Regulatory alterations of daily energy expenditure induced by fasting or overfeeding in unrestrained rats

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SHIBATA, HIROYUKI, AND LUDWIK J. BUKOWIECKI. *Regulatory alterations of daily energy expenditure induced by fasting or overfeeding in unrestrained rats.* J. Appl. Physiol. 63(2): 465–470, 1987.—The consequences of fasting or overfeeding during 2 days on energy expenditure were investigated by continuously monitoring O_2 consumption in unrestrained, unanesthetized rats. O_2 consumption decreased by 15% on the 1st day of fasting and then by an additional 15% on the 2nd day. On the 3rd day, when rats were fed again, energy intake increased by 30% above control (prefasting) values, whereas energy expenditure rapidly increased but no more than control values. On the other hand, when ad libitum fed animals were offered a sucrose solution (32%) for 2 days, energy intake increased by 30% and energy expenditure by 9–12%. On the 3rd day, when the rats were fed with their normal diet, energy intake significantly decreased under control (preoverfeeding) values during one day, but energy expenditure rapidly returned to normal values. The results show that fasting decreases, whereas hyperphagia increases 24-h energy expenditure during the treatments. When the treatments are terminated, energy expenditure rapidly returns to normal values, but fasting induces a postfasting increase of energy intake (during 2 days), whereas hyperphagia, on the contrary, results in a transient decrease of appetite. This indicates that alterations of food intake induce compensatory changes of energy expenditure during the treatments, but that after the treatments, energy balance is normalized via regulatory adjustments in the ratio of energy expenditure over energy intake.

oxygen consumption; starvation; appetite

RESEARCH OVER THE LAST 20 years revealed that homeothermal animals possess an energy buffering system for maintaining body energy constant. French scientists have called this "le pondérostat" (literally translated "body weight-stat") to emphasize the fact that the majority of people maintain a constant body weight throughout life despite great daily variations of energy intake and expenditure. One major component of this energy buffering system resides in the adjustment of energy intake according to the level of energy expenditure. Indeed, it is known that food intake increases when energy expenditure is stimulated by cold exposure (4) or by exercise (mainly in female rats) (5, 6). The opposite situation, adjustment of energy expenditure in function of energy intake, also seems to play an important role. For instance, it has been demonstrated that overfeeding for several weeks increases energy expenditure in humans (1, 7, 19, 21), rats (12, 17), and pigs (8, 10). Likewise, underfeeding or fasting decreases energy expenditure in humans (1, 9) and rats (11, 12).

There is a great variation in the literature about the quantitative effects of hyperphagia (above maintenance levels of energy intake) on energy expenditure. In rats, the increment of energy expenditure induced by hyperphagia varies among different reports from 16 to 89% of the excess energy intake (20). One reason for this divergence among laboratories is that energy expenditure is often measured under unphysiological conditions (in anesthetized or restrained animals, after gavage) or under nonrepresentative situations (i.e., only in the morning, after an overnight starvation). Another reason might be that the capacity for facultative thermogenesis (or regulatory diet-induced thermogenesis) varies among rat strains (18). Indeed, it is unlikely that such a variation (5-fold) can solely be explained on the basis of changes in diet composition affecting obligatory thermogenesis (the specific dynamic action of food). In addition, few studies attempted to analyze the consequences of energy intake alterations on energy expenditure in a continuous manner over long periods of time (several days). We reasoned that by increasing the number of animals, the frequency of measurements as well as the total experimental period, more precise and representative data of energy expenditure could be obtained.

On this basis, it was decided to construct an O_2 consumption apparatus allowing the determination of 24-h energy expenditure in 7–11 animals during several days. Using this apparatus we investigated the consequences of starvation and overfeeding on energy intake and expenditure.

The principal goals of the present study were: *1*) to analyze the effects of starvation (2 days) or overfeeding (2 days) on 24-h energy expenditure, and *2*) to determine whether a 2-day period of fasting or overfeeding was inducing postfasting or postoverfeeding compensatory alterations in energy intake and/or expenditure, and if so, during how much time. The results show that the ratio of energy expenditure over energy intake critically depends on the previous nutritional state of the animal (fasted or overfed) and that regulatory alterations in that ratio may contribute to normalize animal energy content.

METHODS

Animals. Two groups of seven female Sprague-Dawley rats weighing 190–230 g (60–80 days old) were introduced in metabolic cages made from Plexiglas (18 × 10 × 9 cm, inside dimensions) with free access to Purina chow and

tap water (with or without sucrose). The rats could freely turn in their cages, but there was no space for walking. Except for the eating periods (mainly at night), the animals were quietly lying on a grill that was fixed at 2 cm above the bottom of the cage. The cages were cleaned on a daily basis (between 1800 and 1900 h), and food intake values were measured and corrected for spoiled particles. Food was given in small cups that were fixed inside the cages. The cups had a solid bottom and a lateral grill with a small mesh to avoid food spillage. The nipples of the drinking bottles contained a steel ball to prevent dripping. The bottles were periodically checked for tightness. The photoperiod was 12:12 h (0700–1900 h of light period). The air temperature was 25°C, but the body heat generated by the animals increased the temperature inside the cages up to 27°C.

Measurements of O_2 consumption. O_2 consumption was successively estimated every 12 min for 45 s in eight different cages, nonstop during 9–10 days (Fig. 1). One of the cages was left vacant and was used as a reference for measuring room air. Room air (25°C) was continuously pumped (via pump 2, Fig. 1, model AM 5, Apollo, Los Angeles) at a flow of 1.0 l/min (variable-area flowmeters, Cole-Palmer, Chicago) into each cage through a small hole (1.8 cm ID). A portion of the air from each cage was constantly pumped (600 ml/min) by a sampling apparatus (R-2 Flow Control, Amertek Thermox, Pittsburgh, PA) into an O_2 analyzer (model S-3A, Amertek Thermox). The analog outputs from the analyzer were fed into a microcomputer (Apple IIE) equipped with an Adalab interface card and Quick input/output software (Mandel, Rockwood, Ontario, Canada) that recorded and analyzed the data. The microcomputer also controlled a system of three-way valves (Festo, Rexdale, Ontario, Canada), allowing the sequential determination of the O_2 concentration in each of the eight cages. The volumes of the various components of the system were: a cage (1,620 ml), a rat (~200 ml), a food cup (50–60 ml), the space from the sample cage to pump 2, including the inside volume of the flowmeter (100 ml), and, finally, the space from pump 2 to the O_2 analyzer, including the inside volume of the drier filled with Drierite (~20 ml). Particular attention was given to minimize the dead space from the sample cage to the O_2 analyzer (120 ml) in order to increase the frequency and the duration of the measurements. To avoid errors due to flow disturb-

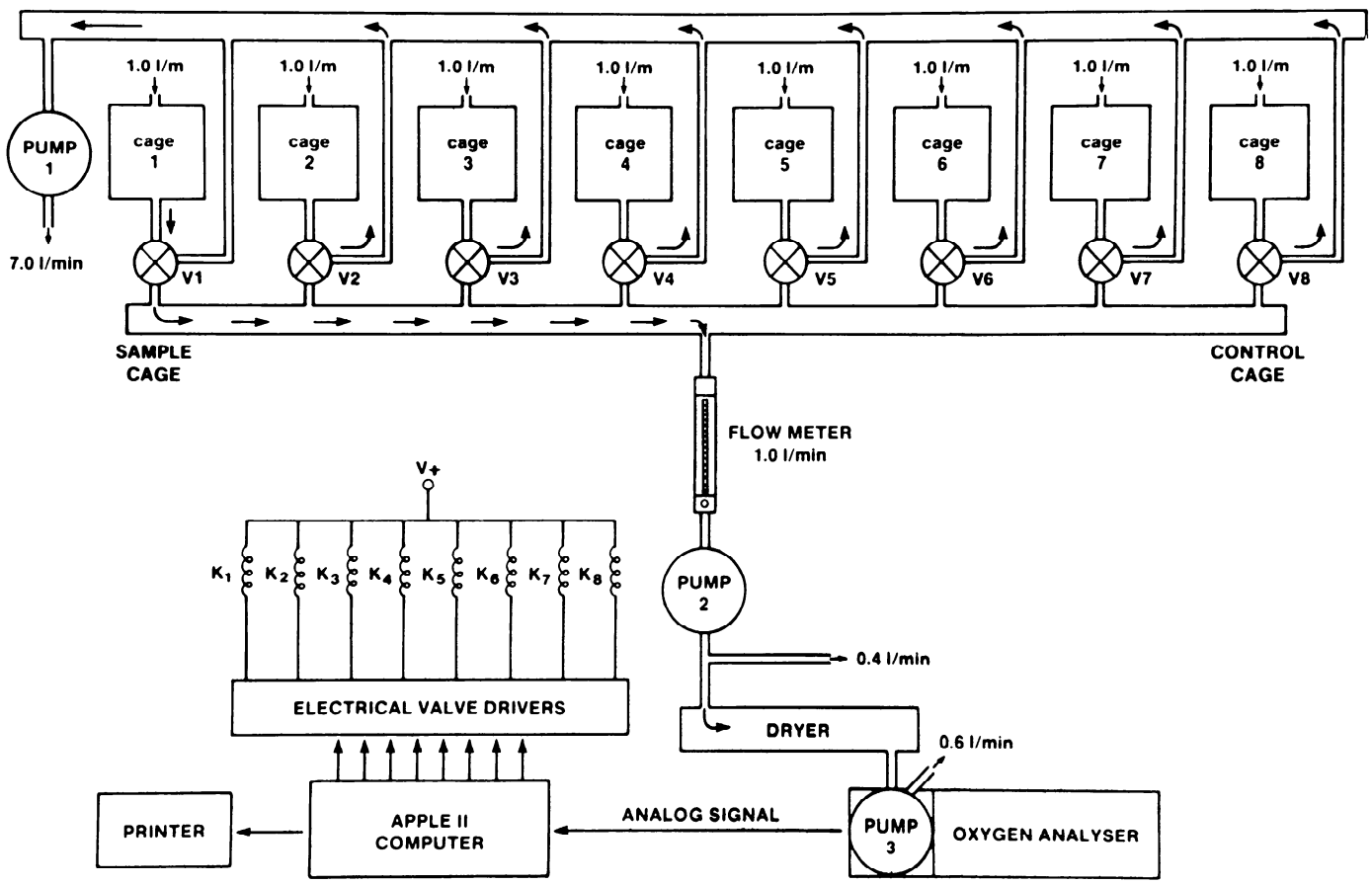

FIG. 1. Flow diagram of apparatus used for measuring O_2 uptake in 8 cages (or more), sequentially, during several days (for details see METHODS). Diagram shows system of 3 pumps aspirating total of 8 l/min of air through 8 cages. *Arrows* indicate airflow when O_2 consumption in cage 1 was analyzed. Under these conditions, 1.0 l/min of air was diverted from cage 1 to O_2 analyzer via pump 2, whereas 7.0 l/min were expelled in room via pump 1. System of 3-way valves controlled by a computer allowed sequential analysis of O_2 uptake in 8 cages. Cage 8 did not contain animals and served as a reference cage. O_2 consumption was determined from difference between values measured in sampling cages and cage 8. System was constructed for determining O_2 consumption in as many as 12 cages, but only 8 were used in present study.

ances resulting from the sequential changes, the first 45 s of readings were discarded from the recordings and only data from the following 45 s were registered. Preliminary experiments revealed that stable and reproducible measurements were obtained with an alternance of 45 s of air flushing followed by 45 s of readings. The system provided 13 measurements/s, and the average value of 585 measurements during 45 s was calculated and recorded. The amount of O_2 consumption was determined by multiplying the airflow through the cages by the difference between the O_2 concentration in an occupied and unoccupied cage (Fig. 1, cages 1 and 8, respectively). The difference in the O_2 concentration between room air and the sampled gas ranged between 0.3 and 1.5%, the lowest values being recorded when the rats were lying quietly in their cages. The volumes of consumed O_2 were expressed in ATP (the conversion factor from ATP to STP, including humidity, varied from 0.910 to 0.922, depending on daily conditions).

Alteration of energy intake. Before the experiment was started, the animals were adapted to their new Plexiglas cages for at least a week. Preliminary experiments revealed that a period of 3–4 days was required for stabilizing values of food intake and daily O_2 consumption. One group of seven rats was subjected to a 2-day period of fasting with free access to water, whereas another group of seven rats was given free access to chow and a sucrose solution (32%), also during 2 days. For the fasting experiment, chow was taken away at 1900 h. For overfeeding, the sucrose solution was given instead of tap water at 1900 h. Measurements of the energy content of the chow and the sucrose solution were obtained with a parr adiabatic calorimeter. The values of the energy content of the chow and sucrose were 17.28 and 16.42 kJ/g, respectively.

Statistics. The statistical significance of the data was evaluated by analysis of variance. When only two means were compared, the unpaired t test was used. P levels of <0.01 and <0.05 were considered significant.

RESULTS

Effects of fasting-refeeding on O_2 consumption and energy intake. Fasting for 1 day decreased the mean O_2 consumption during the same day by 15% (Fig. 2*A*). During the 2nd day of fasting, O_2 uptake dropped by an additional 15%. Thereafter, when the rats were fed again, O_2 consumption rapidly returned to basal levels, but energy intake increased above prefasting values by 20–30% during 2 days before returning to normal levels on the 3rd day.

When the 24-h O_2 uptake data were subdivided for the periods of light and darkness, it was found that O_2 consumption was always higher during the 12-h periods of darkness, even when the animals were deprived of food (Table 1). Although fasting decreased the difference in O_2 consumption between the light and dark periods, it did not change the ratio of energy expended during these two periods. Indeed, O_2 consumption remained ~30% higher at night than during the day in fed as well as in fasted animals. These data clearly indicate that rats do not expend more energy at night simply because they eat more (22). They also suggest the presence of diurnal cycles regulating energy expenditure, regardless of energy intake.

As expected, fasting significantly decreased the body weights of the animals (Table 1). In spite of this, the O_2 consumption values expressed per $kg^{0.75}$ (16) still remained lower in fasted compared with fed animals ($P < 0.01$).

Effects of hyperphagia on O_2 consumption and energy intake. Liquid sucrose feeding increased the total energy intake from sucrose and Purina chow by 30% during 2 days ($P < 0.01$) (Fig. 2*B*). It also increased O_2 consumption by 9 and 12% during the 1st and 2nd day, respectively. Thereafter, when liquid sucrose was substituted by tap water, a transient but significant hypophagia occurred during 1 day ($P < 0.01$). However, O_2 uptake immediately returned to basal values.

Sucrose intake increased O_2 consumption during both dark and light periods (Table 2). However, the ratio of energy expended during the night over that expended during the day was not affected by the hyperphagia. As in the preceding experiment, it remained ~30% more elevated at night than during the day.

Effects of fasting, refeeding, and overfeeding on O_2 consumption/energy intake. The ratio of energy expenditure to energy intake was 21–28% lower during the 2 days following starvation than before starvation ($P < 0.01$) (Table 1), thereby indicating a tendency to conserve energy following calorie deprivation. Likewise, the same ratio was higher after sucrose feeding ($P < 0.01$) (Table 2), showing that energy dissipation relative to energy intake was transiently increased after hyperphagia. However, the O_2 consumption-to-energy intake ratio slightly decreased during the 2 days of sucrose feeding (Table 2), suggesting that increased energy intake was not entirely compensated by an enhanced energy expenditure (Fig. 2).

DISCUSSION

The main objective of the present study was to design a practical O_2 consumption apparatus allowing to test the energy buffering concept (or the pondérostat theory) during several days, simultaneously, in control and experimental animals. The system described in Fig. 1 allows a sequential determination of O_2 consumption in seven rats using a single O_2 analyzer linked to a computer. The computer controlled a system of three-way valves, recorded the data, and analyzed them using commercially available software. With this system, control and experimental animals could be processed in parallel, minimizing the introduction of systematic errors. The introduction of a blank cage (Fig. 1, cage 8) allowed to frequently check the calibration during the course of the experiment. In preliminary experiments, it was found that, for a flow rate of 1.0 l/min, the optimal frequency and duration of readings were 45 s of tubing flushing with air coming from the sample cage, followed by 45 s of measurements (the dead space from the sample cage to the O_2 consumption apparatus was reduced to 120 ml) (see METHODS). With such a frequency, stable and re-

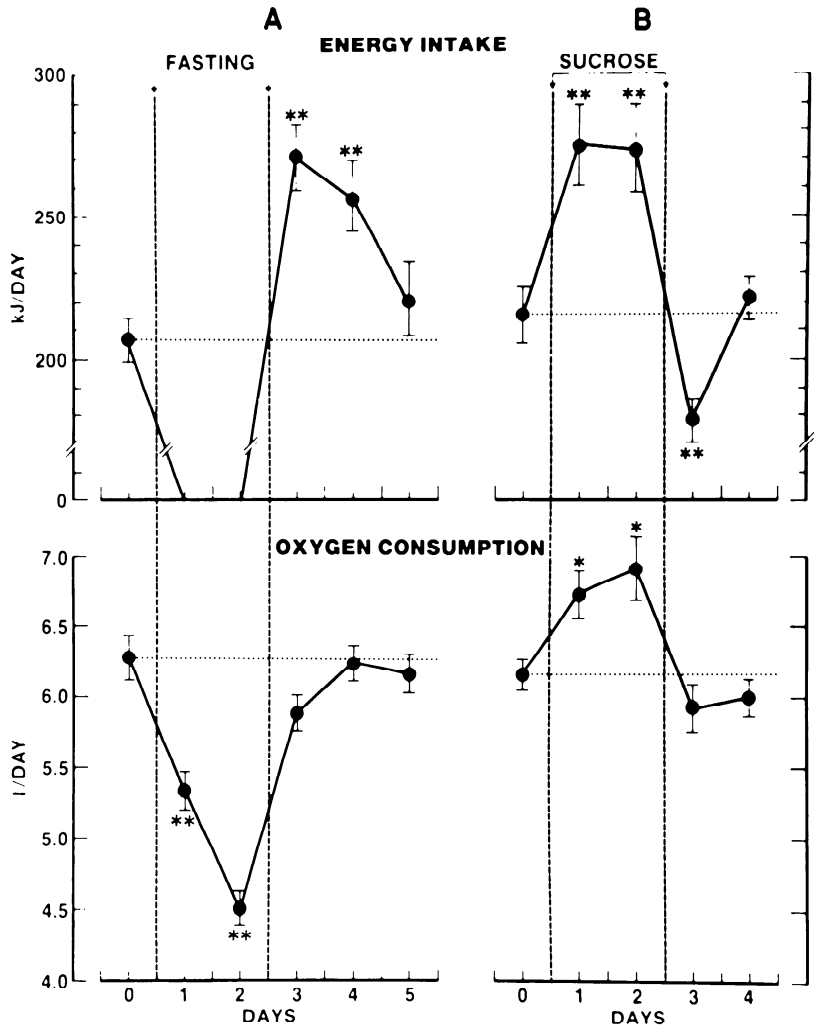

FIG. 2. Comparison of effects of 2-day fasting period (*A*) with 2-day sucrose overfeeding period (*B*) on energy intake and O_2 consumption. Rats had free access to Purina chow and water before and after 2-day period of fasting or overfeeding. Before experiment was started, animals were adapted to their new cages for at least a week, and O_2 consumption values were recorded 3-4 days before *day 0* in order to verify stability and reproductibility of measurements. For other details see METHODS and Tables 1 and 2. Values are means ± SE of measurements obtained during 24 h in 7 rats. Significant differences from control values (*day 0*): * $P < 0.05$; ** $P < 0.01$.

TABLE 1. *Effect of a 48-h period of fasting*

	Day 0	Fasting		Refeeding		
		Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*
O_2 consumption, l/rat						
Whole day	6.27±0.16	5.33±0.13*	4.50±0.12*	5.89±0.11	6.23±0.13	6.16±0.14
Dark period	3.63±0.01	3.01±0.10*	2.52±0.06*	3.31±0.06†	3.52±0.10	3.53±0.08
Light period	2.64±0.07	2.31±0.07*	1.98±0.07*	2.59±0.07	2.70±0.84	2.63±0.06
Difference between dark and light periods	0.97±0.04	0.70±0.10†	0.54±0.03*	0.69±0.07*	0.82±0.04†	0.91±0.05
Dark/light	1.38±0.02	1.30±0.05	1.28±0.02	1.29±0.09	1.30±0.02	1.35±0.02
Energy intake, kJ/day per rat	206.2±7.7	0	0	271.1±11.6*	257.5±12.4*	220.8±13.3
O_2 consumption/energy intake, ml/kJ	30.55±0.72			21.88±0.63*	24.38±0.86*	28.55±2.00
Body wt, g	195.3±4.3	178.1±3.5*	170.0±3.4*	193.3±4.6	195.9±4.5	189.7±3.6
O_2 consumption, $l \cdot day^{-1} \cdot kg^{-0.75}$	21.36±0.43	19.44±0.51*	17.01±0.36*	20.23±0.21†	21.16±0.48	21.41±0.19

Values are means ± SE; *n* (no. of individual experiments performed on separate occasions) = 7 for each group. Significant difference between experimental and control values (*day 0*): * $P < 0.01$; † $P < 0.05$.

producible measurements were obtained. Several other precautions were taken such as alternating rats from cage to cage, changing the position of the calibration cage etc. Nevertheless, the greatest source of variation came from the animals, and it was therefore decided to increase as much as possible the number of animals in each experimental group. The data described in Fig. 2 show that the O_2 consumption measurements were highly reproducible. Indeed, after being significantly perturbed for a few days by starvation or overfeeding, the O_2

TABLE 2. *Effect of a 48-h period of sucrose feeding*

	Day 0	Sucrose		Recovery From Sucrose Feeding	
		Day 1	*Day 2*	*Day 3*	*Day 4*
O_2 consumption, l/rat					
Whole day	6.15±0.11	6.75±0.17†	6.90±0.23†	5.92±0.17	5.99±0.13
Dark period	3.48±0.07	3.70±0.11	3.95±0.17†	3.36±0.14	3.12±0.08
Light period	2.68±0.06	3.04±0.08*	2.95±0.09†	2.56±0.04	2.67±0.06
Difference between dark and light periods	0.77±0.07	0.67±0.08	1.00±0.14	0.80±0.11	0.65±0.04
Dark/light	1.28±0.02	1.22±0.03	1.34±0.05	1.31±0.04	1.24±0.01
Energy intake, kJ/day per rat	215.4±9.5	275.4±14.5*	273.6±16.0*	177.7±7.7*	220.6±7.4
O_2 consumption/energy intake, ml/kJ	28.76±0.71	24.66±0.87*	25.53±1.01†	33.51±1.12*	27.27±0.08
Body wt, g	233.9±2.4	239.3±4.2	239.0±4.1	237.4±3.6	241.0±3.6†
Chow intake, kJ/day per rat	215.4±9.5	128.4±15.4*	121.7±7.4*	177.7±7.7*	220.6±7.4
Water or sucrose solution intake, ml/day per rat	26.9±2.2	28.0±1.9	28.9±2.6	26.6±3.1	32.6±4.5

Values are means ± SE; n (no. of individual experiments performed on separate occasions) = 7 for each group. Significant difference between experimental and control values (*day 0*): * $P < 0.01$; † $P < 0.05$.

consumption values of both experimental groups returned to their original levels (compare *day 0* with *days 4–5*). The following calculations show that rat growth can account for the difference between energy intake and expenditure, as expected for a method estimating energy expenditure with accuracy. The daily energy expenditure during the control period (Tables 1 and 2) ranged from 110 to 120 kJ (taking an equivalent of 20.1 kJ for 11 of O_2 consumed in STP). On the other hand, the estimated daily energy intake (food intake minus caloric loss in feces) was 150–160 kJ (preliminary experiments revealed that the metabolizable energy intake represented 73% of the total food intake). Thus the difference between daily energy expenditure and energy intake (30–40 kJ/day) can be explained by the growth of the rats (1–2 g of weight gain/day).

The present results support the energy buffering concept. They show that short-term fasting or hyperphagia induce compensatory alteration of energy balance not only during but also after treatments. It was found that a decrease in energy intake results in a rapid decrease of energy expenditure, whereas an increase of energy intake yields an increase of 24-h energy expenditure (Fig. 2). This agrees with previously published data showing that long-term hyperphagia generally increases energy expenditure, whereas starvation or food restriction decreases the same parameter (1, 9–12, 17, 19, 21). In addition, the present results suggest that the onset of the effects of fasting (or hyperphagia) on energy expenditure is extremely rapid and may occur within 12 h after the initiation of treatments (Tables 1 and 2). Although energy expenditure was rapidly altered in response to fasting or overfeeding, the magnitude of these alterations did not completely balance the changes in animal energy intake (Tables 1 and 2). Nevertheless, when the 2-day period of fasting (or overfeeding) ended, the energy deficit (for starving animals) or surplus (for hyperphagic animals) continued to be gradually reduced by compensatory alterations both in energy intake and expenditure. Indeed, fasting (during 2 days) induced a postfasting increase of energy intake (also during 2 days), whereas hyperphagia, on the contrary, resulted in a transient decrease of appetite (Fig. 2).

Despite these compensatory alterations, it can be calculated that there was an energy deficit of ~155 kJ at the end of the fasting-refeeding experiment. Indeed, the lack of metabolizable energy intake during the 2 days of fasting (~300 kJ) was only partially compensated by the decrease in energy expenditure during fasting (2.7 liters of consumed O_2 or 50 kJ) and the hyperphagia during the postfasting period (95 kJ). This energy deficit may explain the decrease in the growth rate of the fasted animals (Table 1), which contrasts with the steady increase of body weight of the sucrose fed rats (Table 2). It therefore appears that the marked energy deficit resulting from 2 days of complete fasting requires more than 3 days of refeeding to be completely balanced.

The present results suggest that some component of energy expenditure is regulated to maintain energy content constant. If one compares the data observed 1–2 days after fasting (Fig. 2*A*, *days 3–4*) with those obtained 1–2 days after initiation of sucrose feeding (Fig. 2*B*, *days 1–2*), it can be seen that for a comparable level of increased energy intake (~30% above control values), energy expenditure is much higher during hyperphagia induced by sucrose than during hyperphagia elicited by hunger (refeeding after fasting). This observation agrees with previous reports showing that rats refed after starvation tend to conserve more energy than ad libitum fed rats (2, 3, 13). The enhanced energy retention after refeeding may also be expressed by the ratio of energy expenditure over energy intake. In refed animals, this ratio is much lower than in ad libitum-fed or overfed animals (Tables 1 and 2). The ratio of energy expenditure over energy intake appears to be a function of the previous energy balance state of the animals. These data agree with the recent report showing that energy conservation is enhanced by food restriction (14).

It is generally admitted that there are two main components in energy expenditure: obligatory and facultative thermogeneses. Obligatory thermogenesis can be subdivided in essential, endothermic, and postprandial thermogeneses, whereas facultative thermogenesis includes diet-, cold-, and exercise-induced thermogeneses (15). Under the present experimental conditions, cold-induced thermogenesis was probably minimal because the studies

were carried out close to thermoneutrality (27°C). The alterations in energy expenditure induced by 1 day of starvation (Fig. 2*A*) or overfeeding (Fig. 2*B*) probably reflect changes in postprandial-, diet-, and possibly also exercise-induced thermogeneses. Although the space in the animal cages was reduced to restrict movements (see METHODS), some activity (for instance, activity associated with feeding) could not be eliminated. However, the decrease in energy expenditure observed during the 2nd day of starvation cannot result from a decrease in diet-induced thermogenesis but may be a consequence of decreases in essential and/or endothermic thermogeneses known to be controlled by thyroid hormones (15). Further studies should be carried out to determine the quantitative importance of the various components of energy expenditure in regulating animal energy content.

Finally, it should be pointed out that the total increase in energy expenditure induced by sucrose feeding during 2 days (Fig. 2*B*, *days 1–2*) was 24.8 kJ. This value represents 21% of the excess energy intake measured during the same period (118.2 kJ). On the other hand, energy expenditure after fasting (*days 3–5*) was similar to that of control rats (*day 0*) despite the fact that the animals were significantly hyperphagic (as hyperphagic as sucrose-consuming rats) (Fig. 2*A*, *days 3–5*). Thus, in the present experiments, the increment in energy expenditure induced by overfeeding varied from 0 to 21% of the excess energy intake, depending on the nutritional state of the animals. This kind of variation may help explain, at least in part, the discrepancies among laboratories about the effects of hyperphagia on energy expenditure (20).

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