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Carbohydrate utilization during exercise after high-altitude acclimation: A new perspective

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ABSTRACT **At high altitude (HA), carbohydrate (CHO) is thought to be the preferred fuel because of its higher yield of ATP per mole of O_2. We used indirect calorimetry and D-[6-^{3}H]glucose infusions to determine total CHO and circulatory glucose utilization during exercise in HA-acclimated and sea level (SL) rats. We hypothesized that the percent contribution of CHO to total metabolism ($\dot{V}_{O_2}$) is determined by exercise intensity relative to an aerobic maximum (% $\dot{V}_{O_2max}$). HA rats run under hypoxia ($FIO_2 = 0.12$) showed a decrease in $\dot{V}_{O_2max}$ compared with SL (67.55 ± 1.26 vs. 89.30 ± 1.23 ml kg^{-1} min^{-1}). When exercised at 60% of their respective $\dot{V}_{O_2max}$, both groups showed the same relative use of CHO (38 ± 3% and 38 ± 5% of $\dot{V}_{O_2}$, at the beginning of exercise, in HA and SL, respectively). In both HA and SL, circulatory glucose accounted for ≈20% of $\dot{V}_{O_2}$, the balance was provided by muscle glycogen (≈18% of $\dot{V}_{O_2}$). After 20 min at a higher intensity of 80% $\dot{V}_{O_2max}$, 54 ± 5% (HA) and 59 ± 4% (SL) of $\dot{V}_{O_2}$ was accounted for by CHO. We conclude the following: (*i*) the relative contributions of total CHO, circulatory glucose, and muscle glycogen do not increase after HA acclimation because the O_2-saving advantage of CHO is outweighed by limited CHO stores; and (*ii*) relative exercise intensity is the major determinant of metabolic fuel selection at HA, as well as at SL.**

At high altitude (HA), carbohydrate (CHO) oxidation is classically viewed as the preferred metabolic pathway for aerobic exercise because it provides the highest ATP yield per mole of O_2 (1). This line of reasoning has usually been invoked to explain the effects of HA acclimation on humans. In early experiments, increases in CHO utilization were often simply inferred from changes in plasma glucose (2–4), even though such extrapolations can be misleading (5). Direct measurements of substrate kinetics (6, 7) provided more reliable evidence that glucose flux can be stimulated after acclimation when the experimental subjects are compared at the same absolute work rate. In contrast, other experiments suggested an increase in the use of plasma fatty acids, which was interpreted as a strategy to spare valuable muscle glycogen (8). Thus, no clear and comprehensive picture of altitude-induced changes in metabolic fuel selection is yet available.

Much of our knowledge of the plasticity of fuel supply pathways comes either from endurance training studies in humans (9) or from comparing animals of widely different aerobic capacities (10–12). In both instances, it has been recognized that the pattern of fuel utilization is determined by relative exercise intensity (% $\dot{V}_{O_2max}$) (13, 14). Recent studies have clearly shown that humans (15) and animals (16) derive the same fraction of their total energy from CHO oxidation when they exercise at the same % $\dot{V}_{O_2max}$. Furthermore, the relative importance of CHO increases progressively with exercise intensity, ultimately providing 100% of the energy at $\dot{V}_{O_2max}$.

Aerobic capacity ($\dot{V}_{O_2max}$) is known to decrease by up to 30% after long-term acclimation to HA (17–19), and this response may have obscured the interpretation of earlier results. In previous studies, all the subjects were measured at the same absolute work rate, and therefore acclimated and control groups were compared at different percentages of their $\dot{V}_{O_2max}$. The acclimated subjects were found to rely more heavily on CHOs, but this change in fuel utilization may not be related to HA acclimation because these subjects were exercising at a higher percent of $\dot{V}_{O_2max}$. This suggests that relative exercise intensity is a major determinant of CHO utilization, and that current synthetic models of fuel selection (15, 16) may also apply after acclimation to HA. In this study we have used indirect calorimetry and continuous tracer infusions to quantify CHO metabolism in HA-acclimated rats and SL controls exercising at the same percent of $\dot{V}_{O_2max}$. Our goal was to test the hypothesis that relative exercise intensity determines oxidative fuel selection before and after acclimation, and therefore that animals operating at the same percent of $\dot{V}_{O_2max}$ use proportionally the same amount of CHO to power locomotion.

MATERIALS AND METHODS

Animals. All aspects of this study have been approved by the animal ethics committees of the Universities of British Columbia and Ottawa. The experiments were carried out on 32 female Wistar rats randomly assigned to two groups; one kept under normal sea level (SL) conditions ($FIO_2 = 0.2094$), and the other kept under hypobaric hypoxia simulating HA conditions ($FIO_2 = 0.12$, equivalent to 4,300 m). Starting body mass (M_b) at 5–6 weeks of age was 231 ± 2 g (HA) and 225 ± 2 g (SL). Each group was given free access to food (Rodent Lab Diet, PMI Nutrition Int., St. Louis) and water. Both groups were kept under 12h:12h light/dark photoperiod and housed in groups of two or four per cage at 25°C.

HA rats were acclimated to HA conditions in hypobaric chambers. The pressure was decreased progressively (20) over the first 10 days of acclimation (3 days at 680, 3 days at 600, and 4 days at 580 mmHg) to a final value of 450 mmHg by using a vacuum pump. Rats were kept at this pressure for at least 10 weeks before measurements. The chambers were returned to normoxic conditions for 1–2 h most days for cage cleaning and exercise training. HA and SL rats were trained four times per week at normoxia on an eight lane motorized treadmill, starting at 10 m/min, at a 6° incline, for 45 min per day. Speed and incline were increased to a final training regime of 20

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Abbreviations: HA, high altitude; SL, sea level; $\dot{V}_{O_2max}$, aerobic capacity; CHO, carbohydrate; RMR, resting metabolic rate; RQ, respiratory quotient; M_b, body mass; R_a, rate of appearance; R_d, rate of disappearance.

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m/min, a 10° incline, for 60 min per day. Training lasted 10 weeks and all exercise protocols were performed at a 10° incline.

Respirometry. Measurements of mass-specific oxygen consumption ($\dot{V}_{O_2}$) and CO_2 production ($\dot{V}_{CO_2}$) were made with a flow-through respirometry system (Sable Systems, Henderson, NV). Exercise measurements were made in a Plexiglas-enclosed motorized treadmill (Columbus Instruments, Columbus, OH). The system was found to be accurate to ±1% by burning methanol ($n = 3$). Maximal oxygen consumption ($\dot{V}_{O_2max}$) was measured for each animal (SL rats under normoxic conditions and HA rats under hypoxic conditions, after acclimation). The three criteria used to determine when the animals had reached $\dot{V}_{O_2max}$ were: (*i*) no change in $\dot{V}_{O_2}$ when speed was increased, (*ii*) the rats could no longer keep their position on the treadmill, and (*iii*) the respiratory quotient ($RQ = \dot{V}_{CO_2}/\dot{V}_{O_2}$) reached a value greater than 1 (21). Resting metabolic rate (RMR) was measured before exercise while animals were sitting quietly on the treadmill.

Exercise Protocols. For all protocols, HA ran at $FIO_2 = 0.12$ and SL at $FIO_2 = 0.2094$ after an overnight fast. Running speeds corresponding to 60 and 80% $\dot{V}_{O_2max}$ were calculated for each individual. Values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were continuously measured for 50 or 60 min at 60% $\dot{V}_{O_2max}$ and 25 or 30 min at 80% $\dot{V}_{O_2max}$.

Glucose Kinetics. Because of the more invasive nature of these measurements, glucose kinetics were only quantified at the lower exercise intensity of 60% $\dot{V}_{O_2max}$. After completing the respirometry measurements, the animals were transferred to the Ottawa laboratory, HA rats were again placed in hypobaric chambers and both allowed to recover for a minimum of 5 days. Jugular vein and carotid artery catheters were implanted while the animals were under halothane anesthesia. The catheters were fed approximately 2.5 cm into the vessels and exteriorized at the back of the animal's neck. Catheters were filled with heparinized saline (20 units/ml) and penicillin G (250,000 international units/ml), and sealed with a sterile metal plug. Buprenophine (0.01 mg/kg) was administered before surgery and twice daily postsurgery. Animals were allowed to recover for 3–6 days and buprenophine administration was stopped at least 24 h before any experiment.

On the day of the experiment, extensions were added to both catheters, and the venous line was used for the continuous infusion of D-[6-^{3}H] glucose [32 Ci/mmol (1 Ci = 37 GBq), Amersham]. A priming dose of D-[6-^{3}H] glucose equivalent to 90 min of resting infusion was mixed with 700 μl saline and injected before starting the infusion. Then, the isotope was infused with a calibrated syringe pump (Harvard Apparatus) at a rate of 0.6 ml/h for 60 min at rest, and 1.0 ml/h for 60 min during exercise at 60% $\dot{V}_{O_2max}$ and 5 min during recovery. Resting infusion rates were 843,131 ± 26,613 for SL rats and 807,782 ± 17,329 dpm kg^{-1} min^{-1} for HA rats. To minimize fluctuations in specific activity (22), infusion rates were increased during exercise to 1,390,449 ± 39,212 and 1,346,303 ± 28,882 dpm kg^{-1} min^{-1} in SL and HA, respectively. The arterial catheter was used to take blood samples (100 μl for two of the resting samples and 300 μl for all others) at 45, 50, and 60 min after the start of the resting infusion; at 15, 30, 45, and 60 min during exercise; and at 2 and 5 min postexercise (recovery). All samples where centrifuged immediately and the plasma was stored at −20°C until analysis.

Sample Analysis. Glucose and lactate concentrations were determined at 340 nm by using standard spectrophotometric methods (23). Glucose activity was measured with a Tri-Carb 2500 counter (Packard) on 30 μl plasma after drying under N_2, resuspending in 1 ml dH_2O, and adding ACS-II scintillant (Amersham).

Calculations and Statistics. Values for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were calculated by using the equations of Withers (24). Total CHO oxidation measured by indirect calorimetry was calculated with the equations of Frayn (25), assuming that the contribution of proteins to overall energy expenditure was negligible during exercise in the postabsorptive state (26). Rates of appearance (R_a) and disappearance (R_d) of glucose were calculated according to Steele (27), with a volume of distribution of 125 ml/kg when the nonsteady state equation was used (28). The R_d was used as an approximation of circulatory glucose oxidation because dog (29) and human studies (9) show that 85–100% of R_d is accounted for by oxidation during low-intensity exercise. Results were analyzed by using a *t* test or two-way analysis of variance. Multiple comparisons were made by using a Student–Newman–Keuls or a Bonferroni *t* test. Percentages were arcsine–square–root transformed. Values presented are means ± SEM.

RESULTS

Respirometry and Total CHO Oxidation at 60% $\dot{V}_{O_2max}$. M_b, RMR, and maximum oxygen consumption ($\dot{V}_{O_2max}$) for HA and SL rats are presented in Table 1. HA acclimation did not have a significant effect on M_b ($P = 0.08$) or RMR ($P = 0.38$), but caused a 24% reduction in $\dot{V}_{O_2max}$ ($P < 0.001$). Resting RQ were not different between SL (0.74 ± 0.01) and HA (0.70 ± 0.01). During exercise at 60% $\dot{V}_{O_2max}$, values of $\dot{V}_{O_2}$ (Fig. 1*A*), $\dot{V}_{CO_2}$ (Fig. 1*B*), and total CHO oxidation (Fig. 2*A*) were all lower in HA than in SL ($P < 0.05$). The highest CHO oxidation rate measured was 875 ± 74 μmol O_2 kg^{-1} min^{-1} in SL, but only 682 ± 86 μmol O_2 kg^{-1} min^{-1} in HA (Fig. 2*A*). RQ values were not significantly different between the two groups ($P = 0.20$, Fig. 1*C*) and decreased over time. They went from 0.820 ± 0.008 to 0.765 ± 0.007 in SL and from 0.817 ± 0.014 to 0.752 ± 0.006 in HA. The percent contribution of CHO oxidation to total $\dot{V}_{O_2}$ was not significantly different between the two groups ($P = 0.21$, Fig. 2*B*); during 1 h of exercise it went from 38 ± 3 to 20 ± 2% in SL and from 38 ± 5 to 16 ± 2% in HA (Fig. 2*B*).

Circulatory Glucose Kinetics at 60% $\dot{V}_{O_2max}$. Plasma glucose concentration was not significantly different between the two groups ($P = 0.14$) and it stayed constant during exercise (Fig. 3*A*). Lactate concentration was not different between the two groups, but it increased to 5.09 ± 0.95 mM and 3.87 ± 1.70 mM during exercise in HA and SL rats, respectively (Fig. 3*A*). The average resting R_a glucose was 49 ± 2 μmol kg^{-1} min^{-1} in both groups. During exercise, R_a glucose was significantly lower in HA (54 ± 4 μmol kg^{-1} min^{-1}) than in SL (73 ± 4 μmol kg^{-1} min^{-1}; Fig. 3*C*, $P < 0.001$). R_a represented 19 ± 2% in HA and 20 ± 2% in SL when normalized to total energy expenditure ($\dot{V}_{O_2}$). During exercise, R_d glucose was lower in HA (54 ± 3 μmol kg^{-1} min^{-1}) than in SL (77 ± 4 μmol kg^{-1} min^{-1}; Fig. 4*A*). Circulatory glucose oxidation accounted for 19 and 21% of $\dot{V}_{O_2}$ in HA and SL, respectively (Fig. 4*B*). Resting hematocrit values were higher in HA (44 ± 1, $n = 8$) than in SL (37 ± 2, $n = 10$). Exercise and repeated blood sampling had no significant effect on hematocrit in HA (40 ± 1, $n = 8$) or SL (35 ± 2, $n = 5$) rats.

Respirometry and Total CHO Oxidation at 80% $\dot{V}_{O_2max}$. At the highest exercise intensity, values of $\dot{V}_{O_2}$ (Fig. 5*A*), $\dot{V}_{CO_2}$ (Fig. 5*B*), and total CHO oxidation (Fig. 6*A*) were all lower in HA than in SL ($P < 0.05$). The highest rates of CHO oxidation were measured at the beginning of exercise for SL (2,150 ± 250 μmol O_2 kg^{-1} min^{-1}) and at the end of exercise for HA

Table 1. M_b, RMR and $\dot{V}_{O_2max}$ for HA acclimated and SL control rats

Rats	M_b, g	RMR, ml kg^{-1} min^{-1}	$\dot{V}_{O_2max}$, ml kg^{-1} min^{-1}	*n*
SL	302 ± 6	31.80 ± 1.44	89.30 ± 1.23	13
HA	289 ± 14	30.08 ± 1.16	67.55 ± 1.26*	14

*Significantly different from SL.

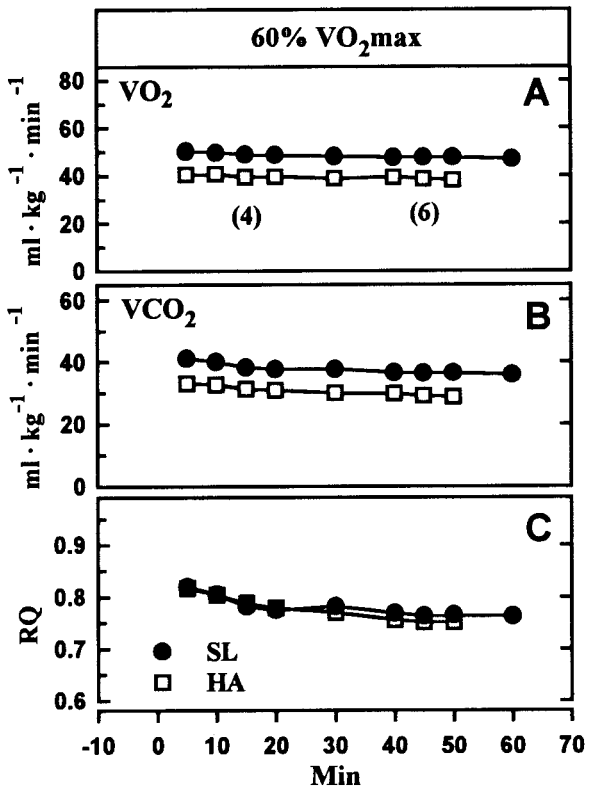

FIG. 1. Oxygen consumption ($\dot{V}_{O_2}$) (*A*), CO_2 production ($\dot{V}_{CO_2}$) (*B*), and respiratory quotient (RQ = $\dot{V}_{CO_2}/\dot{V}_{O_2}$) (*C*) in HA (□; running speed, 9.8 ± 0.6 m/min) and SL control (●; running speed, 16.3 ± 0.3 m/min) rats during exercise at 60% $\dot{V}_{O_2max}$. n = 13 for SL rats; n = 7 for HA rats, except where indicated.

(1,337 ± 225 μmol O_2 kg^{-1} min^{-1}). During exercise, RQ values went from 0.921 ± 0.020 to 0.879 ± 0.013 in SL, and from

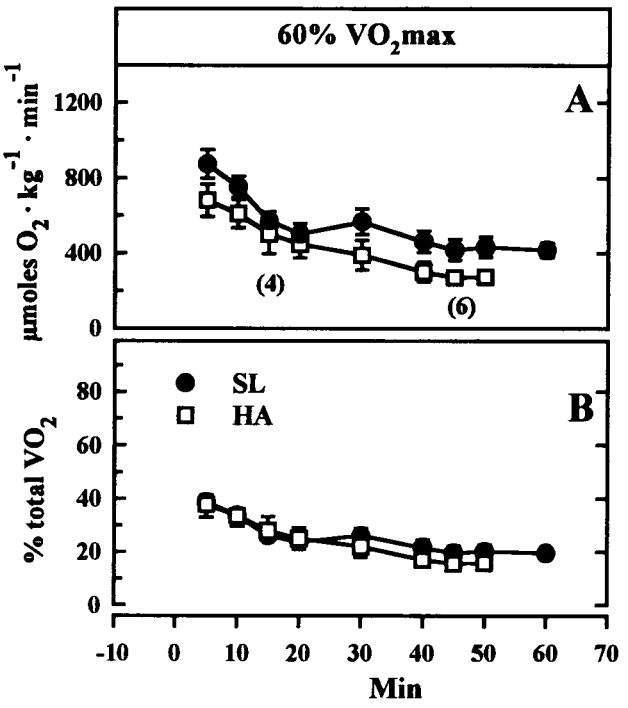

FIG. 2. Total CHO oxidation (μmol O_2 kg^{-1} min^{-1}) (*A*) and expressed relative to total oxygen consumption ($\dot{V}_{O_2}$) (*B*) in rats running at 60% $\dot{V}_{O_2max}$. Symbols are as in Fig. 1.

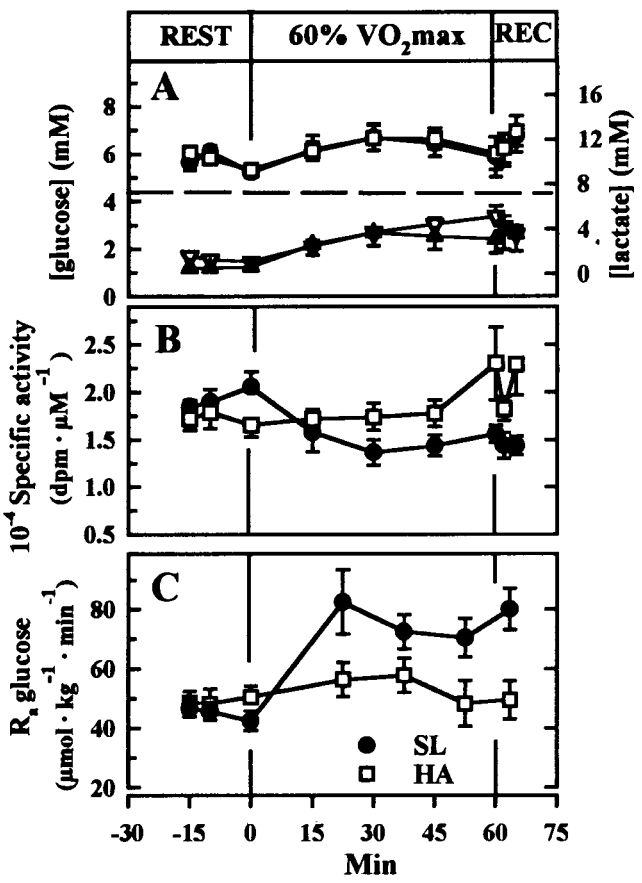

FIG. 3. Plasma concentration (*A*), specific activity (*B*), and rate of appearance (R_a) (*C*) of glucose before, during, and after 60 min of exercise at 60% $\dot{V}_{O_2max}$. *A* also contains plasma lactate concentrations (▽ and ▲, HA and SL, respectively) at rest, during exercise, and in recovery (REC) (n = 8).

0.862 ± 0.016 to 0.866 ± 0.009 in HA. The only significant difference between the two groups was seen at 10 min, RQ being the same for every other time point ($P < 0.05$, Fig. 5*C*). The same was true for the percent contribution of CHO oxidation to total $\dot{V}_{O_2}$; at 10 min it was lower in HA (51 ± 4%) than in SL (68 ± 4%, $P < 0.05$). For all other time periods during exercise, the relative contribution of CHO was the same in the two groups, accounting for 59 ± 4 and 54 ± 5% of total $\dot{V}_{O_2}$ after 20 min in SL and HA, respectively (Fig. 6*B*). In Fig. 7, SL and HA were compared at the same absolute exercise intensity of 17.2 m/min (60% $\dot{V}_{O_2max}$ for SL and 80% $\dot{V}_{O_2max}$ for HA). At this speed, total CHO oxidation and the relative contribution of CHO to total $\dot{V}_{O_2}$ were both significantly higher for HA than for SL ($P < 0.05$, Fig. 7). In 20 min of exercise at 17.2 m/min, CHO oxidation contributed 49 ± 2% of $\dot{V}_{O_2}$ in HA, but only 31 ± 4% in SL (Fig. 7*B*).

DISCUSSION

By comparing animals acclimated to HA with SL controls, this study shows that relative work intensity (% $\dot{V}_{O_2max}$) is the main factor determining fuel selection during exercise. In contrast with several previous reports (2–4, 6, 7), we found that prolonged hypoxia does not cause a significant shift toward higher utilization of CHOs. When running at the same percent of $\dot{V}_{O_2max}$, HA and SL rats derive the same fraction of their total energy from CHO oxidation (Figs. 2*B* and 6*B*). Therefore, current models of fuel selection (15, 16) not only apply to animals of different sizes and aerobic capacities under normoxic conditions but can be generalized to hypoxic environ-

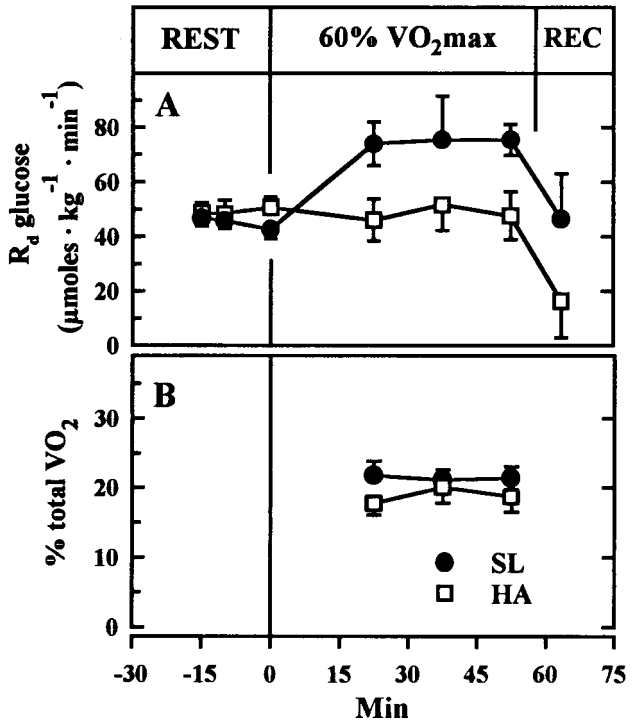

FIG. 4. Rate of disappearance (R_d = rate of oxidation) (*A*) and expressed relative to total $\dot{V}_{O_2}$ (*B*) in HA and SL rats during exercise at 60% $\dot{V}_{O_2max}$. Symbols are as in Fig. 1 (n = 8).

ments. This study of acclimation to hypoxia is the first to eliminate the confounding influence of relative exercise intensity by comparing oxidative fuel utilization in animals working at the same percent of $\dot{V}_{O_2max}$. Previously, experimental groups were compared at the same running speed and acclimated individuals were therefore using a higher proportion of CHO as a consequence of experimental design, not because of acclimation. These earlier observations were confirmed here in control experiments, where the two groups of rats were run at the same absolute speed (17.2 m/min), which represented different relative exercise intensities (60% $\dot{V}_{O_2max}$ for SL and 80% $\dot{V}_{O_2max}$ for HA; Fig. 7).

$\dot{V}_{O_2max}$, RMR, and M_b. Values for RMR and $\dot{V}_{O_2max}$ in SL (Table 1) were similar to those reported previously for other trained rats (30, 31). HA rats running under 12% O_2 had a similar percent reduction in $\dot{V}_{O_2max}$ to that seen in acclimated humans (19) and in untrained white rats under acute hypoxia (32). There was no difference in RMR between HA and SL, which leads to a reduced aerobic scope after acclimation ($\dot{V}_{O_2max}$/RMR = 2.2 for HA vs. 3.6 for SL), and this may have important consequences for the survival of wild animals living in HA environments. Contrary to what was observed in other hypoxia studies on rats (31), HA acclimation did not cause a reduction in M_b in our experiments.

Total CHO Oxidation. Intuitively, one would expect that animals should use a higher proportion of CHO when oxygen availability is low to maximize the ATP yield per mole of O_2 consumed. This does seem to be the case at rest in the cardiac muscle of HA natives, where glucose is used preferentially (33). For exercise at altitude, however, it has been suggested that valuable locomotory muscle glycogen should be spared because CHO represents a relatively small fuel storage (8). Acclimated subjects generally show smaller (8, 34) or similar (35) changes in muscle glycogen than SL controls during exercise. It has been proposed that an increase in lipid (8) or circulatory glucose oxidation (4) is responsible for this effect, but acclimated rats (HA) do not recruit either of these strategies.

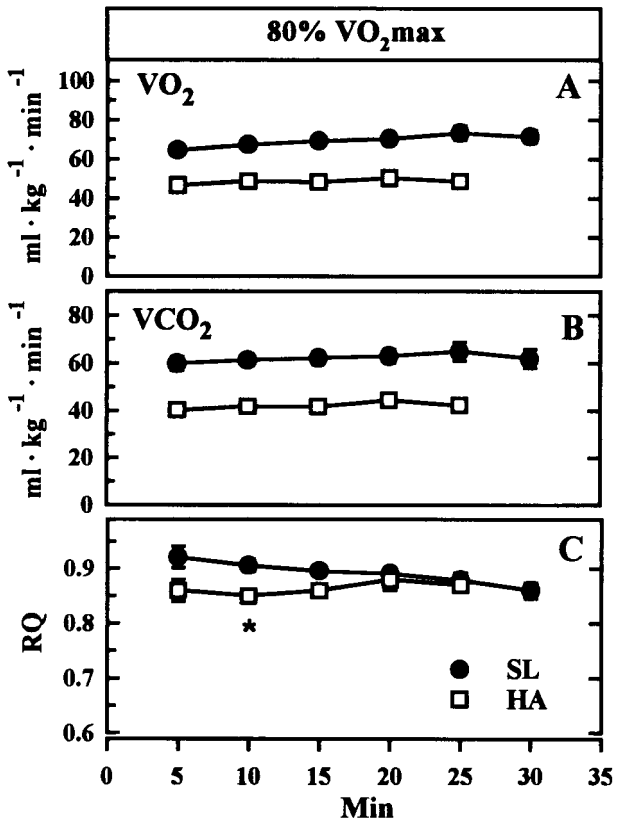

FIG. 5. Oxygen consumption ($\dot{V}_{O_2}$) (*A*), CO_2 production ($\dot{V}_{CO_2}$) (*B*), and RQ (*C*) for HA (running speed = 18.0 ± 0.5 m/min, □) and SL (running speed = 28.0 ± 0.7 m/min, ●) rats during exercise at 80% $\dot{V}_{O_2max}$. *, significantly different than SL [n = 8 (HA) and 11 (SL)].

Total CHO (indirect calorimetry measurements) and circulatory glucose (tracer infusion experiments) are drawn upon to the same extent in HA and SL (Figs. 2*B*, 4*B*, and 6*B*). Acclimated animals may not be able to increase their CHO utilization because they potentially have lower resting stores of muscle glycogen (8), which has been found to increase fat oxidation during exercise at SL (36). Subtracting circulatory glucose oxidation from whole-body CHO oxidation provides a measure of muscle glycogen oxidation. In our experiments, this calculation shows that the relative contribution of glycogen is the same for the locomotory muscles of HA and SL (data not shown). There seems to be active conservation of CHO despite the apparent energetic advantages of its preferential use under HA conditions. In both SL and HA situations, CHO utilization does increase with exercise intensity when O_2-limiting conditions are approached. However, it is not clear whether this higher reliance on CHO is related to increasing the yield of ATP per mole of O_2 or to the fact that the maximal rate of ATP generation is much higher for anaerobic glycolysis than for the oxidation of CHO.

Glucoregulation and Circulatory Glucose Utilization. Plasma glucose concentration was the same in HA and SL (Fig. 3*A*) and did not change significantly with exercise. Both groups had a 1:1 match between hepatic glucose production (R_a, Fig. 3*C*) and glucose uptake by muscle (R_d, Fig. 4*A*), in contrast to previous data on rats (37). Our direct measurements of circulatory glucose utilization reveal that HA have a lower absolute oxidation rate than SL (Fig. 4*A*), and this important effect of acclimation would not have been detected by simple monitoring of plasma concentrations. Consequently, HA and SL derive the same proportion of their total energy from circulating glucose that accounts for ≈20% of $\dot{V}_{O_2}$ in both groups (Fig. 4*B*).

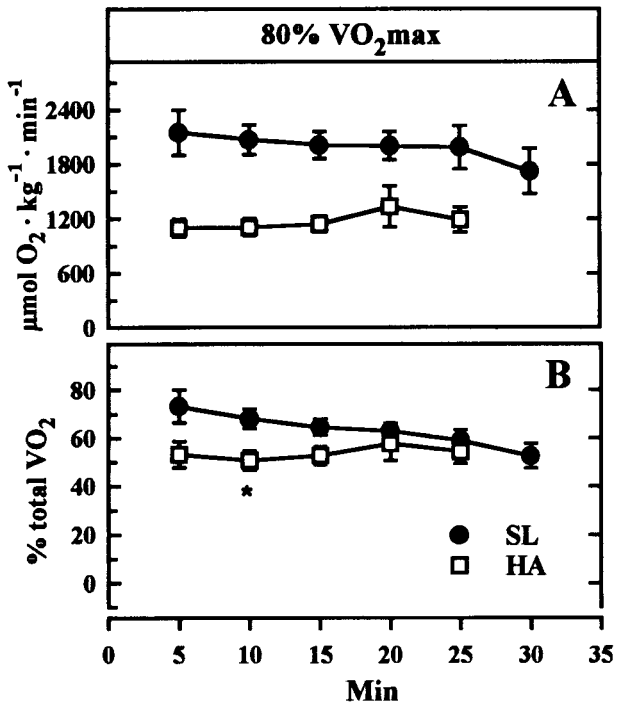

FIG. 6. Total CHO oxidation (in μmol O_2 kg^{-1} min^{-1}) (*A*) and expressed relative to total $\dot{V}_{O_2}$ (*B*) in rats running at 80% $\dot{V}_{O_2max}$. Symbols are as in Fig. 5. *, significantly different than SL [n = 8 (HA) and 11 (SL)].

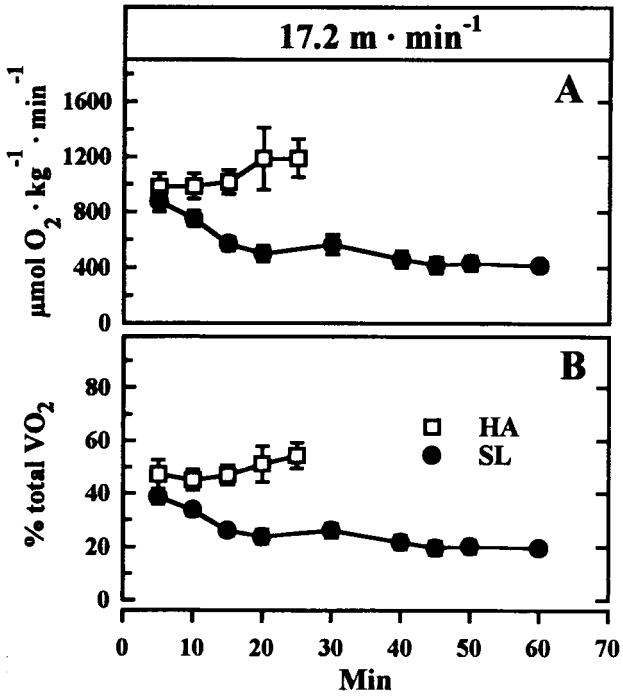

FIG. 7. Total CHO oxidation (in μmol O_2 kg^{-1} min^{-1}) (*A*) and expressed relative to total $\dot{V}_{O_2}$ (*B*) in rats running at the same average absolute speed of 17.2 m/min (SL at 60% $\dot{V}_{O_2max}$, HA at 80% $\dot{V}_{O_2max}$). Symbols are as in Fig. 5.

In recent comparative studies, highly aerobic mammals were found to rely proportionately less on circulatory fuel supply and more on intramuscular substrate stores than their sedentary counterparts (10). At the same percent of $\dot{V}_{O_2max}$, circulatory glucose oxidation accounted for a lower fraction of $\dot{V}_{O_2}$ in highly aerobic dogs than in sedentary goats. In the more aerobic species, an increase in hematocrit reduced the amount of plasma available for circulatory glucose transport and was partially responsible for an increased reliance on muscle glycogen compared with the more sedentary species (12). Hypoxia acclimation caused analogous differences in hematocrit (HA = 44 ± 1%, SL = 37 ± 2%), but HA were still able to maintain glucose transport, and the relative contributions of circulatory glucose and intramuscular glycogen oxidation were equivalent in SL and HA. Dogs have larger muscle glycogen stores than goats, allowing them to support a higher relative contribution of this fuel source (38). In contrast, HA most likely cannot adopt this strategy because acclimation does not lead to an increase, and even tends to lower muscle glycogen content compared with SL controls. During exercise, the relative importance of circulatory fuel sources has been found to decrease as intensity increased (12, 38). This has not been measured after acclimation, but the increase in glucose transporters (39) and glucose transport associated with hypoxic exposure (40) may make it a more important fuel source at higher exercise intensities under these conditions.

Control of Fuel Selection. The mechanisms by which relative exercise intensity controls fuel selection are not yet understood. They are likely complex and probably involve: (*i*) muscle fiber recruitment, (*ii*) hormones (norepinephrine, epinephrine, insulin, glucagon, leptin), (*iii*) fuel cycles (glucose–fatty acid, Cori, and triacylglycerol–fatty acid cycle, among others), and (*iv*) oxygen itself. Furthermore, intricate interactions between these factors makes the interpretation of experimental results much more difficult (41). Very few of these potential regulators have been studied thoroughly at SL and none in HA-acclimated animals exercising at equivalent percentages of $\dot{V}_{O_2max}$. It has been proposed that the observed general pattern of fuel selection is a reflection of how muscle fibers are progressively recruited as work rate goes up (16). At low exercise intensities, slow oxidative (type I) muscles with a high capacity for fat oxidation (42) are recruited. As intensity increases, faster (type II) fibers with higher glycolytic capacity are then activated thus paralleling changes in fuel selection.

The increased reliance on CHO at altitude observed in previous studies is thought to be due, at least in part, to an increase in circulating catecholamines (6, 43). Plasma concentration of norepinephrine correlates with R_a glucose and rises with the percentage of $\dot{V}_{O_2max}$ at SL (14, 43). Therefore, the higher rates of glucose oxidation reported previously (43) were probably not because of acclimation, but to the higher norepinephrine levels of the acclimated animals that were operating at a higher percent of $\dot{V}_{O_2max}$ than the controls (70 vs. 50% $\dot{V}_{O_2max}$). In contrast to SL and other studies using rats (37), there was a blunted response of R_a to exercise seen in HA, suggesting a reduced sympathetic activation after acclimation. Much work has been dedicated to understanding the role of metabolic cycles in the control of fuel selection at SL (44). Unfortunately, it is not known whether some of these cycles are affected by acclimation and further research is needed in this area.

CONCLUSIONS

By eliminating the confounding influence of relative exercise intensity, this study shows that HA acclimation does not cause a significant increase in the use of CHOs. When exercising in hypoxic environments, animals and humans must strike a metabolic compromise to deal simultaneously with low O_2 availability and small CHO reserves. The oxygen advantage provided by CHO must be balanced with the potential depletion of CHO stores. The strategy observed here suggests that the energetic constraint imposed by limited CHO reserves outweighs the O_2-saving advantage of this critical substrate.

Viewed from this "new perspective," a more accurate picture of HA CHO utilization emerges.

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