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ORIGINAL RESEARCH

Effect of L-Carnitine Supplementation on Endurance Exercise in Normobaric/Normoxic and Hypobaric/Hypoxic Conditions

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Objective.—To evaluate the effect of L-carnitine supplementation on improving endurance exercise in normobaric/normoxic and hypobaric/hypoxic environments.

Methods.—Six-week–endurance-trained male Sprague-Dawley rats (n = 24) were randomly divided into 2 groups: control and experimental; the latter group was supplemented with L-carnitine, administered orally in a dose of 100 mg·kg^{-1} body weight. The animals were supplemented for 25 days under ambient normobaric/normoxic conditions and thereafter were exposed to 72 hours of hypobaric hypoxia equivalent to 6100 m. The supplementation was continued during the exposure. "Run to exhaustion" was recorded on day 1 (R1) (presupplementation) and on days 7 (R2), 14 (R3), 21 (R4), and 28 (R5, which followed the last 72 hours of hypoxic exposure) of supplementation. Food intake, body weight, and the biochemical measures of plasma glucose, total cholesterol, and high-density lipoprotein (HDL) cholesterol were recorded.

Results.—There was a significant improvement in endurance exercise, as indicated by an increase in run to exhaustion following L-carnitine supplementation under normobaric normoxia (36%–39%) and hypobaric hypoxia (50%). L-carnitine supplementation had no effect on plasma glucose levels either at sea level or after hypoxic exposure. Total cholesterol was decreased in normoxic and HDL cholesterol was increased in normoxic and hypoxic conditions, indicating a beneficial effect of exercise.

Conclusion.—L-carnitine supplementation improved exercise endurance in rats exposed to normobaric normoxic and hypobaric hypoxic conditions. Such supplementation would be beneficial in delaying the onset of fatigue during prolonged exercise in both conditions, indicating its potentially beneficial use at high altitude.

Key words: endurance exercise, high altitude, L-carnitine

Introduction

Prolonged low-intensity exercise has been characterized by increased utilization of fatty acids, which eventually become the major energy source for muscles. L-carnitine plays a central role during prolonged exercise since it transports activated long-chain fatty acids from the cytosol into the mitochondria for β-oxidation. Without carnitine, long-chain fatty acids cannot enter the mitochrondrial membrane for energy production, but instead accumulate in the cytoplasm, interfering with other metabolic functions.[1] On the other hand, supplementation of L-carnitine is reported to enhance work capacity in experimental animals.[1] However, clinical studies on the effect of L-carnitine supplementation do not provide clear evidence of the beneficial effect of carnitine in exercise.[2]

High-altitude exposure, both acute and chronic, is often characterized by hypophagia, body weight loss, and decrement in exercise capacity.[3] Exposure to high altitude elicits several physiological and metabolic adjustments, including an alteration in substrate metabolism.[4] While most studies have shown carbohydrates to be the preferred fuel in acute hypoxic conditions, some studies also indicate that fat may also be an important fuel at

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high altitude. Young et al[5] have reported higher resting free fatty acids after acute hypobaric/hypoxic exposure (2 hours at 4300 m) in lowlanders. Elevated levels of glycerol, a marker of lipolysis, have also been observed.[6] To aid in increased fat utilization, increased levels of carnitine could offer an advantage in hypoxic conditions. L-carnitine could be a promising compound to enhance physical work capacity in hypoxic conditions. There is limited information on its effects under hypoxic conditions.[7] In view of the potential role of L-carnitine in endurance exercise in rats in the normoxic environment,[1] the present study was conducted. The purpose of this study was to evaluate the effects of exogenous carnitine supplementation on endurance performance under normobaric/normoxic and hypobaric/hypoxic conditions in rats. It was hypothesized that L-carnitine would improve endurance exercise in both conditions. As a secondary objective, plasma glucose was assayed to assess carbohydrate utilization under hypobaric/hypoxic conditions. Keeping in mind the well-known effect of exercise on the lipid profile,[8] the total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol values were also estimated to evaluate the effect of exercise on lipid profile following hypobaric/hypoxic exposure.

Material and methods

EXPERIMENTAL ANIMALS

Adult male albino Sprague-Dawley rats, 14 to 16 weeks of age (n = 24), were obtained from the animal house at the Defence Institute of Physiology and Allied Sciences (DIPAS). Rats were bred and maintained in a well-aerated room with a 12:12-hour light:dark cycle at the animal house facility of the DIPAS in Delhi, India. All experimental procedures were carried out in accordance with the guidelines of the DIPAS Ethics Committee.

DIET

Animal diet consisted of food pellets (Amrut Laboratory Animal Feeds, Pranav Agro Industries Ltd, Delhi, India) with 21% protein, 53% carbohydrate (wheat flour, roasted Bengal pulse, groundnut flour), 4% crude fiber, calcium, phosphorus, and refined oil enriched with stable vitamins A, D3, E, K, B_1, B_2, B_5, B_6, B_{12}, and C. The energy density of the feed was 3.41 kcal·g^{-1}. Food and water were provided ad libitum. The food pellets were provided in a metal cup (120-g capacity) fitted with an antiscatter rim to prevent spillage. The water was provided in 50-mL graduated glass bottles.

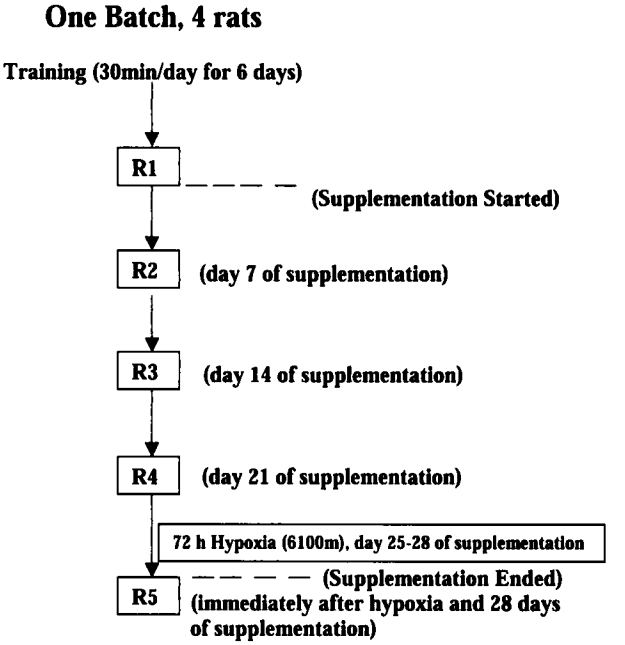

Figure 1. Schematic representation of the experimental protocol.

EXPERIMENTAL DESIGN

The motorized rodent treadmill (Columbus Instruments, Columbus, OH, USA) consisted of a controller unit, motor assembly, 2 running lanes, and 2 grids to deliver electric shocks. The speed and incline of the running belt were increased stepwise during the course of training and were set to a final speed of 27 m·min^{-1} and a 15% incline.[9]

The rats were trained/accustomed to treadmill running for 6 days, for 30 minutes each day, prior to the initiation of supplementation. This duration was found to be sufficient to accustom the animals to treadmill running. After this, "run to exhaustion" time was measured weekly for 5 weeks, at 27 m·min^{-1} speed and a 15% incline. During the exercise, when the rats would slip from the running lane onto the grid as a result of exhaustion, they would be propelled to run again on delivery of an electric shock, which consisted of 200-ms pulses delivered at the rate of 4 pulses·s^{-1} and an intensity of 163 V. Run to exhaustion time was noted as the time from the beginning of exercise until the rats got completely exhausted and remained stationary on the treadmill for longer than 10 seconds.[9]

The protocol for the experiment is represented schematically in Figure 1. All the baseline recordings (ie, run to exhaustion time and biochemical measurements) were carried out 7 days prior to supplementation (R1) in all of the animals. The rats were randomly divided into 2 groups. In the experimental group, L-carnitine

supplementation commenced immediately after R1 and continued throughout the duration of the study (28 days). An aqueous solution of L-carnitine (Sigma Aldrich Chemicals, USA), 100 mg·kg^{-1} body weight was administered orally using an esophageal cannula. The control group was supplemented with an equal volume of distilled water. Subsequent recordings R2, R3, and R4 were carried out after 1, 2, and 3 weeks of supplementation, respectively On day 25, experimental and control groups were exposed to acute hypoxia equivalent to an altitude of 6100 m for 72 hours. Recordings were carried out immediately following hypoxic exposure (day 28, R5).

HYPOBARIC HYPOXIC EXPOSURE

The animals were exposed to hypobaric hypoxia equivalent to a 6100-m–high altitude using an animal decompression chamber (Seven Star Model 700, GDA, Delhi, India) at a temperature of 32 ± 0.5°C and a relative humidity of 50%, with fresh air flow at 5.5 L·min^{-1}. Altitude was attained in 30 minutes with an ascent rate of 200 m·min^{-1}. The level of decompression inside the chamber could be continuously monitored by a mercury manometer (349 mm Hg) and an altimeter, which directly gave the reading of the altitude above sea level. The animals were exposed continuously for 3 days at 23.5 h·d^{-1}. They were brought to sea level between 0930 hours to 1000 hours, at which time their food and water were replenished, their food intake and body weight were recorded, and the supplement solutions were administered.

RECORDINGS

The rats were tested for endurance exercise immediately postexposure (within 5 minutes). The food intake was recorded to the second decimal place; recording occurred daily at the same time in the morning. The food intakes were then subsequently expressed as kcal·100 g^{-1} body weight of the animals. The body weight was recorded every day on a weighing balance with a sensitivity of 0.1 g.

BLOOD SAMPLING AND BIOCHEMICAL ESTIMATION

The animals were anesthetized using anesthetic ether. Postexercise blood samples were drawn from the ophthalmic orbital plexus. The drawing of blood samples coincided with the recording of run to exhaustion time. The samples were collected in heparinized tubes and subsequently centrifuged at 1000*g* for 10 minutes at 4°C. The aliquots of plasma were stored at −70°C to assay TC and HDL cholesterol. Glucose was assayed immediately after separation of plasma to assess the status of carbohydrate utilization under hypoxic conditions. Plasma glucose estimations were carried out using commercially available kits (Boehringer Mannheim GmBH Diagnostica, Penzberg, Germany) based on the glucose oxidase-peroxidase method. Total cholesterol and HDL cholesterol were estimated in the plasma by an enzymatic method using commercially available kits (Source Diagnostics, Shimla, India).

STATISTICAL ANALYSIS

Comparisons between control and experimental groups were made using repeated-measures analysis of variance (2 × 4 mixed model), and further multiple comparisons tests were completed using Student Newman Keul's multiple range tests. The preexposure (R4) and postexposure (R5) comparisons for the same experimental animals were analyzed using paired *t* tests. The level of significance was $P < .05$.

Results

EFFECTS OF L-CARNITINE TREATMENT UNDER NORMOBARIC/NORMOXIC CONDITIONS

(Table 1; Figures 2 and 3)

Run to exhaustion time was significantly increased by ~36% in the experimental group on day 7 (R2) both in comparison to basal value as well as in comparison to the control group. However, there was no further improvement on days 14 (R3) and 21 (R4) of supplementation. Run to exhaustion time was also significantly increased at all time periods (R2–R4) in the experimental group and did not increase significantly in the control group. As shown in Figure 2, there was no significant alteration in food intake recorded before hypobaric hypoxic exposure in both groups. Comparison of body weight between the 2 groups showed a significant decrease in body weight in the experimental group as compared to the control group after days 12, 15, 18, and 21 of supplementation (Figure 3). Table 1 depicts plasma glucose, TC, and HDL cholesterol values.

Comparison of plasma glucose between the experimental and control groups showed no significant differences. There was also no effect of supplementation of L-carnitine and hypobaric/hypoxic exposure on plasma glucose in either group (intragroup comparison). There was no significant difference in TC levels between the control and experimental groups. However, TC showed

Table 1. Effect of L-carnitine supplementation (21 days) on endurance exercise, plasma glucose, and total and HDL cholesterol in normobaric/normoxia conditions§

	R1	*R2*	*R3*	*R4*
Time to exhaustion (min)				
Control (n = 12)	41.3 ± 3.7	38.4 ± 1.6	37.4 ± 2.3	37.6 ± 1.2
Experimental (n = 12)	39.6 ± 2.4	54.0 ± 5.2**†	52.4 ± 3.7**††	55.2 ± 3.5***††
Plasma glucose level (mg·dL^{-1})				
Control (n = 12)	48.8 ± 3.9	48.4 ± 3.9	47.9 ± 3.8	48.5 ± 3.9
Experimental (n = 12)	51.7 ± 6.2	35.1 ± 6.9	36.9 ± 4.7	39.7 ± 7.3
Total cholesterol (mg·dL^{-1})				
Control (n = 12)	74.3 ± 3.3	64.1 ± 3.6†	54.8 ± 3.5†††‡	59.8 ± 4.1†‡
Experimental (n = 12)	73.3 ± 2.9	70.1 ± 5.04	59.9 ± 4.5†‡	50.4 ± 3.2†††‡‡
HDL cholesterol (mg·dL^{-1})				
Control (n = 12)	19.8 ± 0.7	20.9 ± 0.7	21.6 ± 0.5†	19.7 ± 2.0
Experimental (n = 12)	16.7 ± 0.7**	16.8 ± 0.7***	16.8 ± 1.2**	20.3 ± 1.4†‡

§Values are mean ± SEM. R1 indicates presupplementation of L-carnitine recorded after training of rats; R2–R4, readings taken 1, 2, and 3 weeks postsupplementation.

**, ***Experimental vs control $P < .05$, $P < .01$, and $P < .001$, respectively.

†, ††, †††$P < .05$, $P < .01$, and $P < .001$ when compared with respective R1 group.

‡, ‡‡$P < .05$ and $P < .01$ when compared with respective R2 group.

a significant decrease in both groups in comparison with R1 and R2 (intragroup comparison). The values of HDL cholesterol in the experimental group were significantly lower than in the control group at R1 ($P < .01$). There was a significant increase in HDL cholesterol in the experimental group at R4 compared to R1 and R2 ($P < .05$). There was no significant change in HDL cholesterol in the control group (intragroup comparisons).

EFFECT OF L-CARNITINE SUPPLEMENTATION UNDER HYPOBARIC HYPOXIA
(Table 2; Figures 2 and 3)

The run to exhaustion time was higher in the experimental group than in the control group following exposure to hypobaric hypoxia ($P < .05$). There was no significant intragroup change in time to exhaustion following hypobaric hypoxic exposure (R5) in the experimental group. There was an increase in the control group when compared to R4. There was a significant decrease of food intake in both the experimental and control groups ($P < .001$) upon exposure to hypobaric hypoxia (Figure 2). There was a reduction in body weight in both the experimental and control groups after hypoxic exposure ($P < .001$) (Figure 3). As depicted in Table 2, plasma glucose and TC levels did not change significantly after hypobaric hypoxic exposure in both groups. There was a significant increase in HDL cholesterol following hypobaric hypoxic exposure in both the control group ($P < .05$) and the experimental group ($P < .01$).

Discussion

L-carnitine supplementation in the experimental group led to an increase in run to exhaustion time at R4 and R5 compared to the respective control groups (Table 2). The increase in values with respect to R1 was 36.4% at R2 and 39.4% at R4 in the experimental group, whereas no improvement in time to exhaustion was noted in the control group (Table 1). Improved exercise capacity following L-carnitine supplementation in the present study is in agreement with recent work showing improvement in motor performance of rats as measured by in vivo and in vitro recordings, with an increase in endurance exercise following supplementation of L-carnitine along with other ergogenic aids.[10]

The improved endurance exercise following L-carnitine supplementation in prolonged exercise may be beneficial in increasing the total carnitine content of the exercising muscle mitochondria and the total content of acyl-carnitine.[11] These may be limiting factors during such an exercise regimen. It has been reported that muscle carnitine stores are reduced after high-intensity exercise at 70% or greater of the Vo_2max.[1] In the present exercise regimen, although L-carnitine levels were not measured, it appears that the endogenous carnitine mus-

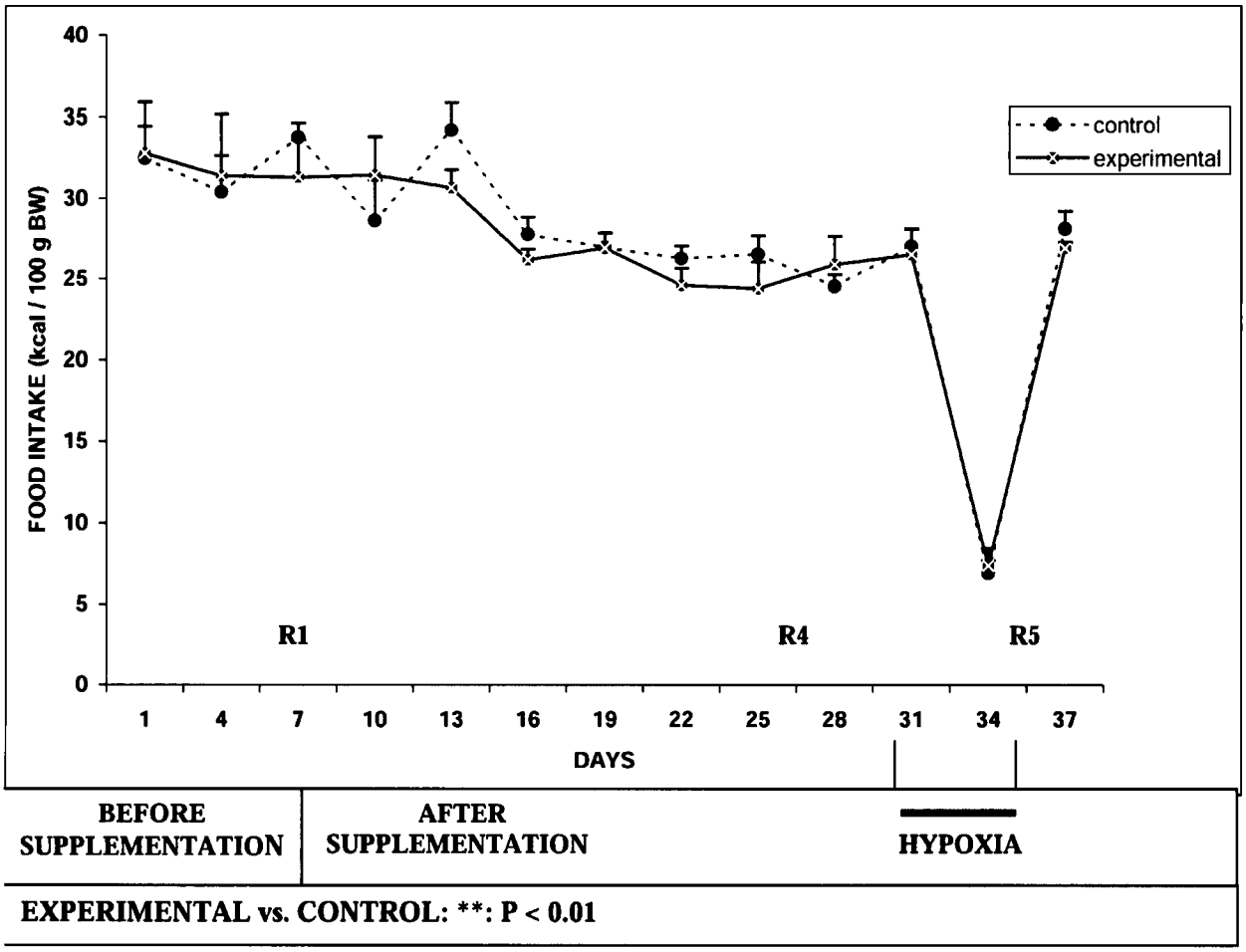

Figure 2. Effect of L-carnitine supplementation on food intake (kcal/100 g body weight) in normobaric/normoxic and hypobaric/hypoxic conditions.

cle reservoir may have been reduced during the exercise. The supplemented L-carnitine may have assisted in the transport of the long-chain fatty acids into the mitochondrial membrane of the exercising muscle, resulting in greater lipid utilization, thereby leading to improved endurance exercise. The findings of the present study are in agreement with those of previous studies that have reported a beneficial effect of supplemented carnitine during prolonged exercise.[12]

The effect of L-carnitine supplementation after 72 hours of hypobaric hypoxia (6100 m) was studied. There was an increase in endurance exercise in the control group. Data indicated that values were most likely increased as a result of the preexposure values that were significantly lower in this group. Our findings are in agreement with a report[13] of an increase in endurance of trained rats upon exposure to hypoxia, which attributed the effect to a reduction in body weight induced by hypoxic exposure. A reduction in body weight in both groups was also a finding of the present study, which could have contributed to the increased endurance exercise. Another study[14] also reported enhanced work efficiency on submaximal exercise within 3 days of acclimatization at 6000 m. Reduced work capacity has been previously found on exposure to high altitude.[15]

In the present study, exercise training per se may have contributed to a lack of any detrimental effect of hypoxia on physical work capacity. It was reported[16] that training may attenuate myocardial beta-adrenoceptor downregulation; the latter contributes to limitation of Vo_2max and preserves cardiac output and Vo_2max at high altitude in rats. However, human studies have shown that upon acute hypoxic exposure athletes have a greater drop in Vo_2max than do nonathletes.[17]

In addition to endurance exercise, hypobaric hypoxia influences food intake and body weight.[19] In the present study, exposure to hypoxia reduced food intake and body weight. Supplementation with L-carnitine had no

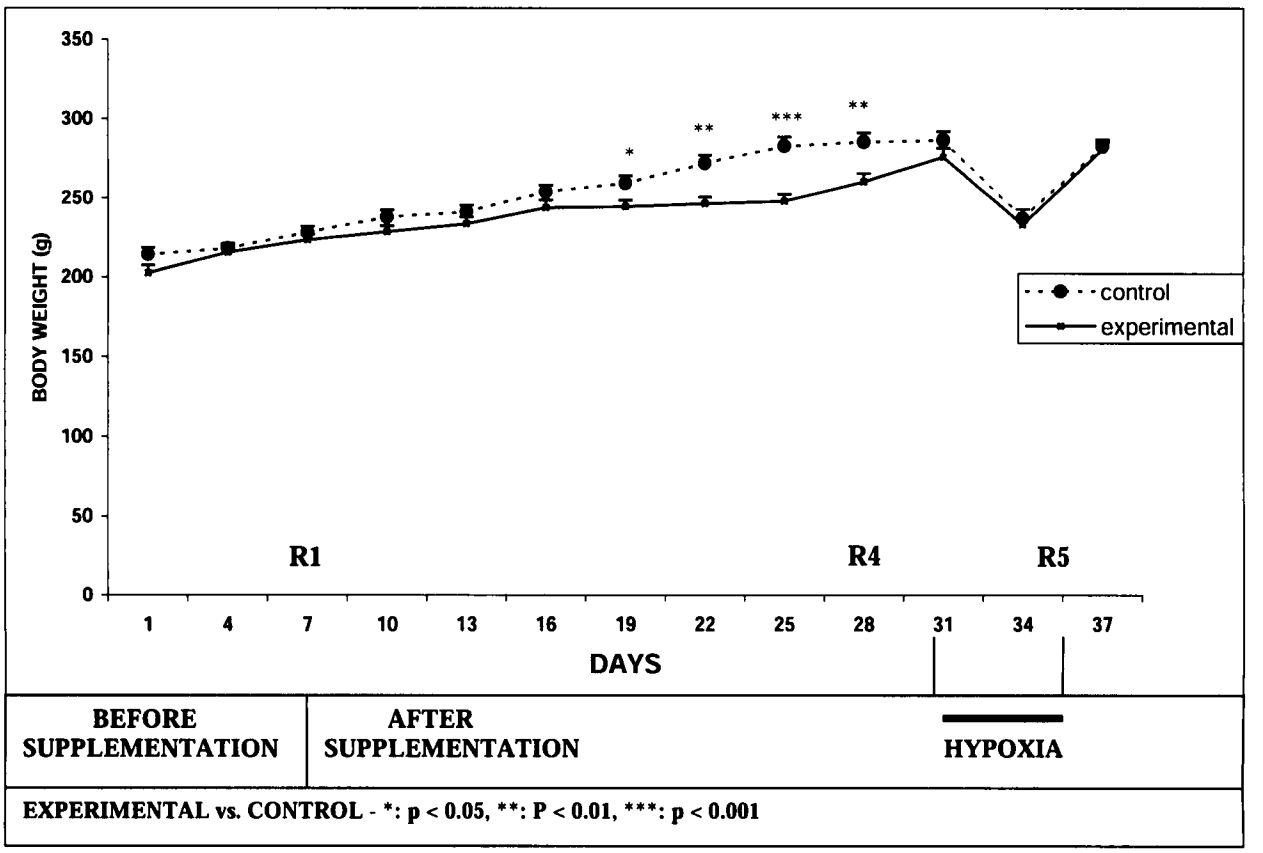

Figure 3. Effect of L-carnitine supplementation on body weight (g) in normobaric/normoxic and hypobaric/hypoxic conditions.

effect on food intake. The reduction in food intake due to high-altitude hypoxia is in agreement with that of our previous studies.[18,19] In the present study, the food intake reduced by 65.6% and 78.4% during hypoxic exposure in experimental and control groups, respectively. The magnitude of the reduction in food intake is in agreement with that observed after a similar hypoxic exposure of the same duration reported in a previous study.[20] A reduction in food intake by 40% was reported after 4 days of exposure at 500 mbar in another recent study in rats.[21]

Body weight loss is another manifestation of hypobaric hypoxia.[18,19] In the present study, weight loss after 72 hours of hypobaric hypoxia was of a similar magni-

Table 2. Effect of L-carnitine supplementation and hypobaric/hypoxic exposure on endurance exercise, plasma glucose, and total and HDL cholesterol‡

		Prehypoxia (R4)	*Posthypoxia (R5)*
Run to exhaustion time (min)	Control (n = 12)	37.58 ± 1.23	48.87 ± 5.18†
	Experimental (n = 12)	55.2 ± 3.5**	60.9 ± 4.8*
Plasma glucose level (mg·dL^{-1})	Control (n = 12)	48.54 ± 3.95	48.3 ± 5.71
	Experimental (n = 12)	39.7 ± 7.25	41.94 ± 7.33
Total cholesterol (mg·dL^{-1})	Control (n = 12)	52.31 ± 5.03	59.8 ± 4.14
	Experimental (n = 12)	50.39 ± 3.2	52.92 ± 4.71
HDL cholesterol (mg·dL^{-1})	Control (n = 12)	19.66 ± 2.04	25.49 ± 2.12†
	Experimental (n = 12)	20.31 ± 1.35	26.09 ± 1.29††

‡Values are mean ± SEM.
*, **Experimental vs control, $P < .05$ and $P < .01$, respectively.
†, ††Prehypoxia vs posthypoxia, $P < .05$ and $P < .01$, respectively.

tude (ie, 19.8% and 17.3%) in the experimental and control groups, respectively. There was a decrease in body weight between day 19 (corresponding to 2 days before R3) and day 28 (R4) in the experimental group compared to the control group; it is possible that this decrease can be attributed to an improvement in endurance exercise following L-carnitine supplementation, leading to an increased oxidation of fat during exercise, which in turn would have contributed to loss of body weight. The simulated hypoxia-induced body weight loss is attributed to hypophagia.[21] Since the hypoxic exposure reduced food intake, and because the effect was of a great magnitude, the reduced body weight was expected.

In the present study, we were interested in assessing carbohydrate utilization by plasma glucose assay. However, neither L-carnitine supplementation nor hypoxic exposure elicited any change in plasma glucose. In the experimental group euglycemia due to glycogen sparing was expected (as a result of increased free fatty acid utilization) during endurance exercise. However, preexercise plasma glucose was not measured for comparison. A higher plasma glucose in the experimental group than in the control group as a result of the glycogen sparing effect would also be expected. A previous report[22] has shown hypoglycemia after a similar exercise protocol in rats whose plasma free fatty acids were raised and who also had a greater run to exhaustion time than controls with normal plasma free fatty acids. Previous studies have reported mild resting hyperglycemia following intermittent hypoxic exposure,[18] whereas a mild hypoglycemia has been reported following chronic exposure.[19,23]

Total cholesterol and HDL cholesterol were also estimated. Endurance exercise reduced the levels of plasma TC in successive weekly recordings taken immediately following exercise performance in both the supplemented and unsupplemented groups of rats. Hypobaric hypoxic exposure (72 hours) had no effect on plasma TC levels. L-carnitine supplementation increased HDL cholesterol levels. This result appears to be linked to the increase in exercise endurance following supplementation. Our findings are in agreement with those of a recent study[24] that reported altered values of lipid metabolites following L-carnitine supplementation in the sample taken at the time of exhaustion after exercise, although no change was recorded in basal conditions. As pointed out, in the present study as well, the blood sample was drawn immediately after endurance exercise. Hypoxic exposure increased the HDL cholesterol levels in both the supplemented and unsupplemented groups. This finding is in agreement with a previous study reporting the same change after high-altitude exposure.[25]

The changes in plasma cholesterol elicited in the present study are well supported by the reports documenting the effects of exercise on plasma lipids.[8] The regulation of substrates during exercise is multifactorial and depends upon 1) dietary and nutritional status; 2) hormonal milieu; 3) exercise mode, intensity, and duration; and 4) training status.[26,27] There is also a marked variability in the response (HDL cholesterol) to the same level of exercise.[28] The effects of exercise on HDL cholesterol also depend upon other baseline factors, such as level of initial HDL cholesterol and triglyceride levels.[29,30]

The present study had the following limitations: 1) the intensity of exercise could not be graded in terms of Vo_2; this is important since fuel utilization and carnitine utilization depend upon exercise intensity[11]; 2) there was no direct measure of fat utilization; 3) pre- and postexercise muscle carnitine concentrations could not be measured; and 4) the recordings were carried out postexposure at sea level, immediately following, not during, the hypobaric hypoxia exposure. Future studies are warranted in these areas. The effect of L-carnitine on physical work capacity during chronic hypoxic exposure should be further evaluated.

In conclusion, L-carnitine supplementation improved physical work capacity in rats exposed to normoxic and hypoxic conditions; this may be attributed to its fat oxidation property, which could potentially delay the onset of fatigue during prolonged exercise.

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