

## Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine<sup>1,2</sup>

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### ABSTRACT

**Background:** The effects of food restriction on energy metabolism have been under investigation for more than a century. Data obtained are conflicting and research has failed to provide conclusive results.

**Objective:** The objective of this study was to test the hypothesis that in lean subjects under normal living conditions, short-term starvation leads to an increase in serum concentrations of catecholamines and thus to an increase in resting energy expenditure.

**Design:** Resting energy expenditure, measured by indirect calorimetry, and hormone and substrate concentrations were measured in 11 healthy, lean subjects on days 1, 2, 3, and 4 of an 84-h starvation period.

**Results:** Resting energy expenditure increased significantly from  $3.97 \pm 0.9$  kJ/min on day 1 to  $4.53 \pm 0.9$  kJ/min on day 3 ( $P < 0.05$ ). The increase in resting energy expenditure was associated with an increase in the norepinephrine concentration from  $1716 \pm 574$  pmol/L on day 1 to  $3728 \pm 1636$  pmol/L on day 4 ( $P < 0.05$ ). Serum glucose decreased from  $4.9 \pm 0.5$  to  $3.5 \pm 0.5$  mmol/L ( $P < 0.05$ ), whereas insulin did not change significantly.

**Conclusions:** Resting energy expenditure increases in early starvation, accompanied by an increase in plasma norepinephrine. This increase in norepinephrine seems to be due to a decline in serum glucose and may be the initial signal for metabolic changes in early starvation. *Am J Clin Nutr* 2000;71:1511–5.

**KEY WORDS** Glucose, healthy volunteers, indirect calorimetry, norepinephrine, respiratory quotient, resting energy expenditure, short-term starvation, Austria

### INTRODUCTION

For more than a century, the effects of food restriction on energy metabolism have been under investigation. Data obtained are conflicting and research has failed to provide conclusive results. As early as 1915, Benedict (1) reported a decrease in metabolic rate of 20–30%, induced by prolonged starvation. This finding was confirmed by further studies (2). Reductions in basal metabolic rate have also been reported after only 2–3 d of starvation (3). Other authors, however, found no decrease or even a moderate increase in resting energy expenditure (4).

Several impressive changes in substrate metabolism during starvation have been described (5, 6). Glucose oxidation decreases markedly during the first day of starvation (7) and fatty acids are mobilized, leading to an increase in plasma concentrations of fatty acids and ketone bodies and to an increased rate of fat oxidation (2, 6).

Because hepatic glycogen stores are depleted after a 24-h fasting period (6), gluconeogenesis is essential for providing glucose to the brain, which does not utilize ketone bodies to cover energy requirements at that time (5). An important factor inducing these changes in substrate metabolism is the decline in blood glucose during the first days of starvation (5). Consequently, insulin secretion decreases, resulting in increased lipolysis and release of amino acids from muscle tissue (5, 8, 9). Amino acids are precursors of gluconeogenesis in the liver during starvation. Hypoglycemia is known to enhance nerve signals from the hypothalamus to the adrenal medulla, which increases serum concentrations of catecholamines (10). Catecholamines stimulate glucose production by the liver (11), stimulate lipolysis (12), and elevate metabolic rates in a dose-dependent fashion (13). However, plasma catecholamine concentrations in early starvation have been reported to remain unchanged (3), to increase (14, 15), and to decrease (4).

Thus, the data available on the effect of short-term fasting on energy metabolism are conflicting. Therefore, we studied resting energy expenditure, substrate metabolism, and hormonal response to an 84-h starvation period in healthy, lean subjects. We tested the hypothesis that in lean subjects under normal living conditions (no hospitalization), short-term starvation leads to an increase in the serum concentrations of catecholamines and thus to an increase in metabolic rate.

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**TABLE 1**Characteristics of healthy, lean subjects on day 1<sup>1</sup>

	All subjects (n = 11)	Women (n = 7)	Men (n = 4)
Age (y)	28 ± 4	27 ± 3	30 ± 4
Body weight (kg)	64.2 ± 13.5	57.7 ± 10.1	75.7 ± 11.5 <sup>2</sup>
Height (cm)	168 ± 9	163 ± 4	176 ± 8 <sup>2</sup>
BMI (kg/m <sup>2</sup> )	22.5 ± 3	21.6 ± 3.2	24.2 ± 1.6

<sup>1</sup> $\bar{x} \pm SD$ .<sup>2</sup>Significantly different from women,  $P < 0.05$ .

## SUBJECTS AND METHODS

### Subjects

Eleven healthy, lean volunteers (7 women and 4 men) participated in the study. The characteristics of the volunteers are shown in **Table 1**. None of the volunteers were smokers. This study was approved by the Institutional Review Board of the University of Vienna. After extensive explanation of the study procedure, all volunteers gave informed consent.

### Experimental protocol

The study was performed on an outpatient basis to keep subjects under normal living conditions. However, the subjects were instructed to perform only necessary physical activities (ie, to avoid sports). They were allowed to drink only fresh water or mineral water without any added sugar during the study period. The first measurement was made after an overnight fast [started at 2100 the previous day (day 1)]. Further measurements were undertaken 36 h (day 2), 60 h (day 3), and 84 h (day 4) after the beginning of starvation. All volunteers entered the metabolic unit at 0700. Measurements were undertaken between 0800 and 0900 in a temperature-controlled room at 26 °C.

### Indirect calorimetry

The subjects laid in bed in a supine position for  $\geq 45$  min before the measurements were started and were instructed to lie quietly until the measurements were completed. Respiratory gas exchange was measured by using computerized open-circuit indirect calorimetry with a ventilated-hood system (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki), as described previously (16). Measurements were made every minute and the results were averaged over 45 min.

**TABLE 2**Results of metabolic studies<sup>1</sup>

	Day 1	Day 2	Day 3	Day 4
UNP (g/d)	7.47 ± 3.6	7.07 ± 2.1	10.94 ± 3.4 <sup>2,3</sup>	7.56 ± 2.3 <sup>4</sup>
$\dot{V}O_2$ (mL/min)	199 ± 45	224 ± 44 <sup>2</sup>	234 ± 45 <sup>2</sup>	229 ± 46 <sup>2</sup>
$\dot{V}CO_2$ (mL/min)	165 ± 35	165 ± 34	167 ± 31	162 ± 32
RQ	0.83 ± 0.05	0.74 ± 0.04 <sup>2</sup>	0.72 ± 0.03 <sup>2</sup>	0.71 ± 0.04 <sup>2</sup>
REE (kJ/min)	3.97 ± 0.9	4.37 ± 0.9 <sup>2</sup>	4.53 ± 0.9 <sup>2</sup>	4.43 ± 0.9 <sup>2</sup>
Nonprotein RQ	0.83 ± 0.06	0.73 ± 0.04 <sup>2</sup>	0.70 ± 0.04 <sup>2</sup>	0.70 ± 0.04 <sup>2</sup>
Weight (kg)	64.2 ± 13.5	63.5 ± 13.3 <sup>2</sup>	62.6 ± 13.2 <sup>2,3</sup>	61.5 ± 13.2 <sup>2,3,4</sup>

<sup>1</sup> $\bar{x} \pm SD$  of data for each day. UNP, urea-nitrogen appearance rate;  $\dot{V}O_2$ , oxygen consumption;  $\dot{V}CO_2$ , carbon dioxide production; RQ, respiratory quotient; REE, resting energy expenditure.<sup>2</sup>Significantly different from day 1,  $P < 0.05$ .<sup>3</sup>Significantly different from day 2,  $P < 0.05$ .<sup>4</sup>Significantly different from day 3,  $P < 0.05$ .

### Calculations

Energy expenditure was calculated from measured oxygen consumption, carbon dioxide production, and urea-nitrogen appearance rate according to the methods of Ferrannini (17) and Frayn (18). The urea-nitrogen appearance rate was calculated from 24-h urinary nitrogen excretion and changes in the body urea nitrogen pool (19).

### Hormone and laboratory measurements

Blood samples were drawn from a cannula inserted in a forearm vein directly after the indirect calorimetry. The cannula was put in place  $\geq 30$  min before the beginning of the measurement. The concentrations of plasma urea, cholesterol, and triacylglycerol were measured by using standard techniques. Urine urea nitrogen was measured colorimetrically (20). Urinary nitrogen was analyzed by using a standard micro-Kjeldahl technique.

All biological markers except insulin were analyzed in duplicate. Insulin was analyzed in triplicate. Glucose concentrations were measured by a glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma fatty acid concentrations were analyzed with a spectrophotometric enzyme kit (BioMerieux-Lyon, Lyon, France). Plasma epinephrine and norepinephrine were separated by HPLC and detected electrochemically according to a modified procedure described previously (21). Insulin was measured with a radioimmunoassay (Biochemical Immunossystems GmbH, Freiburg, Germany).  $\beta$ -Hydroxybutyrate in plasma was analyzed enzymatically as described previously (22).

### Statistics

This study was exploratory. To assess the association of the absolute values between 2 variables over time, Spearman's correlation coefficients for each volunteer were computed (norepinephrine versus resting energy expenditure, epinephrine, glucose, cholesterol, body weight,  $\beta$ -hydroxybutyrate, blood urea nitrogen, fatty acids, insulin, creatinine, respiratory quotient, and triacylglycerol). Subsequently, the resulting distribution of Spearman's correlation coefficients was analyzed: to show significant differences of the means of the obtained Spearman's correlation coefficients from zero, the one-sample  $t$  test or, if appropriate, the Wilcoxon one-sample test, was applied. To show differences in values across time, a repeated-measures analysis of variance (Greenhouse-Geisser test) was used. If the results of the repeated-measures analysis of variance were significant, linear contrasts were used for post hoc testing. All results are

**TABLE 3**  
Biochemical values<sup>1</sup>

	Day 1	Day 2	Day 3	Day 4
Norepinephrine (pmol/L)	1716 ± 574	2134 ± 1079	3409 ± 1349 <sup>2,3</sup>	3728 ± 1636 <sup>2,3</sup>
Epinephrine (pmol/L)	425 ± 180	311 ± 152	395 ± 158	398 ± 257
Insulin (pmol/L)	71 ± 21	71 ± 41	58 ± 19	59 ± 23
Glucose (mmol/L)	4.9 ± 0.5	3.9 ± 0.5 <sup>2</sup>	3.6 ± 0.5 <sup>2,3</sup>	3.5 ± 0.5 <sup>2,3</sup>
Fatty acids (μmol/L)	240 ± 191	616 ± 225 <sup>2</sup>	957 ± 443 <sup>2,3</sup>	1135 ± 575 <sup>2,3</sup>
Triacylglycerol (mmol/L)	0.87 ± 0.3	0.69 ± 0.2 <sup>2</sup>	0.94 ± 0.3 <sup>3</sup>	1.15 ± 0.4 <sup>3,4</sup>
Cholesterol (mmol/L)	4.88 ± 0.6	4.87 ± 0.6 <sup>2</sup>	5.24 ± 0.7 <sup>2,3</sup>	5.45 ± 0.7 <sup>2,3</sup>
β-Hydroxybutyrate (μmol/L)	182.7 ± 262.9	1949.9 ± 1458.7 <sup>2</sup>	4268.9 ± 2717.4 <sup>2,3</sup>	4781.6 ± 3001.6 <sup>2-4</sup>
BUN (mmol/L)	4.58 ± 1	5.59 ± 1 <sup>2</sup>	5.98 ± 1.3 <sup>2</sup>	4.64 ± 2 <sup>4</sup>

<sup>1</sup> $\bar{x} \pm SD$  of data for each day. BUN, blood urea nitrogen.

<sup>2</sup>Significantly different from day 1,  $P < 0.05$ .

<sup>3</sup>Significantly different from day 2,  $P < 0.05$ .

<sup>4</sup>Significantly different from day 3,  $P < 0.05$ .

presented as means ± SDs. A  $P$  value of  $<0.05$  was considered to be significant. For numerical analysis, SAS (release 6.12; SAS institute Inc, Cary, NC) was used.

## RESULTS

All subjects lost weight progressively during the study period (Table 2).

### Substrate concentrations

Mean glucose concentrations decreased and fatty acid concentrations increased significantly on days 2 and 3 and were not significantly different on day 4 (Table 3). Serum concentrations of β-hydroxybutyrate increased constantly during the study period. A decrease in triacylglycerol concentration on day 2 was followed subsequently by an increase on days 3 and 4. The concentration of cholesterol increased during starvation. An increase in the concentration of blood urea nitrogen on days 2 and 3 was followed by a decrease on day 4.

### Energy metabolism

Oxygen consumption and resting energy expenditure increased significantly between days 1 and 2 and remained high until the end of the study (Table 2). Carbon dioxide production rates remained unchanged, whereas respiratory quotients and nonprotein respiratory quotients decreased significantly during the study period. The urea-nitrogen appearance rate was higher on day 3 than on day 2 and was lower on day 4 than on day 3.

### Hormone concentrations

Norepinephrine concentrations increased during the study period. Serum insulin was lower on days 3 and 4 than on days 1 and 2; however, this result was not significant (Table 3). Statistical analysis detected a significant correlation between the concentration of serum norepinephrine and resting energy expenditure, fatty acids, β-hydroxybutyrate, blood glucose, respiratory quotient, and body weight (Table 4).

## DISCUSSION

This study showed that short-term starvation leads to a progressive increase in serum concentrations of norepinephrine, accompanied by an increase in resting energy expenditure,

lipolysis, and ketogenesis in healthy, lean subjects. The concentration of insulin did not change significantly during the study period. Therefore, our results indicate that an increase in serum norepinephrine concentration rather than a decrease in serum insulin concentration initiated by the decline in blood glucose concentration may be the primary initial signal of metabolic changes during early starvation.

Data on energy expenditure during early starvation are conflicting and the mechanisms responsible for the early adaptive response during fasting are not completely understood. A reduction in insulin-mediated inhibition of lipolysis or an increase in catecholamine-stimulated β-adrenergic activity may be an important mechanism for the metabolic adaptation during early starvation (4, 23). This theory is supported by Jensen et al (14), who showed that lipolysis is less completely suppressed by insulin and more readily stimulated by epinephrine. Mansell et al (4) found that the thermogenic response to a 30-min infusion of epinephrine was increased despite an even lower plasma epinephrine concentration achieved after 48 h of starvation. The lipolytic response to epinephrine after fasting in normal-weight and obese volunteers was found to be increased (15). However, the response to norepinephrine was not investigated in both studies.

In our study, epinephrine did not change over time. Norepinephrine increased constantly, whereas insulin did not decrease significantly during starvation. This increase in norepinephrine seems to have been initiated by hypoglycemia, which is known to stimulate the secretion of catecholamines, the effect on norepinephrine being more pronounced than that on epinephrine (10).

The observed progressive increase in norepinephrine concentration could explain the increase in metabolic rate and lipolysis during early starvation in our subjects. The latter finding agrees with the results of a study by Samra et al (24), who found an increased rate of activity of the hormone sensitive lipase and an increased transcapillary efflux of nonesterified fatty acids from adipose tissue during early starvation. Furthermore, an increase in fatty acids leads to increased expression of uncoupling protein 2 and uncoupling protein 3 during starvation (25, 26). An increase in the expression of uncoupling protein 3, which is highly expressed in skeletal muscle, and a direct thermogenic effect of norepinephrine may explain the increased resting energy expenditure (27).

Norepinephrine release from sympathetic nerves within the liver has also been shown to stimulate hepatic glucose production (28). Because gluconeogenesis is energy consuming (29), it

**TABLE 4**  
Description of the distribution of Spearman's correlation coefficients<sup>1</sup>

	Mean	Median	Maximum value	Minimum value	P
NE and REE	0.49	0.6	1	-0.8	<0.05
NE and fatty acids	0.62	0.8	1	0	<0.0005
NE and $\beta$ -hydroxybutyrate	0.64	0.8	1	-0.4	<0.0005
NE and glucose	-0.59	-0.6	0.1	-1	<0.0005
NE and RQ	-0.64	-0.63	0.4	-1	<0.0005
NE and body weight	-0.63	-0.8	0.4	-1	<0.0005

<sup>1</sup>*n* = 11. NE, norepinephrine; REE, resting energy expenditure; RQ, respiratory quotient.

may contribute to increased resting energy expenditure. The increased urea-nitrogen appearance rate on day 3 of our study reflected increased muscle proteolysis. Amino acids generated in proteolysis enter hepatic gluconeogenesis.


Data on catecholamine concentrations in early starvation are conflicting. Unchanged (3), decreased (4), and increased (30, 31) serum concentrations of catecholamines have been described. Our data on norepinephrine agree with those of Jensen et al (14), who found an increased concentration after an 84-h starvation period, and with those of Mansell et al (4), who reported an unchanged concentration after a 48-h starvation period. Although sodium depletion has been discussed as a cause of higher catecholamine plasma concentrations, the decline in plasma epinephrine and norepinephrine after normalization of plasma glucose concentration in fasting subjects to prefasting values is more consistent with the hypothesis that the elevated plasma catecholamine concentrations represent an adrenomedullary response to a decrement in plasma glucose concentration (31). Alternatively, starvation-induced lowering of blood glucose may enhance nerve signals of the hypothalamus to the adrenal medulla, which would increase the serum concentration of catecholamines. Glucose-responsive neurons in the hypothalamic region may play an important role in regulatory mechanisms (10, 32).

Because norepinephrine is synthesized and stored in sympathetic nerve endings, local concentrations likely reflect sympathetic activity more accurately than do the systemic concentrations that were measured in our study (10). As already mentioned, a hyperglycemic response and the mobilization of glycogen in the liver were reported after the stimulation of splanchnic nerves (28). This response was also detected in animals with both adrenal glands removed, indicating the importance of local concentrations of norepinephrine (33). An increased activity of the sympathetic outflow to the adipose tissue in the fasting state, which resulted in an increased hydrolysis of triacylglycerols, was also shown (10).

Our results on resting energy expenditure are in contrast with those of earlier studies, which found a decrease by up to 20% during fasting (1). However, this reduction in the metabolic rate was found during prolonged starvation only and may have been the result of adaptive mechanisms aimed at conserving body mass (6). The lower resting energy expenditure and urea-nitrogen appearance rate on day 4 than on day 3 may reflect the onset of adaptive mechanisms at the transition from brief to prolonged fasting, such as an increased use of alternative substrates. It has been shown that high concentrations of ketone bodies inhibit the rate of protein degradation in muscle (6).

We cannot explain the decline in energy expenditure on day 4 of our study, even though norepinephrine was still rising. Although

not studied by us, it has been suggested that energy deprivation has suppressive effects on the hypothalamus-pituitary-thyroid axis that diminish the metabolic rate (34).

In summary, the present study showed that resting energy expenditure increases in early starvation, accompanied by an increase in serum norepinephrine concentration. This increase in norepinephrine could be the result of a decline in glucose concentrations and may be the primary initial signal of metabolic changes occurring in early starvation. 

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