Abnormal Plasma Carnitine Derivatives Reflecting an Altered Metabolic State in Anorexic Women at Rest and Following Maximal Effort Treadmill Exercise

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Five women diagnosed as having classical anorexia nervosa were studied at rest and following a maximal effort treadmill test prior to (AN-I) and after hospital treatment (AN-II). A group of 14 lean women (matched for age, percent body fat, height, weight, and fitness level as closely as possible) were studied as lean controls (LC). Before treatment, AN-I had significantly less plasma long-chain acyl carnitines than LC (4.59 versus 6.16 μM), whereas short-chain acyl carnitines were nearly twice as high (9.01 versus 4.91 μM, AN-I versus LC) at rest. Following maximal exercise LC women demonstrated a sharp increase in short-chain acyl carnitines (from 4.91 to 8.83 μM), whereas the AN-I group showed no change in these derivatives relative to their resting level (from 9.01 to 10.49 μM). Long-chain acyl carnitines, however, were reduced in AN-I compared with LC after exercise

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(2.37 versus 6.55 μM, respectively). Following hospital treatment short-chain acyl carnitines at rest were reduced toward normal (6.68 μM) in the AN-II, although the long-chain acyl forms still remained lower (3.21 μM) than in the LC (6.16 μM). However, even after hospital treatment the AN-II group did not show the typical increase in short-chain acyl carnitines with an acute bout of exercise.

Anorexia nervosa has been categorized by various researchers into several diagnostic subgroups (Bruch, 1962, 1973; Freighner, 1972). Primary or classical anorexia has become one of the major diseases of young human females between the ages of 13 and 18 years. It has been extensively treated by clinicians with only modest success (Hsu, Crisp, & Harding, 1979). Psychological treatment with adequate nutrition and electrolyte normalization has been the goal (Bargman, 1981; Moore, 1981). Alleviation of the major symptoms can be accomplished, but actual permanent cure is rare (Hsu et al., 1979).

This condition is both metabolically and physiologically similar to starvation. However, several parameters (hormones and metabolites) that are altered by both imposed and self-inflicted starvation (primary anorexia) do not respond in the same manner to adequate nutrient intake and weight gain (Fichter & Pirke, 1984). Proteolysis and amino acid oxidation occur for energy sources in both imposed and self-inflicted starvation that result in a negative nitrogen balance.

Starvation is known to increase the concentration of branched-chain amino acids in plasma within 1 day, and they remain elevated for 1 week. Prolongation of starvation to 2 weeks lowers the concentration to basal levels (Adibi, 1968). In contrast, protein deprivation with adequate caloric intake lowers the plasma concentration of branched-chain amino acids below basal levels within 1 day. The direction of plasma alanine change is opposite that of the branched-chain amino acids. The decrease in alanine has been considered to be an indication of enhanced gluconeogenesis during starvation (Adibi, 1968; Adibi & Drash, 1970), whereas the increase is a function of depressed gluconeogenesis and increased synthesis in protein deprivation (Adibi, Morse, & Amin, 1975; Adibi & Drash, 1970). Changes in renal clearance (Adibi, 1971) and/or intestional absorption (Adibi & Allen, 1970) of the branched-chain amino acids do not appear to account for the plasma concentrations during these dietary states. Prolonged exercise elicits similar metabolic patterns and hormonal changes as observed in imposed starvation. Ingested amino acids are used for protein anabolism and/or are catabolized as fuel for energy.

We have shown that amino acids, especially the branched-chain (which make up about 40% of the minimal daily requirement of indis-

pensable amino acids of man), are transaminated to their keto analogues and/or irreversibly oxidatively decarboxylated to their CoA derivatives in skeletal muscle (liver?) during an acute bout of exercise in chronically trained rats (Lennon et al., 1985). Furthermore, except for Tyr, urea, and ammonia, all amino acids, including alanine, were significantly reduced after 1 hour of treadmill running in the trained rat. Only glutamine was significantly increased, implying that the purine nucleotide cycle was more important than the glucose-alanine cycle for the transportation of nitrogen from the muscle (Lennon et al., 1985). Short-chain acyl carnitines are significantly increased in blood plasma at the same time, suggesting a replenishment of CoA in muscle by shuttling branched-chain fatty acyl derivatives to the liver for gluconeogenesis and/or ketogenesis (D. L. F. Lennon, unpublished data). Sustained exercise of only 30 minutes in the untrained rat has been reported to stimulate skeletal muscle branched-chain keto acid dehydrogenase (EC 1.2.4.4.) basal activity approximately fivefold (Kasperek, Dohm, & Snider, 1985). This increased dehydrogenase activity during sustained exercise could account for our observed increase in both the branched-chain keto-acids (Harper, Miller, & Block, 1984) and the short-chain acyl carnitines. Furthermore, Van Hinsbergh, Veerkamp, and Glatz (1979) have suggested that the branched-chain fatty acyl CoA derivatives may have limited further oxidation potential in skeletal muscle, especially in the human.

The similarity of primary anorexia nervosa to imposed starvation and acute exercise in the trained state, combined with the availability of samples from normal subjects and anorexic patients (both before and after exercise prior to and after hospital treatment), stimulated us to evaluate the possible function of carnitine derivatives in skeletal muscle amino acid oxidation at rest and during exercise.

METHODS

Subjects

Five patients who had lost 20–25% of their premorbid body weight were classified as primary anorexic (AN-I) according to criteria adapted from Freighner et al. (1972). Fourteen healthy, lean, unconditioned females (lean controls, LC) were selected (Einerson, 1983) to closely match age, body composition, and fitness level of the primary anorexic in order to determine if cardiovascular responses were related to body composition. Cardiovascular responses are reported in Einerson (1983). These subjects and patients signed informed consent forms approved by the University of Wisconsin-Madison Medical School Human Subject Committee.

Protocol

Physical characteristics are summarized in Tables 1 and 2 (Einerson, 1983). Percent body fat was determined from body density, which was estimated from the sum of the skinfold thickness at the triceps, supra iliac, and thigh sites (Jackson, Pollock, & Ward, 1980).

Exercise Test Procedure

Dynamic exercise was performed on a motorized treadmill using a modified Balke protocol (Balke & Ware, 1959). Work capacity in METs was estimated from treadmill speed and grade at maximal effort (American College of Sports Medicine, 1980). Blood pressure and heart rate were monitored every minute during the test. The five anorexic patients (AN-I) were tested within five days of admission into a 4 week hospitalization treatment program and 2 days prior to or after hospital discharge (AN-II). The criteria for release were a gain to low normal body weight, normal electrolytes, and expectation that the patient could function in a normal environment.

An indwelling catheter was placed in a warmed antecubital hand vein 10–15 minutes prior to the exercise bout. The blood sample was drawn into heparinized tubes just before exercise and within 3 minutes after the exercise bout.

Carnitine and Lactate Assays

Free and short-chain acyl carnitines (acid-soluble) were determined in blood plasma as previously described (Lennon et al., 1983). Long-chain acyl carnitines (acid-insoluble) were hydrolyzed from the protein pellet and assayed as free carnitine (Lennon et al., 1983). Lactate in blood serum was determined using Strom's modification of the Barker–Summerson method (Strom, 1949).

RESULTS

Physical characteristics of the anorexics before (AN-I) and after (AN-II) hospital treatment are shown in Table. 1. A significant increase in percent body fat with no change in lean body mass occurred during the 4 week hospitalization period in the five anorexic patients (AN-I versus AN-II). All physical characteristics of the AN-II were similar to the LC group after hospitalization (Table 2).

Respiratory exchange ratio did not change after treatment of anorexics (AN-I, 1.19 ± 0.04 (SE), versus AN-II, 1.17 ± 0.05) following maximal exercise and was significantly ($p < .05$) greater than LC (1.09 ±

Table 1. Physical characteristics of the anorexic before (AN-I) and after (AN-II) hospital treatment.

	Weight (kg)		Body Fat (%)		Lean Body Mass (kg)	
Patient	AN-I	AN-II	AN-I	AN-II	AN-I	AN-II
1	47.5	50.9	13.6	16.0	41.0	42.7
2	50.0	49.1	18.3	21.7	40.8	38.4
3	49.4	55.5	11.0	13.6	44.0	47.9
4	29.5	35.5	4.8	7.1	28.1	32.9
5	44.8	52.3	7.1	13.6	41.6	45.2
Mean	44.2	48.6	10.9	14.4	39.1	41.1
SE	3.8	3.4	2.4	2.3	2.8	2.6
p	NS		< 0.05		NS	

Table 2. Physical characteristics of the anorexic group before (AN-I) and after (AN-II) hospital treatment and in the lean controls (LC).

Parameter	AN-I (n = 5)	AN-II (n = 5)	LC n = 14
Age (years)	17.6 ± 1.0[a]	17.6 ± 1.0	18.8 ± 0.6
Height (cm)	166.2 ± 2.3	166.2 ± 2.3	168.0 ± 1.1
Weight (kg)	44.2 ± 3.8	48.6 ± 3.4	51.3 ± 1.2
Body Fat (%)	10.9 ± 2.4	14.4 ± 2.3	14.6 ± 0.5
Lean Body Mass	39.1 ± 2.8	41.4 ± 2.6	43.8 ± 0.9

Note: AN-I versus AN-II, $p < 0.05$; AN-I versus LC, $p < .05$.
[a]Mean and SE.

0.02). Blood lactate levels among these groups did not differ significantly (Table 3). Physical work capacity (METs) was not improved by hospitalization of the AN and remained significantly less than the LC (Table 3).

The effect of exercise on plasma carnitine derivatives in LC females compared with primary anorexic females before (AN-I) and after (AN-II) hospital treatment is shown in Table 4. The LC females responded to the exercise bout with the typical increase in the concentration (from 4.91 to 8.83 μM) and percentage (from 10.4 to 17.8%) of short-chain acyl carnitines observed in other studies (Lennon et al., 1983). Prior to hospital treatment the AN-I females had a significantly higher concentration of short-chain acyl carnitines (9.01 versus 4.91 μM) and percentages (19.0 versus 10.4%) preexercise than the LC. AN-I preexercise short-chain acyl carnitines were nearly identical to the LC subjects' postexercise values. They also had a significantly lower concentration (4.59 versus 6.16 μM) and percentages (9.3 versus 13.6%) of long-chain acyl carnitines. The exercise bout did not induce a significant further release of short-chain acyl carnitines into the plasma of the AN-I. How-

Table 3. Physical work capacity (METs) and blood lactate concentrations in the anorexic group before (AN-I) and after (AN-II) hospital treatment and in the lean controls (LC).

Parameter	AN-I (n = 5)	AN-II (n = 5)	LC (n = 14)
METs			
50%	4.8 ± 0.2[a]	5.1 ± 0.3	6.4 ± 0.2
100%	9.9 ± 0.6	10.2 ± 0.7	12.3 ± 0.3
Lactate levels (m*M*/L) after exercise			
Before treatment	1.0 ± 0.14	1.1 ± 0.11	0.9 ± 0.05
After treatment	7.4 ± 1.57	6.5 ± 0.63	6.4 ± 0.35

Note: AN-I versus LC, $p < .05$; AN-II versus LC, $p < .05$.
[a]Mean and SE.

ever, the percentage of short-chain acyl carnitines was significantly higher than the LC at the end of exercise (21.4 versus 17.8%). There was also a tendency for long-chain acyl carnitines to be metabolized during the exercise bout in the AN-I and AN-II female; thus both the concentration and percentage were reduced when compared with healthy LC. Hospital treatment tended to reduce short-chain acyl carnitine concentrations toward those of LC individuals preexercise, whereas treatment diminished long-chain acyl carnitines still further in the anorexic. The hospital treatment of the anorexic female did not restore the traditional increase in short-chain acyl carnitines observed during exercise in LC females, whereas long-chain acyl carnitines tended to be metabolized to the same extent as seen during the prehospital treatment exercise bout. In normal females long-chain acyl carnitines are not generally lowered in plasma during an exercise bout (Lennon et al., 1983).

Urine samples were collected before and after exercise for only nine normal subjects and two anorexics because of consent problems. LC females had 57.2% short-chain acyl carnitines of total carnitine preexercise and 58.0% postexercise in urine. The two anorexics prior to hospital treatment had 61.8% short-chain preexercise and 67.2% postexercise. Posthospital treatment values increased to 85.9% preexercise and 76.0% postexercise. Owing to the small number of samples in the anorexics, no statistical analyses were conducted. However, these data would suggest increased urinary excretion of the elevated blood plasma short-chain acylated carnitines by the anorexic.

DISCUSSION

The normal increase in the concentrations of short-chain acyl carnitines during an acute exercise bout in humans (Lennon et al., 1983)

Table 4. The effect of exercise on blood plasma carnitine in normal healthy, lean, unconditioned females (LC) compared with primary anorexics before (AN-I) and after (AN-II) hospital treatment.

	Preexercise (μM)					Postexercise (μM)				
	Free	Short-chain	Long-chain	Percent SC	Percent LC	Free	Short-chain	Long-chain	Percent SC	Percent LC
Lean Controls (LC)										
Mean	34.98	4.91	6.16	10.46	13.53	33.61	8.83[a]	6.55	17.75[a]	13.57
SD	6.68	2.39	1.11	3.99	1.87	5.67	3.19	0.97	5.28	2.27
$n = 13$[b]										
Anorexics										
Pretreatment (AN-I)										
Mean	35.82	9.01	4.59	18.96	9.34	35.51	10.49	2.37	21.37	5.21
SD	11.60	1.75	1.68	4.76	2.45	10.92	4.00	1.94	4.20	4.53
p[c]	NS	<0.003	<0.03	<0.001	<0.001	NS	NS	<0.001	<0.04	<0.001
Posttreatment (AN-II)										
Mean	34.65	6.68	3.21	15.27	6.95	32.63	7.73	1.84	18.28	4.33
SD	3.73	1.44	2.02	4.49	4.18	4.88	1.98	1.62	4.32	3.92
p[c]	NS	NS	<0.001	NS	<0.001	NS	NS	<0.001	NS	<0.001
$n = 5$[d]										

[a]Significantly different before versus after exercise, $p < .01$.
[b]One blood plasma sample was lost from this group.
[c]Significantly different from LC.
[d]Same five patients before (I) and after (II) hospital treatment.

and rats (Lennon et al., 1985) is not observed in primary anorexics because they already have elevated concentrations of these derivatives at rest. This resting elevated short-chain acyl carnitine concentration is also present in long term dialysis patients (Lennon et al., 1982). Even after 4 weeks of hospitalization, where a significant weight gain and normalization of electrolytes were the criteria for recovery and further exercise testing, the typical increase in short-chain acyl carnitines was not seen with an acute bout of exercise.

We have observed elevated short-chain acyl carnitines in chronically trained, acutely exercising rats with a concomitant decline in serum branched-chain amino acid concentrations (Lennon et al., 1985). Alanine concentration has also declined, and alanine aminotransferase (E.C. 2.6.1.2) enzyme activity in skeletal muscle is "down regulated," suggesting that after a 1 hour bout of exercise at 75% VO_2max, the glucose-alanine cycle may be of little importance (Ji, Lennon, Nagle, Lardy, & Stratman, 1985). Significant increases in branched-chain keto acids and glutamine are observed in serum at this time. The elevated concentrations of short-chain acyl carnitines in the anorexics most likely reflect increased muscle protein catabolism and oxidation of branched-chain amino acids (Harper et al., 1984) for energy in lieu of free fatty acids, which apparently has not been altered by increased weight gains during hospitalization. On the basis of elevated short-chain acyl carnitines in the resting primary and the treated anorexia and their lack of response to an acute bout of exercise, one would expect all of the skeletal muscle branched-chain keto acid dehydrogenase to be in the active form (Kasperek et al., 1985). Thus, maximum combustion of branched-chain amino acids would be occurring in the anorexic. The branched-chain fatty acyl CoA derivatives may have limited further oxidation potential in human skeletal muscle (Van Hinsbergh, Veerkamp, & Glatz, 1979), thus they would be exported from the cell as branched-chain acyl carnitines. It is suggested that the primary anorexic has a permanently altered protein catabolic pathway induced by hormones or unknown compounds such as neuropeptides. Alterations observed in endocrinological parameters measured to date (DeRosa et al., 1983; Siriathsinshji & Mills, 1985) are probably not the primary factors that are responsible for this metabolic shift. Plasma amino acids and branched-chain keto acids need to be determined in this population for confirmation of this hypothesis. It is known that the weight gained during increased energy intake is primarily a process of adipose tissue deposition as shown by the increase in percent body fat.

Long term dialysis patients do not liberate sufficient free fatty acids owing to a lack of lipoprotein lipase activity, which results in hyperlipidemia (Feldman & Singer, 1975). Thus, the inability to supply suffi-

cient free fatty acids for oxidation in skeletal muscle most likely results in increased catabolism of protein and amino acids for energy. This results in a loss of muscle mass that is also reflected in the higher (two- to threefold) concentrations of short chain acyl carnitines in plasma (Lennon et al., 1986), which is also observed in the anorexics in the present study.

Some similarities exist among the primary anorexic, the dialysis patient, and those sepsis patients requiring total parenteral nutrition (TPN). The TPN sepsis patient apparently remains in a catabolic state with regard to protein, even though more than adequate nitrogen is being supplied. Increasing caloric content with sufficient amino acids only increases adipose deposition and does not alter the protein catabolic state (Cerra, Siegel, & Border, 1983).

Thus, the weight-gaining primary anorexic is in a state of lipogenesis that could be reflected by the decrease in long-chain acyl carnitines in the serum. At the same time the weight-gaining anorexic may still be catabolic regarding protein metabolism as shown by elevated short-chain acyl carnitines at rest. Weight gain, by itself, or normal electrolyte values may be poor criteria to determine whether appropriate metabolic shifts have occurred that may be necessary to alter the anorexic state permanently.

Evidently there has been a shift in metabolic priorities that may reflect control at the higher centers of the brain (Meklenburg, Loriaux, Thompson, Andrews, & Lipsett, 1974). It has been well documented that higher centers of the brain can alter reproductive phenomenon in humans, and it is not unlikely that these centers could be responsible for the metabolic alterations in the anorexic. The physiological and biochemical parameters now used to assess clinical treatment of the primary anorexic are not valid criteria since they do not reflect the inability to permanently alter this catabolic state of skeletal muscle. We need to establish what biochemical relationship exists between this catabolic parameter (short-chain acyl canitines) and plasma neuropeptides in the normal patient, the sepsis patient, and the primary anorexic state. Therefore, refeeding with weight gain and normal electrolyte values may not represent a reorientation of metabolism, but it may require either chemical or psychic alteration of specific neuropeptides to change this metabolic state (Mrosovsky, 1984).

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