Red blood cell lactate transport in sickle disease and sickle cell trait

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**MATERIALS AND METHODS**

**Subjects.** Thirty African-American volunteer subjects were recruited from the University of Alabama at Birmingham (UAB) Comprehensive Sickle Cell Clinic, and surrounding communities in east-central Alabama. Institutional Review Boards of both Auburn University and UAB approved the study. All subjects provided informed consent and were then given a short screening questionnaire. Each group (HbAA, HbAS, and HbSS) consisted of 10 subjects.

**Isolation and preparation of RBCs.** A 20-gauge Vacutainer (Becton Dickinson) system was used to draw blood into two 7-ml heparinized tubes for lactate transport assays. Blood samples were obtained from superficial arm veins using sterile technique. Blood collected at sites away from the laboratory where analyses were performed was stored on ice and transported immediately to the analytical laboratory.

Volunteer subjects from the UAB Comprehensive Sickle Cell Center had previously been determined to have HbsS via gel electrophoresis. All blood samples were subjected to the Sickledex (Ortho Pharmaceuticals) test for HbsS. The Sickledex test served to confirm the presence of HbsS in the sickle cell and sickle cell trait samples and the absence of HbsS in blood samples from control subjects.

Techniques used in our laboratory for preparing RBCs and measuring lactate influx have been described in detail (44, 45). An initial hematocrit was determined for each blood sample (IEC Micro MB centrifuge). Two aliquots (3 ml each) of each blood sample were then centrifuged (1, 7, 13, 29–31). Recently, it has been proposed that *P. falciparum* likely encodes an unusual voltage-dependent ion channel, the plasmodial surface anion channel. It appears that plasmodial surface anion channel accounts for the increased permeability of infected RBCs to key solutes, including lactate (1).

Transport of lactate across the normal, uninfected erythrocyte membrane proceeds by three distinct pathways: 1) non-ionic diffusion of undissociated lactic acid; 2) the band 3 inorganic anion-exchange mechanism; and 3) the monocarboxylate transporter (MCT) pathway (16, 17, 41). In human RBCs, the majority of lactate exchange occurs via the MCT (15, 41). A family of 14 isoforms for the MCT has been identified (22). MCT 1 is the only isoform reported for RBCs (23, 28, 41), except in horse RBCs, where MCT 2 has also been detected (33).

These mechanisms of lactate transport across the membranes of RBCs from sickle cell disease (HbsS) and sickle cell trait (HbsAS) individuals have not been investigated. Therefore, the purposes of this study were to 1) determine the rate and mechanisms of lactate transport into HbsS RBCs and HbsAS RBCs, and 2) compare mechanisms of lactate transport in RBCs of persons with HbsS and HbsA with the mechanisms of lactate transport in a group of control subjects not possessing sickle cell Hb (HbAA).

**Red blood cell lactate transport in sickle disease and sickle cell trait.** *J Appl Physiol* 99: 822–827, 2005. First published May 12, 2005; doi:10.1152/japphysiol.00235.2005—This study determined and compared rates and mechanisms of lactate transport in red blood cells (RBCs) of persons with 1) sickle cell disease (HbsS), 2) sickle cell trait (HbsA), and 3) a control group (HbAA). Blood samples were drawn from 30 African-American volunteers (10 HbsS, 10 HbsA, 10 HbAA). Lactate influx into RBCs was measured by using [1-14C]lactate at six (2, 5, 10, 15, 25, and 40 mM) unlabeled lactate concentrations. The monocarboxylate transporter pathway was blocked by p-chloromercuribenzenesulfonic acid to determine its percent contribution to total lactate influx. Generally, total lactate influx into RBCs from the HbsS group was significantly greater than influx into RBCs from HbsA or HbAA, with no difference between HbsA and HbAA. Faster influx into HbSS RBCs was attributed to increased monocarboxylate transporter activity [increased apparent V_max (V_max) = 4.7 ± 0.6 mol·min⁻¹·ml⁻¹·Hb⁻¹] for HbSS RBCs was significantly greater than V_max of HbSS RBCs (2.9 ± 1.5 mol·min⁻¹·ml⁻¹·Hb⁻¹) and HbAA RBCs (2.0 ± 0.5 mol·min⁻¹·ml⁻¹·Hb⁻¹). K_m (42.8 ± 8 mM) for HbSS RBCs was significantly greater than K_m (27 ± 12 mM) for HbAA RBCs. We suspect that elevated erythropoietin levels in response to chronic anemia and/or pharmacological treatment (erythropoietin injections, hydroxyurea ingestion) is the underlying mechanism for increased lactate transport capacity in HbSS RBCs.

**Sickle cell disease is characterized by intense episodes of pain and hemolytic anemia.** In the United States, it is estimated to affect more than 50,000 persons, with prevalence of the common sickle cell disease variants in African-American live births at ~1 in 375 for sickle cell anemia, 1 in 835 for hemoglobin (Hb) SC disease, and 1 in 1,667 for the sickle β-thalassemia disorders. Approximately 8% of the US African-American population has sickle cell trait, i.e., blood with both normal (HbA) and sickle Hb (HbS) (43). This heterozygous condition for Hbs (HbAS) has been associated with an increased chance of survival following infection with the parasite that causes malaria, *Plasmodium falciparum* (2–4, 21). Malarial infections are believed to have applied selective pressure favoring perpetuation of the Hbs gene in areas where both conditions are endemic (2, 3). The malarial parasite is a homolactate fermenter and produces large quantities of lactic acid through glycolysis (13). The transport mechanisms of normal red blood cells (RBCs) cannot accommodate the quantities of lactic acid produced by the malarial parasite (13). Various alterations in the membranes of RBCs infected with the malarial parasite have been reported that serve to accommodate the metabolic processes of the parasite (1, 7, 13, 29–31). Recently, it has been proposed that *P. falciparum* likely encodes an unusual voltage-dependent ion channel, the plasmodial surface anion channel. It appears that plasmodial surface anion channel accounts for the increased permeability of infected RBCs to key solutes, including lactate (1).

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placed in two 50-ml conical tubes. Each of the two 3-ml blood aliquots was isolated, depleted of lactate, and washed in the same way.

After the final wash with chloride buffer, the RBC pellets from each of the blood sample aliquots were suspended separately in HEPES buffer (90 mM NaCl, 50 mM HEPES, pH 7.4 at 37°C, osmolality ≡ 267 mosmol/kg H2O) equivalent to 30% hematocrit (packed cell volume). The RBC pellet suspended in the HEPES buffer served as the stock RBCs used for influx measurements. One of the stock cell suspensions contained only HEPES buffer. The other stock cell suspension contained 1 mM p-chloromercuriureasulfonic acid (PCMBS) to block the MCT pathway (41). Both the HEPES buffer and the HEPES buffer with PCMBS were adjusted to a pH of 7.4 at 37°C. Hematocrits were determined for both stock cell suspensions for each subject and recorded for use in lactate influx calculations.

**Influx assay.** For each blood sample, the influx medium was prepared by pipetting 75 μl of HEPES buffer into 16 × 100-mm test tubes. The HEPES influx buffer contained [14C]lactate in six unlabeled lactate concentrations ([La^-]; 2, 5, 10, 15, 25, and 40 mM). The RBC stock solutions were exposed to two treatments: 1) HEPES buffer with no blocker to determine total lactate influx, and 2) HEPES buffer plus PCMBS to block the MCT pathway. Test tubes containing the influx medium were covered with Parafilm and stored briefly in a 37°C water bath in preparation for the influx assays.

Twenty-five microliters of the stock RBC suspension (washed, lactate depleted, 30% hematocrit) were added to a 16 × 100-mm test tube containing 75 μl of the HEPES buffer at 37°C. The test tubes were shaken gently by hand for 20 s in the 37°C water bath. The 20-s time interval lies within the phase of linear influx for lactate (14, 44). After 20 s, 5 ml of ice-cold stop solution, MES (150 mM NaCl, 10 mM MES, pH 6.5 at 0°C), were added to each test tube to terminate lactate influx. The test tubes containing RBC suspension, lactate influx medium, and the stop solution were maintained briefly in an ice bath and then centrifuged (4°C, 5 min, 2,000 g). After centrifugation, the supernatant was aspirated, and an additional 5 ml of stop solution (pH 6.5 at 0°C) were added to the RBC pellet. The RBC pellet and stop solution were then centrifuged as above (4°C, 5 min, 2,000 g). Following this second centrifugation, the supernatant was aspirated, and then 0.5 ml of ice-cold 4.2% perchloric acid (HClO4) was added to the RBC pellet to lyse and deproteinize the RBCs. The RBC pellet and perchloric acid were then centrifuged for 5 min (4°C, 2,000 g). Following the final centrifugation, a 0.4-ml sample of supernatant was removed from the deproteinized sample and pipetted into a 10-ml plastic Fisher brand disposable scintillation vial. Five milliliters of water (pH 6.5 at 0°C) were added to the RBC pellet and then 0.5 ml of ice-cold 4.2% perchloric acid (HClO4) was added to the RBC pellet to lyse and deproteinize the RBCs. The RBC pellet and perchloric acid were then centrifuged for 5 min (4°C, 2,000 g). Following the final centrifugation, a 0.4-ml sample of supernatant was removed from the deproteinized sample and pipetted into a 10-ml plastic Fisher brand disposable scintillation vial. Five milliliters of aqueous scintillation fluid (Fisher Scintiverse BD) were then added to the plastic scintillation vials containing the supernatant from the deproteinized samples. The vials containing supernatant were analyzed for [14C]lactate activity in a liquid scintillation counter (Wallac 1515 Winspectral).

In each condition, blank control samples were used to correct for 1) any extracellular radioactivity that might have remained in the RBC pellet after addition of the second stop solution, and 2) transmembrane lactate exchange that may have occurred, despite addition of the stop solution. Standard samples were also prepared in triplicate for each [La^-].

**Calculation of lactate influx.** Measurements of total lactate influx and influx into PCMBs-treated cells were determined for the RBCs from each group (HbAA, HbAS, and HbSS) at all six [La^-] values (2, 5, 10, 15, 25, and 40 mM). All samples were run in triplicate. In all cases, the two measurements closest in value for each specific sample were averaged to determine lactate influx. The aliquot of RBCs in HEPES buffer with no blockers was used to determine total lactate influx. The cells suspended in HEPES buffer containing PCMBs to block the MCT pathway served to estimate the contribution of nonionic diffusion and the band 3 system to lactate influx. The activity of the MCT pathway was calculated by subtracting influx in the presence of PCMBs from total lactate influx at the varying [La^-] values.

Micromoles of lactate influx per milliliter of RBCs per minute were calculated (μmol·ml^-1·min^-1). A packed RBC volume was calculated by multiplying the percent hematocrit of the cell suspension by the 25-μl volume of RBCs. Because the PCMBs treatment inhibited the MCT pathway, influx into the PCMBs-treated RBCs is the sum of lactate transport by the band 3 pathway and nonionic diffusion. Total lactate influx minus influx in the PCMBs-treated cells represents influx via the MCT pathway.

**Statistical analysis.** Lactate influx values ± SE were calculated for each subject under the two treatment conditions (with and without MCT blocker). Mean lactate influx values ± SE were calculated for each of the three groups. Influx values for the MCT pathway were fitted to the Michaelis-Menten equation to determine apparent Vmax (Vmax) and Km for each subject. Mean Vmax and Km values were then determined for each group. All statistical analyses were standard repeated-measures ANOVA performed using SuperANOVA (Abacus Concepts, Berkeley, CA). Pairwise contrasts were used when necessary to determine where significant differences occurred. In all cases, the level of significance was set at the 0.05 level. Linear and curvilinear regression analyses were applied where appropriate using KaleidaGraph software (Synergy Software, Reading, PA).

**RESULTS**

Blood samples were obtained from a total of 30 African-American subjects. Demographic data for the three groups [control (HbAA), sickle cell trait (HbAS), and sickle cell disease (HbSS)] are reported in Table 1.

**Total lactate influx.** Total lactate influx values for RBCs from each of the three groups is shown in Fig. 1A. In general, total lactate influx into HbSS RBCs was significantly faster than influx into either HbAA or HbAS RBCs. The sickle cell group (HbSS) exhibited a significantly faster rate of influx than both of the other groups at 10, 25, and 40 mM [La^-]. Also, at 5 mM [La^-], total lactate influx into HbSS RBCs was significantly faster than total lactate influx into HbAA RBCs. RBCs from the control group (HbAA) and the sickle cell trait group (HbAS) showed no statistically significant differences in total lactate influx at any of [La^-] values tested.

**Influx via the MCT pathway.** Lactate influx via the MCT pathway into HbSS RBCs was significantly greater than lactate influx via this pathway into either HbAA or HbAS RBCs at all [La^-] values except 2 mM. Lactate influx via the MCT pathway into HbAA RBCs and HbAS RBCs did not differ significantly. Lactate influx values through the MCT pathway for all groups are shown in Fig. 1B.

As illustrated in Fig. 1C, none of the RBC groups showed a significant difference in lactate influx values attributable to diffusion and band 3 at any [La^-] tested.

Values for MCT influx were divided by total influx values to calculate the percent contribution of the MCT carrier to total lactate influx. HbSS RBCs showed a greater percentage of...

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<td>All groups</td>
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Values are means ± SE; n, no. of subjects. HbAA, control group; HbAS, sickle cell trait group; HbSS, sickle cell disease group; Hct, hematocrit. *HbSS is significantly different from both HbAA and HbAS, P < 0.05.
Fig. 1. Lactate influx into red blood cells (RBCs) in micromoles of lactate per milliliter of RBCs per minute (μmol·ml⁻¹·min⁻¹) plotted as a function of external lactate concentration (mM). A: total lactate influx; B: lactate influx via monocarboxylate transporter (MCT); C: lactate influx via diffusion plus band 3 [La⁻], lactate concentration; HbSS, sickle cell disease group; HbAS, sickle cell trait group; HbAA, control group. *HbSS significantly greater than both HbAS and HbAA; †HbSS significantly greater than HbAA only: P < 0.05.

Fig. 2. Lactate influx via the MCT as a percentage of total lactate influx, plotted as a function of external [La⁻] (mM). *HbSS significantly greater than both HbAS and HbAA; †HbSS significantly greater than HbAA only: P < 0.05.

maximum rate of lactate influx in μmol·ml⁻¹·min⁻¹) and $K_m$ (the estimated [La⁻] at which one-half of $V_{max}$ is reached) are shown in Table 2. The $K_m$ for HbSS RBCs (42 ± 8 mM) was significantly greater than the $K_m$ for HbAA RBCs (27 ± 12 mM). The $V_{max}$ for HbSS RBCs (4.7 ± 0.6 μmol·ml⁻¹·min⁻¹) was significantly greater than the $V_{max}$ for both the HbAA (2.0 ± 0.5 μmol·ml⁻¹·min⁻¹) and HbAS RBCs (2.9 ± 1.5 μmol·ml⁻¹·min⁻¹).

**DISCUSSION**

Major findings. The two most important findings of this study were that 1) total lactate influx was significantly greater into RBCs from persons with sickle cell disease (HbSS) at various [La⁻] values (5, 10, 25, and 40 mM) than into RBCs from persons with HbAS or HbAA; and 2) the increase in total lactate influx could be attributed to transport via the MCT pathway. $V_{max}$ and $K_m$ for the MCT pathway were also greater in HbSS RBCs. Differences in lactate influx were restricted to the MCT pathway and not evident in combined transport through the band 3 anion-exchange system and nonionic diffusion pathways. No differences were noted in total lactate influx or influx through the MCT pathway between RBCs from subjects with HbAS vs. HbAA.

$V_{max}$ and $K_m$. The increased $V_{max}$ seen in the HbSS RBCs indicates either an increased activity for the MCT carriers on the erythrocyte membranes or an increase in the number of MCT carriers. Unfortunately, we did not quantify MCT 1 proteins via Western blotting analysis, so we cannot clearly distinguish between these possibilities. Furthermore, the higher $K_m$ for lactate transport via the MCT pathway in

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<th>Group</th>
<th>$K_m$ (mM)</th>
<th>$V_{max}$ (μmol·ml⁻¹·min⁻¹)</th>
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<tr>
<td>HbAA</td>
<td>27 ± 12</td>
<td>2.0 ± 0.5</td>
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<tr>
<td>HbAS</td>
<td>34 ± 12</td>
<td>2.9 ± 1.5</td>
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<tr>
<td>HbSS</td>
<td>42 ± 8*†</td>
<td>4.7 ± 0.6*†</td>
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Values are means ± SE. Units for $K_m$ are lactate concentration in millimolar (mM); for apparent $V_{max}$ ($V_{max}$), micromoles of lactate influx per milliliter of red blood cells per minute (μmol·ml⁻¹·min⁻¹). *HbSS is significantly different from HbAA; †HbSS is significantly different from HbAS: P < 0.05.
HbSS RBCs (42 ± 8 mM) indicates that the MCT carrier has a decreased affinity for lactate in RBCs of these subjects. We offer three possibilities relative to these \( V_{\text{max}} \) and \( K_m \) results; they are not mutually exclusive. First, there could be an increase in the density of MCT 1 carriers in the HbSS RBC membrane. Second, perhaps other MCT isoforms were expressed in the membrane. For example, MCT 4 is reported to have a lower affinity for lactate than does MCT 1 in skeletal muscle (27). However, this seems an unlikely explanation. Although we did not confirm that MCT 1 was the only isoform in the RBCs of our subjects, it is the only isoform that has been detected in RBCs (23, 28, 41), except in horse RBCs, where MCT 2 has also been found (33). A third possibility is an increase in membrane content of the glycoprotein CD147. CD147 (neurothelin) has been shown to colocalize with MCT 1 in isolated heart cells, and it has been suggested that it might play a role in regulation of MCT activity, either by directly affecting MCT catalytic activity or by regulating the translocation of MCT to the membrane (23, 32).

Possible mechanisms for changes in lactate transport in HbSS RBCs. Our data generate the question: Why does sickle cell disease (HbSS) lead to an increase in \( V_{\text{max}} \) and \( K_m \) for the MCT pathway in RBCs? Without specific data to answer the question, we can only speculate. We do not know if the increased activity of the MCT in RBCs of persons with sickle cell disease is an inherited characteristic or if the MCT activity increases as a result of stimuli related to the chronic anemia of sickle cell disease. Persons born with HbSS do not suffer the consequences of sickle cell disease during the first year or so of life (9, 12). Fetal Hb (HbF) has a high affinity for oxygen, and it is in a high concentration in RBCs during this time (8, 40). There are no studies examining lactate transport mechanisms in RBCs containing HbF. When the majority of HbF is depleted, persons with sickle cell disease begin to experience the symptoms and complications of chronic anemia related to HbSS.

The presence of HbSS along with the requisite physiological stressors, such as hypoxemia (42), vasoocclusion, increased RBC hemolysis, or metabolic alterations experienced by persons with sickle cell disease, may serve as stimuli for increasing MCT proteins as well as changing their affinity for lactate. Hypoxemia in particular is a favorable candidate. During residence at an altitude of 4,100 m, Danish lowlanders demonstrated threefold and fivefold increases in MCT 1 expression in their RBCs after 2 and 8 wk, respectively (28). Lactate flux across the RBC membrane was not measured (28); this is an important point as there is recent evidence (in horse RBCs) that MCT expression does not necessarily correlate with lactate transport activity (33). However, further evidence of a stimulatory effect of hypoxemia comes from a study of RBC lactate influx in endurance-trained subjects who experienced exercise-induced hypoxemia (EIH) vs. those who did not. Both total lactate influx and MCT-mediated influx were significantly greater in RBCs from EIH vs. non-EIH subjects at 8.1 and 41 mM [La\(^-\)] values (10). Erythropoietin (EPO) may be the underlying factor that enhances lactate transport changes in RBCs of humans exposed to hypoxemia. RBC total and MCT-mediated lactate influxes were significantly increased at [La\(^-\)] of 1.6, 41, and 81.1 mM in nine endurance-trained athletes receiving subcutaneous recombinant human EPO (50 U/kg, ~3,500 units) three times a week for 4 wk (11). The \( K_m \) for lactate influx was unchanged by the EPO injections (11) and was not measured in the study of EIH (10).

Additional provocative evidence for a hypoxemia/EPO connection to enhanced RBC lactate transport is offered by studies of EPO levels in HbSS patients. In the absence of any kind of treatment other than folic acid supplementation, HbSS patients were found to have serum EPO levels that were, on the average, 10 times greater (87 mLU/ml) than those of HbAA control subjects (8.2 mLU/ml) (18). Furthermore, one of our HbSS subjects was receiving EPO injections (20,000 units subcutaneously, two times per week) and another two of our 10 HbSS subjects were undergoing hydroxyurea treatment. In a study of 13 patients with various forms of sickle cell disease, hydroxyurea treatment (1.5 g/day over 7 days/wk) induced increases in serum EPO ranging from 3 to 31 times the basal level (38). In particular, three HbSS patients experienced serum EPO increases from a basal range of 90–284 mLU/ml to a treatment range of 200–1,151 mLU/ml (38). All of this suggests that our HbSS subjects likely had elevated EPO levels.

EPO presumably initiates an increased membrane density of MCT 1, but the mechanism is unknown. Although there are no studies of MCT 1 in this regard, it has been reported that the synthesis of several RBC membrane proteins is dependent on EPO (34, 46, 47). Accordingly, there could be an increased incorporation of transporter proteins during the formation of erythrocytes (28). Because young erythrocytes (reticulocytes) have a higher protein density than mature erythrocytes (19, 39), another possibility is that EPO results in a higher proportion of young erythrocytes (11). Further research is needed to verify or reject these hypotheses.

**Band 3 plus nonionic diffusion.** In the present study, no statistically significant differences were noted among any of the groups for lactate influx through the band 3 anion exchange system combined with diffusion of the undissociated acid. The data for transport through these mechanisms was derived from influx in the presence of PCMBS to block MCT-mediated lactate transport. Our results for these RBC transport mechanisms are consistent with other studies. Neither EPO injections nor EIH induced a change in RBC lactate influx via the combined pathways of band 3 and diffusion (10, 11). It has been further reported that anion transport mechanisms for Cl\(^-\) and SO\(_4^{2-}\) are normal in sickle RBCs and are unaltered by deoxygenation or sickling (25). Possibly incongruent with the above studies is the report that hypoxemia stimulated increases of 1.5- and 3-fold in the RBC membrane density of band 3 protein (specifically anion-exchanger isoform AE1) following exposure to 4,100-m altitude for 2 and 8 wk, respectively (28).

**Physiological implications.** Increased levels of NAD content (35, 48) and hexokinase (37) and glyceraldehyde-3-phosphate dehydrogenase activities (36) have been reported for HbSS RBCs; these elevations might increase the overall rate of RBC glycolysis. If glycolysis in HbSS RBCs were increased, then 2,3-diphosphoglycerate as well as production of lactate would consequently be increased. Both the increased level of 2,3-diphosphoglycerate and the decrease in pH resulting from lactate production would impact the affinity of HbS for oxygen, and thus shift the oxygen-hemoglobin dissociation curve to the right (12). The resulting desaturation would increase the chance of HbS polymers forming within the HbSS RBCs (6, 24) and thus increase the risk of sickling. During such condi-
tions, a greater rate of lactate efflux would be advantageous for maintaining a homeostatic intraerythrocyte pH. The MCT carrier is apparently symmetrical (5, 26, 41), so we assume that our measured increases in lactate influx imply increases in lactate efflux capability in HbSS RBCs. Consequently, the increase in lactate influx rates that we observed might assist the HbSS RBCs in maintaining an optimum pH by allowing for translocation of increased amounts of lactate produced via increased rates of RBC glycolysis. This mechanism might slightly alter the incidence of sickling in HbSS RBCs.

On the other hand, if chronic anemia increases glycolysis in tissues other than RBCs (e.g., skeletal muscle, intestinal tissues, and skin), then a more rapid efflux of lactate from these tissues might also be beneficial, especially from skeletal muscle during physical activity. The increased lactate influx rates for the HbSS RBCs would allow for a faster uptake of lactate into the blood from the tissues mentioned above. The HbSS RBCs could then transport the lactate to other sites (oxidative skeletal muscle, heart) for use as a fuel, or to the liver for gluconeogenesis (20).

In summary, the primary finding of this study was the increased rate of total lactate transport attributable to the MCT pathway seen in the RBCs of persons with sickle cell disease compared with lactate transport in RBCs from other subjects with either sickle cell trait or normal Hb. This was supported by an observed increase in $V_{\text{max}}$ for the MCT pathway in the HbSS group compared with the other two groups. The $K_m$ for the MCT was also increased in the HbSS group. No differences were noted between the groups in the transport of lactate through the band 3 plus diffusion pathways. We suspect that elevated EPO levels in response to chronic anemia and/or pharmacological treatment (EPO injections, hydroxyurea in-...

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