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Persistent suppression of resting energy expenditure after acute hypoxia

Kerstin M. Oltmanns[a,d,*], Hartmut Gehring[b], Sebastian Rudolf[a], Bernd Schultes[c], Ulrich Schweiger[a], Jan Born[d], Horst L. Fehm[c], Achim Peters[c]

[a]*Departments of Psychiatry and Psychotherapy, University of Luebeck, 23538 Luebeck, Germany*
[b]*Department of Anaesthesia, University of Luebeck, 23538 Luebeck, Germany*
[c]*Department of Internal Medicine I, University of Luebeck, 23538 Luebeck, Germany*
[d]*Department of Neuroendocrinology, University of Luebeck, 23538 Luebeck, Germany*

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Abstract

Resting energy expenditure (REE) is known to be influenced by various ambient conditions such as oxygen supply. Investigations in healthy subjects during acute hypoxia revealed a drop in REE, but persistent effects after hypoxia had ended have not been examined so far. Although indirect calorimetry is a well-established method to measure REE, it may lead to false conclusions when hyperventilation, rise in lactate or catecholamines, and decrease of food intake accompany hypoxia. Therefore, we determined REE in healthy men after hypoxia had ended and under conditions of controlled energy supply during a glucose clamp. In a double-blind crossover study design, we induced hypoxia for 30 minutes by decreasing oxygen saturation to 75% (vs 96% in a control session) in 13 healthy men. Indirect calorimetry was performed at baseline and 150 minutes after hypoxia had ended. Plasma glucose was held stable between 4.5 and 5.5 mmol/L, and lactate as well as catecholamine concentrations were monitored. In parallel, we measured alterations in hormones of the hypothalamic-pituitary-thyroid axis, which is one known factor mediating changes in REE. Resting energy expenditure was decreased after hypoxia (from 1656 ± 80 to 1564 ± 97 kcal/d) as compared with the normoxic control condition (1700 ± 82 to 1749 ± 79 kcal/d, $P = .037$), whereas the respiratory quotient remained stable ($P = .79$). Plasma lactate, catecholamine levels, and the pituitary thyroid secretory activity were unchanged after hypoxia ($P > .2$). Our data demonstrate that the REE decrease persists 150 minutes after acute hypoxia, indicating an adaptation of energy metabolism. This should be valued as an additive pathogenic factor in diseases with disturbed energy metabolism.

1. Introduction

Energy homeostasis—in times of growing prevalence of obesity and comorbid diseases—is a central issue of clinical research in metabolism. Total daily energy expenditure (TDEE) comprises resting energy expenditure (REE), diet-induced thermogenesis, and physical activity. Resting energy expenditure, the largest part of total daily energy expenditure (65%-70%) [1], is known to be influenced by various ambient conditions such as oxygen supply. In vitro, oxidative phosphorylation is more efficient at lower than air oxygen saturation levels [2]. In vivo, in obstructive sleep apnea (OSAS), a sleep disturbance with chronic hypoxic manifestation, energy expenditure is increased [3-5] and decreases after treatment with laser-assisted uvuloplasty [5] or continuous positive airway pressure (CPAP) [4]. The rise in energy expenditure in OSAS may be attributed to either hypoxia or to the frequently found obesity, which is known to be characterized by increased energy expenditure [6]. Although the relationship between obesity and increased energy expenditure has been shown [6], the impact of hypoxia, independent from obesity, on energy expenditure is less clarified. In healthy lean subjects, studied over 31 days in a hypobaric chamber corresponding to 4500- to 8848-m altitude, energy expenditure was significantly diminished [7]. The authors attributed the shift toward a negative energy balance to reduced food intake and thereby decreased energy supply, known from previous studies at high altitude [8], rather than to effects of hypoxia itself. Reduced food intake would offer an explanation for the

* Corresponding author. Department of Neuroendocrinology, University of Luebeck, 23538 Luebeck, Germany. Tel.: +49 451 500 3642; fax: +49 451 500 3640.
E-mail address: oltmanns@medinf.mu-luebeck.de (K.M. Oltmanns).

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apparent contradiction between the revealed REE decrease found by Westerterp et al [7] and the fact that hypoxia induces an activation of the sympathetic nervous system [9-11] and thereby an increase in REE [12]. However, previous measurements of REE took place in the course of hypoxia. Persistent effects after normalization of oxygen supply and thereby independent from catecholamine influences or alterations in energy supply were not investigated. Furthermore, one of the main factors regulating REE is the hypothalamic-pituitary-thyroid (HPT) axis [13,14], which has been found to be suppressed by hypoxia [15-20]. We hypothesized that REE decrease is preserved after acute hypoxia had ended, indicating a persistent metabolic adaptation independent of acute stress hormonal activation possibly mediated by suppression of the HPT axis.

One more reason why measurement of REE after the ending of hypoxia seems reasonable is a technical one. The common method to measure REE is indirect calorimetry. This method calculates total energy production of the body by determination of oxygen consumption and carbon dioxide production. In fact, indirect calorimetry can lead to false conclusions in subjects with impaired respiratory gas exchange [1]. Furthermore, hyperventilation and circulating lactate during hypoxia may influence indirect calorimetry [21,22]. Consequently, the determination of REE based on gas exchange under conditions of reduced oxygen supply may not validly reflect the status of energy metabolism. To avoid contamination of REE measurement by changes in gas or lactate concentration during and shortly after hypoxia, we measured REE when these parameters had been normalized again, that is, 150 minutes after hypoxia had ended. Subjects were healthy young men. To control for energy supply, we performed the study during conditions of a euglycemic glucose clamp. Based on our hypothesis that hypoxia-induced suppression of the HPT axis might explain the decreased REE after hypoxia, we simultaneously determined concentrations of thyrotropin, free triiodothyronine (fT_3), and free thyroxine (fT_4) as well as thyroglobulin (TBG). In addition, epinephrine and norepinephrine levels were monitored to control for activation of the sympathetic nervous system.

2. Methods

2.1. Subjects

We included 13 healthy men (24.3 ± 1.0 years [mean ± SEM]) with a body mass index (BMI) of less than 25 kg/m^2 (22.2 ± 0.4 kg/m^2 [mean ± SEM]) in the study. The number of the subjects was based on a power analysis estimating that a sample of 13 subjects was needed to reach a statistical significance of .05 with 94% ("Power and sample size calculation program" by Nathan Enas, MS). Exclusion criteria were respiratory diseases, chronic or acute illness, anxiety disorders, alcohol or drug abuse, smoking, competitive sports, exceptional physical or mental stress, and current medication of any kind. Each volunteer gave written informed consent, and the study was approved by the local ethics committee (ethics committee of the medical faculty, deanery, University of Luebeck, Germany).

2.2. Experimental design and procedure

The subjects participated in a hypoxic and a normoxic condition separated by an interval of at least 4 weeks. Hypoxia (normoxia) was induced while subjects underwent a hyperinsulinemic euglycemic clamp. The order of conditions was balanced across subjects, and experiments were performed in a double-blind fashion. All subjects were requested to abstain from alcohol, not to perform any kind of exhausting physical activity, and to go to bed no later than 11:00 PM on the day preceding the study. On the days of the study, subjects reported to the medical research unit at 11:00 am after an overnight fast of at least 12 hours. The experiments took place in a sound-attenuated room with the subjects lying on a bed with their trunk in an almost upright position (about 60°). A cannula was inserted into a vein on the back of the hand, which was placed in a heated box (50°C-55°C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein of the contralateral arm. Both cannulas were connected to long thin tubes, which enabled blood sampling and adjustment of the rate of dextrose infusion from an adjacent room without awareness of the subject. Baseline blood samples for determining thyrotropin, fT_3, fT_4, TBG, catecholamine, and lactate concentrations were collected, and indirect calorimetry was performed (Deltatrac II, MBM-200 Metabolic Monitor, Datex-Engström Deutschland, Achim, Germany; day to day coefficient of variation [CV] <13%). To convert respiratory gas exchange measurements to energy expenditure, the Deltatrac system uses the following modified Weir equation:

$$EE = (5.5 \times V_{CO_2}) + (1.76 \times V_{O_2}) + (1.99 \times Un)[\text{kcal/day}]$$

with V_{O_2} = oxygen consumption, V_{CO_2} = carbon dioxide production, and Un = urea nitrogen excretion, which is 13 g/d for adults.

After a baseline period of 1 hour, insulin (H-insulin, Hoechst, Frankfurt, Germany) was infused at a continuous rate of 1.5 mU · min^{-1} · kg^{-1}. A 20% dextrose solution was simultaneously infused at a variable rate to control plasma glucose levels. Arterialized blood was drawn at 5-minute intervals to measure plasma glucose concentration (Glucose Analyser, Beckman Coulter, Munich, Germany). Plasma glucose was held stable between 4.5 and 5.5 mmol/L during the clamps.

After 3 hours of the euglycemic clamp, hypoxia was induced for 30 minutes by decreasing oxygen saturation to

75%. (vs 96% on the control condition). During the induction of hypoxia and also during the normoxic control period, participants breathed through a tight-fitting face mask connected to a Trajan 808 (Dräger Medizintechnik, Luebeck, Germany) fresh gas supply, using a valveless high-flow system between 14 and 17 L/min. Inspired oxygen fraction was varied by adjusting oxygen and nitrogen. Oxygen saturation was continuously measured by pulse oxymeter. After 30 minutes, oxygen saturation was quickly normalized. After another 150 minutes, blood samples were collected again for determination of thyrotropin, fT_3, fT_4, TBG, catecholamine, and lactate, and indirect calorimetry was performed.

2.3. Assays

All blood samples were immediately centrifuged and the supernatants stored at −24°C until assay. Plasma thyrotropin, fT_3, fT_4, and TBG were all measured by immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA; thyrotropin, interassay CV <10.0% and intra-assay CV <6.2%; fT_3, intra-assay CV <11.0% and interassay CV <14.1%; fT_4, intra-assay CV <5.8% and interassay CV <6.7%; TBG, intra-assay CV <9.2% and interassay CV <11.0%). High-pressure liquid chromatography was applied to measure plasma epinephrine (intra-assay CV <2.9%, interassay CV <4.2%) and norepinephrine (intra-assay CV <2.6%, interassay CV <3.9%; Chromosystems, Munich, Germany). Plasma lactate concentrations were measured by routine clinical methods.

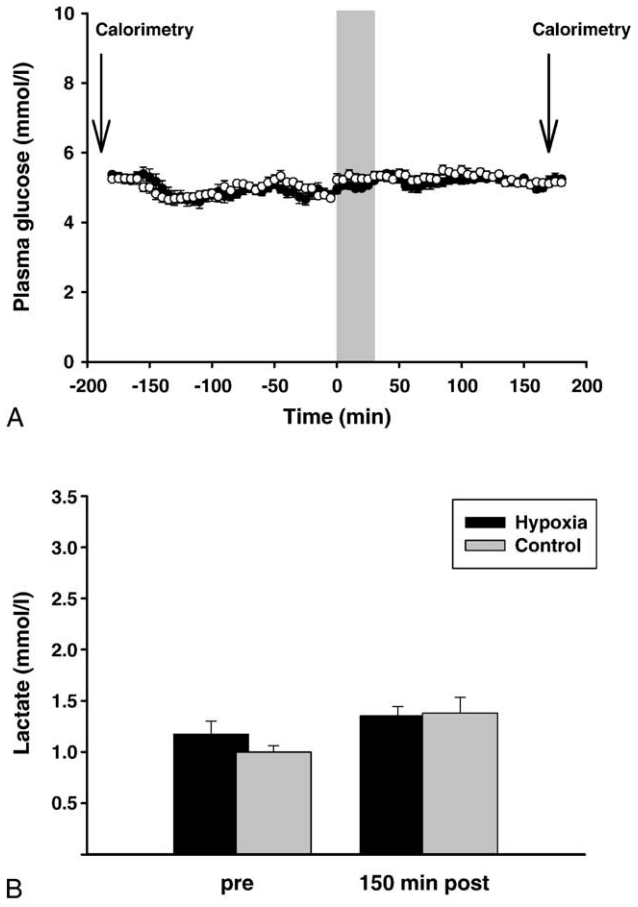

Fig. 1. A, Time course (mean ± SEM) of plasma glucose concentrations during the hypoxic (black circles) and the normoxic (white circles) glucose clamp. Gray area marks the time of hypoxic or normoxic intervention. The hypoxic intervention started at 0 minute. The arrows mark the time points of calorimetry. B, Mean (±SEM) plasma lactate concentrations during the hypoxic (black) and the normoxic (gray) condition. Lactate concentrations were measured at baseline and 150 minutes after hypoxia had ended (n = 13 for each condition; paired *t* test comparison of the changes from baseline, $P = .25$).

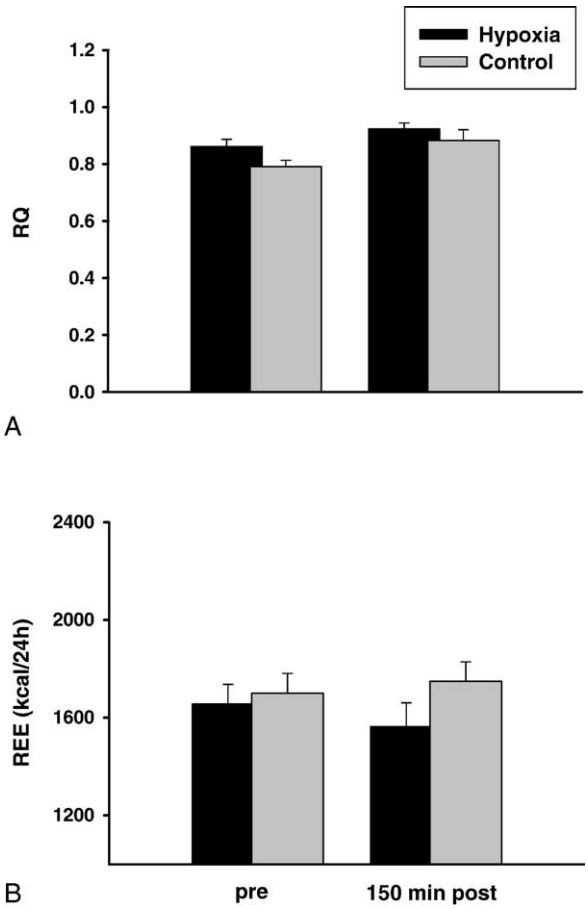

Fig. 2. Mean (±SEM) respiratory quotient (A) and resting energy expenditure (B) during the hypoxic (black) and the normoxic (gray) condition. Measurements were performed at baseline and 150 minutes after hypoxia had ended. (n = 13 for each condition; paired *t* test comparison of the changes from baseline, $P = .79$ for A and $P = .037$ for B).

2.4. Statistical analysis

Values are presented as means ± SEM. Statistical analysis was based on paired *t* test comparison of the changes from baseline (as dependent variable, we used the difference between baseline and postintervention measurement). A *P* value of less than .05 was considered significant.

3. Results

3.1. Oxygen saturation, plasma glucose, catecholamines, and plasma lactate

After induction of hypoxia, oxygen saturation decreased over a period of about 10 minutes and then stayed at a plateau of 74% ± 2%, whereas during the normoxic condition, oxygen saturation remained stable at a mean level of 98% ± 2%. Plasma glucose did not differ between the 2 conditions (5.0 ± 0.1 vs 5.2 ± 0.1 mmol/L; Fig. 1A), although hypoxia, as already published, induced a distinct decrease in the dextrose infusion rate, indicating reduced glucose tolerance as compared with the normoxic control condition [23]. Epinephrine and norepinephrine levels were equal during baseline and showed no alterations at the end of the sessions (P = .22 and .91, respectively). During hypoxia, as already published, epinephrine concentrations were significantly increased [23]. In addition, plasma lactate concentrations, measured at baseline and 150 minutes after hypoxia had ended, were comparable in both treatment conditions (P = .25 for paired t test comparison of the changes from baseline; Fig. 1B).

3.2. Respiratory quotient and resting energy expenditure

Fig. 2 summarizes the main outcome of the indirect calorimetry at baseline and at the end of the sessions. The respiratory quotient increased during both clamps, which was significant for the hypoxic condition (P = .031; paired t test comparison) and a trend during control (P = .090), but paired t test comparison of the changes from baseline did not reveal a significant effect of hypoxia 150 minutes later (P = .79; Fig. 2A).

Resting energy expenditure did not indicate any alterations after hypoxia or normoxia within one session (P > .1 for both), but as compared with the control session, REE clearly decreased after hypoxia (from 1656 ± 80 to 1564 ± 97 kcal/d after hypoxia vs 1700 ± 82 to 1749 ± 79 kcal/d in the control session, P = .037; paired t test comparison of the changes from baseline; Fig. 2B).

3.3. Hypothalamus-pituitary-thyroid axis

In Fig. 3, results of the thyroid hormone responses are illustrated. Free triiodothyronine decreased during control (P = .003), but only tended to decrease after hypoxia (P = .092; Fig. 3A and B), which may reflect the circadian variations of the hormone. Free thyroxine did not change neither in the control session nor after hypoxia (P > .1 for both). However, paired t test comparison of the changes from baseline between both sessions revealed that hypoxia did not have any effect on the hormone concentrations of fT_3 and fT_4 in peripheral blood (P = .24 for fT_3 and P = .89 for fT_4). Thyroglobulin decreased equally during both treatment conditions (P = .047 after hypoxia and P = .003 during control; Fig. 3C). Comparison of the changes in both

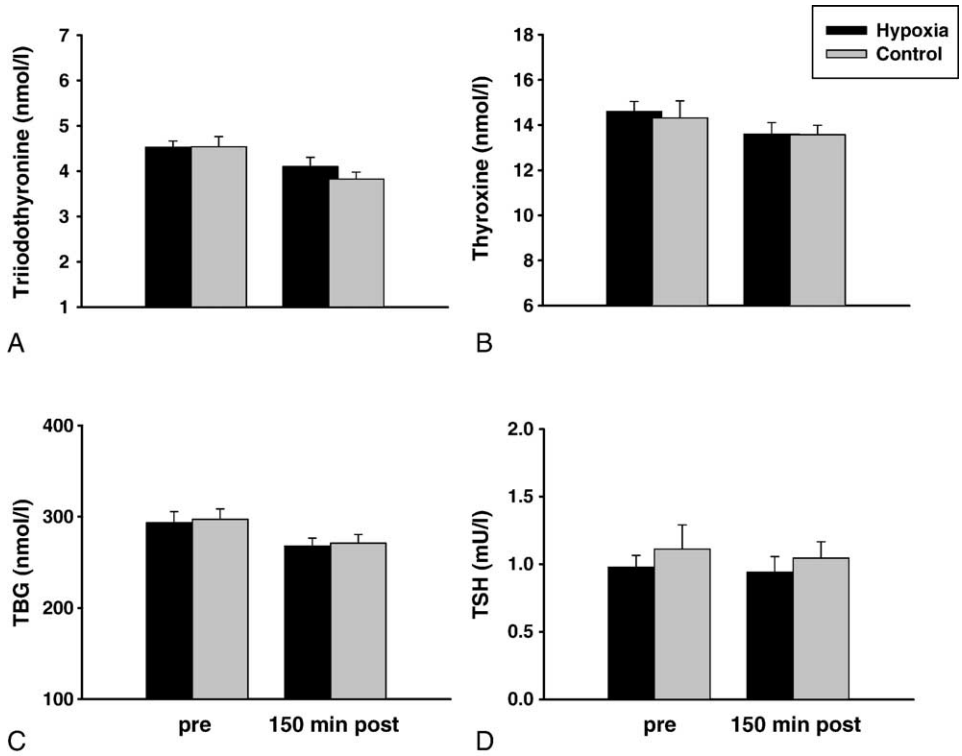

Fig. 3. Mean (±SEM) for triiodothyronine (A), thyroxine (B), thyroglobulin (C), and thyrotropin (D) concentrations during the hypoxic (black) and the normoxic (gray) condition. Measurements were performed at baseline and 150 minutes after hypoxia had ended (n = 13 for each condition; paired t test comparison of the changes from baseline, P = .24 for A, P = .89 for B, P = .87 for C, and P = .37 for D).

conditions demonstrated no effect of hypoxia ($P = .87$). Thyrotropin remained stable throughout the clamps ($P = .58$ after hypoxia and $P = .25$ during control) and was not changed by intermittent hypoxia ($P = .37$ for comparison of both sessions; Fig. 3D).

4. Discussion

Our results demonstrate that the suppression of resting energy expenditure persists 150 minutes after acute hypoxia. These data extend previous observations in rats [24] and humans [7], indicating that REE is decreased during hypoxia. So far, no data exist investigating the long-term effects on energy expenditure after hypoxia had ended.

A possible mechanism by which REE may be regulated is an alteration of the HPT axis, which is known to be suppressed by hypoxia in animal studies in vivo [15-19] and in vitro [20]. Our results do not indicate such a suppression probably because of a relatively short exposure (30 minutes) to hypoxia as compared with the previous interventions where exposure lasted for days and weeks. However, in diseases with chronic hypoxic manifestation, data are conflicting. In chronic obstructive pulmonary disease, fT_3, fT_4, and thyrotropin were not found to be altered in most studies [25-27]. Only one group found that severe airway obstruction is associated with reduced basal and stimulated thyrotropin levels [28]. Similarly, data in OSAS are not consistent. In one study, OSAS was found to be associated with decreased thyrotropin levels as compared with healthy controls [29], whereas in another, fT_4 levels were negatively correlated with baseline OSA severity, and thyrotropin concentration was unchanged at baseline but declined after treatment with CPAP [30]. In contrast, Lanfranco et al [31] demonstrated that fT_3, fT_4 as well as thyrotropin response to TRH were similar in OSAS as compared with those of body mass index–matched or lean controls. However, OSAS is frequently associated with obesity, which in turn is characterized by elevated T_3 [32]. The decrease in fT_3, fT_4, and TBG that we found in our study may reflect the circadian rhythm with nadir concentrations during the afternoon [33], the point of time when the second measurement of REE took place.

Our protocol for measuring REE involved the infusion of glucose and insulin after the first REE measurement. Consequently, one could argue that our second REE measurement did not really reflect REE, but rather REE plus the thermic effect of infused glucose and insulin. However, we did not find an alteration in REE during the control condition wherefore this possibility appears unlikely. Nevertheless, even if we had found a significant REE increase during control, this fact would even strengthen the result of a decrease during the hypoxic session.

Previously, Westerterp and coworkers [7] attributed the decrease of REE during hypoxia to a diminished food intake and thereby energy supply. In our study, blood glucose levels were held stable for a constant energy supply. However, we previously published data from the same study, which demonstrated that glucose infusion rates decreased during hypoxia as compared with control [23]. This finding contradicts previous studies indicating that hypoxia enhances skeletal muscle glucose uptake [34,35]. A discrepancy that has been assigned in our discussion to confounding stress-induced agitation in animal studies and a disconnection from a number of hormonal and neuronal inputs in vitro, respectively [23]. However, there is one fact to add. There is evidence for a differing impact of catecholamines on glucose uptake in skeletal muscle with a stimulatory effect of norepinephrine and an inhibition by epinephrine [36]. Acute hypoxia of a moderate degree predominantly stimulates adrenal medullary epinephrine secretion [36], which might explain our finding of decreased glucose infusion rates during hypoxia associated with an increased epinephrine concentration and unchanged norepinephrine levels [23]. Nevertheless, at the time of REE measurement in the present data, catecholamine concentrations as well as glucose infusion rates were equal in the normoxic and the control condition. To eventually explore the relationship between the change in the rate of glucose infusion and the change in REE, we performed a correlation between the percentage change of these variables that revealed a nonsignificant result ($P = .48$). However, we cannot exclude a causal relationship between a decline of energy uptake and the drop in REE after hypoxia.

Glucose intolerance, causing a decrease in energy uptake as well as hyperglycemia and thereby glucosuria, is associated with a reduced risk of weight gain in nondiabetic subjects, and once people develop diabetes, they tend to lose weight [37]. This correlation may be clarified by an arithmetic example. Presuming that glucosuria ranges between 0 and 80 g/L (our observation in patients with type 2 diabetes mellitus), the energy equivalent of 1 g glucose is 4 kcal, and the urine volume of a diabetic patient amounts between 1 and 4 L/d, then the energy loss of the patients ranges between 0 and 1280 kcal/d. These differences in energy loss apparently exert a significant effect on energy homeostasis and a loss of 1280 kcal/d should lead to a decrease of body weight. Moreover, during glucose intolerance, cellular energy supply by glucose uptake is diminished. In this context, it appears possible that reduced REE acts as energy saving to prevent further weight loss induced by decreased energy supply. In addition, hypoxia leads to a decreased excitability in hippocampal neurons in the brain [38]. Given that, in our study, changes in glucose, lactate, and thyroid activity can be ruled out as factors explaining the drop in REE, one may speculate that REE reduction after hypoxia is a persistent metabolic adaptation mediated by the brain according to the general hypothesis of the neocortex and the limbic system playing a central role in the pathogenesis of a disturbed energy metabolism [39]. Moreover, although the brain is relatively small in relation to the entire body mass, its own energy requirement is huge as compared

with all other organs in the body [40]. Presuming a decreased neuronal activity in the brain during hypoxia [38], a diminished cerebral energy demand may probably suppress total REE as reflected by our data. However, our data cannot prove such hypotheses.

In OSAS, energy expenditure was found to be increased [3-5] and decreases after treatment with laser-assisted uvuloplasty [5] or CPAP [4]. Our results indicate that acute hypoxia causes a decrease in REE. This apparent contradiction to studies in OSAS may be explained by the fact that in OSAS, hypoxia/reoxygenation occurs periodically for years. Therefore, an adaptive mechanism appears possible, which may attenuate REE suppression with progression of the disease. Furthermore, in contrast to our subjects, most patients with OSAS are overweight or obese. This leads us to speculate that the obesity-associated increase of REE in OSAS could override the hypoxia-induced decrease. Probably, an initial decrease in REE at the onset of OSAS may even contribute to overweight in these patients. However, in the present study it is not possible to clarify the physiologic reasons for the greater metabolic efficiency induced by hypoxia. In any case, our results suggest that hypoxia causes alterations in energy metabolism, which persist even after hours. This should be valued as an additive pathogenic factor in diseases with disturbed energy metabolism. Further investigations are desirable to clarify the mechanism of these alterations as well as the relevance for body weight regulation.

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