Relative importance of liver, kidney, and substrates in epinephrine-induced increased gluconeogenesis in humans

Christian Meyer,1,2 Michael Stumvoll, Stephen Welle, Hans J. Woerle, Morey Haymond,3 and John Gerich1

1Departments of Medicine, University of Rochester School of Medicine, Rochester, New York 14642;
2Carl T. Hayden Veterans Affairs Medical Center, Phoenix, Arizona 85012; and 3Baylor College of Medicine, Children's Nutrition Research Center, Houston, Texas 77030

Submitted 4 April 2003; accepted in final form 6 June 2003

Meyer, Christian, Michael Stumvoll, Stephen Welle, Hans J. Woerle, Morey Haymond, and John Gerich. Relative importance of liver, kidney, and substrates in epinephrine-induced increased gluconeogenesis in humans. Am J Physiol Endocrinol Metab 285: E819–E826, 2003; 10.1152/ajpendo.00145.2003.—Splanchnic and renal net balance measurements indicate that lactate and glycerol may be important precursors for epinephrine-stimulated gluconeogenesis (GNG) in liver and kidney, but the effects of epinephrine on their renal and hepatic conversion to glucose in humans have not yet been reported. We therefore used a combination of renal balance and isotopic techniques in nine postabsorptive volunteers to measure systemic and renal GNG from these precursors before and during a 3-h infusion of epinephrine (270 pmol ⋅ kg−1 ⋅ min−1) and calculated hepatic GNG as the difference between systemic and renal rates. During infusion of epinephrine, renal and hepatic GNG from lactate increased 4- to 6-fold and accounted for ∼85 and 70% of renal and hepatic glucose release, respectively, at the end of study; renal and hepatic GNG from glycerol increased ∼1.5- to 2-fold and accounted for ∼7–9% of renal and hepatic glucose release at the end of study. The increased renal GNG from lactate and glycerol was due not only to their increased renal uptake (∼3.3- and 1.4-fold, respectively) but also increased renal gluconeogenic efficiency (∼1.8- and 1.5-fold). The increased renal uptake of lactate and glycerol was wholly due to their increased arterial concentrations, since their renal fractional extraction remained unchanged and renal blood flow decreased. We conclude that 1) lactate is the predominant precursor for epinephrine-stimulated GNG in both liver and kidney, 2) hepatic and renal GNG from lactate and glycerol are similarly sensitive to stimulation by epinephrine, and 3) epinephrine increases renal GNG from lactate and glycerol by increasing substrate availability and the gluconeogenic efficiency of the kidney.

IN HUMANS DURING INFUSION OF EPINEPHRINE, systemic glucose release increases as a result of a transient increase in glycogenolysis followed by a sustained increase in gluconeogenesis (39). Glucose release from glycogenolysis probably occurs only in the liver, because the human kidney normally stores little glycogen (4) and renal cells that could store glycogen lack glucose-6-phosphatase (17). In contrast, both human liver and kidney release glucose via gluconeogenesis (16).

Currently, knowledge regarding the effects of epinephrine on gluconeogenesis in these organs is relatively limited. Specifically, the relative contributions of liver and kidney to epinephrine-stimulated systemic gluconeogenesis are not known, nor is the relative importance of individual substrates used by these organs and the role of increased precursor availability vs. intracellular mechanisms (e.g., altered metabolic pathways).

To our knowledge, the effects of epinephrine on hepatic and renal gluconeogenesis in humans have been investigated in only two studies (39, 42). Sacca et al. (39) used a combination of isotopic and splanchnic net balance techniques and reported the effects of epinephrine on systemic and hepatic gluconeogenesis from lactate and alanine together in five healthy, postabsorptive humans. In that study, infusion of epinephrine increased the combined conversion of lactate and alanine to plasma glucose more than fourfold in both the liver and whole body. However, absolute rates were not reported, and renal gluconeogenesis was not calculated. Nevertheless, one may infer from their splanchnic net balance measurements that lactate was probably a much more important precursor for hepatic gluconeogenesis than alanine (39). In the other study (42), we used a combination of isotopic techniques and renal net balance measurements and determined the effect of epinephrine on renal and hepatic gluconeogenesis (calculated as the difference between systemic and renal rates) from glutamine and alanine in nine postabsorptive humans (42). In that study, epinephrine increased gluconeogenesis from glutamine and alanine selectively in kidney and liver, respectively, but both could account for only a small percentage of renal and hepatic glucose release. However, renal net balance measurements indicate that net uptake of lactate and glycerol could have accounted for ∼50 and 5% of renal glucose release, respectively, suggesting a potentially important role for these precursors.

http://www.ajpendo.org

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Herein, we therefore report the effects of epinephrine on systemic, renal, and hepatic gluconeogenesis from lactate and glycerol. Because these studies were performed under conditions essentially identical to those in our previous report, their combined data allow estimation of the relative importance of lactate, glycerol, glutamine, and alanine during stimulation of renal and hepatic gluconeogenesis by epinephrine. Furthermore, because gluconeogenesis from these precursors normally accounts for the vast majority of overall gluconeogenesis (32), these data also provide information regarding the relative contributions of liver and kidney for epinephrine-stimulated systemic gluconeogenesis.

**METHODS**

**Subjects.** Informed written consent was obtained from nine normal volunteers after the protocol had been approved by The University of Rochester Institutional Review Board. The subjects (6 men, 3 women) were 29 ± 3 yr of age, weighed 68 ± 5 kg, and had a body mass index of 23.1 ± 1.0 kg/m². All subjects had normal physical examinations, routine laboratory tests, and glucose tolerance (World Health Organization criteria) (48). In addition, they had no family history of diabetes mellitus and were not taking any medications known to affect glucose metabolism. For 3 days before the study, all had been on a weight-maintaining diet containing ≥200 g carbohydrate and had abstained from alcohol.

**Protocol.** Subjects were admitted to the University of Rochester General Clinical Research Center between 6:00 and 7:00 PM the evening before experiments, consumed a standard meal between 6:30 and 8:00 PM, and fasted thereafter until experiments were completed.

At 5:30 AM, an antecubital vein was cannulated, and a primed continuous infusion of [6-3H]glucose (−25 µCi, −0.25 µCi/min) was begun in all subjects. In addition, subjects received simultaneous primed continuous infusions of [1-13C]lactate (−1,000 µmol, −10 µmol/min) plus [U-14C]glycerol (−20 µCi, −0.20 µCi/min; n = 3), [1-13C]glucose (−1,000 µmol, −10 µmol/min) plus [U-14C]glycine (−20 µCi, −0.20 µCi/min; n = 3), or [U-14C]glycerol (−20 µCi, −0.20 µCi/min) plus [1-14C]alanine (−2,000 µmol, −20 µmol/min; n = 3). All radioactive isotopes were obtained from Amersham International, and all stable isotopes were obtained from Cambridge Isotope Laboratories (Andover, MA). Isotopic data from alanine and glycine during epinephrine infusion have been published separately (42) and are therefore not included in the present report. At 8:00 AM, an infusion of p-aminohippuric acid (12 mg/min) was started for determination of renal blood flow (RBF). Between 8:00 and 9:00 AM, a renal vein was catheterized under fluoroscopy. The position of the catheter tip was initially ascertained by injecting a small amount of iodinated contrast material and by arterial-renal venous differences of p-aminohippuric acid concentrations during the experiment. At 9:00 AM, a dorsal hand vein was cannulated and kept in a thermoregulated Plexiglas box at 65°C for sampling arterialized venous blood (1). About 1 h later, three blood samples were collected simultaneously from the dorsal hand vein and the renal vein at 30-min intervals (−60, −30, and 0 min) for determination of blood glucose and plasma lactate, glycerol, free fatty acid (FFA), insulin, glucagon, epinephrine, and p-aminohippuric acid concentrations, as well as specific activities/enrichments of [3H]-, [14C]-, and [13C]glycerol, [14C]glycerol, and [13C]lactate by previously described methods (6, 28, 31, 33, 36, 40, 44, 45, 47). At 0 min, a continuous infusion of epinephrine (270 pmol·kg⁻¹·min⁻¹) was begun, which was designed to produce plasma epinephrine concentrations similar to those during hypoglycemia. Subsequently, blood was collected as described above at 30-min intervals for 3 h. Baseline data of hepatic and renal lactate and glycerol gluconeogenesis from all subjects and all glucose data from five of the nine subjects have been included in previous publications (32) (42).

**Calculations.** Arterial [3H]glucose and [14C]glycerol specific activities and arterial [13C]lactate enrichments did not change significantly during the 60-min baseline period (ANOVA), consistent with isotopic steady state having been achieved. However, isotopic steady state was apparently not achieved for [13C]- and [14C]glycerol until −30 min, as evidenced by the fact that values at −60 min, but not at −30 min, were significantly different from those at 0 min (paired Student’s t-test). Consequently, mean values at −30 and 0 min were used for calculations involving [13C]- or [14C]glucose.

Systemic (overall) release (Rₐ) and uptake (Rₜ) of glucose, lactate, and glycerol were calculated using standard steady-state equations at baseline (47), during infusion of epinephrine, kinetics of glucose, lactate, and glycerol were calculated using the non-steady-state equation of DeBodo et al. (13)

\[
Rₐ = \frac{F \times (C₁ + C₂)/2 \times (SA₁ - SA₂)}{(SA₁ + SA₂)/2}
\]

\[
Rₜ = Rₐ - \frac{pV \times (C₂ - C₁)/(t₂ - t₁)}{pV \times (C₄ - C₃)/30}
\]

where F represents the specific isotope infusion rate (dpmin⁻¹ or (µmol·min⁻¹), p the pool volume, V the volume of distribution, C₁ and C₂ the arterial concentrations at sampling times t₁ and t₂, and SA₁ and SA₂ the arterial specific activities at sampling times t₁ and t₂. The pool fraction was set at 0.65 for glucose and lactate and at 0.5 for glycerol; the volume of distribution was set at 200 ml/kg for glucose, 320 ml/kg for lactate, and 600 ml/kg for glycerol (20, 30, 37). For calculation of lactate Rₐ and enrichments (ENR) were used instead of specific activities, and the infusion rate of the lactate tracer was subtracted from the equation above (46).

The proportion of systemic glucose appearance in the steady state due to lactate gluconeogenesis was calculated as (arterial [14C]glucose ENR/arterial [13C]lactate ENR) × 100/2, using the standard precursor-product calculation. The division by 2 corrects for differences in carbon (i.e., lactate has 3, glucose 6 carbons). Systemic lactate gluconeogenesis was calculated as glucose Rₐ multiplied by the proportion of glucose Rₐ from lactate gluconeogenesis (25). During the nonsteady state (i.e., during the epinephrine infusion), whole body lactate gluconeogenesis was calculated using the equation of Chiasson et al. (8) as

\[
\text{glucose } Rₐ \times [13C] \text{ arterial glucose ENR} + pV \times [13C] \text{ arterial glucose ENR} \times \text{ arterial glucose } Rₐ \times \text{ arterial } [13C] \text{glyceraldehyde ENR}_t \times \text{ arterial glyceraldehyde }/30 \text{ min}/[13C] \text{ arterial lactate ENR} \times 2)
\]

where t₁ and t₂ refer to the beginning and end of every 30-min time interval. The previously mentioned pool fraction (p) and volume of distribution (V) for glucose were used.

Renal plasma flow (RPF) was determined by the p-aminohippuric acid clearance technique (6), and RBF was calculated as RPF/(1 – hematocrit). Renal glucose fractional extraction (FX) was calculated as (arterial [6-3H]glucose SA × arterial glucose concentration − renal vein [6-3H]glucose SA × renal vein glucose concentration)/arterial [6-3H]glu-
cose SA × arterial glucose concentration). Renal glucose uptake (RGI) was calculated as RBF × arterial glucose concentration × FX. Renal glucose net balance (NB) was calculated as RBF × (arterial glucose concentration – renal vein glucose concentration). Renal glucose release was calculated as RGI – NB (12). Analogous equations were used for renal net balance, uptake, and release of lactate and glycerol after plasma lactate and glycerol concentrations had been corrected to whole blood values by multiplying by 0.86 and 0.9, respectively (5, 14).

Renal gluconeogenesis from lactate was calculated as RBF × [renal vein [1-13C]glucose ENR × renal vein glucose concentration – [arterial [13C]glucose ENR × arterial glucose concentration × (1 – [3H]glucose FX)/[arterial [13C]lactate ENR × 2)], i.e., production of [13C]glucose divided by the arterial [13C]enrichment of lactate corrected for the different carbon in glucose and lactate. Because gluconeogenesis occurs only in kidney and liver, hepatic gluconeogenesis from lactate was calculated as the difference between systemic and renal rates. Rates of systemic, renal, and hepatic gluconeogenesis from glycerol were calculated by utilizing [14C]glycerol and [13C]lactate specific activities instead of enrichments.

Calculations of renal fluxes assume that data obtained from one kidney represent one-half of both kidneys. In addition, because renal blood flow is high, arterial-renal venous differences in substrate and tracer concentrations are relatively small. Consequently, analytic imprecision in measuring these parameters can lead to errors in calculating renal fluxes, including physiologically impossible values for renal fractional extraction, uptake, and release (15, 31). It was our approach to analyze all data as obtained to avoid possible bias.

Statistical analysis. Unless stated otherwise, data are expressed as means ± SE. Paired two-tailed Student’s t-tests were used to compare the average of data obtained from baseline with the mean of data obtained from the last 60 min of the 3-h epinephrine infusion. A P value < 0.05 was considered statistically significant.

RESULTS

Arterial hormone and substrate concentrations. Plasma concentrations of epinephrine, insulin, and glucagon and blood glucose concentrations were similar in subjects infused with [1-13C]lactate and [U-14C]glycerol at baseline as well as during infusion of epinephrine. Arterial epinephrine concentrations increased from ~270 pM at baseline to ~3,650 pM; arterial glucose and insulin concentrations both increased ~50–60% (both P < 0.01), whereas arterial glucagon concentrations remained unchanged (Fig. 1).

Arterial blood lactate concentrations increased progressively during infusion of epinephrine from ~550 μM at baseline to ~2,200 μM at the end of the epinephrine infusion (P < 0.003; Fig. 2); arterial blood glycerol concentrations increased rapidly from ~75 μM to a peak of ~190 μM at 30 min and subsequently remained nearly constant at ~110 μM (P = 0.02 vs. baseline; Fig. 2). Arterial plasma FFA concentrations followed a pattern similar to that of arterial glycerol, increasing rapidly from 668 ± 60 μM to a peak of 1,488 ± 142 μM at 30 min. Arterial FFA subsequently decreased and were nearly constant during the last 60 min of the epinephrine infusion, averaging 713 ± 60 μM (P > 0.5 vs. baseline).

Systemic turnovers of glucose, lactate, and glycerol. Arterial [3H]glucose and [14C]glycerol radioactivities and arterial [13C]lactate concentrations are given in Table 1. During infusion of epinephrine, systemic glucose release increased from ~12.9 μmol·kg⁻¹·min⁻¹ at baseline to a peak of ~20.5 μmol·kg⁻¹·min⁻¹ at 30 min and subsequently declined to ~15.6 μmol·kg⁻¹·min⁻¹ during the last 60 min of the infusion of epinephrine (P < 0.03 vs. baseline; Fig. 3). Systemic lactate release progressively increased from ~12.0 μmol·kg⁻¹·min⁻¹ at baseline to ~42 μmol·kg⁻¹·min⁻¹ during the last 60 min of the infusion of epinephrine (P < 0.003; Fig. 2); systemic glycerol release increased rapidly from ~2.2 μmol·kg⁻¹·min⁻¹ to a peak of ~4.0 μmol·kg⁻¹·min⁻¹ at 30 min and subsequently remained nearly constant at ~2.8 μmol·kg⁻¹·min⁻¹ from 90 to 180 min (Fig. 2). Systemic uptake of lactate and glycerol followed patterns similar to those of their systemic release (Fig. 2).

Renal blood flow and renal and hepatic glucose release. Renal blood flow decreased 10–20% during infusion of epinephrine in subjects infused with [1-13C]lactate and in those infused with [U-14C]glycerol (both < 0.05; Table 2). Renal glucose net release increased from 0.96 ± 0.26 μmol·kg⁻¹·min⁻¹ at baseline to a peak of 4.5 ± 0.5 μmol·kg⁻¹·min⁻¹ at 30 min and then de-
increased slightly, averaging $3.5 \pm 0.7 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the last 60 min of the infusion of epinephrine ($P < 0.003$ vs. baseline). Arterial and renal venous $[6^{-3}\text{H}]$glucose radioactivities are given in Table 1. Rates of renal and hepatic glucose release during infusion of epinephrine were similar to those previously reported (42). Renal glucose release increased from $-3.2 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at baseline to a peak of $-6.2 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 30 min and averaged $-5.8 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the last 60 min of the infusion of epinephrine ($P < 0.001$ vs. baseline). Hepatic glucose release increased from $-9.7 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to a peak of $-14.3 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 30 min and subsequently decreased to rates similar to baseline ($P > 0.9$; Fig. 3).

**Systemic, renal, and hepatic gluconeogenesis from lactate and glycerol.** Arterial and renal venous $[14\text{C}]$glucose and $[14\text{C}]$glycerol radioactivities and arterial and renal venous $[3\text{H}]$glucose and $[3\text{H}]$lactate concentrations are given in Table 1. At baseline, systemic ($-2.5 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), renal ($-0.85 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and hepatic gluconeogenesis ($-1.6 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) from lactate accounted for 19 ± 1, 35 ± 11, and 16 ± 2% of respective rates of systemic, renal, and hepatic glucose release. All increased gradually during infusion of epinephrine (Fig. 4). At the end of the study, systemic, renal, and hepatic gluconeogenesis from lactate were about four- to sixfold increased (all $P < 0.005$) and accounted for 73 ± 5, 83 ± 7, and 69 ± 6% of systemic, renal, and hepatic glucose release, respectively. The percent contribution of the kidney to systemic gluconeogenesis from lactate remained unchanged during infusion of epinephrine (41 ± 3 vs. 36 ± 6% at baseline, $P = 0.35$).

Baseline systemic ($-0.65 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), renal ($-0.20 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and hepatic gluconeogenesis from glycerol ($-0.45 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) accounted for 4.9 ± 0.8, 6.3 ± 0.9, and 4.8 ± 1.1% of respective rates of systemic, renal, and hepatic glucose release. All increased rapidly during the initial 60 min of epi-

### Table 1. Blood radioactivities/concentrations of labeled glucose, lactate, and glycerol at baseline and during infusion of epinephrine

<table>
<thead>
<tr>
<th>Minutes</th>
<th>-60</th>
<th>-30</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artery</strong></td>
<td>Blood $[^{3}\text{H}]$glucose radioactivity, dpm/ml</td>
<td>2,660 ± 272</td>
<td>2,703 ± 274</td>
<td>2,653 ± 258</td>
<td>2,653 ± 258</td>
<td>2,913 ± 267</td>
<td>3,077 ± 287</td>
<td>3,281 ± 297</td>
</tr>
<tr>
<td></td>
<td>Blood $[^{14}\text{C}]$glucose concentration, μM</td>
<td>20.6 ± 4.4</td>
<td>23.0 ± 5.6</td>
<td>22.9 ± 5.2</td>
<td>25.9 ± 6.0</td>
<td>33.3 ± 9.1</td>
<td>36.5 ± 9.7</td>
<td>40.1 ± 10.5</td>
</tr>
<tr>
<td><strong>Renal vein</strong></td>
<td>Blood $[^{14}\text{C}]$glucose radioactivity, dpm/ml</td>
<td>2,605 ± 271</td>
<td>2,653 ± 277</td>
<td>2,607 ± 256</td>
<td>2,613 ± 253</td>
<td>2,867 ± 267</td>
<td>3,022 ± 285</td>
<td>3,220 ± 298</td>
</tr>
<tr>
<td></td>
<td>Blood $[^{3}\text{H}]$glucose concentration, μM</td>
<td>21.2 ± 3.5</td>
<td>22.9 ± 4.0</td>
<td>23.3 ± 4.0</td>
<td>26.2 ± 4.5</td>
<td>34.1 ± 7.0</td>
<td>37.6 ± 7.7</td>
<td>41.3 ± 8.2</td>
</tr>
<tr>
<td><strong>Artery</strong></td>
<td>Blood $[^{14}\text{C}]$lactate concentration, μM</td>
<td>1,042 ± 127</td>
<td>1,126 ± 150</td>
<td>1,036 ± 118</td>
<td>1,135 ± 108</td>
<td>1,360 ± 104</td>
<td>1,521 ± 123</td>
<td>1,632 ± 133</td>
</tr>
<tr>
<td><strong>Renal vein</strong></td>
<td>Blood $[^{14}\text{C}]$lactate radioactivity, dpm/ml</td>
<td>1,065 ± 135</td>
<td>1,130 ± 152</td>
<td>1,064 ± 124</td>
<td>1,179 ± 118</td>
<td>1,437 ± 118</td>
<td>1,568 ± 127</td>
<td>1,684 ± 138</td>
</tr>
<tr>
<td></td>
<td>Blood $[^{3}\text{H}]$lactate radioactivity, dpm/ml</td>
<td>6.97 ± 2.19</td>
<td>6.65 ± 2.38</td>
<td>7.12 ± 2.47</td>
<td>7.92 ± 3.12</td>
<td>8.10 ± 3.31</td>
<td>8.38 ± 3.36</td>
<td>7.52 ± 2.75</td>
</tr>
<tr>
<td><strong>Artery</strong></td>
<td>Blood $[^{14}\text{C}]$glycerol radioactivity, dpm/ml</td>
<td>4.45 ± 1.21</td>
<td>5.01 ± 1.76</td>
<td>5.77 ± 2.05</td>
<td>5.67 ± 1.97</td>
<td>5.91 ± 2.17</td>
<td>5.47 ± 1.73</td>
<td>5.50 ± 1.50</td>
</tr>
<tr>
<td></td>
<td>Blood $[^{3}\text{H}]$glycerol radioactivity, dpm/ml</td>
<td>209 ± 67</td>
<td>217 ± 72</td>
<td>213 ± 67</td>
<td>226 ± 70</td>
<td>224 ± 71</td>
<td>265 ± 108</td>
<td>248 ± 98</td>
</tr>
<tr>
<td><strong>Artery</strong></td>
<td>Blood $[^{14}\text{C}]$glycerol concentration, μM</td>
<td>199 ± 45</td>
<td>120 ± 54</td>
<td>106 ± 42</td>
<td>116 ± 41</td>
<td>103 ± 39</td>
<td>120 ± 52</td>
<td>104 ± 43</td>
</tr>
</tbody>
</table>

Values are means ± SE.
Renal metabolism of lactate and glycerol. Both net uptake and total uptake of lactate by the kidney increased 3.3- to 3.5-fold during epinephrine infusion (both \( P < 0.001 \)); net uptake and total uptake of glycerol by the kidney both increased 1.2- to 1.4-fold. The increases in renal uptake of lactate and glycerol were wholly due to their increased renal delivery (RBF \( \times \) arterial concentration), since their renal fractional extraction remained unchanged (Table 2). Moreover, the proportion of lactate and glycerol taken up by the kidney that was converted to glucose increased 1.8- and 1.5-fold, respectively, during infusion of epinephrine (both \( P < 0.04 \)), indicating greater renal gluconeogenic efficiency.

Renal uptake of lactate and glycerol accounted for 26 \( \pm 3 \) and 41 \( \pm 4 \%), respectively, of their systemic uptake at baseline and remained unaltered during epinephrine infusion (27 \( \pm 3 \) and 44 \( \pm 7 \%), both \( P > 0.3 \)). Renal release of lactate and glycerol both accounted for a small proportion of their systemic release at baseline and during infusion of epinephrine (Table 2).

**DISCUSSION**

In a previous report (42), we found that in postabsorptive humans, epinephrine selectively increased gluconeogenesis from glutamine in the kidney and that from alanine in the liver but that gluconeogenesis from both of these precursors could account for only a small proportion of renal and hepatic glucose release under these conditions. In the present study, we evaluated the effects of epinephrine on systemic, hepatic, and renal gluconeogenesis from lactate and glycerol and assessed the mechanisms involved in the stimulation of renal gluconeogenesis. Both of these studies were performed under identical conditions [in fact, 5 of the 9 subjects in the present study had been included in our previous report (42)]. Consequently, combined analyses of the data of these studies allow estimation of the relative importance of each of these gluconeogenic precursors during stimulation of renal and hepatic gluconeogenesis by epinephrine in postabsorptive humans.

In the present studies, we found that infusion of epinephrine for 3 h, which resulted in plasma epinephrine levels similar to those observed during hypoglycemia, increased systemic gluconeogenesis from lactate \( \sim 4.8 \)-fold, so that it accounted for 70–75% of systemic glucose release during the last 60 min of the study. Gluconeogenesis from glycerol increased \( \sim 1.6 \)-fold and accounted for 5–10% of systemic glucose release during the same interval. In our previous report (42), systemic gluconeogenesis from glutamine and alanine increased \( \sim 1.7 \)- and \( \sim 3.2 \)-fold and accounted for \( \sim 6 \) and \( \sim 16 \)% of systemic glucose release, respectively, during the infusion of epinephrine (Fig. 5). The sum of gluconeogenesis...

**Table 2. Renal blood flow and renal net balance, fractional extraction, uptake, and release of lactate and glycerol at baseline and during infusion of epinephrine**

<table>
<thead>
<tr>
<th></th>
<th>Lactate (n = 6)</th>
<th>Glycerol (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow, ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1,594 ± 105</td>
<td>1,492 ± 176</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>1,422 ± 132</td>
<td>1,224 ± 207</td>
</tr>
<tr>
<td>P vs. baseline</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal net balance, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5 ± 0.3</td>
<td>0.88 ± 0.16</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>8.8 ± 0.9</td>
<td>1.03 ± 0.17</td>
</tr>
<tr>
<td>P vs. baseline</td>
<td>0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Fractional extraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26 ± 3</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>25 ± 2</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>P vs. baseline</td>
<td>&gt;0.8</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Renal uptake, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.1 ± 0.3</td>
<td>0.90 ± 0.15</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>10.3 ± 0.8</td>
<td>1.25 ± 0.20</td>
</tr>
<tr>
<td>P vs. baseline</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Renal release, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.61 ± 0.21</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>1.48 ± 0.64</td>
<td>0.22 ± 0.09</td>
</tr>
<tr>
<td>P vs. baseline</td>
<td>&gt;0.3</td>
<td>0.081</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of subjects. *Mean of last 2 time points during epinephrine infusion.
sis from these precursors could thus account for all of the increase in systemic glucose release stimulated by epinephrine, indicating that the main process by which sustained hyperepinephrinemia increases glucose release in humans is gluconeogenesis. In addition, these data indicate that lactate is by far the most important precursor for gluconeogenesis under these conditions; alanine seems to be the next important precursor, followed by glycerol and glutamine.

Our findings are consistent with the markedly increased lactate production and lactate gluconeogenesis by epinephrine previously shown in rats (27). In the present study in normal postabsorptive humans, infusion of epinephrine increased systemic lactate production 3.5-fold, so that arterial lactate concentrations averaged 2.2 mM during the last 60 min of the 3-h epinephrine infusion. In contrast, systemic glycerol release increased only 1.3-fold, so that arterial glycerol concentrations averaged 0.11 mM during the same interval. In our previous report (42), alanine concentrations remained unchanged, averaging 0.33 mM during the last 60 min of the 3-h epinephrine infusion, whereas glutamine concentrations decreased slightly to 0.58 mM. Because lactate and glycerol are transported through the circulation by whole blood whereas glutamine and alanine are transported through plasma (5, 9), the delivery of carbons from lactate to liver and kidney was about threefold greater than that from other substrates combined. These observations therefore support the concept that substrate delivery is largely responsible for the increased gluconeogenesis by epinephrine (7, 41). It should be pointed out, however, that increased supply of gluconeogenic substrates by exogenous infusion without concomitant hormonal changes does not normally increase endogenous glucose production and may not necessarily increase overall systemic gluconeogenesis in humans, although it probably alters the substrates used (2, 21, 22, 34, 43). It therefore appears that hyperepinephrinemia overcomes the autoregulation that prevents these increases during merely greater substrate availability.

In the present study, epinephrine increased gluconeogenesis from lactate and glycerol in both kidney (4.0 and 0.20 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) and liver (5.6 and 0.25 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)). By use of absolute rates of renal and hepatic gluconeogenesis from our previous (42) and the present studies, the sum of renal gluconeogenesis from lactate, glycerol, glutamine, and alanine increased by 4.7 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \); the corresponding increment for the liver was 7.2 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). Because gluconeogenesis from these precursors normally accounts for the vast majority of overall gluconeogenesis (32), it may be estimated that liver accounts for 60% and kidney for 40% of the increased systemic gluconeogenesis by epinephrine under the present experimental conditions.

With regard to the mechanisms responsible for the stimulation of renal gluconeogenesis by epinephrine, we found that increased renal uptake of lactate and glycerol and increased renal efficiency of their conversion to glucose were both involved. The increased renal uptake of lactate and glycerol was wholly accounted for by their increased arterial concentrations, since renal blood flow actually decreased and their renal fractional extraction remained unchanged.

We are unable to determine from the present studies whether the increased renal gluconeogenic efficiency was due to direct or indirect effects of epinephrine on the kidney. In vitro studies, in which substrate supply
is constant, have shown that epinephrine directly stimulates renal gluconeogenesis in animal species (18, 23, 26, 29, 35, 38); in contrast, Conjad et al. (11) recently reported that renal gluconeogenesis was unresponsive to direct stimulation by epinephrine in humans. Consequently, the increase in renal gluconeogenic efficiency that we found might have been indirectly mediated. Such a mediating factor might have been increased FFA concentrations, since FFA have been shown to augment the activities of renal gluconeogenic enzymes (3, 19, 24).

Consistent with the view that renal glucose release is normally exclusively due to gluconeogenesis, the combination of our data from the present and our previous report (42) indicates that the sum of renal gluconeogenesis from lactate, glycerol, glutamine, and alanine can account for all of renal glucose release during epinephrine infusion. It is of interest to note that these combined data also indicate that the sum of hepatic gluconeogenesis from these precursors can account for virtually all of hepatic glucose release at the end of the 180-min epinephrine infusion. Although one should interpret the data with caution, since gluconeogenesis from different precursors were determined in different subjects, our findings are in close agreement with those of previous net splanchnic balance measurements in dogs (10) and humans (39) under similar experimental conditions. In the latter study, the sum of net splanchnic uptake of lactate, alanine, and glycerol accounted for ~95% of net splanchnic glucose release during the last 15 min of a 90-min epinephrine infusion. Because net splanchnic glucose release had returned to baseline levels, the findings of that and our studies suggest that, in humans, hepatic glycogenolysis may be suppressed during prolonged epinephrine infusion. Possible explanations for the suppressed hepatic glycogenolysis include inhibition of hepatic glycogenolytic enzymes by increased insulin secretion/hyperglycemia, hepatic glycogen depletion, or hepatic autoregulation, i.e., reciprocal changes in hepatic glycogenolysis and gluconeogenesis.

In conclusion, our findings in postabsorptive humans indicate that, during hyperepiphenylenemia, 1) liver accounts for ~60% and kidney for 40% of the increased gluconeogenesis; 2) lactate is the principal gluconeogenic precursor for both liver and kidney; and 3) the increased renal gluconeogenesis is due to increased substrate availability and greater renal gluconeogenic efficiency.

We thank Becky Miller for excellent editorial assistance, and the nursing and laboratory staff of the General Clinical Research Center for superb help. We also thank Dr. Sreekumaran Nair for analyses of plasma [13C]glucose and [13C]lactate enrichments.

Current address of M. Stumvoll: University of Tübingen, 72076 Tübingen, Germany. Current address of H. J. Woerle: University of Munich, 81377 Munich, Germany.

DISCLOSURES

The present work was supported in part by Division of Research Resources-GCRC Grant 5M01 RR-00044, GCRC Grant RR-00585, and the National Institute of Diabetes and Digestive and Kidney Diseases Grant DR-20411. M. Stumvoll is currently supported by a Heisenberg grant from the Deutsche Forschungsgemeinschaft.

REFERENCES

15. Jensen T, Nurjhan N, Consolini A, and Gerich J. Failure of substrate-induced gluconeogenesis to increase overall glucose
appearance in normal humans. Demonstration of hepatic auto-

23. Kossar P and Saggerson ED. Evidence that catecholamines stimulate renal gluconeogenesis through an alpha1-type of ad-

24. Krebs H, Speake R, and Hems R. Acceleration of renal glu-


36. Nurjhan N, Kennedy F, Consoli A, Martin C, Miles J, and Gerich J. Quantification of the glycolytic origin of plasma gly-


38. Roobol A and Alleynge G. Regulation of renal gluconeogenesis by calcium ions, hormones and adenosine 3’5’-cyclic monophos-


7637, 1976.


47. Wolfe R. Radioactive and Stable Isotope Tracers in Biomedicine: Principles and Practice of Kinetic Analysis. New York: Wiley-
Liss, 1992.

48. World Health Organization Expert Committee. Second Rep-
port on Diabetes Mellitus. Geneva: WHO Technical Report Se-
ries, 1980.