Individual differences in physical activity are closely associated with changes in body weight in adult female rhesus monkeys (Macaca mulatta)

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Sullivan, Elinor L., Frank H. Koegler, and Judy L. Cameron. Individual differences in physical activity are closely associated with changes in body weight in adult female rhesus monkeys (Macaca mulatta). Am J Physiol Regul Integr Comp Physiol 291: R633–R642, 2006. First published April 13, 2006; doi:10.1152/ajpregu.00069.2006.—The increased prevalence of overweight adults has serious health consequences. Epidemiological studies suggest an association between low activity and being overweight; however, few studies have objectively measured activity during a period of weight gain, so it is unknown whether low activity is a cause or consequence of being overweight. To determine whether individual differences in adult weight gain are linked to an individual’s activity level, we measured activity, via accelerometry, over a prolonged period (9 mo) in 18 adult female rhesus monkeys. Weight, food intake, metabolic rate, and activity were first monitored over a 3-mo period. During this period, there was mild but significant weight gain (5.5 ± 0.88%; t = −6.3, df = 17, P < 0.0001), whereas caloric intake and activity remained stable. Metabolic rate increased, as expected, with weight gain. Activity level correlated with weight gain (r = −0.52, P = 0.04), and the most active monkeys gained less weight than the least active monkeys (t = −2.74, df = 8, P = 0.03). Moreover, there was an eightfold difference in activity between the most and least active monkeys, and initial activity of each monkey was highly correlated with their activity after 9 mo (r = 0.85, P < 0.0001). In contrast, food intake did not correlate with weight gain, and there was no difference in weight gain between monkeys with the highest vs. lowest caloric intake, total metabolic rate, or basal metabolic rate. We conclude that physical activity is a particularly important factor contributing to weight change in adulthood and that there are large, but stable, differences in physical activity among individuals.

Exercise; obesity; weight gain; energy balance

Epidemiological studies indicate that body weight and body fat increase through early and middle adulthood such that by late middle age there is an increased percentage of overweight and obese individuals compared with the early adult period (33, 57, 63, 108, 115). Weight gain over the adult years has escalated over the past two decades such that 65% of adults in the United States have a body mass index (BMI) above the healthy range (>25.0 kg/m2) (32). Weight gain and obesity in adulthood have been associated with overall increases in morbidity and mortality (82) and in the risk of diabetes mellitus (23, 33, 53, 115a), gall bladder disease (115a), coronary heart disease (41, 49, 53, 69, 86, 111, 115a), hypertension (53, 115a), stroke (115a), dyslipidemia (115a), osteoarthritis (115a), gout (115a), pulmonary diseases (115a), colon cancer (35), and breast cancer (118).

A large body of epidemiologic data shows an association between low levels of physical activity and a higher rate of adult weight gain, and a greater increase in percent body fat, throughout adulthood (14, 24, 44, 51, 54, 65, 87, 97, 114). However, most of these studies rely on self-reporting of physical activity, and several studies have shown that self-reporting of activity can be inaccurate and problematic (50, 72, 75, 105). Accelerometry, an objective way to monitor physical activity, recently has been used to show that obese children and adults have lower activity levels than their lean counterparts (1, 28, 45, 96, 105, 106). Similarly, studies that objectively measured activity in rodents also showed that obese individuals have lower activity levels compared with lean individuals (21, 60). However, it is unclear from these studies whether low activity is a cause or consequence of obesity. Accelerometry would be ideal for measuring the contribution of individual differences in activity to adult weight gain but would require the wearing of activity monitors during the prolonged periods over which adult weight gain takes place. In fact, two studies in mice that objectively measured activity found that weight gain in adulthood was negatively correlated with activity level (15, 26), supporting the notion that low activity is a cause of obesity.

In the current study, we maintained adult monkeys wearing accelerometers over a prolonged period (i.e., 9 mo), allowing us to determine whether individual differences in adult weight gain differed in monkeys exhibiting low activity vs. high physical activity. Food intake and metabolic rate were measured to allow assessment of the relative contribution of physical activity level to adult weight gain. Results of this study show that of all of the parameters that we measured, an individual’s level of physical activity is the strongest predictor of weight gain in ovarioleomized female monkeys.

Materials and Methods

Animals

Eighteen adult female rhesus monkeys (Macaca mulatta) 9–13 yr of age, weighing between 4.7 and 11.1 kg, and living in individual stainless steel cages (32 × 24 × 27 or 32 × 34 × 27 in.) in a temperature-controlled room (24 ± 2°C) with lights on for 12 h per day (0700–1900) were studied. Approximately 1 yr before initiation of this study, the monkeys had been ovariolecomized and maintained on a high-fat diet (35% fat) to approximate the conditions experienced during a period of weight gain in adult female rhesus monkeys. However, it is unclear from these studies whether low activity is a cause or consequence of obesity. Accelerometry would be ideal for measuring the contribution of individual differences in activity to adult weight gain but would require the wearing of activity monitors during the prolonged periods over which adult weight gain takes place. In fact, two studies in mice that objectively measured activity found that weight gain in adulthood was negatively correlated with activity level (15, 26), supporting the notion that low activity is a cause of obesity.

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by many postmenopausal women in the Western world (112). The high-fat diet was formulated according to the recipe developed by Clarkson and colleagues (94, 112) to study diet-induced atherosclerosis. Monkeys were fed ad libitum with meals provided at ~0915 and 1515. All aspects of the study were reviewed and approved by the Oregon National Primate Research Center Animal Care and Use Committee and were performed according to federal guidelines.

Experimental Design

The goal of this experiment was to determine whether the activity level of an individual is predictive of weight gain over a period of time in adulthood during which food intake is stable and there is slow progressive weight gain. In addition, other parameters known to influence weight gain, such as food intake and metabolic rate, were measured. The experimental period was 9 mo in duration, during which time the activity level of each monkey was measured continuously using a three-way accelerometer. During the first 3 mo of the study, the weight of each monkey was measured weekly, food intake was quantified at each meal, and percent body fat was determined at the beginning and end of the study. Metabolic rate was measured over a 4-h period at the beginning of the study and for 24 h at the end of the first 3 mo. Morning metabolic rate during fasting was compared between the two time points. During the last 6 mo, activity was continuously monitored to allow assessment of the stability of this physiological measure.

Experimental Measures

**Body weight.** Body weight was measured weekly at ~0800, before the morning meal.

Dual-energy X-ray absorptiometry scans. Percent body fat was determined using dual-energy X-ray absorptiometry. Animals were sedated with Telazol (3 mg/kg im; Fort Dodge Animal Health, Fort Dodge, IA) supplemented with ketamine HCl (10 mg/kg im Ketaset; Fort Dodge Animal Health) and were positioned supine on the bed of a Lunar DPX scanner (Lunar, Madison, WI). Total body scans were done in the “pediatric medium” scan mode with a voltage of 76 kV. Lunar software version 3.4 was used to calculate body composition. Two or three scans at each time period were performed per monkey, and body fat was calculated as a percentage of total body mass.

Calorie intake. Each monkey was fed more food than she routinely consumed at each meal to ensure ad libitum food intake. Total food consumption at each meal was recorded daily throughout the study by quantifying the amount of food remaining before the next meal. On 1 day during the study, the total amount of stool excreted in a 24-h period was collected from each monkey by placing a metal pan under each monkey’s cage for 24 h. The amount of stool was weighed, and a representative sample was collected at 0900 the next morning and immediately frozen at −20°C. The caloric content of a sample of stool from the two monkeys that consumed the most calories and the two monkeys that consumed the least number of calories was determined using bomb calorimetry (Kinetics, Franklin, OH) to quantify differences in calories excreted vs. calories absorbed.

Metabolic rate. Metabolic rate of each monkey was measured by placing the monkey in a sealed Lexan and stainless steel metabolic chamber (Columbus Instruments, Columbus, OH) and measuring the amount of carbon dioxide produced and oxygen consumed with a computer-controlled indirect open-circuit calorimeter (Oxymax system; Columbus Instruments). The metabolic chamber was approximately the same size as the monkey’s home cage (inside dimensions: 30 × 24 × 24 in.). To prevent social isolation during metabolic testing, we placed two monkeys familiar with the test monkey in cages across from and in clear view of the animal in the metabolic testing chamber at all times. The familiar monkeys were animals that were housed in the same room as the test monkey before and after metabolic chamber test periods. Before each recording session, the oxygen and carbon dioxide sensors were calibrated with a standard mixture of gases (20.5% oxygen, 0.5% carbon dioxide, and nitrogen balance). Fresh air was pumped into the chamber (12–40 l/min) with an external fresh air pump controlled by a flowmeter (Columbus Instruments) and was circulated within the chamber with a 4-in. fan. The flow rate into the chamber was adjusted for each monkey so that the difference in oxygen concentration between the chamber and the room air was >0.2% and the carbon dioxide level in the chamber was <0.6%. The chamber air was sampled at a rate of 0.5 l/min and was circulated over a water-absorbent (Drierite) column before passing through the oxygen and carbon dioxide sensors. The oxygen and carbon dioxide concentrations of the ambient air and chamber air were recorded every 4 min. Oxygen consumption, carbon dioxide production, and total energy expenditure (kcal) were calculated using Oxymax software version 2.3 (Columbus Instruments). The Oxymax system calculated oxygen consumption (VO2) by taking the difference between input oxygen flow and output oxygen flow. Similarly, carbon dioxide production (VCO2) was calculated by taking the difference between output and input carbon dioxide flows. To determine energy expenditure, we calculated the respiratory exchange ratio (RER), the ratio of VCO2 to VO2, and the energy expenditure (EE) using the following equation: EE = (3.82 + 1.23 × RER) × VO2 × 0.001. Upon study initiation, monkeys were individually placed in the metabolic chamber at 0900 and remained in the chamber until 1300. The day before testing, the monkey was fed its standard meal, and at 1700, all food was removed from the monkey’s cage and the monkey was fasted until completion of metabolic testing. After 3 mo, 24-h metabolic rate of the monkeys was assessed. Monkeys (n = 16) were placed in the metabolic chamber at 1000 and remained in the chamber until 0900 the next morning. Before placement in the chamber, monkeys were fed a standard meal at 0915 and were fed a 114 ± 1-g banana at 1515 while in the chamber. Basal metabolic rate was calculated as the average number of kilocalories expended per hour from 2300 to 0300. This time period was selected because this is when monkeys typically sleep, and this is when heart rate is typically lowest (Cameron J, unpublished observations). In addition, this was the time when monkeys exhibited the lowest number of activity counts in this study. The thermic effect of an isocaloric meal (the banana fed at 1515) was calculated by subtracting basal metabolic rate and activity-associated energy expenditure from total energy expenditure for the 4 h after the banana was consumed. Studies have shown that the majority of energy expended due to meal digestion and processing is within the first 4 h after a meal is eaten (12, 84, 98).

Activity. The naturally occurring activity level of each monkey was assessed using triaxial Actical accelerometers (MiniMitter, Bend, OR). The Actical monitor contains an omnidirectional sensor capable of detecting acceleration in all directions. The sensor integrates the speed and distance of acceleration and produces an electrical current that varies in magnitude depending on a change in acceleration. An increased speed or distance of the acceleration, or a change in direction, produces an increase in electrical current. The activity monitors store this information as activity counts. Each monkey was fitted with a loose-fitting metal collar (Primate Products, Immokalee, FL) with an activity monitor mounted on it, housed in a snug, protective stainless steel box. The monitor was programmed to store the total number of activity counts per minute. These monitors are capable of storing data for up to 45 days. During the study period, monkeys were sedated with ketamine HCl (10–20 mg/kg im Ketaset; Fort Dodge Animal Health), and the data from each activity monitor were downloaded at least every 45 days. After the data were downloaded and saved, the activity monitor was reprogrammed and replaced on the collar. Activity counts recorded from 0700 to 1900 (when lights were on) were considered daytime activity, and activity counts recorded from 1900 to 0700 (when lights were off) were considered nighttime activity. Activity-associated energy expenditure was calculated by determining the energy expended (in kcal) per activity count. This was calculated by measuring total energy...
expenditure at times of day in which there would be little thermic
effect of food contributing to the metabolic rate (from 1400 to 1500
and 1800 to 1900), subtracting basal metabolic rate, and dividing the
remaining energy expenditure by the number of activity counts
occurring during this time period. The number of calories expended
per activity count was multiplied by total daily activity counts to
determine daily activity-associated energy expenditure.

The duration of time that the monkeys were sedentary was assessed
on a representative day from the week of initial activity measurement
by determining how many minutes the monkeys had no activity
counts.

Data Analysis

Activity was analyzed during a representative week at the begin-
nning of the study, after 3 mo, and again after 9 mo. Body weight,
average weekly food intake, and fasted morning metabolic rate were
compared upon study initiation and after 3 mo. The associations
between all measurements (food intake, total energy expenditure,
basal metabolic rate, thermic effect of food, and activity) and weight
gain were determined. Regression analysis demonstrated that lean
body mass was the best predictor of total energy expenditure ($R^2$
= 0.52) and basal metabolic rate ($R^2$ = 0.58); thus, after the raw values
were analyzed, the adjusted residuals also were analyzed for their
association with weight gain.

For all analyses, normality and homoscedasticity were initially
tested. Initially, multivariate regression analysis was used to deter-
mine which variable (basal metabolic rate, activity, and food intake)
was best able to predict weight gain. If data were normally distributed,
paired t-tests were used to evaluate differences between measures
made at two different time points, and repeated-measures ANOVA
was used to evaluate differences in activity measurements made upon
initiation of the study, after 3 mo, and after 9 mo. Independent t-tests
were utilized to assess differences in amount of weight gained by
monkeys divided into groups of the highest and lowest quartiles based
on food intake, activity, and metabolic rate. Correlations between
measurements were determined using Pearson product moment cor-
relation. If data were not normally distributed and could not be
transformed (using a square root or log transformation), then nonpara-
metric tests were utilized. The Wilcoxon signed ranks test was used to
assess differences in nonnormally distributed data over time. Spear-
man’s Rho correlation was used to analyze correlations between
parameters that were not normally distributed. Linear regression
analysis was performed to develop an equation for predicting the
energy expenditure in kilocalories per activity count. Data are pre-

tented as means ± SE. Alpha values were considered significant if
$P < 0.05$. Statistical analyses were performed with SPSS software,
version 13.0 (SPSS, Chicago, Illinois).

RESULTS

During the first 3 mo of the study, the group showed a small
but significant gain in body weight (5.5 ± 0.88%, $t = −6.3$,
df = 17, $P < 0.0001$; Table 1). There were large differences in
weight gain between individual monkeys, with several mon-
keys gaining no weight during this experimental period, whereas others gained up to 13% of their initial weight in 3 mo.
Body fat also increased significantly in the group, from 15.9 ±
3.0 to 18.7 ± 3.4% of total body mass during this time period
($z = −3.17, P = 0.002$; Table 1). Initial body fat was not
correlated with weight ($r = −0.19, P = 0.45$) or fat gain ($r$
= −0.17, $P = 0.51$), and there was no difference in weight gain
or fat gain between the monkeys who were in the leanest vs.
fattest quartile at the beginning of the study ($t = 0.33, df = 8$,
$P = 0.75$; $t = −1.3, df = 8, P = 0.24$ for weight and fat gain,
respectively). In addition, the age of the monkeys was not
related with weight gain ($r = −0.25, P = 0.33$) or fat gain
($r = 0.05, P = 0.86$), and there were no differences in the
amount of weight or fat gained between the youngest and
oldest monkeys ($t = 0.04, df = 8, P = 0.97$; $t = −0.11, df
= 8, P = 0.92$ for weight and fat gain, respectively).

Initially, a multivariate regression analysis determined that
when food intake, basal metabolic rate, and activity were used
as independent variables, body weight gain could not be
significantly predicted ($R^2 = 0.27, F_{3,12} = 1.50, P = 0.27$).
However, activity was a better predictor of weight gain ($P$
= 0.07) than food intake ($P = 0.73$) and basal metabolic rate
($P = 0.87$). Food intake was not significantly changed during
the 3-mo period ($t = 1.04, df = 17, P = 0.31$; Table 1).
Although there were considerable individual differences in the
amount of calories consumed by individual animals (a 5-fold
difference, ranging from 411 to 2,210 kcal/day), the food
intake of individual monkeys was consistent over this 3-mo
time period, such that the initial food intake of each individual
was highly correlated with food intake after 3 mo ($r = 0.95$,
$P < 0.0001$; Fig. 1A). However, food intake did not correlate
with the amount of weight gained by each monkey during this
time period ($r = 0.15, P = 0.56$). In addition, there was no
difference in the weight gain of the quartile of monkeys that ate
the most compared with that of the quartile of monkeys that ate
the least ($t = 0.20, df = 8, P = 0.85$; Fig. 1B). To begin to
look at whether food intake accurately predicts calorie absorp-
tion, we measured the caloric content of the stool in the two
monkeys eating the most and the two eating the least calories.
Mean caloric content of the four stool samples was 1.70 ± 0.28
kcal/g, and the caloric content of the stool samples was corre-
lated with food intake such that the monkeys that ate the most
excreted more calories per gram of stool ($r = 0.95, P = 0.046,
2.1-fold difference between monkeys with the highest and
lowest food intake).

Daily energy expenditure significantly increased from
21.3 ± 2.3 to 28.7 ± 2.9 kcal/h ($t = −3.46, df = 17, P$
= 0.003; Table 1) over the first 3 mo of the experimental period.
Initial daily energy expenditure was correlated with final daily
energy expenditure ($r = 0.68, P = 0.002$; Fig. 2A). Moreover,
the change in daily energy expenditure correlated with weight
gain ($r = 0.47, P = 0.05$) such that the monkeys that gained
the most weight increased their daily energy expenditure the
most. There was a sixfold difference in daily energy expendi-
ture between individual monkeys. However, initial daily en-
ergy expenditure did not correlate with weight gain ($r$
= −0.35, $P = 0.16$), and although percent weight gain was
somewhat higher in the quartile of monkeys with the lowest
daily energy expenditure (7.4% weight gain) compared with
the quartile of monkeys with the highest daily energy expendi-
ture (4.0% weight gain), this was not a significant difference

Table 1. Metabolic parameters across 3 mo of weight gain

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>7.54 ± 0.48</td>
<td>7.94 ± 0.49*</td>
</tr>
<tr>
<td>body fat, %</td>
<td>15.9 ± 3.0</td>
<td>18.8 ± 3.5*</td>
</tr>
<tr>
<td>Food intake, kcal</td>
<td>1,188 ± 129</td>
<td>1,113 ± 105</td>
</tr>
<tr>
<td>Energy expenditure, kcal/h</td>
<td>21.3 ± 2.3</td>
<td>28.7 ± 2.9*</td>
</tr>
<tr>
<td>Activity, counts/day</td>
<td>291,296 ± 35,805</td>
<td>233,651 ± 37,983</td>
</tr>
</tbody>
</table>

Values are means ± SE. Asterisks indicate a significant difference from initial measures.

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Once total energy expenditure was adjusted for lean body mass by regression analysis, there was only a 2.6-fold difference in energy expenditure between individual monkeys. However, adjusted daily energy expenditure did not correlate with weight gain ($r = 0.04$, $P = 0.89$), and there was no difference in weight gain between monkeys in the quartile with the highest adjusted daily energy expenditure compared with the quartile of monkeys with the lowest adjusted daily energy expenditure ($t = 0.04$, $df = 6.1$, $P = 0.97$).

The average basal metabolic rate was $291 \pm 19$ kcal/day and ranged from 172 to 406 kcal/day. On average, basal metabolic rate accounted for 61% of total daily energy expenditure, ranging from 47 to 83% of total energy expenditure in individual monkeys. Basal metabolic rate did not correlate with weight gain ($r = 0.08$, $P = 0.75$), and weight gain was not different between the quartile of monkeys with the highest basal metabolic rate and the quartile of monkeys with the lowest basal metabolic rate ($t = 0.40$, $df = 8$, $P = 0.70$). In addition, basal metabolic rate adjusted for lean body mass with the use of regression analysis was not correlated with weight gain ($r = -0.04$, $P = 0.89$), and there was no difference in weight gain between the quartile that had the highest adjusted basal metabolic rate and the quartile with the lowest adjusted basal metabolic rate ($t = 0.04$, $df = 6.1$, $P = 0.97$).

The mean thermic effect of a 108-calorie meal was $19.9 \pm 3.2$ kcal and ranged from 8.5 to 59.3 kcal (a 7-fold difference) between individual monkeys. There was no significant difference in the weight gain in the monkeys with the highest thermic effect of the meal and the monkeys with the lowest thermic effect of the meal ($t = -1.81$, $df = 8$, $P = 0.11$).

There was an eightfold difference in activity between the most active and most sedentary monkey (Fig. 3), with the most sedentary monkey displaying a mean of 92,110 $\pm$ 7,873 activity counts per day and the most active monkey displaying 770,446 $\pm$ 110,476 activity counts per day. The number of activity counts per day did not change significantly during the 3-mo period ($t = 1.15$, $df = 15$, $P = 0.27$; Table 1), and each monkey’s daily activity level (counts/day) was consistent over time such that the number of activity counts per day initially recorded for each monkey was highly correlated with the number of activity counts per day recorded after 3 mo ($r = 0.79$, $P < 0.0001$; Fig. 4A). There was a significant correlation between the number of daily activity counts and weight gain such that the most active monkeys gained less weight than the least active monkeys ($r = -0.52$, $P = 0.04$). The quartile of

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**Fig. 1.** A: food intake for individual monkeys remained stable. There was a correlation between food intake at study initiation and after 3 mo ($r = 0.95$, $P < 0.0001$). B: however, the quartile of monkeys eating the most food showed the same percent change in body weight as the quartile that ate the least amount of food ($r = -0.20$, $df = 8$, $P = 0.85$).

**Fig. 2.** A: correlation between daily energy expenditure at study initiation and after 3 mo ($r = 0.68$, $P = 0.002$). B: the change in body weight over 3 mo between the monkeys in the top and bottom quartiles of energy expenditure was not significantly different ($t = 2.08$, $df = 8$, $P = 0.07$).
monkeys that were most active gained significantly less weight during the 3-mo period than the quartile of monkeys that were least active ($t_{11005}/H11002 = 2.7$, $df = 8$, $P = 0.03$; Fig. 4B). To follow up this initial finding, we measured activity over an additional 6 mo and found that the number of activity counts per day remained stable ($F_{1,16} = 1.13$, $P = 0.30$) and that the number of activity counts initially recorded for each monkey was highly correlated with the number of activity counts recorded for that monkey after 9 mo ($r = 0.85$, $P < 0.0001$). There was a 10-fold difference in the number of activity counts recorded during the day between individual monkeys, and 96% of total daily activity occurred during daylight hours. Interestingly, although nighttime activity accounted for only 4% of total daily activity, there also was a 10-fold difference in nighttime activity. Nighttime activity was positively correlated with daytime activity such that the monkeys that were the most active during the day were also the most active at night ($r = 0.57$, $P = 0.02$; Fig. 5).

Activity counts correlated strongly with activity-associated energy expenditure (adjusted for body mass) during the time periods from 0200 to 0300 ($r = 0.80$, $P < 0.0001$; Fig. 6) and 0600 to 0700 ($r = 0.74$, $P = 0.001$; data not shown). The regression equation for calculation of activity-associated energy expenditure (AEE) was similar at both times of day [0200–0300: $AEE = (\text{number of activity counts} \times 0.000025) + 0.71$; 0600–0700: $AEE = (\text{number of activity counts} \times 0.000021) + 0.54$]. On average, 0.045 ± 0.006 kcal were expended per kilogram of body weight per 1,000 activity counts. Average activity-associated energy expenditure was 109 ± 14 kcal/day and ranged from 24 to 206 kcal/day. On average, 18 ± 3% of total energy was expended by physical activity, with physical activity accounting for 8–43% of total daily energy expenditure in individual monkeys. The quartile of monkeys that expended the most calories due to activity

**Fig. 3.** The most sedentary monkey (A) was 8 times less active than the most active monkey (B).

**Fig. 4.** A: there was a significant correlation between physical activity at study initiation and after 3 mo ($r = 0.79$, $P < 0.0001$). B: the quartile of monkeys that had the lowest physical activity had significantly greater weight gain than the quartile of monkeys that had the highest physical activity ($r = -2.7$, $df = 8$, $P = 0.03$). *Significant difference in percent change in body weight between groups.

**Fig. 5.** Nighttime activity was significantly correlated with daytime activity ($r = 0.57$, $P = 0.02$).
gained significantly less weight than the quartile of monkeys that expended the least amount of energy due to activity ($t = -2.85$, df = 4.6, $P = 0.04$).

Further analysis of the activity data revealed that there was an inverse correlation between the number of daily activity counts and the number of minutes that the monkeys were completely inactive such that the least active monkeys were inactive more than the most active monkeys ($r = -0.51$, $P = 0.046$). However, there was no correlation between the number of minutes that the monkeys were inactive and weight gain ($r = 0.39$, $P = 0.13$).

**DISCUSSION**

In this study, we objectively measured individual monkeys’ levels of physical activity, as well as other components of energy balance (caloric intake, metabolic rate) over a period of weight gain in adulthood when monkeys were eating a stable diet. There was a slow but significant increase in body weight (5.5%) during the experimental period. However, caloric intake and physical activity level remained stable during this period. The amount of weight gained was predicted by physical activity level such that the most active monkeys gained significantly less weight than the least active monkeys. This finding shows a very strong relationship between an individual’s physical activity level and its tendency to gain weight and suggests that physical activity is an important determinant of body weight gain in adulthood. Activity level differed eightfold between monkeys, but the activity level of an individual was remarkably consistent throughout the 9-mo experimental period, suggesting that activity level is an intrinsic property of an individual.

In this study, the most active individuals were less likely to gain weight than the most sedentary individuals during a period of stable dietary intake in adulthood. This finding supports the epidemiologic data showing that low levels of physical activity predict greater increases in body weight and body fat and that high levels of physical activity prevent or limit weight and fat gain (14, 24, 44, 54, 65, 87, 97, 114). Most of these reports relied on self-reporting of physical activity. However, Levine et al. (62) directly assessed posture allocation in 10 obese and 10 lean individuals and found that obese individuals were seated significantly more than lean individuals and that lean individuals were standing more than obese individuals. Our findings also support findings reporting that activity level in mice is negatively correlated with weight gain (15, 26). Our study represents the first direct measure of activity during a period of adult weight gain in a primate species and strongly indicates that inactivity is an important factor contributing to adult weight gain.

Our findings also are supported by studies that used accelerometry to objectively monitor physical activity and found that obese individuals have lower activity levels than individuals of normal weight (1, 28, 29, 45, 96, 105, 106) and by studies in rodents showing that obese mice have lower activity levels than their lean counterparts (21, 60). However, it has been unclear from these studies whether low activity is a cause or consequence of obesity. Our findings suggest that individual differences in physical activity levels play an important causal role in adult weight gain.

Interestingly, we found large individual difference in nighttime activity (10-fold). This finding is supported by Mehlman et al. (74), who also found a 10-fold range in duration of nighttime activity in free-ranging male rhesus monkeys. This study also showed that nighttime activity was correlated with daytime activity, suggesting that the mechanisms controlling activity at these two time periods are similar. A positive correlation between daytime and nighttime activity is supported by studies in children with attention-deficit hyperactivity disorder, showing that these children are more active than controls during both the day and the night (22). The mechanisms that regulate physical activity are currently not well understood. However, studies have shown that peptides that regulate food intake, such as leptin (76, 83, 89, 90), ghrelin (17, 70), pancreatic polypeptide (58, 77, 107), cholecystokinin (92), the neurotransmitters serotonin (11, 42, 79, 80), glutamate (25, 101), dopamine (30, 89, 100, 117), norepinephrine (19, 89), nitric oxide synthase (27, 47), and β-endorphin (43), and the hormone estrogen (104, 109), all play potential roles in the regulation of physical activity. In addition, several brain regions have been implicated in the regulation of activity, predominantly the reticular activating formation (89). Also, lesion studies have shown that areas of the basal forebrain, ventromedial hypothalamus, paraventricular nucleus, amygdala, and thalamus all play possible roles in activity regulation (89). The mechanisms that regulate nighttime activity have received much less attention. However, two recent studies began to address this issue. Orexin A injection in the paraventricular nucleus increases activity during both the day and night in rats, suggesting that orexin A may play a role in regulating both daytime and nighttime activity (48). Also, central nervous system serotonin turnover has been shown to be inversely correlated with nighttime activity in male rhesus monkeys (74).

Activity-associated energy expenditure was associated with weight gain, and monkeys that expended the most energy by being physically active gained significantly less weight than monkeys that expended the least energy by being physically active. On average, $18 \pm 3\%$ of total energy was expended by physical activity; however, individual differences in the percentage of total energy expenditure due to activity ranged from 8 to 43% of total energy expenditure. This is similar to findings...
in humans showing that the amount of total energy expenditure due to activity averages 30% (110) and ranges from 21 to 51% (61).

Individual differences in the number of calories consumed per day were great and ranged from 411 to 2,210 kcal/day. The number of calories consumed by each monkey remained stable during the experimental period; however, food intake was not predictive of weight gain. This parallels previous studies in humans that failed to find an association between individual caloric intake and individual weight gain or body fat gain (3, 5, 7, 38, 46, 66, 71, 73, 85, 95, 116). This frequent failure to find an association between weight gain and caloric intake may reflect the large role that individual differences in activity level play in regulating body weight. Interestingly, in our study the number of calories excreted per gram of stool was correlated with energy intake such that the individuals with the highest caloric intake excreted twice as many calories per gram of stool. The fact that individuals absorb fewer calories when they consume more calories is well documented in the animal literature (10, 13, 91) but is not generally considered in human studies. Individual differences in energy absorption may contribute to the lack of association between caloric intake and weight gain.

Measurements of energy expenditure in this study were similar to what has been previously reported in rhesus monkeys (9, 55). Daily energy expenditure increased over the period of weight gain and was correlated with change in body weight such that the monkeys that gained the most weight increased their energy expenditure the most. The finding that energy expenditure increases with increased body weight has been documented in studies with humans (4, 16, 36, 78, 88), so it is not surprising that energy expenditure would increase as the volume of metabolically active tissue increases. Although there was a change in energy expenditure, the initial energy expenditure of each individual monkey was correlated with that monkey’s final energy expenditure. However, we found that the weight gain of monkeys with the highest energy expenditure did not differ from the weight gain of the monkeys with the lowest energy expenditure. In addition, when energy expenditure was normalized for lean body mass with the use of regression analysis, there was still no difference in weight gain between the monkeys with the highest adjusted energy expenditure and the lowest adjusted energy expenditure. We note that in no monkey did energy balance (intake minus expenditure) equal zero. Energy that was excreted in the stool and thus not absorbed would account in part for this discrepancy. This has been reported to be 6.3% in rhesus monkeys (56). Energy excreted in urine and in skin cells, hair, and nails also was not accounted for.

We determined that the average basal metabolic rate accounted for 61% of total daily energy expenditure and ranged from 47 to 83% of total energy expenditure in individual monkeys. Similarly, the basal metabolic rate of humans accounts for 60% of total energy expenditure (78, 110), ranging from 22 to 83% (8, 61). Basal metabolic rate also did not predict weight gain in this study. In addition, when basal metabolic rate was adjusted for lean body mass with the use of regression analysis, there was still no difference in weight gain between the monkeys with the highest adjusted basal metabolic rate and the monkeys with the lowest adjusted basal metabolic rate. These findings are supported by previous studies in both humans and mice showing that individuals with a low metabolic rate are not more susceptible to weight gain than individuals with a high metabolic rate (40, 93). However, there are certain populations in which low metabolic rate predicts weight gain. For example, in Pima Indians, low metabolic rate is a risk factor for weight gain (102). In addition, children with stunted growth because of poor nutrition (37) and children with Down syndrome (68) have a lower basal metabolic rate and are more prone to obesity and weight gain than individuals in a control population. Basal metabolic rate accounts for the largest proportion of energy expenditure; however, the lack of relationship between low basal metabolic rate and weight gain suggests that differences in basal metabolic rate within the normal range are not as likely to underlie weight gain as differences in activity.

Ovariectomy (surgical menopause) is associated with changes in energy balance. We have previously shown that ovariectomy is associated with a rapid increase in caloric intake (29%) and weight (~3%) in female rhesus monkeys (99). In addition, it is well documented in small animals (mice, rats, cats; Refs. 2, 20, 31, 34) that ovariectomy leads to a 14–21% increase in weight within several weeks of ovariectomy. Also, it is well documented that along with weight gain, an increase in BMI and an increase in adiposity occur during the menopausal transition in women (18, 39, 52, 64, 67, 103, 113). Thus it is important to note that the monkeys in this study were ovariectomized. It is possible that the relationships between energy balance parameters are different in the ovariectomized vs. the ovary-intact state. Thus caution should be used in extending the findings we report in this study to all weight gain over adulthood. Future studies are needed to objectively measure activity in gonad-intact females and males over periods of adult weight gain.

In conclusion, this study shows that physical activity level is the best predictor of weight gain in adulthood in ovariectomized female monkeys consuming a diet typical of that consumed in the Western world. This finding suggests that the best way to prevent weight gain over adulthood is to focus on living an active lifestyle, as opposed to only dieting. However, even though a high percentage of adults in Western countries are overweight and/or obese, there is little evidence that people are routinely opting for a more active lifestyle. More than 60% of Americans do not participate in the recommended amount of physical activity, and 25% are inactive (59, 81). Although physicians routinely advocate that obese patients adopt a more active lifestyle, the results of this study suggest that this strategy deserves greater emphasis.

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R641

PHYSICAL ACTIVITY LINKED TO WEIGHT CHANGE


