Effect of epinephrine on net lactate uptake by contracting skeletal muscle

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Hamann, Jason J., Kevin M. Kelley, and L. Bruce Gladden. Effect of epinephrine on net lactate uptake by contracting skeletal muscle. J Appl Physiol 91: 2635–2641, 2001.—The purpose of this study was to determine the effect of epinephrine on net lactate (La\(^{-}\)) uptake at constant elevated blood La\(^{-}\) concentration and steady level metabolic rate (O\(_2\) uptake) in the canine gastrocnemius-plantaris muscle in situ. Infusion of La\(^{-}\)/lactic acid (pH 3.5) established a mean arterial blood La\(^{-}\) concentration of \(\sim 10\) mM while normal blood-gas and pH status were maintained as the gastrocnemius-plantaris was stimulated with tetanic trains at a rate of one contraction every 4 s. After steady-state gastrocnemius-plantaris was stimulated with tetanic trains normal blood-gas and pH status were maintained as the lactate metabolism; exercise; β-blockade; canine

skeletal muscle is no longer viewed solely as a producer of lactate (La\(^{-}\)). Isotopic tracer studies (2, 23, 32, 43) have provided evidence indicating that both La\(^{-}\) release into and La\(^{-}\) removal from the blood by skeletal muscle are increased during exercise. In addition, reports have confirmed net La\(^{-}\) uptake by exercising skeletal muscle in humans (7, 32) with an elevated blood La\(^{-}\) concentration ([La\(^{-}\)], where brackets denote concentration). Studies of canine muscle in situ (10–13) have shown that, during both rest and contractions, an elevated blood [La\(^{-}\)] can reverse an initial net La\(^{-}\) output to net La\(^{-}\) uptake. It has also been observed that net La\(^{-}\) uptake by canine muscle in situ increases in proportion to arterial blood [La\(^{-}\)] (10–13, 29). Gladden et al. (12) have observed that increasing the plasma [La\(^{-}\)] causes net La\(^{-}\) uptake to approach a plateau in the high range of the [La\(^{-}\)] studied (\(\sim 20–30\) mM). In the same preparation, when net La\(^{-}\) uptake was measured during steady level conditions with an elevated blood [La\(^{-}\)] (\(\sim 10\) mM), increases in metabolic rate produced increases in net La\(^{-}\) uptake (10). These studies (10–13, 29), as well as others (2, 23, 32, 42, 43), support the idea that net La\(^{-}\) uptake by muscle is dependent on metabolic rate of the muscle and the blood [La\(^{-}\)].

In addition to blood [La\(^{-}\)] and muscle metabolic rate, it seems likely that circulating epinephrine could play a prominent role in determining the rate of La\(^{-}\) uptake by skeletal muscle. The stimulation of muscle glycogenolysis during exercise by epinephrine is supported by investigations utilizing adrenal demedullation (31, 33), epinephrine infusion (17, 37, 40), and β-blockade (4, 8). A consequence of enhanced muscle glycogenolysis is an increase in La\(^{-}\) production. Therefore, it is not surprising that net muscle La\(^{-}\) output, blood La\(^{-}\) rate of appearance, and perhaps La\(^{-}\) clearance, as well, are influenced by circulating epinephrine (3, 14, 17, 24, 39–41). In many instances, β-adrenergic-receptor blockade resulted in a decreased blood [La\(^{-}\)] as well as a decreased net La\(^{-}\) output by muscle (8, 18, 40). In support of these studies, which suggest a causal relationship between muscle and blood [La\(^{-}\)] and epinephrine-β-receptor interaction in exercising humans, high correlations between arterial [La\(^{-}\)] and [epinephrine] have been reported (21, 22, 24, 28). In fact, Mazzeo and Marshall (24) have even observed the inflection points of blood [La\(^{-}\)] and [epinephrine] to occur at the same exercise intensity.

There is clear evidence suggesting a relationship between circulating epinephrine and the production and output of La\(^{-}\) by skeletal muscle. The increasing blood La\(^{-}\) level in many of these studies merely indicates that entry into the blood exceeds removal. Given the importance of skeletal muscle in the removal of

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La\(^-\) during exercise, measurements investigating epinephrine and La\(^-\) uptake are warranted. Under conditions that engender skeletal muscle net La\(^-\) uptake, one could speculate that epinephrine will stimulate endogenous La\(^-\) production, resulting in inhibition of net La\(^-\) uptake. A reversal to net La\(^-\) output might even be possible. However, there have been no systematic investigations of the effect of epinephrine on net La\(^-\) uptake by skeletal muscle. Therefore, it was the purpose of the present investigation to examine the effect of epinephrine on net La\(^-\) uptake by contracting skeletal muscle.

**METHODS**

**Animals.** All procedures for this investigation involving animals were reviewed and approved by the Auburn University Institutional Animal Care and Use Committee. For this study, 12 mongrel dogs (14.5–25.0 kg) of either sex were obtained from the Auburn University Laboratory Animal Health Facility at the College of Veterinary Medicine.

Each animal was obtained after an overnight fast. The animal was anesthetized with pentobarbital sodium (30 mg/kg body wt iv injection), intubated, and transported to the laboratory. Additional doses of pentobarbital sodium were given as needed to maintain a deep surgical plane of anesthesia. The animals were ventilated with a respirator (model 613, Harvard Apparatus) to maintain normal blood-gas values. Rectal temperature was maintained at \(~37°C\) with a heating pad placed under the animal.

**Surgical procedure.** The left gastrocnemius-plantaris muscle group (GP) was surgically isolated, as previously described (10–13, 38). Briefly, a medial incision was made through the skin of the left hindlimb from the midthigh to the ankle. The insertion tendons of the sartorius, gracilis, semitendinosus, and semimembranosus muscles were cut with a heated blade (model D550, Weller) and folded back to expose the GP. All branches of the popliteal vein that did not come from the GP were ligated, and all venous connections from the GP that did not go directly to the popliteal vein were ligated as well. Therefore, all venous outflow (Q) from the GP was isolated to the popliteal vein. The popliteal vein was ligated as well. Therefore, all venous outflow (Q) from the GP was isolated to the popliteal vein. The popliteal vein was cannulated, and Q returned to the animal by means of a reservoir attached to a cannula in the left jugular vein. Q was directed from the cannula to the jugular reservoir by using a venous return line. Blood flow was measured with an inline type ultrasonic flow transducer (T106, Transonic Systems) placed in the venous return tubing. The flowmeter-transducer combination was calibrated with a graduated cylinder and a stopwatch before and during each experiment. Venous blood samples were taken from a T connector placed in the cannula exiting the left popliteal vein. In addition, to ensure vascular isolation, all branches of the popliteal artery that did not go directly into the GP were doubly tied and ligated. Thus arterial supply to the GP was exclusively by way of the popliteal artery.

The right femoral artery and vein were isolated by an inguinal incision. The right femoral artery was cannulated and connected to a pressure transducer (model RP-1500, Narco Biosystems); this line was also used to obtain arterial blood samples. The right femoral vein was cannulated, and the cannula terminated with a Y connector. This venous cannula provided the route for infusion of the La\(^-\)/lactic acid and epinephrine solutions. The La\(^-\)/lactic acid infusion consisted of a 725 mM L-(+)-lactic acid (2-hydroxypropionic acid, sarcotic acid) solution made by diluting a 30% aqueous solution (L-1875, Sigma Chemical) with deionized water. The pH of the infusion was adjusted to 3.5 at 37°C with saturated NaOH to maintain normal blood acid-base status during infusion (13). This solution was infused via a peristaltic pump (model 312, Gilson Minipuls 3) at a rate of 0.245 mmol·kg body wt\(^{-1}\)·min\(^{-1}\) for the first 10 min of infusion and then decreased to 0.133 mmol·kg body wt\(^{-1}\)·min\(^{-1}\) thereafter. Arterial [La\(^-\)] was monitored with a portable La\(^-\) analyzer (Accusport), and the infusion schedule was altered as necessary to maintain an elevated arterial whole blood concentration around 10 mM. The epinephrine infusion was made immediately before infusion by adding 1.5 mg active principle of epinephrine bitartrate (E-4375, Sigma Chemical) to a stock solution containing 60 ml of normal saline (NaCl 0.9 g/100 ml) with 2.0 mg/ml ascorbic acid (A-1417, Sigma Chemical) as an antioxidant. In all of the experiments, the same empirically determined epinephrine infusate schedule was used. The epinephrine solution was infused via a syringe pump (model 55–1111, Harvard Apparatus) at a rate of 0.32 μg·kg body wt\(^{-1}\)·min\(^{-1}\) for 30 s. After this period, the infusion rate was decreased to 0.15 μg·kg body wt\(^{-1}\)·min\(^{-1}\) for the remainder of the experiment. In 6 of the 12 experiments, propranolol (P-8688, Sigma Chemical) was dissolved in a normal saline solution and given in a bolus dose of 1.0 mg/kg body wt by way of the jugular cannula. Blood coagulation was prevented by intravenous heparin (2,000 U/kg) given through the jugular cannula immediately postsurgery before any cannulations.

A portion of the calcaneus, with the two tendons of the GP attached, was cut away for connection to an isometric myograph. The two tendons were clamped around a short metal rod and connected via a short section of aluminum pipe (29 mm diameter) and a universal joint coupler to the myograph load cell (interface SM-250, Narco Biosystems). The universal joint coupler was used to ensure that the muscle always pulled directly in line with the load cell, thus preventing the application of torque to the load cell. The load cell was calibrated with known weights before each experiment. The GP was covered with saline-soaked gauze and a thin piece of plastic to prevent drying and cooling. Both the femur and the tibia were fixed to the base of the myograph using bone nails and connecting rods. A turnbuckle strut was placed parallel to the muscle between the tibial bone nail and the arm of the myograph to minimize flexing of the myograph, which would decrease the measured force production. The sciatic nerve was exposed and isolated near the GP. The distal stump of the nerve, \(~1.5–3.0\) cm in length, was pulled through an epoxy electrode containing two wire loops for stimulation.

To evoke muscle contractions, the nerve was stimulated by supramaximal square-wave pulses of 4.0- to 6.0-V amplitude and 0.2-ms duration (Grass S48 stimulator) and isolated from ground by a stimulus isolator (Grass SIU8STB). Before each experiment, the GP was set to optimal length by progressively lengthening the muscle as it was stimulated at a rate of 0.2 Hz until a peak in developed tension (total minus resting tension) was observed. For the contraction protocol of the experiments, isometric tetanic contractions were evoked by stimulation with trains of stimuli (200-ms duration, 50-Hz frequency) at a rate of one contraction every 4 s. This contraction protocol was used to elevate metabolic rate to a steady level for a prolonged period of time.

**Experimental protocols.** Once surgical isolation of the GP was complete, all cannulas and equipment were in place, and optimal length was determined, the muscle was allowed to rest for a minimum of 10 min while blood gases and pH were measured. When these values were within normal limits, La\(^-\)/lactic acid infusion commenced. After an equilibration of the arterial [La\(^-\)] at \(~10\) mM, the GP was stimulated to...
contract submaximally until a steady state in oxygen consumption was reached and maintained for 15 min (total contraction period ~35 min; control). Subsequently, there was a 35-min period during which the [La−] was still maintained at ~10 mM and the muscle continued to contract, but epinephrine was also infused to reach an arterial level of ~3.5 ng/ml (Epi). Because epinephrine was determined to influence net La− uptake in the contracting GP, additional experiments were performed. These experiments were similar in all respects (time, infusion schedules, etc.) to the aforementioned experiments, except that propranolol was given in a bolus dose 10 min preceding the infusion of epinephrine (Pro).

Measurements. Outputs from the flowmeter, pressure transducer, and load cell were recorded on a strip chart recorder (Narcomat 40, Narco Biosystems) for monitoring and analysis. Additionally, output from the load cell was fed into a computerized data-acquisition system (PowerComputing Powerbase 240 Macintosh clone; GW Instruments, Superscope II; IntruNet model 100B A/D converter). Five and thirty minutes into each experimental period (control, Epi, and Pro), muscle force production was measured and averaged over 30 s. Heart rate was periodically monitored by using the arterial pressure tracing.

A minimum of three steady-state arterial and venous (a-v) samples, separated by 5 min, was collected no earlier than 20 min into the contraction protocol before epinephrine infusion. Steady state was defined as a variation in measured variables of <5% over a 5-min interval. During the 35-min contraction period with epinephrine infusion, simultaneous a-v samples were taken at 2, 5, 10, 15, 20, 25, 30, and 35 min after the first observable arterial pressure response to epinephrine. All blood samples were collected anaerobically in 3.0-ml plastic syringes. About 1.0 ml of blood was placed in a spot plate, and 0.4 ml were immediately transferred from the spot plate into each of duplicate test tubes containing 2.0 ml of ice-cold 4.2% perchloric acid. The tubes were vortexed and stored on ice until the end of the experiment. At the end of the experiment, the tubes were centrifuged at 4°C, and the supernatant from each sample was stored at ~80°C until analysis for [La−] by a modification of standard spectrophotometric methods (15).

After the 1.0 ml of blood was dispensed, as noted above, the syringe containing the remaining 2.0 ml of blood was capped and stored on ice for a short time before being analyzed for PO2, PCO2, and pH with a blood-gas analyzer (IL 1304). In addition, samples were analyzed for [Hb] and percent saturation of Hb with a calibrated CO-oximeter (IL 282) set for dog blood. Oxygen uptake (VO2) and net La− uptake by the GP were calculated from blood flows and a-v concentration differences.

An additional 1.5-ml arterial blood sample was collected during steady-state contractions before epinephrine infusion and at ~5 and ~30 min into epinephrine infusion. This sample was dispensed into a 1.5-ml Eppendorf tube containing 30 µl of a catecholamine preserving solution (250 mM EGTA; 200 mM reduced glutathione; sodium heparin, 30 U/ml blood), lightly vortexed, and centrifuged. The supernatant was transferred to Eppendorf tubes and stored at ~80°C for later analysis of plasma [epinephrine] and [norepinephrine]. [Epinephrine] and [norepinephrine] were determined by using the single-isotope derivative method (36). This method is based on quantitative conversion of epinephrine and norepinephrine to their labeled O-methyl derivatives, isolation of the derivative by solvent extraction, thin-layer chromatography, and oxidation to vanillin.

After each experiment, the muscle was removed from the animal, dissected free of connective tissue, and weighed. The muscle was then dried in an oven at 80°C to determine its percentage of water.

Statistics. Differences among the variables measured in this study were determined with a two-way (2 conditions × 9 sample times) ANOVA with repeated measures across time (0, 2, 5, 10, 15, 20, 25, 30, 35 min). Appropriate post hoc contrasts were used when necessary to determine where significant differences occurred. A significance level of 0.05 was used for all analyses in this investigation. Data are reported as means ± SE.

RESULTS

Table 1 shows mean values for major variables that were measured in the Epi as well as the Pro experiments. The mean control data for the two series of experiments were not different in terms of the major variables measured. There were no significant differences in VO2 between the two trials at any time. Although steady-state VO2 in Pro was numerically lower than in the other measures, the difference was not statistically significant.

In accordance with the experimental protocol, epinephrine infusion increased the arterial [epinephrine] in both Epi and Pro. The infusion of epinephrine in this investigation resulted in an increased arterial blood concentration of this amine that is on the high end of the physiological range observed in dogs exercising at moderate intensity (27). These values are also well within the range observed in exercising humans (24, 26) and rats (14, 25) in vivo. Five minutes into epinephrine infusion, the arterial concentration was elevated to 2,985 ± 949 and 3,570 ± 752 pg/ml for the Epi and Pro series, respectively. Steady-state arterial [epinephrine] in both trials were slightly but insignificantly higher than the 5-min values.

As planned, La− infusion resulted in an elevated arterial [La−] of ~10 mM in all experiments. During Epi, there was a slight but significant increase in the arterial [La−] over the course of the experiments. Despite this slight increase in arterial [La−], the a-v [La−] difference decreased significantly from the control to steady state. To the contrary, Pro resulted in a gradual rise in the a-v [La−], which became significantly greater than the control after 10 min of epinephrine infusion and remained elevated for the remainder of the experiment.

The blood flow response to epinephrine infusion as a function of time is shown in Fig. 1. Infusion of epinephrine during Epi resulted in a significant rise in Q˙, which reached a peak of 642.9 ± 37.7 ml·kg−1·min−1 5 min into the infusion. After 5 min of Epi, Q gradually declined to the elevated steady-state Q shown in Table 1. Conversely, Pro significantly decreased Q during epinephrine infusion. By the second minute of epinephrine infusion, Q had significantly decreased to 414.5 ± 28.5 ml·kg−1·min−1 from the control (544 ± 21 ml·kg−1·min−1) and continued to decline slowly to steady state.

As expected, La− infusion and the resulting increase in arterial [La−] elicited a large net La− uptake during
Table 1. Steady-state values for arterial blood gases, acid-base, resistance, flow rate, pressure, \([\text{La}^-]\), developed tension, \(\dot{V}_O_2\), (a-v)\(\text{Cl}_{\text{La}}\), and [catecholamine]

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Epi</th>
<th>Control</th>
<th>Pro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q, ml·kg(^{-1})·min(^{-1})</td>
<td>506 ± 13(^a)</td>
<td>585 ± 17(^b)</td>
<td>544 ± 21(^a)</td>
<td>373 ± 19</td>
</tr>
<tr>
<td>(P_{\text{aO}_2}), Torr</td>
<td>98 ± 4</td>
<td>98 ± 2</td>
<td>103 ± 4</td>
<td>107 ± 6</td>
</tr>
<tr>
<td>(C_{\text{aO}_2}), %vol</td>
<td>20.1 ± 0.9</td>
<td>22.8 ± 1.0</td>
<td>18.7 ± 0.8</td>
<td>19.7 ± 1.0</td>
</tr>
<tr>
<td>(P_{\text{aCO}_2}), Torr</td>
<td>38.3 ± 1.5</td>
<td>42.1 ± 1.2</td>
<td>38.9 ± 1.7</td>
<td>40.6 ± 1.9</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.01</td>
<td>7.39 ± 0.01</td>
<td>7.37 ± 0.03</td>
<td>7.40 ± 0.03</td>
</tr>
<tr>
<td>([\text{HCO}_3^-]), mM</td>
<td>22.9 ± 0.3*</td>
<td>24.9 ± 0.8</td>
<td>21.8 ± 1.0*</td>
<td>24.5 ± 1.0</td>
</tr>
<tr>
<td>Arterial pressure, Torr</td>
<td>143 ± 8</td>
<td>159 ± 11</td>
<td>144 ± 7*</td>
<td>180 ± 8</td>
</tr>
<tr>
<td>Resistance, PRU</td>
<td>0.286 ± 0.016</td>
<td>0.272 ± 0.013†</td>
<td>0.268 ± 0.012*</td>
<td>0.494 ± 0.027</td>
</tr>
<tr>
<td>Tension, kN/kg wet muscle</td>
<td>3.58 ± 0.13</td>
<td>3.38 ± 0.11</td>
<td>3.75 ± 0.43</td>
<td>3.20 ± 0.39</td>
</tr>
<tr>
<td>(\dot{V}_O_2), ml·kg(^{-1})·min(^{-1})</td>
<td>69.2 ± 5.4</td>
<td>68.8 ± 4.6</td>
<td>69.9 ± 6.7</td>
<td>60.1 ± 5.2</td>
</tr>
<tr>
<td>Arterial [(\text{La}^-)], mM</td>
<td>11.0 ± 0.4*</td>
<td>12.9 ± 0.5</td>
<td>10.0 ± 0.5</td>
<td>11.1 ± 0.9</td>
</tr>
<tr>
<td>(a-v)(\text{Cl}_{\text{La}}), mM</td>
<td>1.44 ± 0.08*</td>
<td>0.91 ± 0.06†</td>
<td>1.26 ± 0.07*</td>
<td>1.75 ± 0.07</td>
</tr>
<tr>
<td>Net (\text{La}^-) uptake, mmol·kg(^{-1})·min(^{-1})</td>
<td>0.756 ± 0.043*</td>
<td>0.527 ± 0.040</td>
<td>0.703 ± 0.061</td>
<td>0.658 ± 0.070</td>
</tr>
<tr>
<td>[Epinephrine], pg/ml</td>
<td>89 ± 33*</td>
<td>3,509 ± 1,026</td>
<td>62 ± 44*</td>
<td>3,895 ± 794</td>
</tr>
<tr>
<td>[Norepinephrine], pg/ml</td>
<td>121 ± 32</td>
<td>184 ± 48</td>
<td>89 ± 23*</td>
<td>178 ± 28</td>
</tr>
</tbody>
</table>

Values are means ± SE of \(n = 6\) dogs. Epi, epinephrine infusion without propranolol; Pro, epinephrine infusion following propranolol; Q, venous outflow; \(P_{\text{aO}_2}\), arterial \(P_{\text{O}_2}\); \(C_{\text{aO}_2}\), content of arterial \(O_2\); \(P_{\text{aCO}_2}\), arterial \(P_{\text{CO}_2}\); \([\text{La}^-]\), lactate concentration; PRU, peripheral resistance units (Torr·ml\(^{-1}\)·kg\(^{-1}\)·min\(^{-1}\)); (a-v)\(\text{Cl}_{\text{La}}\), arteriovenous lactate concentration difference; \(\dot{V}_O_2\), oxygen uptake. Brackets denote concentration. *Significant difference between Epi and its control and Pro and its control. †Significant difference between Epi steady state and Pro steady state.

The control net \(\text{La}^-\) uptake averaged 0.756 ± 0.043 and 0.703 ± 0.061 mmol·kg\(^{-1}\)·min\(^{-1}\) for Epi and Pro, respectively (Table 1). Net \(\text{La}^-\) uptake for both conditions as a function of time is depicted in Fig. 2. In the Epi series, epinephrine infusion resulted in a significant decrease in net \(\text{La}^-\) uptake compared with the control at all sample times. In the Pro series, epinephrine infusion had no significant effect on net \(\text{La}^-\) uptake compared with control conditions.

Figure 3 illustrates the change in net \(\text{La}^-\) uptake from the control values at every sample time for both Epi and Pro. The negative values indicate a decrease in net \(\text{La}^-\) uptake compared with control conditions. The change in net \(\text{La}^-\) uptake observed during Epi was significantly greater than the change observed during Pro for every sample time. Although the values are not significantly different, the change in net \(\text{La}^-\) uptake over the course of the Epi experiments suggests a trend toward the control net \(\text{La}^-\) uptake values. This visual trend of net \(\text{La}^-\) uptake during Epi is consistent with the work of Rennie et al. (30), which provides evidence...
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that suggests that phosphorylase activation at the onset of contractions is reversed with continued contractions and can be reactivated with epinephrine (adrenaline) infusion.

The percentage of muscle tissue that was water at the end of the experiments was similar to that found in previous studies in this preparation (10–12). Percentage of water averaged 75.8 ± 0.6 and 75.7 ± 0.5% after Epi and Pro, respectively.

DISCUSSION

The most significant finding of this investigation was that epinephrine infusion significantly inhibited net La− uptake in the contracting canine GP during exposure to an elevated arterial [La−]. In addition, propranolol given in a bolus dose before epinephrine infusion abolished the decrease in net La− uptake brought about by epinephrine infusion (Fig. 3). Because the effect of epinephrine infusion on net La− uptake could be abolished by prior administration of propranolol, it appears that the effect of epinephrine on net La− uptake is related to epinephrine-β-receptor interaction. To our knowledge, this is the first investigation to address directly the role of epinephrine on La− uptake by skeletal muscle and to provide evidence as to whether β-receptor activation mediates alterations in La− uptake by skeletal muscle caused by epinephrine.

There is no direct evidence with which to explain the observed decrease in net La− uptake due to Epi in this investigation. On the basis of previous research examining the effect of epinephrine on net La− output in canine GP (39–41), it is reasonable to suggest that the decrease in net La− uptake observed in this study was due to a mass action effect resulting from an increased rate of glycogenolysis and glycolysis and a concomitant increase in endogenous La− production. An increase in endogenous La− production would increase intramuscular [La−]. This increase in the intramuscular [La−], along with the associated decrease in pH, could inhibit La− transport into the muscle (9, 35). In addition, the elevated rate of glycogenolysis could lead to a decreased flux of La− to pyruvate through lactate dehydrogenase and decrease the ability of the muscle to metabolize exogenous La− once it is taken up. Previous studies investigating the role of epinephrine in skeletal muscle metabolism have provided evidence that epinephrine activates glycogenolysis (1, 31, 33, 37). A consequence of epinephrine-mediated enhancement of glycogenolysis is an increase in La− production and output by skeletal muscle. Furthermore, administration of a β-receptor blocking agent has been shown to attenuate the rate of La− production and output by skeletal muscle during contractions and exercise (8, 18, 40). These results support the above hypothesis.

An alternate postulate is that epinephrine might directly inhibit sarcolemmal La− transport, thereby decreasing net La− uptake. The major portion of La− transport across the muscle sarcolemmal membrane is facilitated by protein-linked monocarboxylate transporters. The monocarboxylate transporter displays typical saturation kinetics and has been characterized as being bidirectional, symmetrical, stereospecific, and facilitating flux along pH and concentration gradients (9, 34, 35). La− transport is, therefore, a potentially significant rate-controlling step in La− uptake. This has led to much debate as to whether La− transport, La− utilization by muscle, or a combination of both control La− uptake by skeletal muscle (9). Presently, there is no evidence with which to confirm or refute the idea that epinephrine may affect La− transport.

There are at least two notable limitations to the present study. First, there are no control data on resting muscle, and it is possible that other mechanisms, such as changes in [Ca2+], could alter La− transport and metabolism during contractions compared with rest. Second, muscle [La−] measurements before and after Epi would have been informative and might have been able to confirm our hypothesis of a mass action enhancement of endogenous La− production on net La− uptake. It should be noted, however, that a steady state of net La− uptake was essential for the purposes of this study. Our previous experience (unpublished observations) with this muscle preparation strongly suggests that the steady state of net La− uptake is very sensitive to manipulations such as biopsy sampling.

Other results of the present investigation support the notion that mean Q˙ is not typically an important factor in determining the rate of net La− uptake. Q˙ was significantly elevated above the control level by the second minute of the Epi experiments and peaked at a flow rate ~27% higher than the control 5 min into Epi before declining slightly to the steady-state value. The Epi steady-state Q˙ still remained significantly greater than the control Q. Despite this elevated Q, net La− uptake was significantly decreased at all sample times. In contrast, net La− uptake remained unchanged from the control values during the Pro experiments, even though flow rate was significantly decreased to ~66%
of the control flow by minute 2 of epinephrine infusion, and $Q$ continued to decline throughout the remainder of the trial. These findings are consistent with those of Gladden et al. (11), who observed no significant effect on net $La^-$ uptake when $Q$ was increased up to $\sim 165\%$ of the normal spontaneous blood flow in the isolated GP. Under these experimental conditions, it seems reasonable to conclude that mean blood flow, within the physiological range for this preparation, plays a minor role in determining net $La^-$ uptake. On the basis of the present investigation, as well as previous findings (9–12), it can be proposed that the changes in metabolic rate of the muscle, arterial $[La^-]$, membrane transport, and transmembrane pH gradient play a much more significant role than blood flow in regulating net $La^-$ uptake.

In the present study, if all of the $La^-$ taken up were oxidized as a fuel, the net $La^-$ uptake would have accounted for $74.5 \pm 0.1\%$ of the total $V_O^2$ during control conditions and $56.3 \pm 0.1\%$ during Epi steady state. During the Pro experiments, net $La^-$ uptake could have accounted for $69.8 \pm 0.1\%$ of the total $V_O^2$ during control conditions and $74.4 \pm 0.1\%$ during Pro steady state (for calculations, see Ref. 10). Recent experiments in our laboratory examining the metabolic fate of $La^-$ taken up by the contracting GP have provided evidence that $La^-$ oxidation is indeed the primary fate of $[14C]La^-$ submaximal contractions (\textasciitilde 20\% peak $V_O^2$ for this preparation); arterial $[La^-]$ was similar to the levels used in the present study (20). During this metabolic fate study (20), $La^-$ oxidation accounted for \textasciitilde 83\% of the $La^-$ that was taken up. Previous studies in dogs (5, 19), rats (6), and humans (16, 23) have also provided evidence that $La^-$ oxidation is prevalent during steady-state exercise. On the basis of this evidence and the calculations above, we assume that oxidation was the primary fate of $La^-$ taken up by the contracting GP in our experiments.

To assess the role of epinephrine-$\beta$-receptor interaction in the determination of net $La^-$ uptake, propranolol was administered in 6 of the 12 experiments in this investigation. As a marker of $\beta$-blockade, heart rate was monitored during the Pro experiments. The dose of propranolol given in this investigation resulted in a significant decrease in heart rate, from 165 $\pm$ 6 beats/min for control to 146 $\pm$ 6 beats/min after administration of propranolol. During Pro, epinephrine infusion had no effect on heart rate at any sample time. Along with the finding that propranolol abolished the decrease in net $La^-$ uptake observed during Epi, heart rate data suggest that full $\beta$-blockade was achieved by the administered dose of propranolol used in these experiments.

In conclusion, the results of the present investigation suggest that epinephrine has a profound effect on net $La^-$ uptake by contracting skeletal muscle in situ exposed to an elevated blood $[La^-]$. $\beta$-Adrenergic blockade via propranolol abolished the decrease in net $La^-$ uptake brought about by epinephrine infusion. Therefore, under the conditions studied in the present investigation (10 mM arterial $[La^-]$, high [epinephrine], and one tetanic contraction per 4 s), the evidence suggests that epinephrine reduces the ability of skeletal muscle to remove $La^-$ from the blood. Furthermore, the effect of epinephrine is apparently mediated by $\beta$-adrenergic receptors.

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