Lactate delivery (not oxygen) limits hepatic gluconeogenesis when blood flow is reduced

Ken D. Sumida,1 Jerry H. Urdiales,2 and Casey M. Donovan2

1Chapman University, Department of Biological Sciences, Orange; and 2University of Southern California, Department of Kinesthetics, Los Angeles, California

Submitted 19 July 2004; accepted in final form 31 August 2005

Lactate delivery (not oxygen) limits hepatic gluconeogenesis when blood flow is reduced. Am J Physiol Endocrinol Metab 290: E192–E198, 2006. First published September 6, 2005; doi:10.1152/ajpendo.00319.2004.—The purpose of this study was to determine, using the isolated liver perfusion technique, whether the limiting factor for hepatic gluconeogenesis (GNG) from lactate was precursor delivery or oxygen availability during reduced flow rates of 0.85 or 0.60 ml·min−1·g liver−1. After a 24-h fast, three different experimental protocols were employed. Protocol 1 examined the impact on GNG when reservoir lactate concentration was maintained but oxygen delivery was elevated via increases in hematocrit (Hct). Elevating the Hct from 22.5 ± 0.8% to 30.9 ± 0.4% at a blood flow of 0.89 ± 0.01 ml·min−1·g liver−1 increased the oxygen consumption (VO2) but did not augment GNG. Similarly, when the Hct was elevated from 22.5 ± 0.8% to 41.5 ± 0.7% at 0.59 ± 0.04 ml·min−1·g liver−1, VO2 was increased, but GNG was unaffected. Protocol 2 examined the impact on GNG when Hct was maintained but precursor delivery was elevated via increases in reservoir lactate concentration ([LA]). Specifically, elevating the [LA] from 2.31 ± 0.07 to 3.61 ± 0.33 mM at a flow rate of 0.82 ± 0.04 ml·min−1·g liver−1 significantly increased GNG. Similarly, elevating the [LA] from 2.31 ± 0.07 to 4.24 ± 0.37 mM at a flow rate of 0.58 ± 0.02 ml·min−1·g liver−1 increased GNG. Finally, we examined the impact of increasing both the oxygen and lactate delivery (Protocol 3). Again, VO2 was elevated with increased oxygen delivery, but GNG was not augmented beyond that observed with elevations in lactate delivery alone, i.e., Protocol 2. The results indicate that, during decrements in blood flow, GNG is limited primarily by precursor delivery, not oxygen availability.

Using the isolated liver perfusion technique, we (21) recently reexamined the impact of blood flow restrictions on hepatic lactate uptake and GNG. In that study, both lactate uptake and GNG were observed to be robust over a wide range of flow rates, with substantial decrements occurring only when the flow fell below 1 ml·min−1·g liver−1. In this prior study, we could not determine whether precursor delivery or oxygen supply was the limiting factor that resulted in the eventual decline in hepatic GNG at flow rates below 1 ml·min−1·g liver−1. Iles et al. (8) provided an insight by elevating the lactate concentration (i.e., precursor delivery) at a single, low flow rate. They observed that the reduction in lactate uptake induced by the low flow was partially alleviated by the elevation in precursor availability, but glucose production and oxygen consumption (VO2) remained unaffected (8). To date, no study has fully dissociated substrate delivery from oxygen availability in examining the impact of reduced flow rates on hepatic GNG.

By use of the same preparation as our previous report (21), isolated rat livers were perfused with lactate (2.5 mM) and glucagon (250 μg/ml) at two distinct flow rates below 1 ml·min−1·g liver−1. With this model, we sought to distinguish between reductions in oxygen delivery and precursor delivery with respect to their impact on hepatic GNG at these low flow rates. To achieve this objective at low flow rates, we normalized oxygen delivery by adjusting the perfusate hematocrit (Hct) or precursor delivery by adjusting the lactate concentration. This approach allowed for an explicit examination of hepatic GNG where flow, precursor delivery, and oxygen availability could be specifically distinguished.

METHODS

Three sets of experiments (n = 5–6 per protocol) were conducted utilizing a total of 17 female Wistar rats (240–300 g). All animals were housed individually in a temperature-controlled room and maintained on a 12:12-h light-dark cycle with food and water provided ad libitum. Animals were fasted for 24 h before experiments to deplete liver glycogen stores, thereby minimizing glucose production from glycogenolysis.

Surgical isolation of the liver (20) and the perfusion chamber/apparatus has been previously described in detail (4). As before, all perfusions were single pass where the perfusion medium consisted of Krebs-Henseleit buffer with 25 mM sodium bicarbonate, dialyzed bovine serum albumin (30 g/l, fraction V, Sigma Chemical), 2.5 mM calcium chloride, and fresh bovine erythrocytes. The final Hct was 20%, and the pH was checked to ensure a range of 7.1–7.4. The perfusate was then separated into two reservoirs with the first reser-
Blood samples for blood pH/gas analysis (Radiometer BMS3 Mk2) adjustments in flow from the second reservoir during the experiment. Every 5 min between 0.04 ml

Vor containing only the perfusate medium with no added substrate, whereas lactate (2.5 mM), [U-14C]lactate (10,000 dpm/ml, ICN), and glucagon (250 μg/ml, Sigma) were added to the second reservoir. Both reservoirs were maintained at 37°C via a water bath.

After the surgical isolation, the flow was adjusted to ~2 ml·min⁻¹·g liver⁻¹ and a 30-min “washout” period was initiated using the first reservoir. Upon completion of the washout period, the perfusion was switched to the second reservoir with the appropriate flow adjustment and maintained for the next 30 min. At minute 45, after the reservoir switch and flow adjustment, blood samples were collected every 5 min up to minute 60 to establish steady-state GNG rates. At minute 60, the flow was again adjusted and maintained for the next 30 min. At minute 75, blood samples were again collected every 5 min between minutes 75 and 90. Thus each liver received two adjustments in flow from the second reservoir during the experiment. Blood samples for blood pH/gas analysis (Radiometer BMS3 Mk2) and 14CO2 evolution were collected every 15 min, whereas the Hct was determined every 20 min. After all perfusions, the liver was rapidly excised, weighed, freeze-clamped with aluminum tongs precooled in liquid nitrogen, and stored at −70°C for subsequent analysis.

**Protocol 1: Hct elevation.** To ascertain the impact of oxygen availability on GNG during flow rate reductions, we altered the oxygen delivery via elevations in the Hct. The experimental procedures were as described above, with the following modifications. At minute 30, additional erythrocytes were added to the second reservoir yielding a Hct of 30.9 ± 0.4% with the flow rate adjusted to 0.89 ± 0.01 ml·min⁻¹·g liver⁻¹. At minute 60, flow was decreased to 0.59 ± 0.04 ml·min⁻¹·g liver⁻¹, and additional erythrocytes were added to elevate the Hct to 41.5 ± 0.7%. Thus, in these experiments (n = 6), precursor delivery fell with reductions in flow rate, whereas oxygen delivery was relatively maintained via elevations in Hct.

**Protocol 2: lactate elevation.** To ascertain the impact of precursor delivery on GNG during flow rate reductions, we normalized the precursor delivery via elevations in lactate concentration. In this second set of experiments (n = 5), the perfuse flow was adjusted at minute 30 to 0.82 ± 0.04 ml·min⁻¹·g liver⁻¹ with the lactate concentration elevated to 3.61 ± 0.33 mM. At minute 60, the flow rate was decreased to 0.58 ± 0.02 ml·min⁻¹·g liver⁻¹ with the lactate concentration elevated further to 4.24 ± 0.37 mM. Thus, in these experiments, oxygen delivery fell with reductions in flow rate, whereas precursor delivery was largely maintained.

**Protocol 3: lactate elevation and Hct elevation.** To ascertain whether increasing the oxygen delivery might further augment gluconeogenesis during perfusions with elevated precursor concentrations, we superimposed the Hct elevations in Protocol 1 upon the increases in lactate concentrations in Protocol 2. In this final set of flow reduction experiments (n = 6), the perfuse flow was again adjusted at minute 30 to 0.85 ± 0.07 ml·min⁻¹·g liver⁻¹, with the lactate concentration elevated to 3.64 ± 0.20 mM and the Hct raised to 31.5 ± 0.5%. At minute 60, the flow rate was decreased to 0.59 ± 0.06 ml·min⁻¹·g liver⁻¹, however, the lactate concentration was elevated to 4.13 ± 0.17 mM, and the Hct was increased to 42.7 ± 0.9%.

**Chemical analyses.** Blood samples were collected in chilled test tubes containing sodium fluoride and heparin. A portion of the blood sample was centrifuged, and aliquots of the supernatant were taken for the analysis of alanine aminotransferase (ALT, EC 2.6.1.2) activity (16). The remaining blood sample was deproteinized in 8% perchloric acid and neutralized with potassium hydroxide (KOH). The supernatant was deproteinized in 8% perchloric acid and neutralized with potassium hydroxide (KOH). The supernatant was deproteinized in 8% perchloric acid and neutralized with potassium hydroxide (KOH).

---

**Table 1. Perfusate characteristics and indexes of liver integrity**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Relative Flow, ml/min · g liver⁻¹</th>
<th>Reservoir [LA], mM</th>
<th>Hct, %</th>
<th>Bile Production, ml</th>
<th>Blood pH</th>
<th>Tissue Water, %</th>
<th>Tissue Protein, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 6)</td>
<td>0.59 ± 0.04</td>
<td>2.66 ± 0.09</td>
<td>41.5 ± 0.7</td>
<td>0.55 ± 0.11</td>
<td>7.21 ± 0.01</td>
<td>71.7 ± 0.2</td>
<td>167 ± 8</td>
</tr>
<tr>
<td>2 (n = 5)</td>
<td>0.89 ± 0.01</td>
<td>2.58 ± 0.07</td>
<td>30.9 ± 0.4</td>
<td>0.55 ± 0.11</td>
<td>7.21 ± 0.01</td>
<td>71.7 ± 0.2</td>
<td>167 ± 8</td>
</tr>
<tr>
<td>3 (n = 6)</td>
<td>0.58 ± 0.02</td>
<td>4.24 ± 0.37</td>
<td>23.0 ± 0.5</td>
<td>0.64 ± 0.09</td>
<td>7.22 ± 0.01</td>
<td>71.4 ± 0.3</td>
<td>180 ± 8</td>
</tr>
<tr>
<td></td>
<td>0.82 ± 0.04</td>
<td>3.61 ± 0.33</td>
<td>23.0 ± 0.5</td>
<td>0.64 ± 0.09</td>
<td>7.21 ± 0.01</td>
<td>71.4 ± 0.3</td>
<td>180 ± 8</td>
</tr>
<tr>
<td></td>
<td>0.59 ± 0.06</td>
<td>4.13 ± 0.17</td>
<td>42.7 ± 0.9</td>
<td>0.67 ± 0.07</td>
<td>7.19 ± 0.02</td>
<td>71.9 ± 0.8</td>
<td>168 ± 13</td>
</tr>
<tr>
<td></td>
<td>0.85 ± 0.07</td>
<td>3.64 ± 0.20</td>
<td>31.5 ± 0.5</td>
<td>0.67 ± 0.07</td>
<td>7.19 ± 0.02</td>
<td>71.9 ± 0.8</td>
<td>168 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SE. [LA], lactate concentration; Hct, hematocrit. There were no significant differences in bile production, blood pH, tissue water, or tissue protein content between protocols.

---

**Fig. 1. Impact of elevating hematocrit (Hct) to 30.9 ± 0.4% at a flow rate of 0.89 ± 0.01 ml·min⁻¹·g liver⁻¹ and reservoir lactate concentration of 2.58 ± 0.07 mM (Protocol 1) vs. a Hct of 22.0 ± 0.8% at a flow rate of 0.86 ± 0.03 ml·min⁻¹·g liver⁻¹ and reservoir lactate concentration of 2.31 ± 0.07 mM (from Ref. 21) on hepatic gluconeogenesis (GNG), lactate uptake (LAup), O2 consumption (VO2), radioactive glucose production (14C-Glu), and radioactive CO2 production (14CO2). Note: flow rate and reservoir lactate concentration between Protocol 1 and those of our previous study were not significantly different, whereas Hct was significantly elevated (P < 0.05). Values are means ± SE. *Significant difference (P < 0.05).**
Fig. 2. Impact of elevating Hct to 41.5 ± 0.7% at a flow rate of 0.59 ± 0.04 ml·min⁻¹·g liver⁻¹ and reservoir lactate concentration of 2.66 ± 0.09 mM (Protocol 1) vs. Hct of 22.0 ± 0.8% at a flow rate of 0.59 ± 0.03 ml·min⁻¹·g liver⁻¹ and reservoir lactate concentration of 2.31 ± 0.07 mM (from Ref. 21) are depicted for comparison. Briefly, using the identical experimental protocol, we previously perfused livers from female Wistar rats (of the same age and weight as identified in the current study) with a reservoir lactate concentration of 2.31 ± 0.07 mM, a blood Hct of 22.0 ± 0.8%, and decrements in flow corresponding to 0.86 ± 0.04 ml·min⁻¹·g liver⁻¹. ANOVA was employed to analyze the impact of oxygen availability or lactate delivery on the dependent measures (e.g., GNG, VO₂, [¹⁴C]glucose production, and lactate uptake). Tukey’s post hoc analysis was used (where appropriate), and statistical significance was accepted at P < 0.05. All values are expressed as means ± SE.

Fig. 3. Impact of elevating reservoir lactate concentration to 3.61 ± 0.33 mM at a flow rate of 0.82 ± 0.04 ml·min⁻¹·g liver⁻¹ and Hct of 23.0 ± 0.5% (Protocol 2) vs. reservoir lactate concentration of 2.31 ± 0.07 mM at a flow rate of 0.86 ± 0.03 ml·min⁻¹·g liver⁻¹ and Hct of 22.0 ± 0.8% (from Ref. 21) on Hepatic GNG, LAlp, VO₂, [¹⁴C]Glu, and [¹⁴CO₂]. Note: flow rate and Hct between Protocol 2 and those of our previous study were not significantly different, whereas reservoir lactate concentration was significantly elevated (P < 0.05). Values are means ± SE. *Significant difference, P < 0.05.
ml·min⁻¹·g liver⁻¹. These flow rates were not significantly different from the flow rates examined in the current study. The purpose of this prior study was to examine the impact of flow rate reductions on hepatic lactate uptake and GNG. Maximal GNG, 0.88 ± 0.02 μmol·min⁻¹·g liver⁻¹, and VO₂, 2.97 ± 0.19 μmol·min⁻¹·g liver⁻¹, did not significantly differ when the flow rate was above 1 ml·min⁻¹·g liver⁻¹. However, as flow rates decreased to 0.86 ± 0.03 and 0.59 ± 0.03 ml·min⁻¹·g liver⁻¹, GNG, lactate uptake, [¹⁴C]glucose production, ¹⁴CO₂ evolution, and VO₂ fell proportionately. As such, these data will be depicted in the figures to aid in the comparison and interpretation with the current results.

Elevating only the Hct (Protocol 1) to 30.9 ± 0.4% at a flow rate of 0.89 ± 0.01 ml·min⁻¹·g liver⁻¹ or to 41.5 ± 0.7% at a flow rate of 0.59 ± 0.04 ml·min⁻¹·g liver⁻¹, resulted in VO₂ of 2.98 ± 0.24 and 2.96 ± 0.21 μmol·min⁻¹·g liver⁻¹, respectively. In our prior study (21), using a Hct of 30.8 ± 0.8% with the perfusate lactate concentration at 2.31 ± 0.07 mM, resulted in a GNG of 0.62 ± 0.04 and 0.45 ± 0.04 μmol·min⁻¹·g liver⁻¹ and a VO₂ of 2.02 ± 0.15 and 1.84 ± 0.10 μmol·min⁻¹·g liver⁻¹ at flow rate reductions of 0.86 ± 0.03 and 0.59 ± 0.03 ml·min⁻¹·g liver⁻¹, respectively. In the current study, the augmented VO₂ attributable to the elevation in Hct represents a 48 and 61% increase for the flow rates of 0.86 and 0.59 ml·min⁻¹·g liver⁻¹, respectively (Figs. 1 and 2).

Despite the elevation in VO₂, GNG was unaffected compared to those of our prior study (21) where the lactate concentration was significantly elevated (P < 0.05). Values are means ± SE. *Significant difference, P < 0.05.
to the enhanced precursor delivery, elevations were also observed for $[14C]$glucose production, lactate uptake, $14CO_2$ production and $VO_2$ (Figs. 3 and 4).

Simultaneous elevations in Hct with elevated lactate concentrations, i.e., Protocol 3, did not lead to any further increase in hepatic GNG compared with elevated lactate concentrations alone (Protocol 2). Elevating the Hct to 31.5 ± 0.5% but maintaining a lactate concentration of 3.64 ± 0.20 mM and a flow rate reduction of 0.85 ± 0.07 ml·min$^{-1}$·g liver$^{-1}$ did not significantly elevate GNG, 0.89 ± 0.05 μmol·min$^{-1}$·g liver$^{-1}$ compared with what we observed in Protocol 2. In like manner, elevating the Hct to 42.7 ± 0.9% but maintaining a lactate concentration of 4.13 ± 0.17 mM and a flow rate reduction of 0.59 ± 0.06 ml·min$^{-1}$·g liver$^{-1}$ did not significantly elevate GNG, 0.56 ± 0.04 μmol·min$^{-1}$·g liver$^{-1}$ As previously observed, the elevation in Hct increased the $VO_2$ at both flow rates without augmenting the $[14C]$glucose production, lactate uptake, or $14CO_2$ production (Figs. 5 and 6).

Final glycogen concentrations for all experiments were not significantly different from the final glycogen content observed after the washout period (Fig. 7). Under these conditions, the minimal glycogenolysis supports that the hepatic glucose production is primarily derived via GNG. In addition, when radioactive tracers are used to follow metabolic pathways, as performed in the current study, some of the tracer will inevitably be found in glycogen. However, the amount of $[14C]$lactate incorporation into $[14C]$glycogen, expressed as a percentage of $[14C]$lactate uptake, was 1.1 ± 0.2% and was not significantly different between experimental protocols. Thus glycogen was not a major source for glucose appearance, nor was it a primary source for lactate removal.

**DISCUSSION**

The current findings demonstrate that reductions in GNG from lactate, attributable to decrements in hepatic blood flow, are primarily due to compromised precursor delivery, not oxygen availability. At reduced flow rates of 0.85 and 0.60 ml·min$^{-1}$·g liver$^{-1}$, GNG decreased significantly. The observation that the measured rates of glucose production reflect GNG rates was confirmed by two lines of evidence, i.e., the lack of significant liver glycogenolysis during any experiment (Fig. 7) and the corresponding incorporation of $[14C]$lactate into $[14C]$glucose. When oxygen delivery was increased, normalizing $VO_2$ (Protocol 1), there was no impact on either GNG or $[14C]$glucose production (Figs. 1 and 2). In contrast, elevating precursor delivery (Protocol 2) led to significant increases in GNG (Figs. 3 and 4). The fact that oxygen delivery was not limiting for hepatic GNG under the current conditions was further confirmed when oxygen delivery was increased along with precursor delivery (Protocol 3). Although this led to an increase in $VO_2$, it had no impact on GNG or $[14C]$glucose production beyond what was observed with the increase in precursor delivery alone, i.e., Protocol 2 (Figs. 5 and 6).

Elevating the Hct augmented the oxygen delivery and resulted in significant increases in $VO_2$ (Figs. 1, 2, 5, and 6). However, the additional consumption of oxygen is apparently not obligatory for enhanced GNG. Under the current conditions, $VO_2$ appears well above what is required to sustain GNG alone, i.e., 2–3 times what is required for glucose synthesis. The site(s) responsible for the additional $VO_2$ remains to be elucidated. However, hepatic metabolism involves numerous other synthetic processes, such as ureagenesis, glutamine formation, and cholesterol synthesis. Furthermore, other cell types, such as nonparenchymal cells, Kupffer cells, and endo-
thelial cells, reside within the liver. Although not measured, these additional metabolic processes or other cell types could conceivably explain the extra oxygen consumed by the liver. Finally, the liver is abundant in extramitochondrial oxidase systems that may also contribute to the increased VO₂ with elevated oxygen delivery (18).

There are a limited number of studies that have attempted to distinguish the relationship between hepatic flow and hepatic function using the isolated liver perfusion technique. Keiding et al. (9) varied the flow and Hct in perfused rat livers using galactose elimination as the marker for metabolic function. At flow rates below 0.9 ml·min⁻¹·g liver⁻¹, they reported parallel reductions in both galactose elimination and oxygen uptake. Pastor et al. (14) isolated and perfused rat livers with glutamine at various flow rate reductions and examined oxygen supply dependence on urea production (their marker of liver function). They reported that urea production was dependent on both glutamine concentration and oxygen availability and becomes limited at the same critical oxygen delivery. Although we did not seek to examine other aspects of hepatic function beyond GNG, it is interesting to note that GNG can be augmented with increased precursor delivery at flow rates previously observed to suppress other hepatic functions. This observation suggests that the liver is capable of suppressing other functions to maintain glucose output (i.e., autoregulation). Consequently, the elevated use of one gluconeogenic precursor results in the attenuated use of another (12, 23), where the rate of hepatic glucose production via GNG is closely related to the rate of systemic glucose uptake.

We acknowledge that discretion needs to be exercised when extrapolating the current results to humans. From previous observations on exercising humans, elevating the precursor concentration via exogenous infusions did not increase hepatic GNG (12, 23). It is important to note that, under these moderate-intensity exercise conditions where hepatic blood flow and blood glucose concentration were not severely compromised, the liver is capable of regulating glucose output (i.e., autoregulation). Consequently, the elevated use of one gluconeogenic precursor results in the attenuated use of another (12, 23), where the rate of hepatic glucose production via GNG is closely related to the rate of systemic glucose uptake. However, autoregulation within the liver can be augmented when hepatic glycogen levels become depleted. McCraw et al. (11), using the liver perfusion technique on 24-h-fasted rats, demonstrated that hepatic gluconeogenic rates from lactate were elevated in the absence, compared with the presence, of glucose in the perfusate. Although hepatic autoregulation plays an important role to help resist hypoglycemia in the absence of significant blood flow limitations, our understanding of autoregulation during marked reductions in liver blood flow remain to be elucidated. Previous studies in both humans (13) and rats (21, 22) suggest that the liver can serve as a large reserve for lactate disposal during significant flow rate reductions, culminating in elevations in GNG. Collectively, the current results indicating that precursor delivery is the limiting factor for hepatic GNG during marked blood flow reductions suggest that the liver can increase its autoregulatory response. Specifically, under conditions where glucose is absent in the perfusate and liver glycogen is depleted, hepatic GNG appears to have priority over other hepatic functions. In support, elevating precursor delivery concomitantly augments hepatic GNG in the presence of compromised perfusion flows most likely attributable to a downregulation in some metabolic processes to upregulate glucose production. Admittedly, our use of a supra-physiological concentration of glucagon to stimulate hepatic GNG during flow rate reductions prevents a clear delineation between hormonal and nonhormonal responses in enhancing hepatic autoregulation. However, to the extent that our results can be applied to humans, it underscores the capacity of the liver to meet the systemic demands upon glucose and contribute to the prevention of severe hypoglycemia even in the presence of markedly reduced hepatic blood flows.

Although the perfusion of an isolated liver offers an invaluable technique in the investigation of hepatic function, the current results warrant some caution. It should be noted that the high PO₂ we used is above what is observed in vivo. Under these conditions it is possible that oxygen delivery was not adequately compromised. However, it has previously been demonstrated that the supply of oxygen could be limiting at oxygen tensions in the hepatic vein below 30 mmHg (24). Data from our prior report (Fig. 7 in Ref. 21) indicate that the venous oxygen tension was below 30 mmHg at flow rates lower than 1 ml·min⁻¹·g liver⁻¹. In addition, Iles et al. (7, 8), using the isolated liver perfusion preparation in rats, demonstrated a significant decline in oxygen uptake at low flow rates using a high PO₂ comparable to ours. Given all these factors, oxygen delivery appears to be sufficiently compromised in this preparation. Finally, as with all studies employing animal models, we cannot rule out the possibility that there may be species differences.

In summary, the current results support previous observations that decrements in flow eventually lead to a reduction in hepatic GNG (7, 8, 17, 21, 22). These findings further demonstrate that, in glucagon-stimulated perfused livers, it is the reduction in precursor delivery and not oxygen availability that limits GNG. Normalizing oxygen delivery via elevations in Hct, albeit resulting in significantly higher rates of VO₂, had no impact on hepatic glucose production. In contrast, normalizing precursor delivery at low flow rates led to a restoration of gluconeogenic rates despite a decrease in VO₂. Thus, in the presence of reduced hepatic blood flow, the liver can augment its autoregulatory response giving rise to a robust capacity for GNG to assist in the maintenance of euglycemia.

GRANTS

This study was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant no. DK-48000.

REFERENCES