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Metabolic rate and fuel utilization during sleep assessed by whole-body indirect calorimetry

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Abstract

The purpose of this study was to examine metabolic rate and substrate oxidation during sleep in relation to time of sleep and sleep stage. Twelve male subjects free from sleep-disordered breathing slept for 469 ± 8.7 (mean ± SE) minutes until natural awakening in a whole-body indirect calorimeter, and polysomnographic documentation of sleep was recorded. Energy expenditure decreased during the first half of the night, reached a nadir (a 35% decrease), and remained relatively stable until awakening. Similarly, fat oxidation decreased from the onset of sleep. On the other hand, carbohydrate oxidation showed no remarkable changes from the onset of sleep but began to increase before awakening. Because distribution of sleep stages is not uniform throughout the night, with rapid-eye-movement (REM) sleep tending to appear later in the sleep, effect of sleep stage on energy metabolism was isolated by analysis of covariance with time as a covariate. Subsequent comparison of metabolic rate by 1-way analysis of variance with Bonferroni post hoc analysis revealed that energy expenditure during REM sleep was significantly greater than that during sleep stages 2 and 3/4 (stage 2, 25.248 ± 0.961; stage 3/4, 24.825 ± 0.935; REM, 25.712 ± 0.928 kcal kg^{-1} fat-free mass d^{-1}). Carbohydrate oxidation during REM sleep was significantly greater than that during sleep stage 3/4 (stage 3/4, 12.229 ± 1.071; REM, 13.986 ± 1.291 kcal kg^{-1} fat-free mass d^{-1}). Respiration quotient was statistically different among sleep stages, but Bonferroni post hoc analysis failed to identify significant differences (stage 2, 0.850 ± 0.010; stage 3/4, 0.846 ± 0.011; REM, 0.861 ± 0.013). The increases in energy expenditure and carbohydrate oxidation during REM sleep are consistent with a notion that changes in energy metabolism in brain are manifested as small fluctuations in whole-body energy metabolism during sleep.

1. Introduction

Human 24-hour energy expenditure has 3 major components: resting energy expenditure, thermic effect of food, and energy cost of physical activity. The basal energy expenditure is the largest component of total energy expenditure in sedentary individuals (60%-75% of total energy expenditure) [1]. Therefore, it is always considered to be a fundamental basis for computing the daily energy expenditure. For calculation of daily energy requirement, energy cost of sleep is often assumed to be equal to resting energy expenditure, according to the Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University recommendations [2]. However, this might be an oversimplification of the sleep metabolic rate because previous studies observed downward trend in energy expenditure as the night progresses and upward elevation before awakening [3]. Furthermore, sleep itself is a complicated process; and a person alternatively goes through 2 different types of sleep called *non–rapid-eye-movement* (NREM) sleep and *rapid-eye-movement* (REM) sleep. *Rapid-eye-movement sleep* is defined by absence of tonic muscle tone, eye movements, and appearance of low-voltage electroencephalographic activity similar to that seen during waking [4]. The mental activity of human REM sleep is associated with dreaming [5]. Rapid-eye-movement sleep is accompanied by an

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increase in cerebral blood flow, oxygen, and glucose uptake [6]. Non–rapid-eye-movement sleep and REM sleep continue to alternate through the night, and the NREM-REM cycle is approximately 90 to 110 minutes. Wakefulness within sleep usually accounts for less than 5% of the night. Stages 1, 2, 3, and 4 and REM generally comprise 2% to 5%, 45% to 55%, 3% to 8%, 10% to 15%, and 20% to 25% of the night, respectively [5].

Previous studies using indirect calorimetry with polysomnographic documentation of sleep suggested a relationship between sleep stage and energy metabolism. Some, but not all, studies in which sleeping metabolic rate was measured using a ventilated face mask or hood observed higher metabolic rate during REM and drowsiness/light sleep (stages 1 and 2) compared with that during NREM and deep sleep (stages 3 and 4), respectively [7-11]. Use of a face mask or a hood might interfere with the quality of sleep by affecting the comfort of the subjects. To improve the quality of sleep during the measurement, small open-circuit indirect calorimeter was developed by Fontvieille et al [3]. Diffusion of expired gas into the chamber, volume of which was 1022 L, limited time resolution of the system; and energy metabolism was calculated every 5 minutes. In their study, only those 5-minute periods containing at least 80% of a constant sleep stage were considered for analysis; and significant differences in metabolic rate between REM and stage 3 (REM > stage 3) and stages 2 and 3 (stage 2 > stage 3) were reported.

In addition to energy expenditure, indirect calorimetry provides respiration quotient (RQ), which indicates the type of substrate oxidized [12]. However, changes in RQ during sleep have received less attention; and one study suggested lower RQ during sleep stage 3 compared with all the other stages (REM and stages 1, 2, and 4) [3]. Changes in RQ before awakening have not been reported, although there is a general agreement among authors that energy expenditure starts to rise toward morning [9-13].

To improve the quality of sleep during the measurement, the present study measured sleeping metabolic rate in a room-sized human calorimeter, which was equipped with sensitive gas analyzer and new algorithm for improved transient response [14], addressing the following questions: (1) Is there difference in energy expenditure, RQ, and substrate of oxidation among sleep stages? (2) How does substrate of oxidation (carbohydrate vs fat) change during downward trend in energy expenditure as the night progresses and upward elevation before the subjects wake up?

2. Methods

2.1. Subjects

Twelve male subjects were recruited in this study. All subjects were free from respiratory and cardiac pathology, and none of them was taking any medications or supplements. Before this study began, the nature, purpose, and risks of the study were explained to all the subjects; and informed written consent was obtained. The study was approved by the local ethics committee of the University of Tsukuba.

2.2. Protocol

The subjects were required to abstain from alcohol, drugs, beverage containing caffeine, naps, and strenuous exercise during the daytime. Although meal before sleep was not controlled in the present study, consuming food within 3 hours of bedtime was inhibited. On arrival at the laboratory at 8:00 PM, each subject was instrumented with electrodes to measure central and occipital electroencephalography (C3/A2, C4/A1, O1/A2, O2/A1), chin electromyogram, eye electrooculographic activity (right and left electrooculographic), and electrocardiogram. In addition, sensors for oronasal thermistor, nasal pressure, and tracheal microphone were attached. The subject was also fitted with inductive belts around the rib cage and abdomen for the detection of respiratory movements, and pulse oximeter was positioned on index or middle finger. While the subject quietly lay on the bed, resting metabolic rate before sleep was measured for 30 minutes; and the subject continued to lie on the bed until sleep began. The measurement continued until the subject woke up.

2.3. Sleep stages

A standard polysomnogram [15] was recorded on Alice 5 1848 (RESPIRONICS, Murrysville, PA). The records were coded, and 30-second epochs were used to score sleep stages according to conventional criteria [15,16] by an investigator without knowledge of the conditions or order of the records.

2.4. Indirect calorimetry

The airtight chamber located at the University of Tsukuba measures 2.00 × 3.45 × 2.10 m and has an internal volume of 14.49 m^3. It has 1 entrance door and an air lock for food supply. Air in the chamber is pumped out at a rate of 70 L min^{-1}. Temperature and relative humidity of incoming fresh air were controlled at 25.0°C ± 0.5°C and 55.0% ± 3.0%. The chamber is furnished with an adjustable hospital bed, a desk, a chair, a wash basin, and a toilet.

Concentrations of oxygen (O_2) and carbon dioxide (CO_2) in outgoing air were measured with high precision by online process mass spectrometry (VG Prima δB; Thermo Electron, Winsford, United Kingdom). Precision of mass spectrometry, defined as the standard deviation for continuous measurement of calibration gas mixture (O_2, 15%; CO_2, 5%), was less than 0.002% for O_2 and CO_2. At every minute, O_2 consumption and CO_2 production rates were calculated using algorithm for improved transient response [14]. Computation of metabolic rate can be viewed as reconstructing unknown signal (metabolic rate)

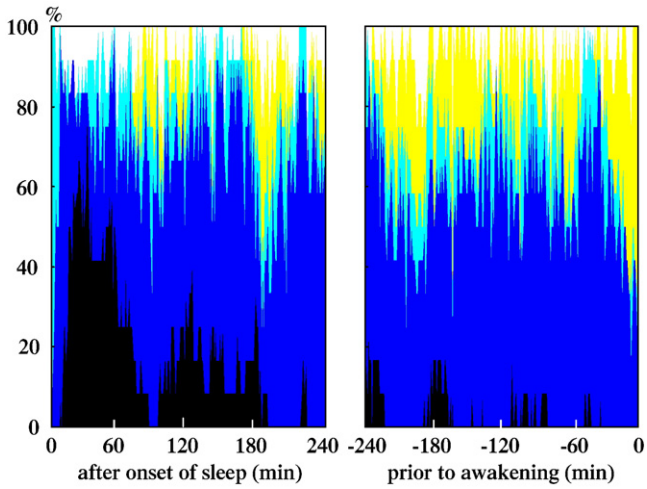

Fig. 1. Distribution of sleep stages in 12 subjects for the initial 4 hours (left) and the last 4 hours (right) of sleep. Percentage of subjects in awake stage (□), stage 1 (■) , stage 2 (■), stage 3/4 (■), and REM (■) changed along time of sleep. In the initial 4 hours, subjects in stage 3/4 were observed more than those in REM sleep. On the contrary, distribution of REM sleep increased, whereas stage 3/4 decreased in the last 4 hours of sleep.

from the known causally related effects of the signal (gas concentration in the chamber). When dealing with linear time-invariant systems, like chamber of whole-body calorimeter, the computation of input signal from the effects is called deconvolution [17]. However, direct solution of the deconvolution problem can be ill conditioned; that is, a small percentage error in the data is amplified in a much larger percentage error in the estimate. In our new algorithm for human calorimeter, the Phillips-Tikhonov regularization approach was adopted. Details of the algorithm are described in Appendix A.

From O_2 consumption and CO_2 production rates, energy expenditure, RQ, and carbohydrate and fat oxidation were calculated according to the equations described by Weir [18] and Ferrannini [19], respectively.

2.5. Statistical analysis

Data in the text, tables, and figures are given as means ± SE. To evaluate time course of metabolic rate and substrate of oxidation, repeated-measures 1-way analysis of variance (ANOVA) were used. Because duration of sleep in each subjects was different, the ANOVAs were applied for the initial 4 hours and the last 4 hours of sleep.

Effect of sleep stage on energy metabolism was evaluated through the following steps. First, to synchronize sleep stage with energy metabolism, measurements of energy metabolism were advanced by 2 minutes, taking into account the response of open-circuit indirect calorimeter. Energy metabolism was measured at 1-minute intervals, and only those 1-minute periods of constant sleep stage were considered for the analysis. In this analysis, stage 1 was excluded because of unstable sleep with much noise by the muscle tonus and intermingling with wake. Epochs with body movements and the subsequent 3 minutes, and with respiratory event such as apnea and hypopnea were ruled out. Second, effect of sleep stage on energy metabolism was isolated by analysis of covariance with time of sleep as a covariate; and the representative value of each sleep stage was obtained for each subject. Finally, comparison of metabolic rate and substrate of oxidation among sleep stages was made by repeated-measures 1-way ANOVA followed by Bonferroni post hoc test. A power analysis, using the standard deviation of our data, suggested that 12 participants would be needed to detect the following differences—0.5 kcal kg^{-1} fat-free mass (FFM) d^{-1} in energy expenditure, 0.017 in RQ, 1.3 kcal kg^{-1} FFM d^{-1} in carbohydrate oxidation, and 1.5 kcal kg^{-1} FFM d^{-1} in fat oxidation—between sleep stages with an α value of .05 and a power of 0.80.

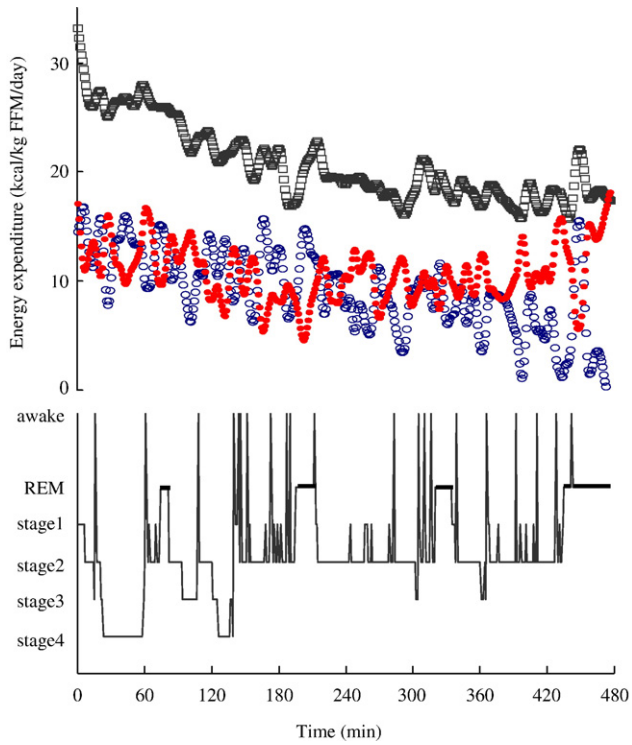

Fig. 2. Changes in energy metabolism and sleep stages during 1 night for 1 subject. Energy expenditure (□) and oxidation of carbohydrate (●) and fat (○) are shown in the upper panel. Sleep stages (awake, REM sleep, or sleep stages 1-4) are shown in the lower panel. The subject experienced frequent but short awake stage (20 times and mean duration of the stage wake as 20 seconds in this case) judging from the polysomnogram recording at 30-second intervals, although the subject was unaware of it. This example demonstrates the following: (1) Sleep architecture showed a normal pattern: stage 3/4 sleep occupied less time in the second NREM-REM cycle and disappeared from later cycles; sleep stage 2 expanded to occupy the NREM portion of the cycle; REM episodes became longer across the night. (2) Energy expenditure decreased during the first part of the night. (3) Carbohydrate oxidation increased during the second and fourth REM sleep of the night. (4) In contrast with downward trend in energy expenditure and fat oxidation, carbohydrate oxidation began to increase well before the subject woke up.

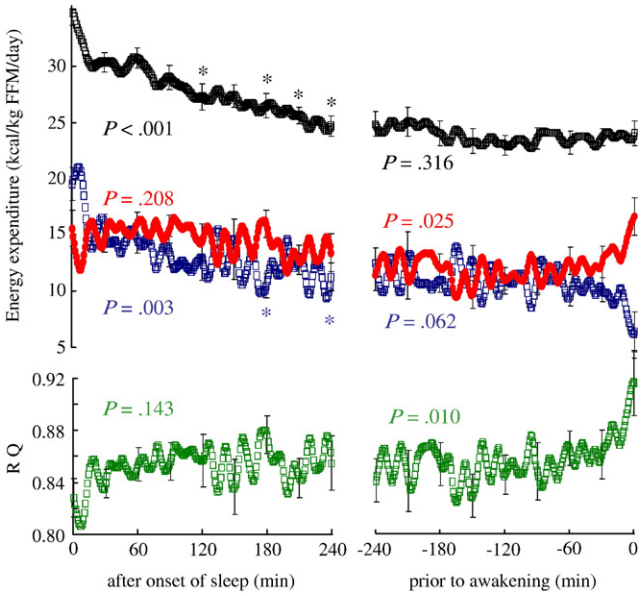

Fig. 3. Mean energy metabolism in 12 subjects throughout the night for the initial 4 hours (left) and last 4 hours (right) of sleep. Energy expenditure (□) and oxidation of carbohydrate (●) and fat (□) are shown in the upper panel. Respiratory quotient is shown in the lower panel (□). Statistical analyses were performed on data every 30 minutes by 1-way ANOVA, followed by Bonferroni post hoc tests. *P* values for repeated-measures 1-way ANOVA are shown on the figure. *Significant difference from onset of sleep ($P < .05$) by Bonferroni post hoc test.

Statistical analysis was performed using SPSS statistical software (Version 14.0; SPSS Japan, Tokyo, Japan), with the level of statistical significance set at 5%.

3. Results

Because sleep-disordered breathing such as obstructive sleep apnea syndrome and primary snoring [16] was not observed, data from the all 12 subjects (age, 22.5 ± 1.1 years; height, 173.4 ± 1.0 cm; weight, 71.7 ± 4.2 kg; body mass index, 23.6 ± 1.1 kg/m^2; FFM, 58.1 ± 2.4 kg) were used for statistical analysis. The total sleep time, time in bed, and sleep efficiency (total sleep time/time in bed) were 469 ± 8.7 minutes per night, 551.8 ± 13.3 minutes per night, and 85.4% ± 1.9%, respectively. The percentage of sleep time spent in each sleep stage for the group as a whole (9.3% ± 1.4% in stage 1, 52.2% ± 2.3% in stage 2, 11.4% ± 1.1% in stage 3/4, and 13.3% ± 0.9% in REM) was within the previously reported reference range [3]. Distribution of sleep stage was not uniform throughout the night, with REM sleep tending to appear later in the sleep (Fig. 1).

An example of changes in sleep stages and energy metabolism during a night is shown in Fig. 2. In contrast with downward trend in energy expenditure and fat oxidation, carbohydrate oxidation began to increase well before the subject woke up in this case. Because duration of sleep in each subject was different, average ± SE of energy metabolism was calculated for the initial 4 hours (Fig. 3, left) and the last 4 hours (Fig. 3, right) of the sleep. There was a downward trend in energy expenditure as the night progressed, and statistical analysis applied on data at every 30 minutes revealed the following: Energy expenditure differed over time ($P < .001$ for the time effect from the onset of sleep by ANOVA; Fig. 3, left); and Bonferroni post hoc analysis indicated that metabolic rate at 120, 180, 210, and 240 minutes after the onset of sleep was significantly lower than that during the first minute of the sleep ($P < .05$; Fig. 3, left). Respiratory quotient ($P = .010$ for the time effect before awakening by ANOVA) and carbohydrate oxidation ($P = .025$) seemed to increase toward the end of sleep, particularly during 30 minutes before awakening (Fig. 3 right). On the other hand, fat oxidation decreased over time from the onset of sleep ($P = .003$ by ANOVA; Fig. 3, left); and the downward trend seemed to continue until awakening, although it was not statistically significant ($P = .062$ by ANOVA; Fig. 3, right). Bonferroni post hoc analysis indicated that fat oxidation rate at 180 and 240 minutes after the onset of sleep was significantly lower than that during the first minute of sleep ($P < .05$).

To isolate the effect of sleep stage on energy metabolism, data were analyzed by analysis of covariance, followed by repeated-measures 1-way ANOVA with Bonferroni post hoc statistical analysis. The differences in energy expenditure ($P = .001$ for main effect of sleep stage by 1-way ANOVA), carbohydrate oxidation ($P = .010$), and RQ ($P = .050$) among 3 sleep stages were statistically significant. Bonferroni post hoc test indicated significant differences in energy expenditure between stage 2 or stage 3/4 and REM ($P < .019$ and $P = .002$, respectively) and in carbohydrate oxidation between stage 3/4 and REM ($P = .05$), but failed to identify differences in RQ among sleep stages (Table 1).

Table 1
Energy metabolism in different sleep stage

Sleep stage	Stage 2	Stage 3/4	REM	*P* value
Energy expenditure (kcal kg^{-1} FFM d^{-1})	25.248 ± 0.961*	24.825 ± 0.935*	25.712 ± 0.928	.001†
RQ	0.850 ± 0.010	0.846 ± 0.011	0.861 ± 0.013	.050†
Carbohydrate oxidation (kcal kg^{-1} FFM d^{-1})	12.836 ± 1.023	12.229 ± 1.071*	13.986 ± 1.291	.010†
Fat oxidation (kcal kg^{-1} FFM d^{-1})	12.394 ± 1.123	12.581 ± 1.291	11.709 ± 1.354	.252

* Significant difference from REM ($P < .05$) by Bonferroni post hoc test.
† Significant effect of sleep stage by repeated-measures 1-way ANOVA, *P* values of which are shown in the table.

4. Discussion

The room-sized human calorimeter was used in the present study because it may provide a more comfortable sleep environment for the subjects. This is clearly demonstrated by the sufficient length of sleep (469 ± 8.7 minutes per night) with better sleep efficiency (85.4% ± 1.9%) in the present study. Sleep efficiency was not reported in previous studies [5,7-20] except one [11], in which it was 77.1% ± 2.4% and the value was lower than the lower limit of normal value (82.8%) [21]. To our knowledge, time course of RQ during sleep has never been reported, although that of O_2 consumption, CO_2 production, and energy expenditure has been reported in previous studies [22-24]. This paucity of literature for time course of RQ during sleep reflects technical difficulties of whole-body indirect calorimetry due to the small amplitude of the signal in relation to the size of the room. Small error in measurement of gas concentration is amplified in a much larger error in O_2 consumption and CO_2 production rate, and RQ estimate suffers from errors in both O_2 consumption and CO_2 production. By adopting a nonparametric deconvolution as a new noise suppression algorithm and installing sensitive gas analyzer, the present study reported changes in RQ during sleep in a whole-body indirect calorimeter. The main findings of the present study were that energy expenditure and carbohydrate oxidation were greater in REM sleep compared with those in stages 2 and 3/4 and that carbohydrate oxidation increased before awakening.

Our findings are consistent with previous ones in which the differences in O_2 consumption between REM and NREM sleep were observed using hood to collect expired air [8,9]. For statistical reason, further comparison of energy metabolism among stages in NREM sleep was not possible in the present study. Fragmental evidence of previous reports suggests that O_2 consumption during deep sleep (stages 3 and 4) are lower than that during shallow sleep (stages 1 and 2) [5,7,8], but the differences are subtle and not always observed [10,11]. In addition, the present study showed that the increase in energy expenditure during REM sleep was accompanied by an increase in carbohydrate oxidation. Brain's major fuel is glucose, and brain glucose metabolism accounts for more than 50% of systemic glucose utilization during the postabsorptive period [25]. Because of the major contribution the brain plays in total glucose consumption, it is reasonable to assume that changes in brain activity affect substantial part of whole-body glucose metabolism. During REM sleep, increments in cerebral blood flow, glucose, and/or O_2 uptake have previously been noted [26-30]. Thus, the increase in central nervous system electrical activity and energy metabolism seemed to be reflected as fluctuations in whole-body energy metabolism during sleep in man.

When viewed with a longer scale in time, the relation between energy metabolism in central nervous system and that in the whole body was not straightforward. First, one might expect increases in energy expenditure and carbohydrate oxidation as the night progresses because dominant sleep stage shifts from deep to REM sleep. However, systemic glucose utilization declines during the sleep; and this decline is largely accounted for by reduced brain glucose metabolism in man [28]. Part, but not all, of the fall in systemic glucose turnover could be blocked by keeping subjects awake through the night [31]. Second, it is also reasonable to assume that prolonged fasting during the night shifts energy source from carbohydrate to fat. When gluconeogenesis plays a role, about 0.1 g of fatty acid is oxidized to provide for the energetic cost of this endergonic reaction to synthesize each gram of glucose from alanine [19]. Third, energy metabolism during the first part of the night is affected by thermic effect of food, which subjects consumed before sleep in normal conditions including our experiment. In the present study, energy expenditure and fat oxidation decreased during the first 4 hours, but remained relatively constant during the last 4 hours of the sleep. Thus, downward trend in energy expenditure was parallel to that in fat oxidation, suggesting a contribution of energy metabolism in peripheral tissue but not that in central nervous system. Consistent with this notion, the rate of decrease in sleeping metabolic rate is negatively correlated to body weight (correlation coefficient, −0.829), body mass index (−0.896), and FFM (−0.798) [32]. The physiologic significance of factors such as body mass, thermic effect of food, and duration of sleep in determining downward trend in energy expenditure during sleep remains to be determined.

The increase in RQ before awakening was accompanied by an increase in carbohydrate oxidation. As REM sleep becomes dominant sleep stage during this period of sleep, the increase in carbohydrate oxidation is partly explained by a physiologic sleep architecture (Fig. 1). However, the average increase in carbohydrate oxidation during the final hour of the sleep (13.23 ± 1.16 at 1 hour before and 17.06 ± 1.62 kcal kg^{-1} FFM d^{-1} immediately before awakening) was greater than the differences in sleeping metabolic rate between REM sleep and the other sleep stages (Table 1); and one can assume additional factors to enhance carbohydrate oxidation before awakening. Because estimates of carbohydrate oxidation by indirect calorimetry reflect net balance of glucose oxidation and synthesis, the increase in carbohydrate oxidation suggests the increase in oxidation of glucose from glycogenolysis or dietary carbohydrate but not from gluconeogenesis [19]. Therefore, we assumed that the increase in carbohydrate oxidation before awakening reflected enhanced oxidation of glucose released from glycogen. Rates of glucose production and utilization have previously been observed to increase during the final hour of sleep in normal subjects [33]. Such increments occur during the hours of 5:00 AM to 8:00 AM in general and are thought to be related to secretion of growth hormone during the first hours of sleep [31]. In patients with insulin-dependent diabetes, this increase in endogenous glucose production generally results in a rise in plasma glucose

concentration and is referred to as the *dawn phenomena* [34]. The possible involvement of growth hormone in the dawn phenomena suggests that gluconeogenesis is also enhanced during the final hour of sleep, although gluconeogenesis is invisible to indirect calorimetry. Because continuous glucose monitoring has recently become available [35], it remains to be clarified if the increase in energy metabolism and carbohydrate oxidation is exaggerated in diabetic patients with dawn phenomena.

In summary, the present study with young subjects free of sleep-disordered breathing revealed that energy metabolism and carbohydrate oxidation were enhanced during REM sleep compared with NREM sleep. The increase in carbohydrate oxidation was also observed before awakening. Sleeping metabolic rate is the component of energy expenditure that explains a large proportion of total daily energy needs in individuals, but the contribution of a low sleeping metabolic rate to the etiology of obesity is undecided. Furthermore, obesity is often a risk factor and possibly a cause of sleep apnea; but it is also likely that sleep apnea increases the risk for weight gain [36,37]. Detailed analysis of obese subjects with and without obstructive sleep apnea remains to be determined.

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Appendix A

The symbols used throughout are consistent with those used by Brown et al [38], and volume and flow rate were assumed to be corrected to standard temperature pressure dry (STPD).

Variables:

F: flow rate, liters per minute (STPD)
f: fractional concentration
R: rate of gas production, liters per minute (STPD)
t: time, minutes
V: volume of chamber, liters (STPD)

Subscripts:

i: incoming
o: outgoing
G: any gas

Algorithm

Concentration of a gas at t and its rate of appearance at time τ (Ra[τ]) is related by a convolution integral.

$$\int_{-\infty}^{t} h(t-\tau)\mathrm{Ra}(\tau)d\tau \tag{1}$$

where the function $h(t)$ describes the input-output behavior of the chamber and is called the *impulse response of the system*. The inverse problem to solve is

$$\Delta Vf_{GO}(t) = \int_{0}^{t} h(t-\tau)R_G(\tau)d\tau \tag{2}$$

where $Vf_{GO}(t) = Vf_{GO}(t) - \int_{-\infty}^{t} h(t-\tau)Fif_{Gi}(\tau)d\tau$, and can be estimated from chamber volume and gas concentration of outgoing air (δVf_{GO}). Adopting matrix notation, mass of gas in the chamber (c) derived from the metabolism is

$$c = Hu \tag{3}$$

where c is a vector of dimension n containing output function sampled at times $t_1 < t_2,\ldots, t_n$ ($t_1 > 0$); u is a vector of dimension n containing the metabolic rate sampled at times $\tau_1 < \tau_2,\ldots, \tau_n$ ($\tau_1 = 0$; $\tau_i = t_{i-1}$ for $i = 2,\ldots, n$) and assumed to be piecewise constant; H is a $n \times n$ lower triangular matrix of impulse response, whose entries are given analytically by

$$H_{ij} = \begin{cases} 0 & (i<j) \\ \left(1-e^{-\lambda}\right)/\lambda & (i=j) \\ \left\{\left(1-e^{-\lambda}\right)/\lambda\right\}e^{-\lambda\left(\tau_i-\tau_j\right)} & (i>j) \end{cases} \tag{4}$$

where λ is F/V. Each nonzero element describes the output of the model at time t_i when all initial conditions are zero and the input is a pulse of a unit amplitude between t_{j-1} and t_j. Because direct solution of the deconvolution problem can be ill conditioned, our new algorithm for human calorimeter adopted the Phillips-Tikhonov regularization approach. The regularized estimate u is defined as

$$u = \arg\min\left[(y-Hu)^T B^{-1}(y-Hu) + \gamma u^T Q^T Q u\right] \tag{5}$$

where y denotes the n-dimension vector of the noisy data, and its measurement error was assumed uncorrelated ($E[e] = 0$, $\mathrm{Cov}[e] = B$). Q is the square Toeplitz matrix ($n \times n$) whose first column is $[1, -2, 1, 0,\ldots, 0]^T$ [39]. Regularization parameter γ is an arbitrary nonnegative parameter that controls the degree of smoothing of the solution. The first term on the right-hand side in Eq. 5 measures the fidelity to the data, whereas the second term is introduced to penalize the roughness of the estimate. The closed-form solution of Eq. 5 is

$$u = \left(H^T B^{-1} H + \gamma Q^T Q\right)^{-1} H^T B^{-1} y \tag{6}$$

Assuming that the accuracy of the gas concentration measurement was known (SD = 0.002%), regularization parameter γ was tuned until [39,40]

$$\mathrm{SSU} = q(\gamma)/\gamma \tag{7}$$

where SSU is sum of the squared estimate and

$$q(\gamma) = \mathrm{trace}\left[B^{-1/2}H\left(H^TB^{-1}H + \gamma Q^TQ\right)^{-1}H^TB^{-1/2}\right] \tag{8}$$

Validation of the algorithm against known input, such as CO_2 infusion and ethanol combustion tests, has been reported [14].

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