Role of hepatic $\alpha$- and $\beta$-adrenergic receptor stimulation on hepatic glucose production during heavy exercise

ROBERT H. COKER, MAHESH G. KRISHNA, D. BROOKS LACY, DEANNA P. BRACY, AND DAVID H. WASSERMAN

Department of Molecular Physiology and Biophysics and Diabetes Research and Training Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Coker, Robert H., Mahesh G. Krishna, D. Brooks Lacy, Deanna P. Bracy, and David H. Wasserman. Role of hepatic $\alpha$- and $\beta$-adrenergic receptor stimulation on hepatic glucose production during heavy exercise. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E831–E838, 1997.—The role of catecholamines in the control of hepatic glucose production was studied during heavy exercise in dogs, using a technique to selectively block hepatic $\alpha$- and $\beta$-adrenergic receptors. Surgery was done >16 days before the study, at which time catheters were implanted in the carotid artery, portal vein, and hepatic vein for sampling and the portal vein and vena cava for infusions. In addition, flow probes were implanted on the portal vein and hepatic artery. Each study consisted of a 100-min equilibration, a 30-min basal, a 20-min heavy exercise (−85% of maximum heart rate), a 30-min recovery, and a 30-min adrenergic blockade test period. Either saline (control; $n = 7$) or $\alpha$ (phentolamine)- and $\beta$ (propranolol)-adrenergic blockers (Blk; $n = 6$) were infused in the portal vein. In both groups, epinephrine (Epi) and norepinephrine (NE) were infused in the portal vein during the blockade test period to create supraphysiological levels at the liver. Isotope ([3-3H]glucose) dilution and arteriovenous differences were used to assess hepatic function. Arterial Epi, NE, glucagon, and insulin levels were similar during exercise in both groups. Endogenous glucose production ($R_g$) rose similarly during exercise to $7.9 \pm 1.2$ and $7.5 \pm 2.0 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in control and Blk groups at time = 20 min. Net hepatic glucose output also rose to a similar rate in control and Blk groups with exercise. During the blockade test period, arterial plasma glucose and $R_g$ rose to $164 \pm 5 \text{ mg}\cdot\text{dl}^{-1}$ and $12.0 \pm 1.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively, but were essentially unchanged in Blk. The attenuated response to catecholamine infusion in Blk substantiates the effectiveness of the hepatic adrenergic blockade. In conclusion, these results show that direct hepatic adrenergic stimulation does not participate in the increase in $R_g$, even during the exaggerated sympathetically response to heavy exercise. Catecholamine, adrenergic blockade; endogenous glucose production.

The aim of this study was to examine the effect of the catecholamines on $R_g$ during heavy exercise, using a selective hepatic adrenergic receptor blockade technique that produces only minimal extrahepatic effects. This method utilizes the infusions of the $\alpha$- and $\beta$-adrenergic blockers, phentolamine and propranolol, respectively, into the hepatic portal vein of chronically catheterized and instrumented conscious dogs exercising at a high intensity.

METHODS

Animals and surgical procedures. Experiments were performed on a total of 13 overnight-fasted mongrel dogs (mean wt 21.5 ± 0.5 kg) of either sex that had been fed a standard diet (Pedigree beef dinner and Wayne Lab Blox; 51% carbohydrate, 31% protein, 11% fat, and 7% fiber based on dry wt). The dogs were housed in a facility that met American Association for the Accreditation of Laboratory Animal Care guidelines, and the protocols were approved by the Vanderbilt University Animal Care Subcommittee. At least 16 days before each experiment, a laparotomy was performed under general anesthesia (0.04 mg kg$^{-1}$ atropine and 15 mg kg$^{-1}$ pento-barbital sodium presurgery; 1.0% isoflurane inhalation anesthetic during surgery). An incision in the neck region allowed the isolation of the carotid artery, into which a Silastic catheter (0.04 in. ID) was inserted and advanced to the aortic arch for sampling and hemodynamic measurements during experiments. Silastic catheters (0.03 in. ID) were inserted into the vena cava for infusion of indocyanine green and [3-3H]glucose. Last, a Silastic catheter (0.03 in. ID) was inserted into the splenic vein and positioned so that the catheter tip rested just beyond the point where the splenic and portal veins coalesce. This catheter was used for the intraportal infusions of phentolamine and propranolol and the infusion of catecholamines during the final period of the...
steady state. After completion of the exercise period, the increased by 2.5-fold during the heavy exercise period to continued throughout the study. The tracer infusion rate was constant-rate indocyanine green infusion (0.1 mg·m⁻²·min⁻¹) which point it remained for the remainder of the study. A norepinephrine were infused into the portal vein at rates of 0.40 and 1.0 µg·kg⁻¹·min⁻¹, respectively, from t = 50 to 80 min.

All studies were conducted in dogs after an 18-h fast. The free catheter ends and flow probe leads were accessed through small skin incisions made under local anesthesia (2% lidocaine; Astra Pharmaceutical Products, Worcester, MA) in the abdominal and neck regions on the morning of the experiment. Catheters were then aspirated and flushed with saline. The exposed catheters were connected to Silastic tubing, which was secured to the back of the dog with quick-drying glue.

Experimental procedures. Experiments consisted of a tracer and dye equilibration period (-130 to -30 min), basal period (-30 to 0 min), heavy exercise period (0 to 20 min), recovery period (20 to 50 min), and catecholamine infusion period (50 to 80 min). A primed (50 µCi) infusion (0.30 µCi/min) of [³⁵S]glucose was initiated at time (t) = -130 min and continued throughout the study. The tracer infusion rate was increased by 2.5-fold during the heavy exercise period to minimize changes in glucose specific activity in the nonsteady state. After completion of the exercise period, the [³⁵S]glucose infusion rate was returned to the basal rate, at which point it remained for the remainder of the study. A constant-rate indocyanine green infusion (0.1 mg·m⁻²·min⁻¹) was also started at t = -130 min and continued throughout the study. Indocyanine green was used as a backup method of blood flow measurement if the Doppler probes did not provide a clear signal and as confirmation of hepatic vein catheter placement. There was no Doppler flow probe failure in these studies. Two protocols were performed (Fig. 1). In the blockade protocol, the α- and β-adrenergic receptor blockers, phentolamine and propranolol, were infused intraportally from t = -50 to 80 min at rates of 2 and 1 µg·kg⁻¹·min⁻¹, respectively. To test the effectiveness of the blockade, norepinephrine and epinephrine were infused at rates of 0.40 and 0.20 µg·kg⁻¹·min⁻¹, respectively, from t = 50 to 80 min. In the control protocol, animals were handled and prepared identically except that vehicle alone (saline and ascorbate) was infused. Heart rates were monitored by a transducer connected to the carotid arterial catheter.

Blood sample collection and processing. Arterial blood samples were drawn every 5 min during the basal period and at 1- and 2.5-min intervals during the first 5 and the last 15 min of heavy exercise, respectively. Arterial blood samples were drawn every 5 min during the recovery and blockade test periods. Portal vein and hepatic vein blood samples were drawn every 10 min during the basal period, every 5 min during the exercise period, at 10 and 30 min of the recovery period, and every 10 min during the blockade test period.

Plasma glucose concentrations were determined by the glucose oxidadase method, using a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). For the determination of plasma glucose radioactivity, samples were deproteinized with barium hydroxide and zinc sulfate and centrifuged. The supernatant was then evaporated to remove ³H₂O and reconstituted in 1 ml water and 10 ml scintillation fluid [Ecolite (+)-ICN Biomedical, Irvine, CA]. Radioactivity was determined on a Beckman liquid scintillation counter. Blood samples were deproteinized (0.5 ml blood in 1.5 ml of 4% perchloric acid), and whole blood lactate, alanine, and glyceral concentrations were determined, using standard enzymatic methods (13), on a Monarch 2000 Centrifugal Analyzer (Lexington, MA). Free fatty acids (FFA) were measured with the use of the Wako FFA C test kit (Wako Chemicals, Richmond, VA) on the centrifugal analyzer. Immunoreactive glucagon (3,500 mol wt) was measured in plasma samples containing 500 kallikrein inhibitory units (KIU)/ml Trasylol (FBA Pharmaceuticals, New York, NY), using a double-antibody system modified from the method developed by Morgan and Lazarow (17) for insulin. Plasma samples for norepinephrine and epinephrine were collected into tubes containing ethyleneglycol-bis(β-aminoethyl ether)-N,N,N',N''-tetraacetic acid and glutathione, centrifuged at 4°C, and stored at -70°C for subsequent analysis, using high-performance liquid chromatography. Catecholamine concentrations were calculated based on linear regression, using dihydroxybenzylamine as an internal standard. With the use of this method, the coefficients of variation were 5% and 7% for norepinephrine and epinephrine, respectively. Plasma cortisol was measured with the Clinical Assays Gamma Coat radioimmunoassay kit (Travenol-Gene Tech Diagnostics, Cambridge, MA) with an interassay coefficient of variation of 6%.

Materials. [³⁵S]Glucose was obtained from NEN (Boston, MA). Glucagon and ¹²⁵I-labeled glucagon were obtained from Novo Research Institute (Copenhagen, Denmark). Standard insulin and ¹²⁵I-labeled insulin were obtained from Linco Research (St. Louis, MO). Indocyanine green was purchased from Hynson, Westcott, and Dunning (Baltimore, MD). Enzymes and coenzymes for metabolite analyses were obtained from Boehringer Mannheim Biochemicals and Sigma Chemical.

Fig. 1. Heavy exercise protocol utilizing hepatic adrenergic blockade and control groups. *Epinephrine and norepinephrine were infused into the portal vein at rates of 0.20 and 0.40 µg·kg⁻¹·min⁻¹, respectively. **Isotope infusion was increased 2.5-fold during exercise [time (t) = 0–20 min]. ***Phentolamine and propranolol were infused into the portal vein at rates of 2 and 1 µg·kg⁻¹·min⁻¹, respectively, from t = -50 to 80 min.
Calculations. Net hepatic lactate balance (NHLB), net hepatic alanine uptake (NHAU), and net hepatic glucose output (NHGO) were determined according to the formula \( \text{HAF} \times ([A] - [H]) + \text{PVF} \times ([P] - [H]) \), such that [A], [P], and [H] are the arterial, portal vein, and hepatic vein substrate concentrations, and HAF and PVF are the hepatic artery and portal vein blood flows. Hematocrits were measured at each multiple catheter sampling point to correct for changes in red cell volume. The sign was reversed for the calculation of NHGO so that net output would be a positive number. Endogenous Ra was calculated, using the two-compartment approach described by Mari (14). Changes in specific activity were minimized during the exercise period by increasing the infusion rate of \( [3^{-3}] \)glucose by 2.5-fold to increase the accuracy of the Ra calculation (19).

Statistical analysis. Superanova (Abacus Concepts, Berkeley, CA) software installed on a Macintosh Power PC was used to perform statistical analysis. Statistical comparisons between groups and over time were made, using analysis of variance designed to account for repeated measures. Time points were specifically examined for significance, using contrasts solved by univariate repeated measures. Statistics are reported in the corresponding table or figure legend for each variable. Data are presented as means ± SE; n = 7 dogs for control and n = 6 dogs for blockade.

RESULTS

Arterial epinephrine and norepinephrine concentrations. Catecholamine values for five of the seven control experiments have been published previously (4). Plasma epinephrine rose (\( P < 0.05 \)) in control experiments from 165 ± 41 to 530 ± 100 pg/ml at 20 min of exercise. In the blockade group epinephrine levels were not different (\( P > 0.05 \)) from controls, increasing from 207 ± 27 to 495 ± 85 pg/ml at 20 min of exercise (Fig. 2). Plasma norepinephrine increased (\( P < 0.05 \)) from 416 ± 96 to 1,093 ± 182 pg/ml at 20 min of exercise in control experiments and from 365 ± 68 to 1,109 ± 258 pg/ml at 20 min of exercise in the blockade group (Fig. 2). There was no difference in the exercise response between groups. No significant differences were noted in plasma epinephrine or norepinephrine between the groups during recovery or the blockade test period.

Arterial insulin, glucagon, and cortisol concentrations. No significant differences in plasma insulin were noted between the two groups throughout the basal, exercise, or recovery periods. However, plasma insulin was significantly higher in the control group compared with the blockade group because of hyperglycemia during the blockade test period (Fig. 3). Plasma glucagon rose similarly in both groups during exercise and was not significantly different between groups throughout the remainder of the experiment (Fig. 3). Plasma cortisol was higher in the blockade group compared with the control group during the basal period (\( P < 0.05 \)). Otherwise, there was no significant difference between protocols (Table 1).

Arterial glucose concentration and kinetics. Arterial plasma glucose was similar in both control and blockade groups during the basal, exercise, and recovery periods. During the blockade test period, arterial plasma glucose was greater (\( P < 0.05 \)) in the control group (164 ± 5 mg/dl at t = 60 min) than the blockade group (126 ± 4 mg/dl at t = 60 min; Fig. 4). NHGO was also similar in both groups during the basal, exercise, and recovery periods. During the blockade test period, NHGO was greater (\( P < 0.05 \)) in the control group (8.5 ± 3.3 mg·kg\(^{-1}\)·min\(^{-1}\) at t = 60 min) compared with the blockade group (3.0 ± 0.9 mg·kg\(^{-1}\)·min\(^{-1}\) at t = 60 min; Fig. 4). Ra rose similarly from 3.1 ± 0.2 and 3.0 ± 0.2 mg·kg\(^{-1}\)·min\(^{-1}\) during the basal period to 7.9 ± 1.2 and 7.5 ± 2.0 mg·kg\(^{-1}\)·min\(^{-1}\) at 20 min of exercise in the control and blockade groups, respectively. Ra was also similar during the recovery periods. However, Ra was higher (\( P < 0.05 \)) during the blockade test period in the control group (10.9 ± 1.2 mg·kg\(^{-1}\)·min\(^{-1}\) at t = 60 min) compared with the blockade group (4.1 ± 0.3 mg·kg\(^{-1}\)·min\(^{-1}\) at t = 60 min; Fig. 5).

Arterial lactate concentrations and NHLB. Mean basal arterial lactate was less in the control group (478 ± 58 \( \mu \)mol/l) than in the blockade group (674 ± 150 \( \mu \)mol/l). Arterial lactate rose to a significantly greater level in the control group (1.315 ± 75 \( \mu \)mol/l at t = 20 min) than the blockade group (881 ± 84 \( \mu \)mol/l at t = 20 min) during the exercise period. Arterial lactate remained elevated (\( P < 0.05 \)) in the control group during the recovery period. Arterial levels during the blockade test period were not different between the two groups (Fig. 6). NHLB in both control and blockade groups shifted similarly from net uptake during the basal period to net output during exercise. NHLB was similar...
during the recovery and blockade test periods in the control and blockade groups (Fig. 6).

Arterial alanine concentrations and NHAU. Arterial alanine was higher in the control group at t = 30 min and during the recovery period (P < 0.05). No significant differences were present during the blockade test period between the two groups (Fig. 7). NHAU was less (P < 0.05) in the control group (1.4 ± 0.3 µmol·kg⁻¹·min⁻¹ at t = 20 min) than the blockade group (3.6 ± 0.7 µmol·kg⁻¹·min⁻¹ at t = 20 min) during exercise. No significant differences in NHAU were seen during the recovery or blockade test periods (Fig. 7).

Arterial FFA and glycerol concentrations. Arterial FFA was significantly higher in the blockade group at t = 20 min during the exercise period. Otherwise, both FFA and glycerol levels responded similarly in the two groups (Table 1).

Heart rate and blood flow. Heart rate increased by 118 ± 6 and 121 ± 3 beats/min at 20 min of exercise in the control and blockade groups, respectively (Fig. 8). Heart rate did not increase during the blockade test period in either group, indicating that splanchic escape of the catecholamines was minimal. Blood flow measurements for five of the seven control experiments

Table 1. Plasma cortisol and free fatty acids

<table>
<thead>
<tr>
<th>Time, min: Mean Basal</th>
<th>Exercise</th>
<th>Recovery</th>
<th>Blockade Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td><strong>Plasma cortisol, µg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.0 ± 0.5</td>
<td>5.0 ± 0.9</td>
<td>5.6 ± 1.0</td>
</tr>
<tr>
<td>Blockade</td>
<td>4.4 ± 0.7*</td>
<td>5.1 ± 0.7</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td><strong>Plasma free fatty acids, µeq/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>837 ± 128</td>
<td>658 ± 80</td>
<td>691 ± 77</td>
</tr>
<tr>
<td>Blockade</td>
<td>699 ± 95</td>
<td>659 ± 70</td>
<td>681 ± 83</td>
</tr>
<tr>
<td><strong>Blood glycerol, µmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>86 ± 10</td>
<td>147 ± 16</td>
<td>153 ± 16</td>
</tr>
<tr>
<td>Blockade</td>
<td>73 ± 11</td>
<td>122 ± 15</td>
<td>151 ± 24</td>
</tr>
</tbody>
</table>

Values are means ± SE for 7 control and 6 adrenergic blockade dogs. *Significantly different from control group (P < 0.05).
Hepatic artery blood flow was less \( (P < 0.05) \) in the control group \( (5 \pm 1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \) compared with the blockade group \( (11 \pm 1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \) during the basal period. Hepatic artery blood flow was also less \( (P < 0.05) \) during the recovery period in the control group. However, there was no significant difference in hepatic artery blood flow between the two groups during the exercise and blockade test periods (Table 2). In contrast, portal vein blood flow was higher \( (P < 0.05) \) in the control group compared with the blockade group during exercise and the blockade test period (Table 2). Total hepatic blood flow was not significantly different between the two groups during the course of the experiment.

**DISCUSSION**

The results of this study demonstrate that the exercise-induced increment in \( R_a \) is not critically dependent on adrenergic receptor stimulation during heavy exercise. The use of frequent sampling, arteriovenous difference techniques, and improved tracer methods coupled with local delivery of \( \alpha \)- and \( \beta \)-adrenergic blockers to the liver permitted a more precise assessment of the role of catecholamines during exercise. These findings in the dog support studies conducted in humans that
failed to show an effect of catecholamines on Ra during heavy exercise (11, 12, 24). The attenuation of sympathetic nerve activity to the liver and adrenal medulla, using celiac ganglion blockade during heavy exercise (~75% maximum oxygen uptake), did not affect Ra (11). In addition, liver transplant patients who are free of hepatic innervation have a normal Ra response to heavy exercise (~82% maximum oxygen uptake) (12).

Last, systemic infusion of a β-adrenergic blocker, propranolol, does not attenuate the rise in Ra during exercise at 100% of maximum oxygen uptake (V\textsubscript{O\textsubscript{2}} max) (24). The interpretation of these previous studies was complicated by the use of a patient population or by the nonspecific nature of the methods used to prevent hepatic adrenergic stimulation. The present study provides strong support for the assertion that catecholamine actions mediated through hepatic adrenergic receptors do not play an essential role in mediating the increase in Ra during heavy exercise. This conclusion is supported by a study in the adrenalectomized rat that showed that the breakdown of hepatic glycogen during high-intensity exercise was independent of epinephrine replacement (15).

Previous studies have shown that the fall in insulin and the increase in glucagon are the major determinants of the increase in Ra during moderate exercise (25). In the present study, heavy exercise resulted in similar arterial glucagon and insulin levels in both the control and blockade groups. It is important to recognize that the glucagon levels in the portal vein to which the liver is mainly exposed increase considerably more than those in the artery (26). It is noteworthy, however, that Ra still increases during cycling in humans in whom systemic glucagon and insulin were clamped at basal levels, using the pancreatic clamp technique (23). These investigators deduced indirectly from these studies that catecholamines must be important. This conclusion contrasts with results obtained when they tried to assess catecholamine action directly, using β-adrenergic blockade during heavy exercise.

The potential for the catecholamines to stimulate Ra is dependent on their levels at the liver. This is determined by catecholamine delivery via the circulation and/or sympathetic nerve activity (norepinephrine). The gut extracts ~50% of the plasma catecholamine concentration delivered to it by the blood during rest and heavy exercise (4). This results in portal vein levels that are ~50% of the arterial epinephrine levels. Plasma norepinephrine concentration in the portal vein remains comparable to arterial levels, despite gut norepinephrine extraction, because of sympathetic innervation of the gut and spillover of norepinephrine into the portal vein. In addition, marked increases in hepatic norepinephrine spillover during heavy exercise show that sympathetic drive to the liver is increased (4).

Even though norepinephrine levels at the liver are higher than epinephrine levels, the effectiveness of norepinephrine in stimulating adenylate cyclase is lower than that of epinephrine in the dog (5). Thus the reason that adrenergic stimulation is less effective in stimulating Ra during heavy exercise than has previously been postulated (16) is that arterial epinephrine levels overestimate those at the liver and norepinephrine is less effective compared with epinephrine in stimulating Ra.

The hepatic adrenergic blockade was designed to achieve completeness and selectivity. That the hepatic adrenergic blockade was virtually complete was shown by the attenuation of the rise in Ra in the blockade group during the portal vein infusion of catecholamines. Ra increased approximately threefold during the catecholamine infusion in the control group. In contrast, Ra was unchanged in the blockade group during the catecholamine infusion period. Other differences in the blockade and control groups (circulating glucose and insulin) are probably secondary to the higher Ra during the blockade test in controls. That the hepatic adrenergic receptor blockade was largely selective to the liver was demonstrated by similar glycerol and FFA responses during exercise in the present study. Local sympathetic nervous activity elicits fat mobilization (10), whereas the blockade of sympathetic nerves attenuates glycerol and FFA responses to heavy exercise (11). In addition, catecholamines have marked effects on pancreatic hormone secretion. The similar glucagon and insulin responses in both groups further support that the extrahepatic effects of the portal vein adrenergic blocker infusion are small. Peripheral α-adrenergic receptor blockade of the pancreas would increase insulin secretion, whereas β-adrenergic blockade would decrease insulin secretion (21, 22). In addition, an α- and/or β-adrenergic blockade would be expected to attenuate the increase in glucagon during exercise (22). Thus the local delivery of adrenergic blockers to the liver did not seem to affect pancreatic hormone secretion. The local nature of the hepatic blockade is also seen by the equal heart rate responses

---

**Table 2. Hemodynamic measurements**

<table>
<thead>
<tr>
<th>Time, min:</th>
<th>Mean Basal</th>
<th>Exercise</th>
<th>Recovery</th>
<th>Blockade Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Control</td>
<td>25 ± 2</td>
<td>20 ± 1</td>
<td>18 ± 0</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Blockade</td>
<td>20 ± 2</td>
<td>16 ± 1*</td>
<td>14 ± 2*</td>
<td>14 ± 1*</td>
</tr>
<tr>
<td>Control</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Blockade</td>
<td>11 ± 1*</td>
<td>9 ± 3</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE for 7 control and 6 adrenergic blockade dogs. *Significantly different from control group (P < 0.05).
to exercise in both groups, since blockade of β-adrenergic receptors by propranolol has been shown to decrease heart rate during exercise by 60% (1). Portal vein administration of adrenergic blockers localizes their action to the liver, and their efficient extraction by the liver reduces their systemic effects (9). In addition, the local irrigation of the liver with adrenergic blockers allows the infusion rate to be markedly reduced over that utilized during peripheral infusion. Therefore, it is likely that only small amounts of the adrenergic blockers are available to extrahepatic tissues.

Although the hepatic adrenergic blockade was far more selective than could be obtained by using conventional approaches, there was still evidence that there may be systemic effects of the blockers. During heavy exercise, arterial lactate was higher in the control group than the blockade group. Because net hepatic balance of lactate was similar in both groups, lactate formation must be reduced or lactate clearance must be greater in the blockade group at an extrahepatic site. β2-Adrenergic receptors mediate the epinephrine-stimulated increase in glycogenolysis and, by doing so, stimulate muscle lactate release (7). It may be that enough propranolol is escaping from the splanchnic bed to attenuate this response.

NHAU fell during heavy exercise in controls. This decrease may be due to a potent stimulation of hepatic glycogenolysis and glycolytic flux during short-term (27), high-intensity exercise. This could decrease NHAU by causing an opposing increase in alanine efflux from the liver. Evidence for an increase in hepatic glycolytic flux is seen by the parallel increase in net hepatic lactate output. It is unlikely that NHAU is decreased because of a direct stimulation of the A transport system, which mediates hepatic membrane alanine transport, since glucagon, its major endocrine agonist (2), is increased. A surprising finding was that hepatic adrenergic blockade prevented the fall in NHAU during heavy exercise. This implies that the fall in NHAU is mediated, in some way, by hepatic adrenergic stimulation. It is hard to relate this effect of adrenergic stimulation to an overall effect on hepatic glycogenolysis and glycolysis, since net hepatic glucose and lactate output responses were still intact. Regardless, it is unlikely that the net hepatic glucose and lactate output responses were still intact. Regardless, it is unlikely that the greater NHAU in the blockade group could have had a major effect on Ra by providing more substrate for the gluconeogenic pathway. This is because the increase in Ra during short-term exercise is due to an increase in hepatic glycogenolysis (25), and the additional carbon due to the differences in NHAU is small relative to the increment in Ra.

Another interesting finding was the increased basal arterial cortisol response in the blockade group compared with the control group. This difference was not present during exercise. The stimulatory effect of intraportal blocker administration on basal cortisol levels suggests that hepatic afferents may play a role in the regulation of cortisol secretion. It is unlikely that this increase in cortisol had a significant impact on the interpretation of this short study, since cortisol must remain elevated for a longer duration to have metabolic effects (8). Even if increased cortisol levels were studied over an extended time period, the relative importance would probably be minor, since the hormone serves to amplify the capacity for gluconeogenesis and glycogen synthesis, neither of which operates at high rates during heavy exercise. In addition to basal cortisol levels, blood flow distribution was also altered by intraportal blocker administration. Although the total hepatic blood flow was the same in the two groups, portal vein blood flow made up 82 and 63% of the total blood flow in the control and blockade groups, respectively. It is conceivable that the increased blood flow in the hepatic artery may be due to phentolamine entering the systemic circulation and the adrenergic blockade of α-receptors, which cause vasoconstriction. The decrease in portal vein blood flow may be compensatory for the increase in hepatic artery blood flow. It is important to recognize that the exercise-induced blood flow responses were similar in the two groups. The metabolic effects of this redistribution in blood flow, if any, will require further investigation.

The present study utilizes rapid arterial sampling, arteriovenous difference techniques, improved tracer methodology, and a selective hepatic adrenergic receptor blockade to determine the role of the catecholamines in control of hepatic glucose output during heavy exercise. The effectiveness of the adrenergic blockade was illustrated by the demonstration that the blockade eliminated the increases in Rα and NHGO resulting from a combined norepinephrine and epinephrine challenge. Minimal extrahepatic effects of the adrenergic blockade are supported by the similar insulin, glucagon, glycerol, FFA, and heart rate responses to heavy exercise in control and adrenergic blockade groups. In conclusion, under conditions in which glucagon, insulin, and plasma glucose levels are equal, the Rα and NHGO responses to heavy exercise are unaffected by hepatic adrenergic receptor blockade. This demonstrates that the catecholamines do not play an essential role in mediating the increase in Rα during heavy exercise.

We are grateful to Pamela Venson, Eric Allen, Wanda Snead, Robert Allison, and Thomas Becker for excellent technical assistance. This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant R01-DK-50277.

Address for reprints requests: R. H. Coker, Dept. of Molecular Physiology and Biophysics, Vanderbilt Univ. School of Medicine, Nashville, TN 37232.

Received 11 March 1997; accepted in final form 7 July 1997.

REFERENCES


