor.

Interestingly, the reciprocity between gluconeogenesis and glycogenolysis only occurred during the last hour of the study. In the first hour, glucagon still exerted a major GLY effect, even in the presence of elevated epinephrine and GNG precursors. Glucagon’s effect on GLY flux was inhibited only after GNG flux had risen, implying that it was the increase in gluconeogenesis that inhibited glycogenolysis. Note that, although glucagon’s effect on glycogenolysis is known to wane with time (3, 23), glycogenolysis is still significantly elevated after 4 h compared with a hyperglycemic control group, and as such substantial inhibition was possible (21).

The effect of GNG precursor infusion on the components of hepatic glucose production has been studied in the presence of basal hormone levels. Infusions of lactate (11), alanine (14), and glycerol (50) in dogs were able to increase GNG flux without altering total glucose production (thus implying reciprocal inhibition of glycogenolysis). These results support the present study, in which infusion of precursors (lactate and alanine), in the presence of elevated epinephrine and glucagon, resulted in stimulation of gluconeogenesis, inhibition of glycogenolysis, and no change in glucose production [either net hepatic glucose production or whole body glucose Ra compared with elevated epinephrine and glucagon without precursor infusion (21)]. Thus precursor availability is able to reciprocally affect these processes, regardless of the hormonal environment (i.e., basal or elevated glucagon and epinephrine). Studies in humans seem to support this conclusion. Lactate infusion resulted in increased gluconeogenesis with no change in total glucose production (25). Likewise, infusion of alanine alone (51), or glycerol and alanine concurrently (24), was not able to change total glucose production. Originally, it was thought that the lack of a rise in glucose production, despite an increase in GNG precursor availability, might have resulted from a decrease in gluconeogenesis from the other precursors (24, 44). However, it was subsequently determined that it is the reciprocal fall in glycogenolysis that prevents an increase in glucose production (11, 25). Interestingly, two recent studies involved infusing lactate in humans during rest and exercise (33, 34). Overall glucose production did not change with increased precursor supply during rest in...
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either study, which is consistent with the previously described literature. Moreover, during exercise, the relative rates of gluconeogenesis and glycogenolysis increased and decreased, respectively, in response to lactate infusion, indicating interregulation of the processes (33).

Glucagon has been shown to increase small, neutral amino acid transport into hepatocytes via A transporters (26–28). The fact that glucagon increases efficiency of alanine uptake, in addition to intrahepatic conversion of alanine to glucose (45), explains the fact that the net hepatic alanine uptake rose to a greater extent in G + Epi + P than Epi. There was also a tendency in the present study for lactate uptake to reach an approximately threefold greater rate by the end of the study when glucagon was elevated (Epi = 3.5 ± 5.0, G + Epi + P = 9.7 ± 3.3 μmol·kg⁻¹·min⁻¹). Although this difference was not statistically significant, it is likely that a threefold larger uptake is physiologically important. In fact, statistically significant differences are difficult to obtain for lactate measurements, as this parameter is inherently variable. At any rate, the increase in efficiency of lactate uptake was expected because glucagon increases overall GNG efficiency in vivo (45) by stimulating both transcription and activation of hepatic GNG enzymes (16, 29, 36, 37). The most likely explanation for our failure to detect an increase in lactate fractional extraction, and for the failure of previous studies (12, 45) to do so, is that the variance of the measurement created a signal to noise problem.

The elevations in the GNG and GLY parameters in this study are not likely to have resulted from changes in plasma NEFA levels. NEFA are known to increase gluconeogenesis in vivo (2, 6, 10, 38, 46, 49), but the increase in NEFA was not greater in the G + Epi + P group than in the Epi group or in the glucagon and epinephrine alone (without precursor infusion) group from our previous study (21). Thus NEFA levels cannot explain the elevated rates of GNG flux to G-6-P and the decrease in net hepatic glycogenolysis that occurred in the presence of glucagon, epinephrine, and precursors. It appears that the precursors alone, not NEFA, were able to significantly increase gluconeogenesis and completely inhibit glycogenolysis in the present studies.

In conclusion, simply raising plasma glucagon and epinephrine levels resulted in additive effects of the two hormones on net hepatic glucose production and did not alter the GNG and GLY contributions to glucose production. The addition of GNG precursors (lactate and alanine) to the system did not increase NHGO further, and the effects of the hormones remained additive (change in AUCs of the 4-h experimental period: 1,178 ± 57 mg/kg with both hormones, and 1,000 ± 43 mg/kg with both hormones and GNG precursor infusion). However, increasing the availability of GNG precursors changed the effects of the hormones on the two components of hepatic glucose production. Specifically, the effect of the hormones on gluconeogenesis was potentiated, and the effect on glycogenolysis was inhibited, when additional precursors were made available during the hormone infusion. This would serve to protect liver glycogen stores when GNG substrates are available for conversion to glucose. A final point is that, under stress conditions, such changes in glucagon and epinephrine would undoubtedly be accompanied by changes in insulin, resulting in a smaller increment in plasma glucose, and it remains to be seen whether in the presence of hyperinsulinemia and lower glucose levels the interaction of glucagon and epinephrine would be altered.

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DISCLOSURES

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