Faster lactate transport across red blood cell membrane in sickle cell trait carriers

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Sickle cell anemia is a genetic abnormality of red blood cells (RBCs) that affects more than 150 million individuals, mainly of African origin. In the French West Indies, 1 of 300 newborns is affected by this disease (10). Affected individuals have RBCs containing an abnormal hemoglobin (Hb) S with a reduced affinity for O2 (25). Sickle cell trait (SCT) is characterized by the heterozygous presence of Hb A and Hb S (AS genotype). The prevalence of SCT is ~8% in the African-American population (3), reaching up to 40% in some West African populations (27).

SCT is generally considered benign, not being associated with clinical symptoms in physiological conditions (26). However, numerous incidents, severe injuries (rhabdomyolysis, splenic syndrome, tissue necrosis, renal deficiency), and unexplained sudden death during exercise have been reported, albeit anecdotally (18). The physical and physiological behavior of exercising SCT carriers (AS) remains equivocal, and controversial data have been documented. Although the presence of Hb S should result in lower aerobic capacity, most studies have reported similar aerobic performances in AS and controls (1, 13, 20, 24). Impaired O2 delivery to muscles from AS RBCs during exercise could result in a greater participation of anaerobic metabolism in exercising muscles. This should lead to an earlier rise in blood lactate concentration ([La]) as noted in subjects with abnormal O2 transport (34). However, most studies matching AS and normal Hb (AA) subjects in terms of both physical performance and physical activity demonstrate lower blood [La] in AS during incremental exercise (1, 13, 24).

A recent study from Connes et al. (7) strongly suggested that a high level of RBC lactate transport activity might compensate the rise in blood [La] induced by exercise, leading to hypolactatemia. Moreover, faster lactate influx into AS RBCs than into AA RBCs has been suggested (30) to explain the occurrence of sudden death under strenuous conditions in some SCT individuals (8), but this has never been specifically demonstrated. The aim of the present study was thus to investigate RBC lactate transport activity in AS and AA subjects having the same level of aerobic physical fitness. We particularly focused the study on the RBC lactate transport activity via the major lactate transport pathway, the monocarboxylate transporter (MCT-1) pathway.

MATERIALS AND METHODS

Subjects

Nine AS subjects and seven AA subjects participated in the present study. The physical and hematological characteristics of the subjects are summarized in Table 1. All were students at the Faculty of Sports

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in the University of the French West Indies and Guyana and took part in the same training program. They practiced athletic activities regularly (12 ± 2.1 h/wk) but never at a high level. The subjects who did not have the required training status or who were unwilling to follow the study protocol were excluded.

Protocol

At the beginning of the university year (2004–2005), all new students of the Faculty of Sports underwent Hb screening. Nine AS subjects were detected in this screening program and included in the study. Subjects with anemia and/or α-thalassaemia were excluded. The subjects were informed of the procedures and purposes of the study, which was approved by the local Ethics Committee, and gave written consent to participate. All were from the French West Indies (Martinique, Guadeloupe) and French Guyana. Venous blood samples were obtained from AA and AS in rest conditions to assess hematological parameters and RBC lactate transport activity. The two groups also performed a progressive and maximal exercise test to determine the maximal O2 consumption (V\(_{\text{O2max}}\)), the maximal aerobic power output (MAP), and blood [La] at rest and at maximal exercise.

SCT Diagnosis and Blood Analysis

To test for the Hb type, venous blood was drawn into tubes containing EDTA and screened by isoelectric focusing. The results were confirmed by citrate agar electrophoresis. The various hemoglobinins were isolated and quantified by high-performance liquid chromatography. A test of solubility confirmed the presence of Hb S. The various haemoglobin-containing EDTA and screened by isoelectric focusing. The results were confirmed by citrate agar electrophoresis. The various haemoglobinins were isolated and quantified by high-performance liquid chromatography. A test of solubility confirmed the presence of Hb S.

Maximal Exercise Test and Blood Lactate Analysis

The progressive and maximal exercise test began with a 3-min warm-up at 60 W. Pedalling speed remained constant (at 70 rpm) throughout testing, and the load was increased by 30 W every minute until V\(_{\text{O2max}}\) was reached. Oxygen uptake (V\(_{\text{O2}}\)) was considered maximal if at least three of the following criteria were met: 1) a respiratory exchange ratio of >1.10; 2) attainment of age-predicted maximal heart rate [210 − (0.65 × Age)] ± 10%; 3) an increase in V\(_{\text{O2}}\) lower than 100 ml with the last increase in work rate; and 4) an inability to maintain the required pedalling frequency (70 rpm) despite maximum effort and verbal encouragement. A 5-min recovery period was then implemented with 2 min of pedalling and 3 min of rest. Fingertip arterialised blood microsamples were taken with a lancet (B-D micro-Fine, Becton Dickinson) for lactate analysis at rest and at V\(_{\text{O2max}}\). The blood [La] was determined with an instrument for the total lactate influx buffer containing 

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### Table 1. Anthropometric and hematological data in AS and AA subjects

<table>
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<tr>
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<th>AS (n = 9)</th>
<th>AA (n = 7)</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>24.1±3.2</td>
<td>19.6±0.5</td>
</tr>
<tr>
<td>Height, cm</td>
<td>181.3±1.7</td>
<td>179.0±1.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.0±3.4</td>
<td>68.9±2.7</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.7±0.2</td>
<td>14.5±0.3</td>
</tr>
<tr>
<td>Hct, %</td>
<td>42.0±0.7</td>
<td>42.0±0.9</td>
</tr>
<tr>
<td>Hb S, %</td>
<td>38.0±0.8</td>
<td>38.0±0.8</td>
</tr>
<tr>
<td>Ret, %</td>
<td>0.96±0.07</td>
<td>1.19±0.15</td>
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Values are means ± SE. Hb, hemoglobin; Hct, hematocrit; Ret, reticulocytes; AA, normal hemoglobin group; AS, sickle cell trait group. There were no significant differences between groups.

Transport of lactate across the erythrocyte membrane proceeds by three distinct pathways: 1) nonionic diffusion (NI) of the undissociated acid; 2) the band 3 system, an inorganic anion-exchange system; and 3) the MCT-1-mediated pathway (22). In the present study, we measured total lactate influx, MCT-1-mediated influx, and influx via band 3 and NI together.

Five milliliters of venous blood were drawn from each subject into heparinized vacueters and used immediately. The techniques for preparation of RBCs and lactate influx measurements were modified from previously published methods (28, 29). The initial Hct was determined for all blood samples. Half (2.5 ml) of each blood sample was transferred to a 50-ml conical tube.

The RBCs were isolated by centrifugation at room temperature (20°C, 10 min, 1,000 g). The plasma and buffy coat were removed by aspiration, leaving only the RBC pellet. The pellet was then depleted of lactate by inversion mixing with 30 volumes of chloride buffer (150 mM NaCl, 10 mM Na-Tricine, pH 8.0 at 37°C, osmolality ~315 mosmol/kg H2O) and incubation in a water bath for 30 min at 37°C. At the end of the incubation, the RBCs were sedimented at room temperature (20°C, 10 min, 1,000 g) and the supernatant was removed by aspiration. The cells were then washed twice with chloride buffer. After the final wash, the RBC pellets were separately suspended (hematocrit 30%) in HEPES buffer (90 mM NaCl, 50 mM HEPES, pH 7.4 at 37°C, osmolality ~267 mosmol/kg H2O). This suspension was divided into two aliquots, each containing 1 ml. One of the two stock cell suspensions contained no lactate transport inhibitors. One millimolar p-chloromercuribenzoic acid (PCMB; Sigma, Sigma-Aldrich) was added to the second stock cell suspension to inhibit the MCT-1-mediated pathway. The two aliquots were incubated in a water bath for 30 min at 37°C, and Hct was determined in a sample of each stock cell suspension.

**Influx Assay**

**Total lactate influx.** Twenty-five microliters of stock cell suspension were incubated in 75 μl of HEPES influx buffer for 20 s at 37°C. The HEPES influx buffer contained 

\[ ^{14} \text{C} \text{La} \] (200 disintegrations/min×1nmol×1) at four unlabeled [La] values of 2, 10, 50, and 100 mM, pH 7.4, with final concentrations, respectively, of 1.6, 8.1, 41, and 81.1 mM. The incubation was stopped with 5 ml of an ice-cold stop solution [150 mM NaCl, 10 mM Na-2-(N-Morpholino)ethanesulfonic acid, pH 6.5] and tubes were immediately iced. The cells were spun by centrifugation (4°C, 10 min, 1,000 g) and were washed twice with the ice-cold stop solution to eliminate extracellularradioactivity. After the final centrifugation, RBCs were lysed and deproteinized with 0.5 ml of 4.2% perchloric acid and centrifuged (4°C, 10 min, 1,000 g). Then, 0.4 ml of the supernatant was pipetted into scintillation vials containing 5 ml of scintillation liquid (Amersham Biosciences) and counted in a liquid scintillation counter (Packard 1900CA liquid scintillation analyzer).

**MCT-1-mediated lactate influx.** The cells were suspended in HEPES buffer containing PCMB to block the MCT-1 pathway. Tubes were treated exactly as for the total lactate influx assay.

In all conditions, blank controls were run to test the residual extracellularradioactivity, as well as to correct for any transmembrane lactate exchange that might have occurred despite the ice-cold stop solution.

All measurements were made in triplicate.
Calculation of Lactate Influx

With PCMBs inhibiting the MCT-1 pathway, influx measured in the PCMBs-treated erythrocytes is the sum of lactate transport via the band 3 pathway and NI. Therefore, MCT-1-mediated lactate influx was estimated by subtracting the influx into the PCMBs-treated RBCs from the total lactate influx (MCT-1-mediated lactate influx + band 3-mediated lactate influx + NI-mediated lactate influx).

Lactate influx was calculated in nanomoles of lactate per milliliter of cells per minute. The percentage of contribution from the MCT-1 pathway was calculated by dividing MCT-1 lactate influx by the corresponding total lactate influx.

The Michaelis-Menten coefficients for MCT-1, i.e., the constant of Michaelis-Menten (Km) and the maximal lactate transport capacity for MCT-1 (Vmax), were determined by curve fitting using GraphPad prism 4 for Windows.

Statistical Analysis

Values are means ± SE. A Student’s t-test was used to compare anthropometric data, VO2 max, maximal heart rate, MAP, hematological parameters (Hb concentration, Hct, and percentage of reticulocytes), and Michaelis-Menten coefficients for MCT-1 between the two groups. Blood [La] was compared between the two groups at rest and at maximal exercise using a two-way (group x time) ANOVA for repeated measures. A two-way (group x concentrations) ANOVA for repeated measures was also used to compare the different pathways of RBC lactate transport activity in AS and AA. Pairwise contrasts were used when necessary to determine where significant differences occurred. Statistical significance was established at α = 0.05. StatView software was used to perform statistical analysis.

RESULTS

Anthropometric Characteristics, Hematological Data, and Exercise Response

The AS and AA groups were similar for anthropometric data (age, height, and weight), hematological data (Table 1), and maximal exercise responses (VO2 max, maximal heart rate, and MAP) (Table 2). The blood [La] did not differ between the two groups and increased during exercise to reach similar values in AS and AA (Table 2).

RBC Lactate Transport Activity

Total lactate influx into erythrocytes increased significantly with the increase in external [La] in both groups (P < 0.001) (Fig. 1). AS had greater values of total lactate influx into erythrocytes than AA at 1.6, 41 (P < 0.05), and 81.1 mM (P < 0.001). At moderate external [La], i.e., 8.1 mM, there was no significant difference between the two groups.

MCT-1-mediated lactate influxes also increased with external [La] in both groups (P < 0.001). RBC lactate transport activity was higher in AS than in AA at low and high external [La], i.e., 1.6, 41 (P < 0.05), and 81.1 mM (P < 0.001) (Fig. 2).

The fractional contribution of MCT-1 to total lactate influx decreased with external [La] (Table 3).

Band 3- and NI-mediated lactate influxes are reported in Table 4. Whatever the external [La], no statistical difference was observed between the two groups.

As shown in Fig. 3, Vmax for MCT-1 was significantly higher in AS compared with AA (P < 0.05). However, there was no statistical difference for Km, which was identical for the two groups (Fig. 4).

DISCUSSION

The main findings of the present study were that 1) total lactate influxes and MCT-1-mediated lactate influxes were significantly higher in SCT carriers than in the control group at 1.6, 41, and 81.1 mM of external [La]; and 2) the Vmax of the MCT-1 pathway was significantly higher in AS than in AA.

Although Skelton et al. (29) did not find great differences between lactate transport activity in aerobically trained subjects, sprinters, and untrained subjects, they observed faster lactate transport activity at 1.6 mM in the aerobic group compared with the sprinters and untrained individuals and higher total lactate influx at 41 mM in the sprinters compared with the untrained subjects. This suggests that training status

Table 2. Maximal exercise responses and blood lactate concentrations in AS and control subjects

<table>
<thead>
<tr>
<th>VO2max, m/min/kg-1</th>
<th>HRmax, beats/min</th>
<th>MAP, W</th>
<th>[La] test, mM</th>
<th>[La] maximum, mM</th>
</tr>
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<tbody>
<tr>
<td>AS (n = 9)</td>
<td>38.6±2.6</td>
<td>177± 2</td>
<td>276.7±13.9</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>AA (n = 7)</td>
<td>45.3±1.9</td>
<td>177±10</td>
<td>284.3±5.7</td>
<td>2.0±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. VO2max, maximal oxygen uptake; HRmax, maximal heart rate; MAP, maximal aerobic power output; [La], lactate concentration. There were no significant differences between groups.

Fig. 2. Monocarboxylate transporter (MCT-1)-mediated lactate influx into RBCs of AS and AA groups at 4 external [La]. Values are means ± SE. Significant differences between AS and AA at 1.6, 41, and 81.1 mM [La]: *P < 0.05; **P < 0.001.

Fig. 1. Total lactate influx into red blood cells (RBCs) of sickle cell trait (AS) and control (AA) subjects measured at 4 external lactate concentrations ([La]). Values are means ± SE. Significant differences between AS and AA at 1.6, 41, and 81.1 mM [La]: *P < 0.05; **P < 0.001.
and aerobic physical fitness might influence the activity of RBC lactate transport (even if the influence is minor). This hypothesis is supported by an animal study that demonstrated that RBC lactate influx varied with the aerobic capacity of the animals (28). In the present study, we therefore carefully chose control subjects with the same aerobic physical fitness and anthropometric parameters as the AS group. The $V_{O2\ max}$ and MAP values noted in the present study were not very high but were similar in the two groups, indicating that AS and controls had the same aerobic capacity and training status. Indeed, the differences found between the groups for the RBC lactate transport activity cannot be explained by physical fitness differences.

The higher RBC lactate transport activity reported in AS compared with AA at 1.6, 41, and 81.1 mM seems to be directly related to the higher MCT-1-mediated lactate influx found in AS. It remains unclear why we failed to find a significant difference at 8.1 mM of external [La]. However, at this [La] in both groups, this lack of difference and the greater variability in the individual results of both groups might be linked. We chose to focus on MCT-1 because this has been reported to be the major pathway of lactate influx into RBCs (22, 28), a result confirmed in our study (Table 3). We did not find a difference between the two groups for the band 3 plus NI pathways.

The greater $V_{\text{max}}$ observed for MCT-1 in AS compared with AA suggests either increased MCT-1 activity on the RBC membranes or a greater expression of MCT-1 transporters. The hypothesis of higher MCT-1 content in AS will need confirmation by Western blotting. An increased MCT-1 activity would not be due to the presence of younger cells in the AS RBC population since the reticulocyte percentage did not differ between AS and AA (Table 1). Greater activity could be the result of the presence of some effector of MCT-1. One possibility proposed by Pattillo and Gladden (21) for sickle red cells is that the amount of CD147 (neurothelin), a chaperone that is thought to regulate the MCT-1 activity, could be greater in AS. The lack of difference in $K_m$ between the two groups indicates that MCT-1 had the same affinity for lactate in both groups.

The values found for RBC lactate transport activity at high external [La] and for $V_{\text{max}}$ were lower than the values reported by previous studies in humans (6, 7, 21, 29). In horses, some studies reported that RBC lactate transport activity might be dependent on the breed (32, 33). In humans, Skelton et al. (29) proposed that the differences observed for RBC lactate transport activity between a group of African-American sprinters and other groups composed of Caucasians were possibly related to differences in ethnic origin. The subjects tested in the present study were exclusively composed of students from the French West Indies and French Guyana, whose populations are of African origin but characterized by a high degree of racial intermixing. Ethnic differences rather than the accuracy of the measures may thus be at the origin of the lower values found in the present study for $V_{\text{max}}$ and RBC lactate transport activity at high [La]. We used exactly the same methodology as Skelton et al. (28, 29) and Connes et al. (6, 7). Moreover, the fractional contribution of MCT-1 to total lactate transport activity decreased with the rise in external [La], reflecting the saturation properties of the MCT-1 pathway, as already reported by previous studies (6, 7, 9, 21, 28, 29).

Our results contrast with those of the recent study from Pattillo and Gladden (21), who investigated RBC lactate transport activity in sickle cell disease, SCT, and healthy subjects. They found higher MCT-1-mediated lactate influx in subjects with sickle cell disease compared with the other two groups. However, they observed no difference between SCT carriers and healthy subjects. The reasons for the differences between our results and those of Pattillo and Gladden are unknown at present.

### Table 3. Fractional contribution of monocarboxylate transporter to total lactate influx at four [La]

<table>
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<th>[La] (mM)</th>
<th>AS ($n = 9$)</th>
<th>AA ($n = 7$)</th>
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<tr>
<td>1.6</td>
<td>93 ± 1</td>
<td>92 ± 1</td>
</tr>
<tr>
<td>8.1</td>
<td>89 ± 2</td>
<td>86 ± 3</td>
</tr>
<tr>
<td>41.0</td>
<td>73 ± 2</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>81.1</td>
<td>59 ± 3</td>
<td>48 ± 3</td>
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Values are means ± SE (in %). There were no significant differences between groups.

### Table 4. Band 3- and NI-mediated lactate influx into RBCs measured at four external [La] in AS and AA groups

<table>
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<th>[La] (mM)</th>
<th>AS ($n = 9$)</th>
<th>AA ($n = 7$)</th>
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<tbody>
<tr>
<td>1.6</td>
<td>19.6 ± 3.2</td>
<td>10.9 ± 2.3</td>
</tr>
<tr>
<td>8.1</td>
<td>76.9 ± 5.7</td>
<td>82.7 ± 10.9</td>
</tr>
<tr>
<td>41.0</td>
<td>376.0 ± 25.4</td>
<td>348.3 ± 65.2</td>
</tr>
<tr>
<td>81.1</td>
<td>843.9 ± 60.4</td>
<td>729.1 ± 75.9</td>
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Values are means ± SE (in nmol·ml$^{-1}$·cells$^{-1}$·min$^{-1}$). No significant differences were observed between groups.
this time (21). However, it is notable that the main difference between the two studies is the level of physical fitness in the groups. If training status and aerobic physical fitness influence the activity of RBC lactate transport (7, 28, 29), one assumes that final conclusions could not be drawn from Pattillo and Gladden’s study (21) regarding the role of exercise on RBC lactate transport activity in SCT carriers.

Juel et al. (17) showed that chronic hypoxia increases MCT-1 expression in RBCs. Erythropoietin, the production of which can be stimulated by hypoxia and hypoxemia (19, 23), is known to increase MCT-1-mediated lactate influx (7). Hypoxia and erythropoietin could thus be involved in the synthesis of MCT-1 in AS red cells, but further studies are needed to prove this effect.

Another factor that might explain the greater lactate transport in AS RBCs, as advanced by Pattillo and Gladden (21), is related to *Plasmodium falciparum*. This malarial parasite, endemic to areas where both sickle cell disease and malaria rage, is a holomalarial fermenter and produces large quantities of lactic acid in infected cells (21). The presence of this parasite in infected RBCs causes alterations in the cell membranes that accommodate the metabolic processes of *P. falciparum*. A more efficient lactate transport across the RBC membrane might be a genetic adaptation to malarial exposure, although the subjects participating in the present study were not infected by *P. falciparum*. Further studies will be necessary to test this hypothesis.

The physiological effect of a high MCT-mediated lactate influx is likely to be an increase in lactate and H⁺ fluxes from plasma to erythrocytes. During exercise, the accumulation of lactate and H⁺ within the muscle contributes to the appearance of fatigue (11, 15). The increased storage of lactate and ions in RBCs reduces the levels of these ions in plasma, leading to a greater gradient from interstitial fluid to plasma, and potentially improves the rate of release from muscle (17). This greater total amount of lactate anions and hydrogen ions taken up by erythrocytes might lead to a better redistribution in different places in the body (7). These mechanisms are thought to delay or limit fatigue and hence to improve exercise performance (7). Indeed, the higher RBC lactate transport activity might delay muscle fatigue and improve exercise performance in AS to compensate the impaired blood oxygen transport capacity due to the presence of Hb S.

The higher total and MCT-1-mediated lactate influxes observed in AS could also explain why some studies have described significantly lower blood [La] after the 4 mM lactate threshold in AS subjects (13, 31). Other investigations have reported higher [La] during the last two increments of a graded test (12), but this contrasting result may be explained by a heterogeneous training status and differences in physical fitness between the tested subjects (12). Bile et al. (1) and Sara et al. (24) noted a significantly lower blood [La] during a ramp exercise test in sedentary and trained AS, respectively. In these studies, AS were carefully matched with a control group for physical activity and physiological performance (1, 24). Based on the “lactate shuttle” mechanism (4, 5), the pathophysiological process involved in the lowered lactate in AS subjects during incremental exercise could be due to both greater uptake by RBCs and greater utilization by muscles. The lactate taken up by RBCs is then redistributed among the different body parts. According to Connes et al. (7), greater RBC lactate transport activity might compensate the rise in blood [La] induced by exercise, leading to hypolactatemia. In the present study, we failed to find a difference between AS and AA in blood [La] at rest or maximal exercise. Unfortunately, we did not determine the blood [La] kinetics during exercise, and it is thus possible that AS had lower blood [La] than AA during lower intensity exercise but not at maximal exercise. Similar results were reported in athletes treated with erythropoietin: they had higher RBC lactate transport activity and lower blood [La] at submaximal intensity during a ramp exercise test but the same maximal [La] (7).

However, greater RBC lactate transport activity in AS should also lead to greater lactate and H⁺ accumulation in RBCs, resulting in severe intra-erythrocytic lactic acidosis (14). As suggested by Smith et al. (30), a greater lactate influx into the RBCs of AS than of AA could be involved in the reported cases of sudden death in SCT carriers after strenuous exercise (8). Excessive uptake of lactate by AS RBCs could trigger the sickling process because of the subsequent dehydration caused by activation of the volume- and pH-dependent K⁺/Cl⁻ cotransport channels (30). This may lead, in turn, to hypoxia through microvascular obstruction and, sometimes, to fatal medical complications (8, 30).

The data in the present study show that the RBCs from SCT carriers have increased lactate transport activity via the MCT-1 pathway. The MCT-1 of RBCs from AS might be either overexpressed or differently regulated, perhaps via CD147. This study indicates the complexity of lactate clearance in SCT carriers. However, lactate transport via RBCs is only an intermediary step in lactate homeostasis. Muscle, which is the primary site of lactate production and combustion, plays a great role in the regulation of lactate metabolism during exercise (4). Further research should investigate the expression of the different isoforms of MCT in RBCs and skeletal muscle.

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