Dietary Influences on Nonexercise Physical Activity and Energy Expenditure in C57BL/6J Mice

Jun Ho Kim, Yooheon Park, Daeyoung Kim, and Yeonhwa Park

Abstract: It is well established that the lack of physical activity can lead to weight gain or obesity. However, there is limited information on influences of diet components on physical activity. Thus the purpose of this study was to investigate the role of major dietary components on energy expenditure by affecting nonexercise physical activity in C57BL/6J mice. All mice were assigned to 1 of the following 4 dietary groups based on their body weight and baseline physical activity; low fat/normal protein, high fat/normal protein, low fat/low protein, or low fat/high protein. After 3 mo, the highest weight gain was observed in animals fed with high-fat/normal-protein diet, and the caloric intake was significantly lower in low-fat/high-protein diet-fed mice compared to other groups. However, there were no significant changes in nonexercise physical activity during experimental periods in all groups. The respiratory quotient and energy expenditure were not significantly different among the dietary groups. These findings suggest that diet-induced obesity is not explainable by levels of physical activity and energy expenditure.

Keywords: diet, energy expenditure, mice, obesity, physical activity

Practical Application: The understanding the link between diet and nonexercise physical activity would provide important knowledge that will potentially assist appropriate food choices to control obesity and its related health problems.

Introduction

Obesity is a result of a sustained mismatch between energy intake and expenditure. In mammals, energy expenditure is comprised of 3 main components including resting metabolic rate, thermoregulatory demands, and physical activity (Simoncic and others 2008). Physical activity is the most variable component of energy expenditure and, therefore, has been the target of behavioral interventions to control body weight in humans (Jakicic and Otto 2005).

It is well established that physical inactivity can lead to obesity, however, it is not clear if diet-induced obesity correlates with physical inactivity resulting in excessive weight gain. Several animal studies using a voluntary running wheel showed that physical activity is rather enhanced with high-fat diet-induced weight gain especially in polygenic fat or high runner lines of mice (Simoncic and others 2008; Meek and others 2010). These results imply involvement of high-fat diet in providing necessary fat as a fuel to help sustain prolonged exercise. However, others did not show consistent results for voluntary activity with high-fat diet (Bjursell and others 2008; Vaanholt and others 2008; Basterfield and others 2009). Bjursell and others (2008) reported a decrease in locomotor activity when C57BL/6J mice were on a high-fat western diet, and Vaanholt and others (2008) reported no change in home-cage activity in high-fat diet-fed males or females that were housed without wheel access. Basterfield and others (2009) observed no significant changes in wheel running and decreases in voluntary-cage activity with more sleep time when mice were exposed to high-fat diet compared to low-fat diet-fed mice. Therefore, the relationship between diet-induced obesity and physical activity is inconsistent, and there is limited information about influences of dietary components on physical activity.

Thus, the purpose of this study was to investigate the role of major dietary components on nonexercise physical activity, such as grooming, feeding, walking around, and so on, monitored under normal housing conditions. These reflect a normal sedentary lifestyle in humans. This study would help provide important information for understanding the link between diet and physical activity that may contribute to prevent obesity and obesity-related health problems.

Materials and Methods

Animals and diet

Male 8-wk-old C57BL/6J mice (The Jackson Laboratory, Bar Harbor, Maine, U.S.A.) were housed in individual wire-bottomed cages in a windowless room with a 12-h light–dark cycle, under a protocol approved by the Institutional Animal Care and Use Committee of the Univ. of Massachusetts Amherst. After a 1-wk adaptation period, all mice were subjected to measurement of nonexercise physical activity and respiratory quotient (RQ) as baseline data (week 0). Then animals were assigned to 1 of the following 4 dietary groups based on their body weight and baseline

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physical activity to minimize variations among the tested groups: low fat/normal protein, high fat/normal protein, low fat/low protein, or low fat/high protein.

The semipurified powdered diets were obtained from Harlan Laboratories (Madison, Wis., U.S.A.) and kept frozen until use. Animals were provided with diet and water freely and freshly twice per week. The compositions of treatment diets are presented in Table 1. Mice were maintained on treatment diet for 12 wk, and body weight and food intake were recorded weekly. In the end of study, the mice were fasted for 4 h and sacrificed by CO_2 asphyxiation. Internal organs (liver, heart, kidney, spleen, and adipose tissues) were weighed.

Activity measurement: nonexercise movement

Nonexercise physical activity was monitored using LoliTrack Quatro Video Tracking Software Version 1.0 (Loligo Systems, Tjele, Denmark) with an infrared camera. The mice were placed into special clear cages (30 × 46 × 40 cm) individually during the dark phase (6:00 p.m. to 5:00 a.m.) once biweekly with free access to diet and water (provided as HydroGel®, Clear H_2O, Portland, Maine, U.S.A.). This cage was larger than a typical mouse cage and was used to prevent a restriction in the numbers and positioning of activity monitors that could be caused by using a small size cage (Wittert and others 2005). The mice to be tracked were placed against a contrasting background and the software assigned an X, Y coordinate pair to the center of the contrasting objects. The program found all pixels within the range of 640 × 80 pixels and calculated the center X and Y coordinates of these pixels. The time-stamped X and Y coordinates were written into a data file to 5 times per second, and then the data were imported into Excel for analysis. Movement data for 9 h (8:00 p.m. to 5:00 a.m.), excluding first 2 h (6:00 to 8:00 p.m.) of early phase as adapting to surroundings, were analyzed. To determine changes in the activity pattern throughout the experiment, dark phase activity was expressed as percentage of total activity based on their baseline data obtained at week 0.

Table 1–Composition of experimental diets (g/kg).

Ingredients	Low-fat/ normal protein	High-fat/ normal protein	Low-fat/ low protein	Low-fat/ high protein
Casein	200	243	100	500
L-Cystine	3	3.7	1.5	0
Corn starch	423.302	221.56	499.902	172.902
Maltodextrin	135	135	155	100
Sucrose	100	100	100	100
Soybean oil	48	198	49	45
Cellulose	50	50	53	44
Mineral mix (W/O Ca, P), AIN-93-MX (TD 98057)	13.388	16	13.388	13.388
Calcium carbonate	5.6	6.7	3.4	12.2
Calcium phosphate dibasic	9.2	11	12.3	0
Vitamin mix, AIN-93-VX (TD 94047)	10	12	10	10
Choline bitartrate	2.5	3	2.5	2.5
TBHQ	0.01	0.04	0.01	0.01
kcal/g	3.6	4.4	3.6	3.6
Protein, % kcal	19.5	19.5	9.8	47.9
Carbohydrate, % kcal	68.1	39.8	77.8	39.7
Fat, % kcal	12.4	40.8	12.4	12.4

Energy expenditure and RQ

Energy expenditure was measured by an indirect calorimetric method, using a Metabolic Monitoring System (Qubit System, Kingston, Ontario, Canada). All animals were placed into this system individually once biweekly for 23 h (10:00 to 9:00 a.m.) with free access to diet and water as HydroGel®. Data were presented as RQ and energy expenditure. RQ is the ratio of V_{CO_2} produced to V_{O_2} consumed. Energy expenditure at week 12 was calculated from RQ data as: energy expenditure = $(3.815 + 1.232 \times \text{RQ}) \times V_{O_2}$ (Choi and others 2007). To eliminate the influence of body size variation, total energy expenditure was expressed as adjusted value for lean body mass as covariate (Choi and others 2011). Lean body mass was obtained by measuring carcass weights without guts and adipose tissues in abdominal area.

Statistical analyses

Data were analyzed by one-way ANOVA followed by a *post hoc* GLM procedure and least square means options of the SAS software for Windows release 9.2 (SAS Inst. Inc., Cary, N.C., U.S.A.) on the W32_VSHOME platform. Analysis of covariance (ANCOVA) with final body mass or lean body mass as covariate was used to test for differences in adipose depot, organ weight, and energy expenditure among different dietary groups. Homogeneity of regression assumptions were tested and met in each analysis. The adjusted mean values for the 4 experimental groups were further compared using the Tukey–Kramer's method in SAS. Repeated measures ANOVA using SAS PROC MIXED was performed for data in Figure 1. Data are shown as the mean ± S.E. The P values < 0.05 were reported as statistically significant.

Results

Body weight and caloric intake

The final body weight was the highest in the high-fat diet group (high-fat/normal-protein), which was significant compared to the low-fat/normal-protein and low-fat/high-protein groups but not to low-fat/low-protein group (Table 2). Caloric intake was significantly lower in the high-protein diet group (with low fat) than other dietary groups during the experimental period.

Tissue weights

Total adipose tissue weights including epididymal, mesenteric, and retroperitoneal adipose tissue were the highest in the high-fat/normal-protein group and the lowest in the low-fat/high-protein group ($P = 0.0128$ for diet effect between 2 treatments, Table 3). High-protein feeding significantly increased the weights of liver and kidney compared to the other 3 groups ($P < 0.0001$ for overall effect of diet on liver weight) and high-fat or high-carbohydrate (low-fat/low-protein) groups ($P = 0.0017$ for overall effect of diet on the kidney weight), respectively. No differences were observed in heart and spleen weights among all treatment groups.

Nonexercise physical activity

To evaluate the effects of dietary components on nonexercise physical activity, voluntary movement during dark cycle was observed throughout the experimental period (Figure 1A, 1B, 1C, and 1D). Animals fed high-fat (normal-protein) and high-protein (low-fat) diets showed increasing tendency of physical activity during the experimental period compared to their baseline, although not statistically significant among all dietary groups. Mice fed low-fat/normal-protein and low-fat/low-protein diets

showed decreasing tendency compared to their baseline, but overall there was no significant changes in physical activity for the diets ($P = 0.2415$) or time ($P = 0.1121$) in all tested groups. Repeated measurement analysis showed that trends of increased activity over time for animals fed high-protein (low-fat) compared to normal-protein (low-fat) and low-protein diets, although not linear pattern (Figure 1E, $P = 0.11$ for the interaction effect between diet and repeated time).

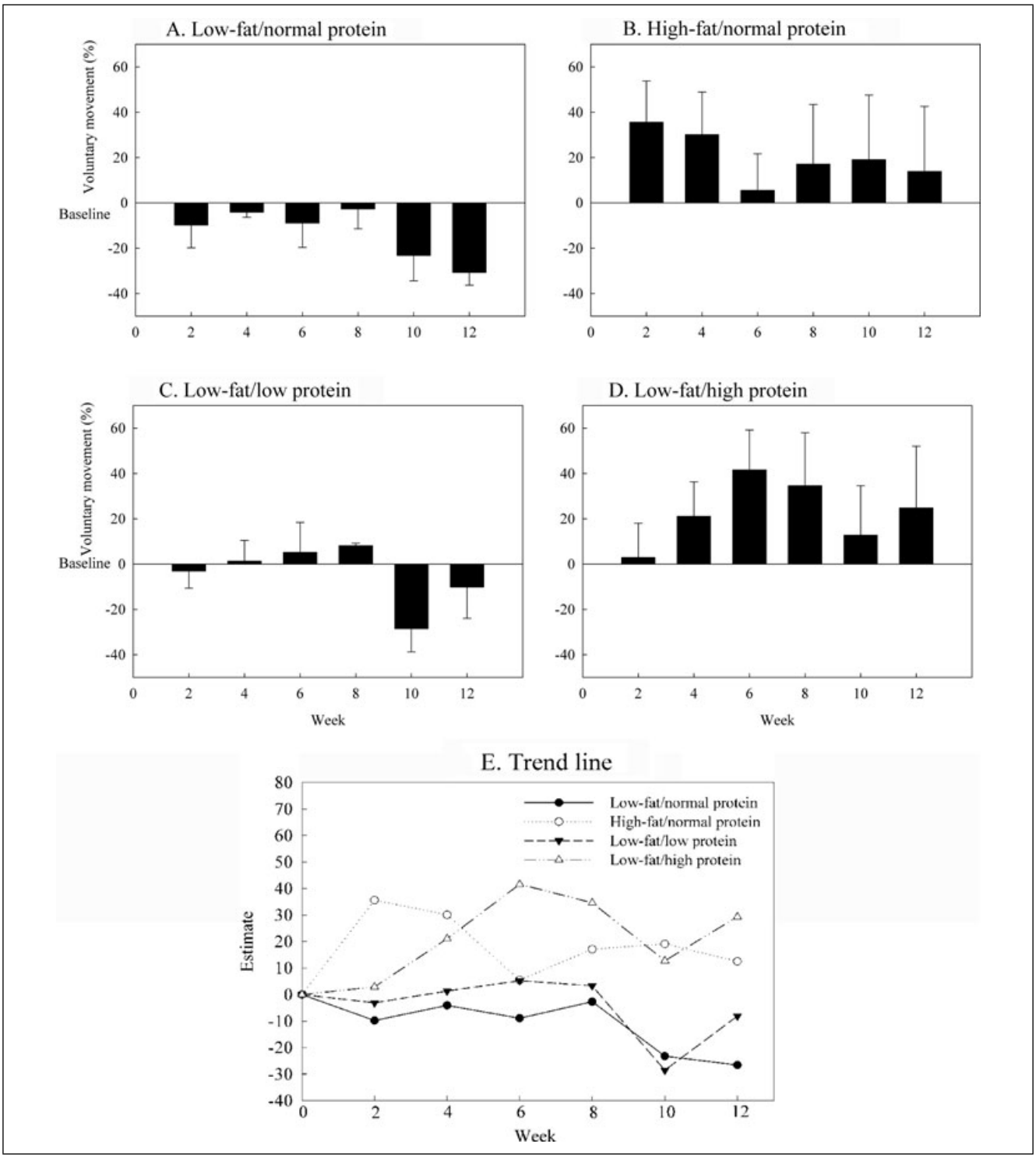

Figure 1–Effects of treatment diets on nonexercise physical activity in mice. 8-wk-old male C57BL/6J mice were fed 1 of the treatment diets for 12 wk. Physical activity was monitored between 8 p.m. and 5 a.m. at week 0 (baseline) and measured biweekly afterward. Values represent the percentage of increase or decrease of voluntary movement based on their baseline measured at week 0. Values are mean ± S.E. ($n = 5$). Subpart (E) shows trend lines of physical activity changes in each dietary group, which were analyzed by repeated measures ANOVA using SAS PROC MIXED. There were no significant differences in physical activity among all treatment groups ($P = 0.2415$ for diet effect, $P = 0.1121$ for time effect, and $P = 0.11$ for the interaction effect).

RQ and energy expenditure

RQ (throughout the experimental period) and total energy expenditure (at week 12) during both light and dark cycles did not show significant differences among the dietary groups ($P > 0.05$; Figures 2 and 3). There were no significant differences in the values of RQ and energy expenditure between light and dark cycles, although the values were slightly higher during dark cycle than light cycle.

Discussion

Several mice strains such as C57BL/6J, C57L/J, and SWR/J have been used in a voluntary exercise paradigm (Lerman and others 2002; Lightfoot and others 2004; Turner and others 2005), and C57BL/6J is especially characterized as having a genetic predisposition for the development of dietary-induced obesity when given access to a high-fat diet (Brownlow and others 1996; Rossmeisl and others 2003). This study was designed to evaluate the dietary effects on the changes of energy expenditure with physical activity in C57BL/6J mice. Physical activity has been typically tested by using a tool to measure activities, such as a running wheel, that involve more than normal leisurely movements. In this study, for the measurement of normal physical activity, nonexercise voluntary movement was recorded in their home cage without any wheel access during dark cycle.

As expected, high-fat diet-fed mice were the heaviest with the highest fat mass among the dietary groups but there was no significant difference in final body weight between high-fat and high-carbohydrate (low-fat/low-protein) diet groups. Previously, Brownlow and others (1996) observed a significant increase in body weight in high-fat diet compared with high-carbohydrate diet in male C57BL/6J mice after 4 mo of feeding trial even with similar caloric intake, which is different than our results. However, among high-carbohydrate diets, high-starch diet (similar to diet used in our study) fed mice were heavier than high-sucrose diet-fed mice in the same report (Brownlow and others 1996). Others reported that there was no difference in body weights in rats fed high-carbohydrate diet containing equal amounts of starch and sucrose compared with rats fed high-fat diet for 7 wk (Chang and others 1995). Thus, inconsistent observations between diet and weight gain may be in part due to the difference in feeding duration as well as the type of carbohydrate in the treatment diets.

The studies examining voluntary activity in animals fed high-fat diet have shown various responses. There are reports demonstrating increased voluntary activity, especially running, associated with high-fat diet feeding (Zhou and others 2005; Meek and others 2010). This could be accounted for by a sufficient supply of lipid sources required as a substrate for energy production during exercise. Fatty acid oxidation in muscular mitochondria followed by aerobic reactions of the tricarboxylic acid cycle are adequate to generate a large proportion of the ATP required for muscular contraction during prolonged exercise (Fushiki and others 1995). Hickson and others (1977) found that high-fat diet can serve to increase the duration of moderate physical activity by sparing glycogen, the depletion of which is considered to be a cause of fatigue.

In contrast, we did not observe any significant changes of nonexercise activity by any dietary treatments including high-fat diet for 3 mo. This is consistent with Brownlow and others (1996) reporting high-fat or high-sucrose diet did not induce the change in home-cage movement in male C57BL/6J and A/J mice. Moreover, our results indicated that there were no significant differences in RQ and energy expenditure during both light and dark cycle among dietary groups. We speculate that nonexercise form of physical activity might be primarily influenced by behavioral regulation via neurohormonal system rather than fuel utilization. This is based on reports that activation of the sympathetic nervous system is required to enter torpor as well as to initiate lipid mobilization (Youngstrom and Bartness 1998; Ruschke and others 2009). Moreover, defective hypothalamic melanocortin system blocks a normal torpor response with impairment of energy expenditure, and the hypothalamic neurotransmitters, including dopamine, norepinephrine, and serotonin, are also important

Table 2–Body weight and caloric intake of mice fed treatment diets.

	Dietary group			
	Low-fat/ normal protein	High-fat/ normal protein	Low-fat/ low protein	Low-fat/ high protein
Initial weight (g/mouse)	26.0 ± 0.7	25.3 ± 0.9	25.5 ± 0.7	25.9 ± 0.7
Final weight (g/mouse)	33.0 ± 0.9^{b}	38.1 ± 1.8^{a}	$35.4 \pm 1.7^{a,b}$	33.1 ± 1.4^{b}
Weight gain (g/mouse/12wk)	7.0 ± 0.2^{b}	12.8 ± 0.9^{a}	$10.0 \pm 1.1^{a,b}$	7.2 ± 0.7^{b}
Caloric intake (kcal/mouse/12wk)	1259 ± 39.3^{b}	$1281 \pm 36.1^{a,b}$	1303 ± 23.3^{a}	1184 ± 30.0^{c}

Values represent means ± S.E. ($n = 5$).
[a,b,c]Means with different superscripts within the same row are significantly different ($P < 0.05$).

Table 3–Organ and adipose tissue weights of mice fed treatment diets.

	Dietary group			
	Low-fat/normal protein	High-fat/normal protein	Low-fat/low protein	Low-fat/high protein
Adipose tissue (g)				
Epididymal	$1.22 \pm 0.15^{a,b}$	1.58 ± 0.17^{a}	$1.24 \pm 0.15^{a,b}$	0.87 ± 0.15^{b}
Mesenteric	0.33 ± 0.06	0.44 ± 0.06	0.37 ± 0.06	0.32 ± 0.06
Retroperitoneal	0.29 ± 0.06	0.46 ± 0.06	0.39 ± 0.05	0.23 ± 0.06
Total	$1.84 \pm 0.19^{a,b}$	2.49 ± 0.21^{a}	$1.99 \pm 0.18^{a,b}$	1.42 ± 0.19^{b}
Organ (g)				
Liver	1.24 ± 0.03^{b}	1.10 ± 0.03^{c}	1.24 ± 0.03^{b}	1.47 ± 0.03^{a}
Heart	0.18 ± 0.01	0.18 ± 0.01	0.17 ± 0.01	0.18 ± 0.01
Kidney	$0.49 \pm 0.02^{a,b}$	$0.41 \pm 0.03^{b,c}$	0.38 ± 0.02^{c}	0.53 ± 0.02^{a}
Spleen	0.08 ± 0.00	0.07 ± 0.00	0.07 ± 0.00	0.07 ± 0.00

Values represent means ± S.E. ($n = 5$). Means are adjusted for final body mass using the ANCOVA analysis.
[a,b,c]Means with different superscripts within the same row are significantly different ($P < 0.05$).

determinants for the control of motivation, emotion, and reward behaviors (Wankhade and others 2010). In addition, recent research supports the hormonal regulation, including leptin, of nonexercise physical activity in various animal models (Levine and others 2003; Wittert and others 2005; Knaba and others 2009; Morton and others 2011). Thus, our results in this report imply that the neurohormonal regulation of nonexercise physical activity in mice may not be affected by dietary treatments for at least the duration in this study.

We observed no differences in total energy expenditure among the dietary groups, which is consistent with a previous report of a lack of a relationship between diet-induced obesity and physical inactivity in both human and animal models (Eck and others 1990; Brownlow and others 1996). It has been reported that nonexercise activity thermogenesis (NEAT) correlates inversely with fat gain, which is representing energy expenditure with activities of daily living, including spontaneous muscle contraction, nonexercise movement, and fidgeting (Wittert and others 2005), although it was recently suggested that this definition of NEAT should be more narrowly corrected in order to facilitate study of logically and operationally separable components of energy expenditure (Garland and others 2011). Additionally, Jenkins and others (2006) observed an increase in sleep time (nonrapid eye movement sleep) in male C57BL/6J mice fed with a high-fat diet (obese) compared to mice fed with a regular chow (nonobese). Therefore, it is possible that NEAT with nonexercise physical activity responds differently according to the body fat level and we did not observe any difference in energy expenditure since animals in our study were not overweight or obese.

There are reports that high-protein feeding enhanced physical performance by decreasing muscle protein degradation and increasing muscle endurance, although the evidence is not consistent (Zdanowicz and others 1995; Williams and others 2003; Berardi and others 2008; Rowlands and Wadsworth 2011). In this study, animals fed high-protein diets showed steadily increasing tendency of nonexercise physical activity by week 6, but overall there were no significant increases. van Norren and others (2009) reported that supplementation with a specific combination of high-protein, leucine, and fish oil normalized impaired nonexercise physical activity with improving muscle performance in the tumor-bearing mice, but no effects of the single nutrients were observed. In light of these findings, the effects of high-protein feeding on the regulation of physical activity should be examined more closely in future studies.

In conclusion, the present study indicates no macronutrient influence on nonexercise physical activity and energy expenditure in C57BL/6J mice for the duration in this study. This implies that there are potentially other factors contributing to physical

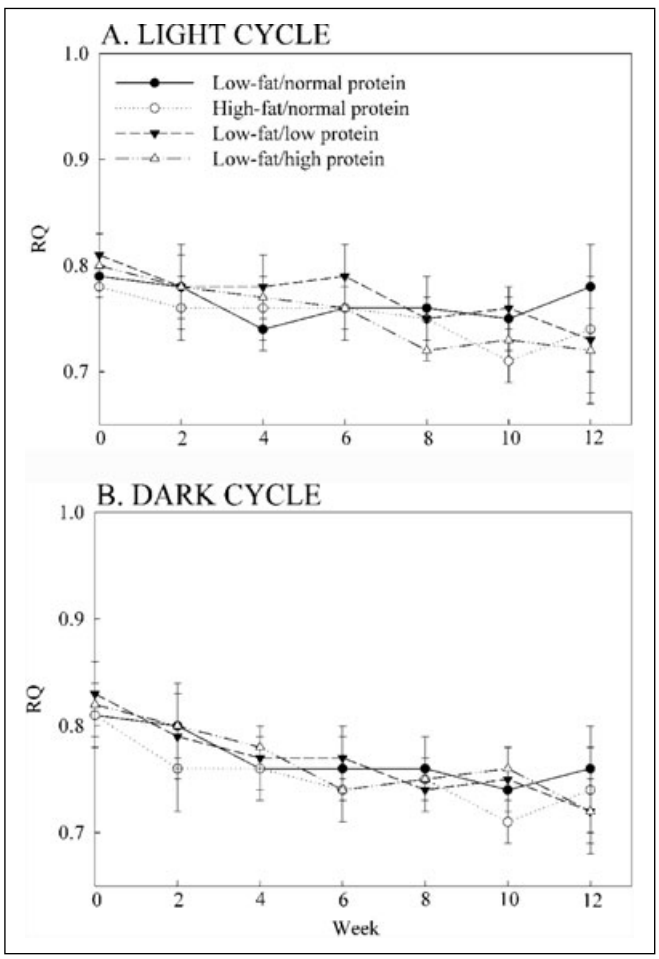

Figure 2–Effects of treatment diets on respiratory quotient (RQ) in mice; 8-wk-old male C57BL/6J mice were fed 1 of the treatment diets for 12 wk. RQ was measured biweekly. Values represent RQ during light or dark cycle after treatments. Values are mean ± S.E. ($n = 5$).

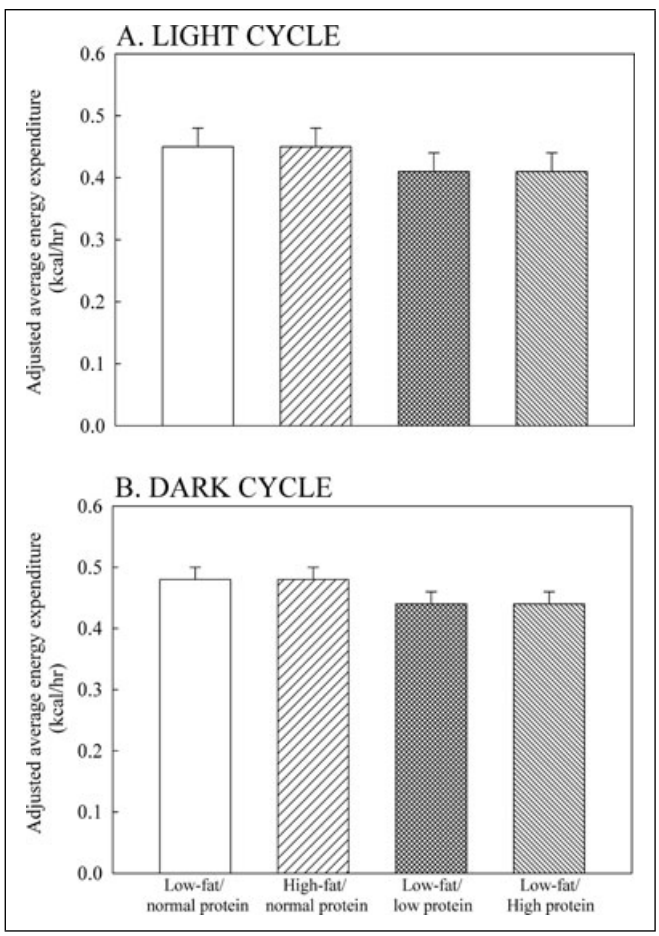

Figure 3–Effects of treatment diets on energy expenditure in mice; 8-wk-old male C57BL/6J mice were fed 1 of the treatment diets for 12 wk. Energy expenditures were determined at week 12. Values are mean ± S.E. ($n = 5$). Means are adjusted for lean body mass using the ANCOVA analysis.

inactivity prior to or simultaneous with obesity development. Further research that monitors the changes of physical activity, along with physiological mechanisms, by the combination of macronutrients will be needed to provide more information for understanding the obesity epidemic.

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