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Effects of L-carnitine administration on $\dot{V}_{O_{2max}}$ and the aerobic-anaerobic threshold in normoxia and acute hypoxia

V. Wyss, G. P. Ganzit, and A. Rienzi

Institute of Sports Medicine, Corso Sebastopoli 123, I-10137 Turin, Italy

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Summary. Seven healthy young male adults were subjected to a total of 56 tests to ascertain the effects of L-carnitine (L-C) and a placebo (P) on ventilation, O_2 intake ($\dot{V}_{O_2}$), CO_2 output, heart rate, blood pressure and serum lactic acid, non-esterified fatty acid, glycerol and glucose during strenuous and aerobic/anaerobic threshold-level treadmill exercise. The tests were made in conditions of normoxia ($O_2 = 20.9\%$) and hypoxia ($O_2 = 13.0\%$, equivalent to 3,500 m above sea level). The only clear difference was in the respiratory quotient (RQ = 0.883, SD 0.025 vs 0.904, SD 0.035) after L-C and P administration respectively ($P < 0.01$), under normal oxygenation and 0.861, SD 0.052 following L-C vs 0.926, SD 0.040 after P ($P < 0.01$) in acute hypoxia at $\dot{V}_{O_2}$ levels around the anaerobic threshold. The lower RQ values of the L-C-treated subjects during hypoxia indicate a lower rate of carbohydrate transformation.

Key words: L-Carnitine administration - Aerobic-anaerobic threshold - Treadmill exercise - Normoxia - Hypoxia

Introduction

The efficacy of L-carnitine (L-C) as a therapeutic agent has been confirmed in ischaemic myocardiopathy (Cherchi 1978; Di Monaco 1980; Ferrari 1984), arrhythmia (Gaita 1982), myopathy (Angelini 1976; Markesbery 1977; Siliprandi 1983), repeated haemodialysis (Siliprandi 1983) and diphtheric intoxication (Siliprandi 1983).

Physiological evaluation of endogenous carnitine during muscular exertion has shown that, at 50% of maximal oxygen uptake ($\dot{V}_{O_{2max}}$), acyl-carnitine increases in the plasma and is simultaneously reduced in the muscles (Bohmer et al. 1966; Marconi et al. 1985). In the rat, training determines a shift of carnitine content between kidneys, liver, muscles and heart (Lennon and Mance 1986), with exogenous carnitine localizing mainly in the ischaemic myocardium (Liedtke and Nellis 1979). Increased muscular concentration of carnitine-palmityltransferase has also been postulated in trained rats (Baldwin and Tipton 1972; Baldwin et al. 1975; Norum 1964). In man, training can cause slightly increased muscular carnitine (Lennon et al. 1983; Morgan et al. 1971). These data match the findings reported by Eclache et al. (1979) and Marconi et al. (1985) in response to L-C administration: the former identified an increased duration of muscular effort at 80% of $\dot{V}_{O_{2max}}$ with an accompanying reduction of the respiratory quotient (RQ), while a $\dot{V}_{O_{2max}}$ increase of about 6% without variation of the RQ was reported by the latter. Greater availability of the carrier would facilitate the use of fatty acids as an energy source, with a consequent saving of glycogen. This advantage should theoretically, be more pronounced in acute hypoxia, when availability of plasma fatty acids is higher than at an equivalent exercise intensity in normoxia (Jones et al. 1972; Young et al. 1982), the reasons being higher circulatory concentrations of catecholamines (Havel 1965) and increased sympathetic activity (Havel and Carlson 1963; Rosell and Ballard 1971).

The aim of this study was to ascertain whether oral administration of L-C to healthy young subjects in normoxia and acute hypoxia ($O_2 = 13\%$) affects:

1. Exercise endurance $\dot{V}_{O_{2max}}$, lactic acid accumulation
2. The level of the aerobic/anaerobic threshold
3. The RQ and lactacidaemia patterns during 30-min sustained threshold-level exertion and the subsequent recovery period.

Methods

Subjects. Tests were performed on seven healthy male subjects whose informed consent was obtained. None of the subjects had

Offprint requests to: V. Wyss

been engaged in regular training or competitions. Their average age was 22.2 years, SD 2.3 height 183.4 cm, SD 3.5, mass 73.6 kg, SD 4.6, and adipose tissue 12.8%, SD 3.2%.

Details of experiment. Exercise was performed on a treadmill (3–30 km·h^{-1}, 0%–28% gradient), with a reduction from 20.9% O_2 to 13.0% O_2 (equivalent to about 3,500 m above sea level). The reduction was obtained by gradually introducing nitrogen into the closed-circuit spirometer (Magna-Test Dargatz-Hamburg) and at the same time subtracting circulating air, until O_2 concentration reached 13%, measured by an internal paramagnetic oxygen meter. The dilution of normal air with nitrogen lasted about 2 min which was necessary to obtain a uniform mixture. The volume was kept constant during the whole test by feeding O_2 into the closed circuit. The inspiratory tube was connected to a paramagnetic O_2 analyser and an infra-red CO_2 analyser (Morgan, London), to measure O_2 and CO_2 concentrations in the inspired air, while the expiratory tube was fitted with a manual-control valve so that the expired air could be collected (for a whole number of breaths) in a 15-l rubber bag and piped on to the gas analysers.

The O_2 concentration of 2–3 air samples was tested before the subject started to breathe through the circuit. Further samples were tested at regular 3-min intervals during both normoxia and hypoxia.

Heart rate (HR) was continuously monitored by V5 ECG (Cardioline ETA 40 Remco, Milan, Italy) from shortly before the start of the treadmill exercise until the end of recovery. Blood pressure (BP) was measured by a Riva-Rocci sphygmomanometer. Determination of the aerobic-anaerobic threshold was based on the ventilation: O_2 uptake ratio ($\dot{V}_E$: $\dot{V}_{O_2}$), at increasing exercise intensities (Wasserman et al. 1973; Davis et al. 1976).

Blood samples were taken from the antecubital vein without a tourniquet. Serum glycerol was assayed by the Eggstein enzymatic method (Biochemia Kit, Boehring Mannheim GmbH, Mannheim, FRG). Serum nonesterified fatty acids (NEFA) were assayed by the NEFA quick "BHY" enzyme test Boehring Mannheim Yamanouchi, Tokio, Japan), glycaemia by Trinder's method (Biochemia Kit), and plasma lactate by Noll's enzyme test (Biochemia kit).

Statistical evaluation was performed by means of Student's *t*-test for paired data.

Experimental protocol. The experimental conditions were double-blind. Subjects took tablets, identical in appearance and taste, of either 1.036 g L-C and excipient or excipient alone [placebo (P)]. Dosage was 3 tablets daily (one every 8 h) of L-C or P for the 7 days prior to the start of the tests and for the 15–18 days of their duration.

The subjects were treated on a cross-over basis, i.e. a course of one type of tablet being followed, after a 7-day interval, by administration of the other. Throughout the study, subjects maintained a daily food intake of 2,700–2,800 kcal (11,300–11,719 kJ), provided by varied but chemically equivalent diets.

Exercise tests were performed during the morning, from April to July 1986. The test environment was a laboratory, with the temperature ranging between 21° and 24° C, an atmospheric pressure between 730 and 744 mmHg and humidity between 45% and 65%. The subjects were connected to the closed-circuit and subjected to the following test sequence:

1. Measurement of $\dot{V}_E$, $\dot{V}_{O_2}$ and carbon dioxide output ($\dot{V}_{CO_2}$), at rest in a standing position, electrocardiogram (ECG) for determination of HR, BP, venous blood sampling for basal lactic acid, NEFA, glycerol and glucose.
2. Strenuous exercise (SE) comprising treadmill exercise at a steady speed of 5.5 km·h^{-1} with gradient increase, from horizontal, of 2% every 3 min, to continue uninterrupted until exhaustion. Continuous $\dot{V}_E$ and HR measurements were made for each exercise intensity, while expired air samples of O_2 and CO_2 evaluation were taken every 3 min during exercise. The BP was measured in the first 15–30 s of recovery. Spirometer and ECG recordings continued at regular intervals during recovery. Venous blood samples for the tests listed above were collected at 3 and 30 min, with an additional sample for lactate alone at 15 min.
3. Threshold-level exercise (TE), following a rest period of not less than 2 h from the conclusion of SE, when each subject completed a period of 30-consecutive-min treadmill exercise at a speed of 5.5 km·h^{-1} and at the established aerobic/anaerobic threshold gradient. Exercise was interrupted only by a 2-min break at the 15th min for venous blood-sample collection and BP recordings. The gradient could be varied to a limited extent according to $\dot{V}_{O_2}$ and HR. The $\dot{V}_E$ and HR were continuously monitored and expired gases analysed every 3 min during exercise.

A final blood sample was collected at the end of the exercise period. Each subject underwent the test in normoxic conditions (20.9% O_2) and in hypoxia (13% O_2), with an interval of 4–7 days between sessions to avoid a cumulative training effect. Each subject repeated both the normoxia and the hypoxia tests twice, once after L-C and once after P. Overall, 28 exercise tests were performed in conditions of normoxia and 28 in hypoxia.

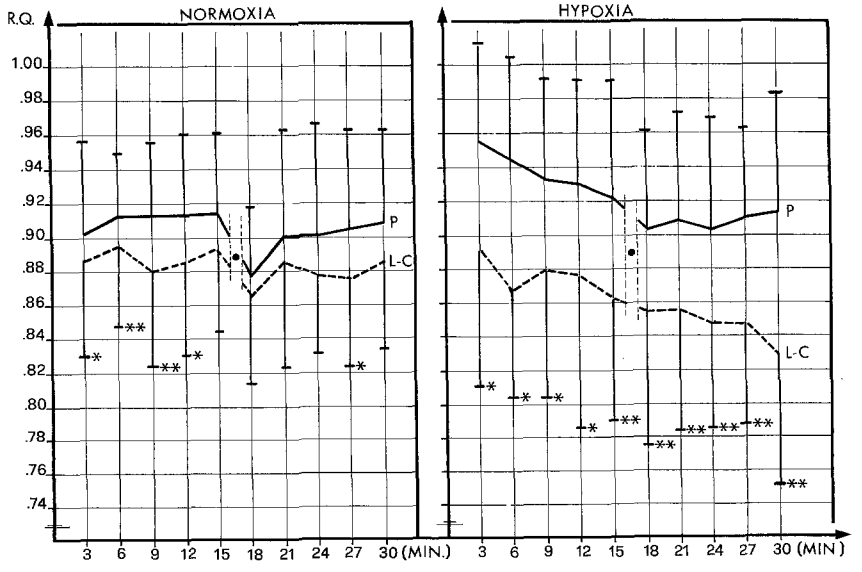

Fig. 1. Respiratory quotient (RQ) (mean and SD) during anaerobic threshold exercise tests in normoxia and hypoxia, following administration of L-carnitine (*L-C*) (——) and placebo (*P*) (——) with 2-min break for blood collection. * $P<0.05$; ** $P<0.01$

Results

At rest

There was no difference, following L-C and P, in $\dot{V}_E$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, RQ, HR, BP and blood concentrations of lactic acid, NEFA, glycerol and glucose, whether in normoxia or in hypoxia.

Strenuous exercise

As shown in Table 1 there was no significant difference, whether in normoxia or in acute hypoxia, in terms of duration of exercise endurance, maximum power, total energy output, decrease in energy output in the switch from normoxia to hypoxia, $\dot{V}_E$, $\dot{V}_{O_{2max}}$, RQ, HR and BP. The $\dot{V}_{O_{2max}}$ was 3.55 l·min^{-1} (normoxia) and 2.86 l·min^{-1} (hypoxia) following L-C, against 3.54 l·min^{-1} and 2.91 l·min^{-1} after P, the reduction being 19.4% and 17.8% respectively.

The RQ remained in the range 1.007–1.079, with no significant variations according to differences in test conditions. Lactacidaemia after strenuous exercise (Table 2) was about six times higher than at rest in conditions of normoxia, with a further slight increase during acute hypoxia. The NEFA increased to 2–2.5 times basal values in both normoxia and acute hypoxia. Glycaemia also increased by 20%–25% in both normoxia and hypoxia, with no significant difference between treatments. The recovery process for all the parameters considered was comparable after L-C and P (Table 2). In particular lactate recovery kinetic showed the normal decrease in concentration from the 5th to 30th min.

Aerobic/anaerobic threshold

The aerobic/anaerobic threshold was reached in conditions of normoxia after about 25 min exercise at increasing intensities, at over 160 W following both L-C and P. In hypoxia, the threshold was reached after about 21 min at 128 W in subjects treated with L-C and at 138 W following P. Threshold $\dot{V}_{O_2}$ in normoxia was below $\dot{V}_{O_{2max}}$, by 24.51% following L-C and by 19.78% after P. In hypoxia, the percentage differences were 18.1% following L-C and 18.3% after P. These differences were not significant. The RQ, while slightly lower in the tests following L-C than after P treatment, was in all cases higher than 0.9.

Table 1. Spiro-ergometric and cardiocirculatory parameters (mean and SD) at the final exercise intensity of a strenuous exercise test (duration and total energy indicated) in normoxia and acute hypoxia following L-carnitine (L-C) or placebo (P) administration. Hypoxia-normoxia percentage difference indicated for each parameter

		Normoxia		Hypoxia		$\frac{\text{Hypoxia-Normoxia}}{\text{Normoxia}} \cdot 100$	
P	(%)	L-C	P	L-C	P	L-C	(%)
Power (W)		236	231	197	198	−16.4	−16.4
	SD	33	28	30	33	4.2	5.4
Duration of exercise (min)		35.1	34.3	30	29.4	−14.5	−12.5
	SD	4.5	3.6	4.4	4.4	4.1	3.9
Total energy (kJ)		253.2	239.8	180.8	181.6	−28.6	−24.2
	SD	63.7	50.7	52.8	55.6	9.7	8.6
Maximum $\dot{V}_E$ (l·min^{-1})		117.2	117.2	120.5	116.7	2.8	− 0.3
	SD	21.1	19.2	17.3	19.9	6.09	14.8
Maximum $\dot{V}_{O_2}$ (l·min^{-1})		3.55	3.54	2.86	2.91	−19.4	−17.8
	SD	0.40	0.27	0.25	0.25	5.1	5.5
Maximum $\dot{V}_{CO_2}$ (l·min^{-1})		3.58	3.54	2.98	2.95	−16.7	−16.7
	SD	0.31	0.38	0.37	0.49	10.9	13.8
RQ		1.025	1.017	1.007	1.079	− 1	0.5
	SD	0.040	0.054	0.062	0.029	8.7	5.4
HR (beats·min^{-1})		173.9	173.6	167.8	168.8	− 2.9	− 2
	SD	10.6	3.6	9.3	9.0	2.1	4
BP (mmHg)		171/71	170/69	167/73	167/68	—	—
	SD	9/5	10/6	4/6	4/6		

No statistically significant differences between L-C and P for any parameter in either O_2 regime. $\dot{V}_E$ = ventilation; $\dot{V}_{O_2}$ = oxygen uptake; $\dot{V}_{CO_2}$ = carbon dioxide output; RQ = respiratory quotient; HR = heart rate; BP = blood pressure

Table 2. Serum lactate, non-esterified fatty acid (NEFA), glycerol and glucose (mean and SD) in normoxia and hypoxia, at rest, following strenuous exercise and at 15th and 30th min of recovery following L-carnitine (L-C) or placebo (P) administration. Same parameters at 15th and 30th min of aerobic/anaerobic threshold-level exercise.

				Rest	Exercise maximum	Recovery 15th min	Recovery 30th min	Threshold 15th min	Exercise 30th min
Lactate ($mmol \cdot l^{-1}$)	Normoxia	L-C		1.4	8.8	5.3	3.0	3.7	3.1
			SD	0.7	3.3	2.3	1.2	1.6	0.9
		P		1.5	8.1	4.4	2.6	3.5	3.0
			SD	0.7	1.7	1.1	1.0	1.4	1.4
	Hypoxia	L-C		1.5	9.9	5.6	3.1	4.0	3.8
			SD	0.6	2.3	1.5	0.7	1.6	1.3
		P		2.1	9.1	5.5	2.8	4.8	4.4
			SD	0.8	1.5	0.9	0.5	0.8	1.1
NEFA ($mmol \cdot l^{-1}$)	Normoxia	L-C		183	450	—	309	—	1172
			SD	46	105		120		293
		P		260	473	—	282		1251
			SD	71	134		87		314
	Hypoxia	L-C		201	447	—	297	—	1247
			SD	49	128		135		369
		P		202	530	—	264	—	1055
			SD	92	237		84		423
Glycerol ($\mu mol \cdot l^{-1}$)	Normoxia	L-C		69.5	177	—	116	—	297
			SD	18.4	42.3		29.3		70.5
		P		77.1	183	—	117	—	288
			SD	17.3	45.6		29.3		76
	Hypoxia	L-C		69.4	169	—	104	—	290
			SD	11.9	31.5		22.8		97
		P		74.9	178	—	109	—	279
			SD	16.3	42.3		17.4		85.8
Glucose ($mmol \cdot l^{-1}$)	Normoxia	L-C		4.2	5.7	—	4.6	—	4.9
			SD	0.5	1.0		0.7		0.8
		P		4.3	5.5	—	4.35	—	4.9
			SD	0.4	1.2		0.9		0.8
	Hypoxia	L-C		4.3	5.8	—	4.75	—	4.75
			SD	0.9	0.8		0.70		0.6
		P		4.3	5.5	—	4.3	—	4.8
			SD	0.7	0.9		0.8		1.0

No statistically significant differences between L-C and P for any parameter

Aerobic/anaerobic TE for 30 mins

During the 30-min TE (Table 3) all subjects, whether in normoxia or hypoxia and following L-C or P, maintained the exercise intensities identified during strenuous exercise. The lactate concentrations at the 15th and 30th min showed that exercise did not exceed the anaerobic threshold. The $\dot{V}_E$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, HR and BP were in all respects comparable following L-C and P. The only certain difference was that in the RQ, which was 0.883 following L-C against 0.904 following P in normoxia ($P<0.01$) and 0.861 after L-C against 0.926 following P in acute hypoxia ($P<0.01$) (Fig. 1).

Discussion

Our data match the findings of other authors, in that, while duration of exercise, haematological parameters and the aerobic/anaerobic threshold did not differ significantly between treatments in either normoxia or hypoxia, RQ evaluation showed a far higher lipid metabolism rate after L-C during sustained TE, in both hypoxia and normoxia.

The L-C is considered to be a specific carrier of activated fatty acids across the internal mitochondrial membrane, so that they can undergo chemical transformation (Bressler and Katz 1965; Chase et al. 1965; Norum 1964; Quagliarello et al. 1967). It can thus interfere with the metabolism of other compounds only by the indirect effect on these processes of an increased lipid uptake. As a result, in conditions of strenuous exercise reached by a gradual increase of the exercise intensities every 3 min, the predominantly carbohydrate content of the metabolic uptake prevents excess L-C from acting. Marconi et al. (1985) reported a 4% increase of $\dot{V}_{O_{2max}}$

Table 3. Spiroergometric and cardiocirculatory parameters (mean and SD) in continuous aerobic/anaerobic threshold-level exercise (duration and total energy indicated) in normoxia and acute hypoxia following L-carnitine (L-C) and placebo (P) administration. Hypoxia-normoxia percentage difference indicated for each parameter

		Normoxia		Hypoxia		$\frac{\text{Hypoxia-Normoxia}}{\text{Normoxia}} \cdot 100$	
P	(%)	L-C	P	L-C	P	L-C	(%)
Threshold (W)		164	167	131	138	−19.9	−17.3
	SD	28	29	33	32	9.9	5.4
Duration of exercise (min)		30	30	30	30		
Total energy (kJ)		1766	1804	1414	1491	−19.9	−17.3
	SD	306	313	356	349	9.9	5.4
$\dot{V}_E$ ($l \cdot min^{-1}$)		75.6	77.7	74.0	81.3*	− 2.0	+ 4.6
	SD	10.7	13.7	12.5	12.8	9.5	1.2
$\dot{V}_{O_2}$ ($l \cdot min^{-1}$)		2.72	2.80	2.15	2.28	−20.9	−19.0
	SD	0.24	0.27	0.31	0.23	5.3	7.3
$\dot{V}_{CO_2}$ ($l \cdot min^{-1}$)		2.52	2.55	1.98	2.16	−21.4	−15.3
	SD	0.36	0.35	0.32	0.25	9.2	10.6
RQ		0.883	0.904**	0.861	0.926**	− 2.5	+ 2.5
	SD	0.025	0.035	0.052	0.040	5.8	4.8
HR ($beats \cdot min^{-1}$)		156.6	157.5	151.6	155.1	− 3.2	− 1.6
	SD	13.1	3.9	10.2	9.0	4.2	6.8
BP (mmHg)		150/72	151/73	146/69	149/71		
	SD	6/3	6/3	10/6	7/5		

L-C and P comparison: * $P<0.05$, ** $P<0.01$. Definitions as in Table 1

which they attributed to pyruvate dehydrogenase stimulation, probably caused by a decrease in the acetyl-coenzyme A:coenzyme A (acetyl CoA:CoA) ratio; they conclude that L-C cannot have any effect on brief, intense exercise performance and recommended that it be studied in sustained exercise of limited intensity. When TE is performed in normoxia, endogenous L-C is usually sufficient.

For L-C administration to be useful, exercise must be such that:

1. Lipids can be used as an energy source
2. Lipid availability is ready and plentiful
3. There is a relative shortage of endogenous L-C

The findings of Eclache et al. (1979), showing a clear lenghtening of the duration of 80% $\dot{V}_{O_{2max}}$ effort after exogenous L-C are probably related to partial or complete fulfilment of the above criteria. Other results concerning the benefits of exogenous L-C in paraphysiological or pathological conditions, whether experimental (Cherchi 1978; Lennon et al. 1983) or clinical (Di Monaco 1980; Ferrari 1984; Froberg et al. 1971), are also consistent, albeit in varying degrees, with these requirements.

Our observations matched those of other authors in this respect. Prevalent lipid uptake after L-C was indicated in both normoxia and hypoxia by reduced RQ values, while lower lactacidaemia after L-C, particularly in acute hypoxia indicated high lipid availability. These findings give legitimate grounds for postulating reduced carbohydrate metabolism in the anaerobic phase.

Previous authors have attributed these metabolic variations (Fritz 1963; Markwell 1973) to freeing of pyruvic dehydrogenase (PDH) by carnitine-CoA-acetyltransferase, so that acetyl-CoA can be removed and oxidative catabolism of the carbohydrate molecule be facilitated. The stabilizing effect of short chain carnitine esters on the CoA-mitochondrial pool could also favour PDH activity (Brass and Hopple 1980; Bremer 1983). Siliprandi (1983) also postulates that a greater quantity of activated acetyls is stored in the cell, available for immediate oxidation without prior adenosine 5′-triphosphate-mediated activation.

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