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ORIGINAL ARTICLE

Variation of food availability affects male striped hamsters (*Cricetulus barabensis*) with different levels of metabolic rate

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Abstract

In the present study, we examined metabolic, morphological and neurochemical changes in male striped hamsters (*Cricetulus barabensis*) in response to variations in food availability. Males with low and high levels of metabolic rate (MR: L-MR and H-MR, respectively), defined by their activity MR, were compared. In Experiment 1, 36-h food deprivation was found to significantly decrease MR levels, body fat content, mass of small and large intestines, and leptin gene expression in the white adipose tissues in male hamsters. Interestingly, L-MR males displayed decreased MR during both the day and night phases of circadian cycles, whereas H-MR males only showed a decrease in MR during the day (resting phase). These data indicate that individual differences in physical activity were associated with animals' different metabolic responses to food deprivation. In Experiment 2, both groups of males went through a 4-week fasting and re-feeding (re) paradigm. H-re males showed a persistent high level of MR, with decreased body fat content and a trending decrease in leptin mRNA expression, compared to L-re males. Together, our data indicate that male striped hamsters with different levels of physical activity display altered, adaptive changes in response to variations in food availability. The neurochemical involvement of such adaptive changes needs to be further studied.

Key words: fasting, food deprivation, leptin, metabolic rate, re-feeding

INTRODUCTION

Food shortage is prevalent in the life history of small mammals (Ehrhardt *et al.* 2005; Gutman *et al.* 2006). In response to changes in food availability, animals usually make adaptive behavioral and physiological adjustments which, in turn, are critical for their survival and reproductive success (Alvarenga *et al.* 2005; Zhao & Cao 2014; Zhao *et al.* 2014). For example, during food shortages, rodents may display alternative behavioral adaptations by increasing food foraging and/or resting longer and more frequently to decrease energy expenditure (Gutman *et al.* 2007; Auer *et al.* 2016). The display of such behavioral strategies occurs in a photoperiod-dependent and circadian-dependent manner; nocturnal animals may increase foraging during the dark (active) phase but rest more during the light (resting) phase of the day (Wen *et al.* 2018).

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Food intake and energy balance are important for animals' growth, survival and reproductive success (Hammond & Diamond 1997; Bacigalupe & Bozinovic 2002). It has been shown that animals' physical activity and the associated energy expenditure play a critical role in regulating their energy balance (Thorburn & Proietto 2000; Halsey *et al.* 2015). The total metabolic rate (MR) refers to the level of an individual's overall energy expenditure and consists of the resting and activity MRs (Halsey *et al.* 2015). While the former is usually used to measure basal metabolic demands of the organs, the latter (activity MR) is primarily due to the energy expenditure associated with increased organ activity related to muscle contractions (Halsey *et al.* 2015). The activity MR has also been reported to be correlated with animals' physical activity (Rezende *et al.* 2005; Careau & Garland 2012; Li *et al.* 2015; Toscano & Monaco 2015). Interestingly, large individual differences in physical activity have been reported in many animals (Careau & Garland 2012; Seebacher & Walter 2012). In general, a high level of physical activity is usually associated with a high level of activity MR (Careau & Garland 2012; Li *et al.* 2015; Toscano & Monaco 2015; Auer *et al.* 2016).

Food deprivation (FD) has been shown to affect behavior, morphology and physiology, especially for small rodent species. For example, Swiss mice [*Mus musculus* (Linnaeus, 1758)] and striped hamsters [*Cricetulus barabensis* (Pallas, 1773)] increased their activities during FD (Zhao & Cao 2009). Fasting has been reported to reduce body mass, body fat and resting MR in a variety of rodent species, including Swiss mice, striped hamsters and Brandt's voles [*Lasiopodomys brandtii* (Radde, 1861)] (Zhan *et al.* 2009). Fasting-related morphological changes in the metabolic and digestive organs have also been reported in many rodent species (Gao *et al.* 2013). Furthermore, FD has been found to affect hormonal and neurochemical systems that are involved in behaviors and energy metabolism and balance. For example, the level of serum leptin (a hormone that is mainly produced by adipocytes and has been implicated in energy expenditure and balance) has been shown to decrease in food-deprived animals (Mercer *et al.* 1998; Schneider *et al.* 2000; Mustonen *et al.* 2008; Speakman & Mitchell 2011; Gao *et al.* 2014) and such decreased serum leptin was associated with decreased fat mass as a result of fasting (Ahima *et al.* 2000). FD also increased hypothalamic gene expression of neuropeptides such as neuropeptide Y (NPY) and agouti-related protein (AgRP) in the golden spiny mouse [*Acomys russatus* (Wagner, 1840)] (Gutman *et al.* 2008). Interestingly, leptin supplement attenuated food restriction-enhanced gene expression of NPY and AgRP in the hypothalamus of striped hamster, indicating that leptin may play a key role in mediating responses to fasting (Zhao & Cao 2014; Wen *et al.* 2018). It is also interesting to note that re-feeding after fasting may induce post-fasting hyperphagia (Xie *et al.* 2012) and restore body mass and resting MR of the fasting animals (Zhao *et al.* 2009; Zhao & Cao 2009). However, serum leptin levels did not show compensatory increases during re-feeding in Syrian hamsters [*Mesocricetus auratus (*Waterhouse, 1839)] (Bartness 1997; Schneider *et al.* 2000) and Siberian hamsters [*Phodopus sungorus* (Pallas, 1773)] (Day & Bartness 2003).

The striped hamster is a rodent species widely distributed in northern China, Russia, Mongolia and Korea (Zhang & Wang 1998; Song & Wang 2003). They are nocturnal animals that are active mainly during the first half of the night (Vosko *et al.* 2009). In summer, striped hamsters do not store food and feed mainly on stems and leaves of plants (Zhang & Wang 1998; Zhang *et al.* 2015). Therefore, they have to make physiological and behavioral adaptations when experiencing food shortages in the natural environment (Zhang & Wang 1998). Data from previous studies have shown that food restriction alters activity behaviors of striped hamsters (Zhao *et al.* 2013). However, it is still unknown how these animals respond to FD and whether individual differences in physical activity influence their responses to FD. In the present study, we compared male striped hamsters with low or high levels of MR, to examine their metabolic and morphological changes in response to 36 h of FD. We also examined the gene expression of several neuropeptides in the hypothalamus and leptin from adipose tissue. Furthermore, the hamster's responses to 4 weeks of repeated fasting and re-feeding were also examined. We hypothesized that striped hamsters can make adaptive changes in their bodily functions in response to variations in food availability, and such responses may differ among individuals with different levels of physical activity and associated energy demands.

MATERIALS AND METHODS

Experimental subjects

Subjects were adult, male striped hamsters from our laboratory-breeding colony. Hamsters were housed individually in plastic cages (29 cm × 18 cm × 16 cm) with sawdust bedding and maintained in a room illuminated

on a 12:12 h light: dark cycle (lights on at 0800) under a constant temperature of 23 ± 1 °C. Water and pellet rodent chow (Beijing KeAo Feed, Beijing, China) were provided *ad libitum*. All experimental procedures were conducted in compliance with the Animal Care and Use Committee of the Institute of Zoology, Chinese Academy of Sciences.

Experimental design

At the onset of the study, one hundred and 4 adult male hamsters at 4–5 months of age with an average body weight around 27.3 g were screened for their MR at 2000–0200 hours. These animals were subsequently rank-ordered by their MR values. Thirty animals from each of the low (L) and high (H) ends of the MR measurement were assigned as L-MR (body mass ranged from 23.1 to 30.1 g) and H-MR (body mass ranged from 23.9 to 33.5 g) groups, respectively. Animals in these 2 groups differed significantly at their MR measurements (L-MR: 4.13 ± 0.08 mLO_2/h and H-MR: 6.06 ± 0.06 mLO_2/h; t_{58} = 18.85, P < 0.0001). These subjects were subsequently assigned into 1 of the following 2 experiments. Experiment 1 was designed to test the effects of FD on hamsters with different MR levels. A total of 20 L-MR and 20 H-MR subjects were randomly assigned into 1 of the 2 treatment groups that received food *ad libitum* (AD) or were food-deprived for 36 h (FD). Consequently, 4 experimental groups were created: L-AD, L-FD, H-AD and H-FD (with 10 subjects in each group). Experiment 2 was designed to test the effects of fasting and re-feeding on hamsters with different MR levels. L- MR (n = 10) and H-MR (n = 10) subjects were food-deprived for 24 h and then re-fed for 6 days. They went through this 7-day-cycle for 4 weeks. Thus, 2 experimental groups were created as L-re and H-re.

Total metabolic rate

The MR was quantified as the rate of oxygen consumption, using an O_2 measuring module high-speed sensor unit (994620-CS-HSP-01) for calorimetric measurements open-flow respirometry system (TSE, Germany), as described in our previous study (Wen *et al.* 2017; Wen *et al.* 2018). Briefly, air was pumped at a rate of 1000 mL/min through a cylindrical sealed Perspex chamber at 23 °C (same to the indoor temperature). Gases leaving the chamber were dried and sampled using an oxygen analyzer at a flow rate of 380 mL/min. The data were collected every 10 s by a computer connected analogue to digital converter, and analyzed using standard software (TSE, Germany). MR was corrected to standard temperature and air pressure conditions and expressed as mLO2/h (McNaught & Wilkinson 1997). Animals were pre-adapted to the metabolic chamber for 1 h before measurement started. In Experiment 1, MR was monitored throughout the entire experimental period (36 h starting at 2000 hours on the 1st day of the treatment). In Experiment 2, the 6-h MR measurement started at 2000 hours on the day when 4 weeks of fasting and re-feeding treatment was finished.

Body composition and body fat content

After the MR measurement, subjects were killed, and their trunk blood was collected. The whole brain was separated carefully and frozen on tin foil on dry ice. The hypothalamus was carefully dissected and stored in liquid nitrogen. Subcutaneous fat was harvested rapidly and also stored in liquid nitrogen. The stomach, small and large intestines, and caecum were separated and weighed (to 1 mg) without their contents. The liver, heart, lung, spleen and kidneys were also removed and weighed (to 1 mg). The remaining carcass was weighed to obtain wet mass. All of the tissues, organs and carcass were dried in an oven at 60 °C for 2 weeks to constant mass, and reweighed (to 1 mg) to determine dry mass. Total body fat was extracted from the dried carcass by ether extraction in a Soxhlet apparatus, and the weight difference before and after extraction was taken to calculate the fat mass of the carcass (Zhao & Wang 2006).

Real-time quantitative *reverse transcription* polymerase chain reaction analysis

Gene expression of agouti-related protein (AgRP), neuropeptide Y (NPY), cocaine-regulated and amphetamine-regulated transcript (CART), and pro-opiomelanocortin (POMC) in the hypothalamus, as well as subcutaneous adipose tissue leptin and hormone-sensitive lipase (HSL) were measured. Total RNA was extracted from the hypothalamus and subcutaneous fat, respectively, using TRIzol reagent (TAKARA, Dalian, China), and then was diluted to the same concentration across individuals in the 4 groups. Real-time *reverse transcription* polymerase chain reaction (RT-qPCR) analysis was carried out as described previously (Zhao *et al.* 2014). The cDNA samples (2 μL) were used as a template for the subsequent PCR reaction using gene-specific primers (Suppl. Table S1). The final reaction volume of 20 μL contained 10 μL of 2× SYBR Premix EX Tag TM (TAKARA), 2 μL cDNA template, 0.4 μL of forward prime and reverse primer (final concentration

0.2 μM per primer, Table 1). The qPCR was performed using the Roche LightCycler 480 Real-time qPCR System (Forrentrasse CH-6343 Rotkreuz, Switzerland). After an initial polymerase activation step at 95 °C for 60 s, amplification was followed by 40 cycles (95 °C for 5 s, 55 °C for 30 s and 72 °C for 30 s). The reaction was finished by the built-in melt curve. All samples were quantified for relative quantity of gene expression by using actin expression as an internal standard.

Body mass and food intake

The body mass of hamsters in Experiment 2 was measured daily (at 1600 hours) using a Sartorius balance (to 0.1 g), while subjects' food intake was also measured and calculated as the mass of food missing from the hopper, minus food residues mixed in the bedding (Cameron & Speakman 2010). The body mass and food intake were gradually increased during re-feeding. On days 4–7 of each week, body mass and food intake reached a stable level with some fluctuations. Therefore, we calculated the average value of days 4–7 as weekly body weight and food intake, and then compared the values with the baseline before the fasting.

Data analysis

Data were expressed as means ± SEM and analyzed by SPSS 20.0 statistical software. Two-factor (MR × FD) ANOVAs were performed for MR data in Figure 2a, and 3-factor mixed design ANOVA (MR × FD × phase) for Figure 2b and c, followed by a Student–New-

Table 1 The main effect of metabolic activity and food deprivation on body composition of striped hamster

	Metabolic rate			Food deprivation		
	L	H	*P*	AD	FD	*P*
Dry mass (g)						
Liver	0.321 ± 0.018	0.334 ± 0.024	ns	0.336 ± 0.021	0.318 ± 0.020	ns
Heart	0.038 ± 0.001	0.037 ± 0.002	ns	0.039 ± 0.002	0.036 ± 0.001	ns
Lung	0.051 ± 0.001	0.049 ± 0.002	ns	0.050 ± 0.002	0.049 ± 0.002	ns
Spleen	0.010 ± 0.001	0.006 ± 0.001	*	0.007 ± 0.001	0.009 ± 0.001	ns
Kidneys	0.082 ± 0.004	0.082 ± 0.003	ns	0.086 ± 0.004	0.078 ± 0.003	ns
SI	0.145 ± 0.009	0.133 ± 0.007	ns	0.164 ± 0.007	0.113 ± 0.004	**
LI	0.062 ± 0.005	0.056 ± 0.003	ns	0.068 ± 0.005	0.049 ± 0.002	**
caecum	0.039 ± 0.002	0.041 ± 0.002	ns	0.042 ± 0.002	0.037 ± 0.002	ns
Stomach	0.076 ± 0.004	0.077 ± 0.003	ns	0.084 ± 0.003	0.068 ± 0.002	**
Carcass	6.588 ± 0.405	6.364 ± 0.275	ns	7.055 ± 0.229	5.844 ± 0.413	*
Wet mass (g)						
Liver	0.928 ± 0.056	0.966 ± 0.083	ns	1.085 ± 0.072	0.791 ± 0.042	**
Heart	0.148 ± 0.005	0.150 ± 0.011	ns	0.164 ± 0.008	0.132 ± 0.005	**
Lung	0.206 ± 0.005	0.209 ± 0.006	ns	0.220 ± 0.004	0.193 ± 0.004	**
Spleen	0.123 ± 0.082	0.106 ± 0.081	ns	0.186 ± 0.106	0.037 ± 0.014	ns
Kidneys	0.328 ± 0.015	0.316 ± 0.012	ns	0.341 ± 0.010	0.302 ± 0.016	*
SI	0.612 ± 0.047	0.563 ± 0.032	ns	0.715 ± 0.027	0.449 ± 0.025	*
LI	0.211 ± 0.012	0.220 ± 0.010	ns	0.248 ± 0.009	0.179 ± 0.008	**
Caecum	0.176 ± 0.012	0.179 ± 0.007	ns	0.197 ± 0.007	0.156 ± 0.011	**
Stomach	0.334 ± 0.020	0.311 ± 0.011	ns	0.335 ± 0.009	0.310 ± 0.023	ns
Carcass	16.751 ± 0.542	16.500 ± 0.494	ns	17.870 ± 0.389	15.256 ± 0.460	**

Data are means ± SEM. *$P < 0.05$, **$P < 0.01$; ns, non-significant ($P > 0.05$). AD, *ad libitum*; FD, food deprivation; H, high; L, low; SI, small intestine; LI, large intestine.

man Keuls (SNK) post-hoc test. The effects of MR and FD on fat content, body composition, neuropeptide gene expression in the hypothalamus and subcutaneous fat (in Figs 3 and 4 and Table 1) were analyzed using 2-way ANOVA (MR × FD) followed by the SNK test. In Experiment 2, differences in the body mass and food intake between L-re and H-re groups over the 4 weeks were tested using one-way ANOVA with repeated measures (Fig. 5). Group differences in the MR, fat content, body composition and neuropeptide gene expression were examined by *t*-test (Figs 6 and 7 and Table 2). Significance was set at $P < 0.05$.

Table 2 Body composition in striped hamster subjected to 4 weeks fasting and refeeding

	L-re	H-re	*t*	*P*
Dry mass (g)				
Abdominal fat	0.079 ± 0.006	0.054 ± 0.008	−2.49	*
Heart	0.041 ± 0.002	0.042 ± 0.002	0.37	ns
Liver	0.282 ± 0.010	0.306 ± 0.015	1.32	ns
Lung	0.052 ± 0.002	0.049 ± 0.003	−0.83	ns
Spleen	0.006 ± 0.001	0.007 ± 0.001	0.66	ns
Kidneys	0.088 ± 0.003	0.085 ± 0.004	−0.48	ns
Stomach	0.096 ± 0.004	0.094 ± 0.003	−0.43	ns
SI	0.182 ± 0.005	0.208 ± 0.011	2.23	*
LI	0.079 ± 0.004	0.070 ± 0.004	−1.55	ns
Caecum	0.053 ± 0.003	0.048 ± 0.002	−1.60	ns
Carcass	8.412 ± 0.367	7.161 ± 0.344	−2.49	*
Wet mass (g)				
Abdominal fat	0.098 ± 0.005	0.065 ± 0.009	−3.19	**
Heart	0.172 ± 0.005	0.173 ± 0.008	0.02	ns
Liver	0.897 ± 0.029	0.970 ± 0.048	1.31	ns
Lung	0.215 ± 0.007	0.214 ± 0.007	−0.06	ns
Spleen	0.033 ± 0.003	0.028 ± 0.003	−1.24	ns
Kidneys	0.333 ± 0.011	0.332 ± 0.013	−0.04	ns
Stomach	0.376 ± 0.012	0.376 ± 0.009	0.01	ns
SI	0.740 ± 0.024	0.877 ± 0.040	2.95	**
LI	0.269 ± 0.010	0.274 ± 0.013	0.25	ns
Caecum	0.228 ± 0.010	0.228 ± 0.010	−0.06	ns
Carcass	18.205 ± 0.556	17.319 ± 0.575	−1.11	ns

Data are means ± SEM. *$P < 0.05$, **$P < 0.01$; ns, non-significant ($P > 0.05$). SI, small intestine; LI, large intestine.

RESULTS

Experiment 1

Total metabolic rate

Circadian patterns of MR for all 4 experimental groups are illustrated in Figure 1. As there was a strong correlation between MR and activity behavior, the increased MR during the night suggested that activity started after lights were off and continued all night. When the lights were shining, animals became sedentary throughout the day, indicated by considerably decreased MR. L-MR groups had lower levels of O_2 consumption in comparison to H-MR groups ($F_{1,960} = 10.41$, $P < 0.01$, Fig. 2a). FD decreased the rate of O_2 consumption in the L-MR, but not H-MR groups ($F_{1,960} = 38.48$, $P < 0.01$, Fig. 2a). When data were organized into 3 phases (phase 1: 0–12 h; phase 2: 12–24 h; phase 3: 4–36 h; Fig. 2b),

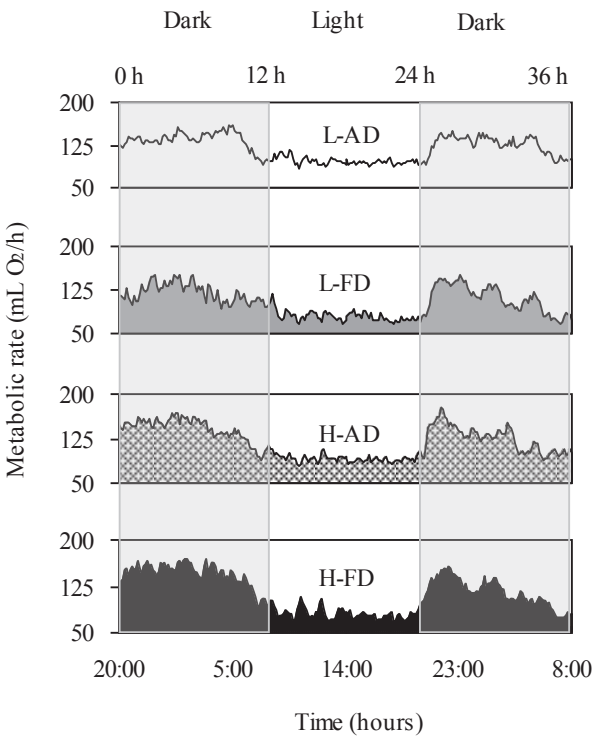

Figure 1 Mean metabolic rates of male striped hamsters changed across the 36-h experiment. Grey areas indicate the dark phase in a day. H-AD, group with high activity metabolic rate and *ad libitum* feeding; H-FD, group with high activity metabolic rate and food deprivation; L-AD, group with low activity metabolic rate and *ad libitum* feeding; L-FD, group with low activity metabolic rate and food deprivation.

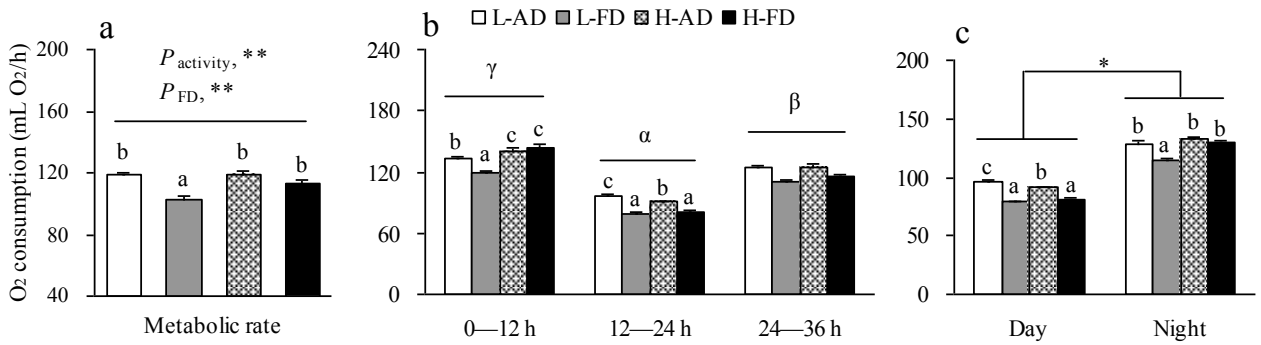

Figure 2 Effects of subject's activity and food deprivation on the metabolic rates (MR) in male striped hamsters. (a) Subjects activity ($P_{activity}$) and food deprivation (P_{FD}) significantly affected the overall levels of MR. Significant interaction was also found; food deprivation decreased MR in L-activity, but not H-activity, males. (b) Phase-dependent effects of subject's activity and food deprivation were found on MR. Males showed the highest levels of MR in Phase 1 (0–12 h) and the lowest levels of MR in Phase 3 (24–36 h) during the 36-h experiment. Greek letters indicate significant phase differences. (c) Males also displayed higher levels of MR during the night, compared to the day, of circadian cycles. Alphabetic letters indicate group differences by the post-hoc tests. *$P < 0.05$; **$P < 0.01$. Data are expressed as mean ± SEM. H-AD, high activity metabolic rate with *ad libitum* feeding; H-FD, high activity metabolic rate with food deprivation; L-AD, low activity metabolic rate with *ad libitum* feeding; L-FD, low activity metabolic rate with food deprivation.

a clear pattern emerged. The MR level during phase 1 was significantly higher compared to the other 2 phases, while the MR level during phase 3 was also higher than during phase 2 ($F_{2,638} = 885.10$, $P < 0.01$; Fig. 2b). Interesting effects of MR, FD and MR-FD interaction were found in a phase-dependent manner. For example, during phase 1, H-MR groups showed higher levels of MR compared to the L-MR groups ($F_{1,316} = 65.22$, $P < 0.01$), and FD significantly decreased MR in the L-MR, but not H-MR, groups ($F_{1,316} = 6.57$, $P < 0.01$). FD was effective in reducing MR in both L-MR and H-MR groups in phase 2 ($F_{1,316} = 279.81$, $P < 0.01$) and phase 3 ($F_{1,316} = 27.55$, $P < 0.01$), respectively. In phase 2, a significant interaction was also observed ($F_{1,316} = 17.52$, $P < 0.01$; Fig. 2b) in which L-AD males had a higher level of MR compared to H-AD males and both groups of FD males. No MR-FD interaction was found in phase 3.

Striped hamsters showed lower MR levels during the light phase (day) than the dark phase (night) of the day ($t_{643} = 108.29$, $P < 0.01$; Fig. 2c). Significant MR-FD interactions were found during the day ($F_{1,316} = 17.52$, $P < 0.01$) and night ($F_{1,316} = 8.18$, $P < 0.01$), respectively (Fig. 2c). FD significantly decreased MR levels for both L-MR and H-MR groups during the day but had such effects only for the L-MR group during the night (Fig. 2c).

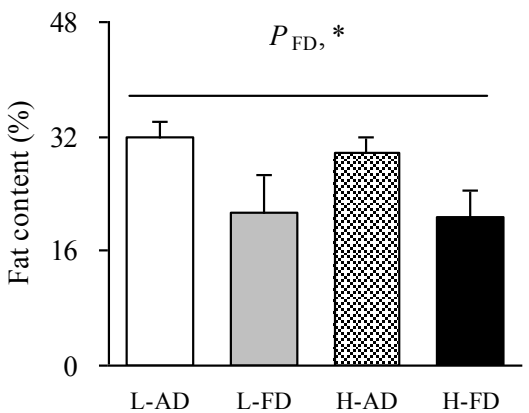

Figure 3 Food deprivation significantly decreased carcass fat content in male striped hamsters (P_{FD}*: $P < 0.05$). Data are expressed as mean ± SEM. H-AD, high activity metabolic rate with *ad libitum* feeding; H-FD, high activity metabolic rate with food deprivation; L-AD, low activity metabolic rate with *ad libitum* feeding; L-FD, low activity metabolic rate with food deprivation.

Body composition

Fat content of the carcass was significantly affected by FD ($F_{1,34} = 7.48$, $P < 0.01$, Fig. 3); FD groups had lower levels of fat content than AD groups (Fig. 3).

The body fat content was affected neither by subjects' MR ($F_{1,34}$ = 0.15, P > 0.05) nor by MR-FD interaction ($F_{1,34}$ = 0.05, P > 0.05; Fig. 3). FD resulted in significant decreases in the dry and/or wet masses of the carcass and of most of the organs measured (Table 1). In contrast, metabolic activities did not affect the measurements of the body composition (Table 1).

mRNA expression

Gene expression of a variety of neuropeptides in the hypothalamus, as well as of HSL and leptin in the subcutaneous fat, were examined. No group differences were found in any of the measured neuropeptide genes, including AgRP, NPY, CART, POMC and HSL (Fig. 4). FD tended to increase the hypothalamic AgRP mRNA expression but this effect was not statistically significant ($F_{1,34}$ = 3.82, P = 0.06, Fig. 4a). FD resulted in a significant decrease in the level of leptin mRNA expression in the fat ($F_{1,34}$ = 8.27, P < 0.05; Fig. 4f), but no effects were found for the subjects' activity and interaction with food availability.

Experiment 2

The body mass fluctuated consistently with the fasting-refeeding paradigm; it decreased following fasting and then bounded back throughout the days of re-feeding (Fig. 5a,c). No overall group differences were found for body mass during the 4-week experimental period (Fig. 5b). However, the food intake was significantly affected by phases ($F_{4,72}$ = 31.75， P < 0.05; Fig. 5d). Both L-re and H-re hamsters showed significant increases in their food intakes in phases 1, 3 and 4, compared to the baseline level. Group differences at the basal levels of MR remained after the 4 weeks fasting–re-feeding experience. H-re subjects had a significantly higher level of MR compared to L-re subjects (t_{14} = 2.61, P < 0.05;

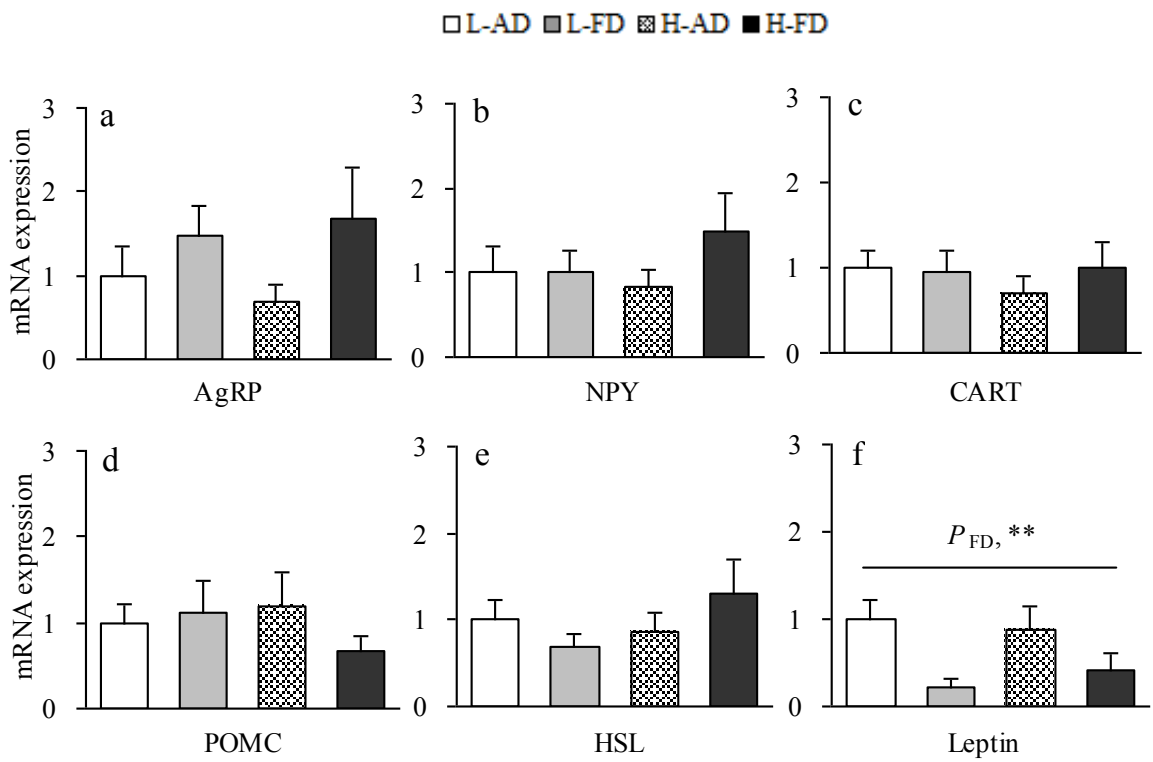

Figure 4 Gene expression of neuropeptide Y (NPY) (a), agouti-related protein (AgRP) (b), cocaine-regulated and amphetamine-regulated transcript (CART) (c) and pro-opiomelanocortin (POMC) (d) in the hypothalamus, and of hormone-sensitive lipase (HSL) (e) and leptin (f) in the subcutaneous fat of male striped hamsters. Data are expressed as mean ± SEM. H-AD, high activity metabolic rate with *ad libitum* feeding; H-FD, high activity metabolic rate with food deprivation; L-AD, low activity metabolic rate with *ad libitum* feeding; L-FD, low activity metabolic rate with food deprivation.

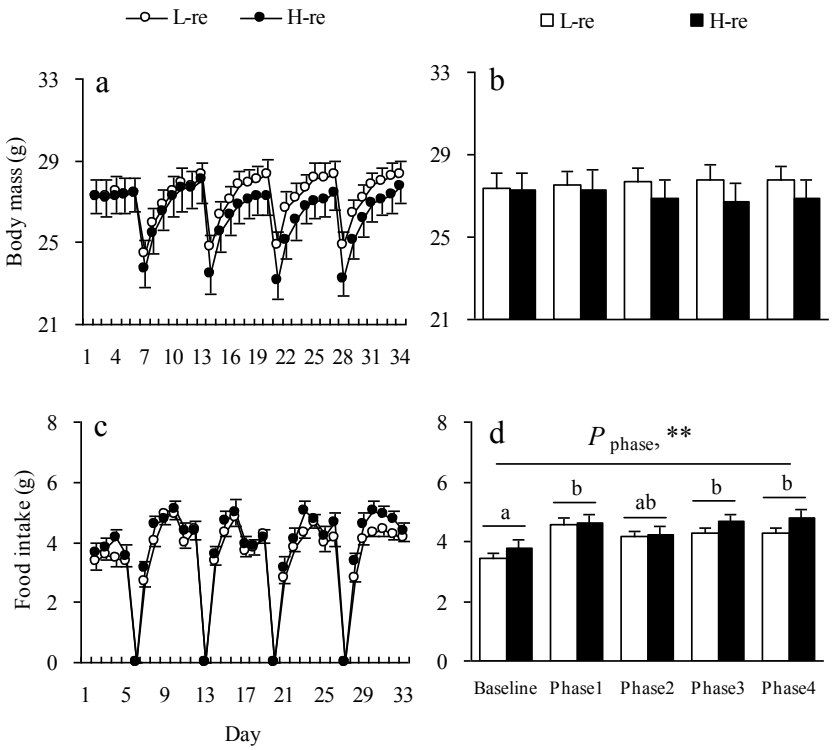

Figure 5 Body mass (a and b) and food intake (c and d) of male striped hamsters over the 4 weeks of repeated fasting and re-feeding. The 4-week experimental period was divided into 5 phases (b and d). Significant differences were found in food intake among different phases compared to the baseline (P_{phase}: $^{**}P < 0.01$). Alphabetic letters indicate phase differences by the post-hoc tests. Data are expressed as mean ± SEM. H-re, males with high activity metabolic rate; L-re, males with low activity metabolic rate.

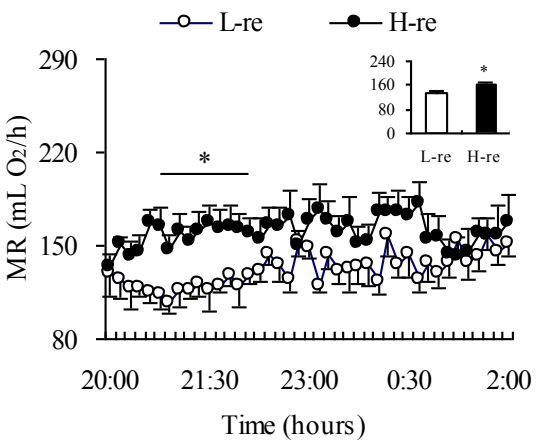

Figure 6 Metabolic rates of male striped hamsters over the 6-h measurement following 4 weeks of repeated fasting and re-feeding experiment. The insert indicates overall group differences. $^{*}P < 0.05$. Data are expressed as mean ± SEM. H-re, males with high activity metabolic rate; L-re, males with low activity metabolic rate.

Fig. 6). A group difference was also found in body fat content ($t_{1,18} = 3.35$, $P < 0.05$), which decreased significantly in the H-re, compared to the L-re, group (Fig. 7a). Consistently, H-re hamsters had a lower level of abdominal fat than L-re hamsters (Table 2). H-re hamsters also had heavier small intestines than L-re group (Table 2). Finally, no group differences were found in the gene expression of HSL and leptin in subcutaneous fat (Fig. 7b) and that of the hypothalamic neuropeptides (Fig. 7c).

DISCUSSION

Previous studies have shown that striped hamsters can make adaptive changes to cope with fluctuations of food resources (Zhao *et al.* 2013; Zhang *et al.* 2016; Wen *et al.* 2018). In the present study, our data show that male striped hamsters displayed metabolic, morphological and hormonal changes in response to 36-h FD. Most interestingly, L-MR and H-MR hamsters showed similar morphological and hormonal changes but different metabolic responses to FD. Furthermore, L-MR and H-MR hamsters differed in their responses to 4 weeks of fasting and re-feeding. Together, our data suggest that male striped hamsters with different levels of MR can display both similar and different adaptive strategies in response to variations in food availability.

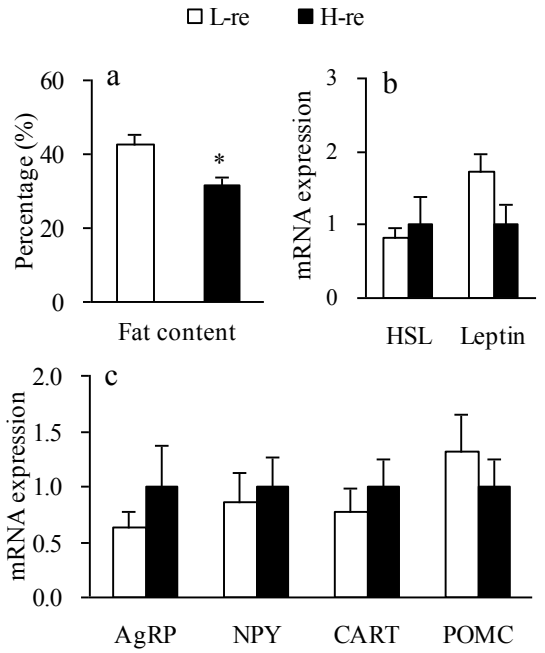

Figure 7 Carcass fat content (a), and gene expression of hormone-sensitive lipase (HSL) and leptin in the subcutaneous fat (b) and of neuropeptide Y (NPY), agouti-related protein (AgRP), cocaine-regulated and amphetamine-regulated transcript (CART) and pro-opiomelanocortin (POMC) in the hypothalamus (c) in male striped hamsters. Data are expressed as mean ± SEM. H-re, males with high activity metabolic rate; L-re, males with low activity metabolic rate.

Metabolic changes

In the present study, male hamsters, despite FD, displayed circadian patterns on the measured MR activity that were synchronized with the light/dark phases of circadian cycles. These data are consistent with data from previous studies on the striped hamsters (Zhao 2012) as well as on other rodent species (Green *et al.* 2008; Branecky *et al.* 2015). Our data also show that males that experienced FD displayed significant decreases in their MR compared to the control males that had *ad libitum* feeding. These data suggest that in adaptation to the prolonged FD, male striped hamsters can reduce energy expenditure by decreasing metabolic activities: a phenomenon that has been well documented in a variety of rodent species, including chipmunks (*Tamias minimus* Bachman, 1839) (Gutman *et al.* 2007), dormice [*Glis glis* (Linnaeus, 1766)] (Cornish & Mrosovsky 1965), deer mice (*Peromyscus*) (Blank & Desjardins 1985) and Yunnan red-backed vole [*Eothenomys miletus* (Thomas, 1914)] (Zhu *et al.* 2016). The reduced MR under conditions of limited food availability or FD can play important roles in conserving energy, sustaining animals' lives, and even enhancing their reproductive success (Brzek *et al.* 2016; Rimbach *et al*. 2016).

Most interestingly, this FD effect on MR differed in individuals with different levels of physical activity. L-MR hamsters showed reductions in the overall MR as well as in the MR during both the dark and light phases of a circadian circle. However, H-activity hamsters showed a decrease in the MR only during the light phase of a circadian circle, but neither in the dark phase of the circle nor in the overall MR level. Individual differences in MR are determined by complex intrinsic factors that affect animals' physiological and behavioral traits (Majdak *et al.* 2014). Although these factors are still unknown in striped hamsters, our data indicate that hamsters with different MR are fundamentally different in their metabolic responses to FD. The disappearance of the FD effect on H-MR hamsters during the night phase is interesting. The pestrid hamsters are nocturnal animals. One possibility is that H-MR hamsters need to maintain a high level of MR, regardless of FD, to sustain organ and body activities. It is also possible that H-MR hamsters are more resistant to FD compared to their L-MR counterparts.

Morphological changes

Our data illustrate several morphological changes associated with 36-h FD. FD males had significant decreases in body fat content, as well as in the mass of small and large intestines, compared to the control males. Such morphological changes have been reported in striped hamsters even when they have experienced food restriction of 90% and 60% for 4 weeks (Zhao 2012). Food restriction or FD also led to similar changes in other species, such as yunnan red-backed vole (Gao *et al.* 2013) and tree shrew [*Tupaia belangeri* (Wagner, 1841)] (Gao *et al.* 2014). Decreases in body fat content may be due to increased mobilization of stored energy in compensating for prolonged FD (Ahima *et al.* 1996; Doring *et al.* 1998; McCue 2010). In addition, decreases in the size of internal organs, such as small and large intestines, observed in the present and previous studies (Wen *et al.* 2018; Zhao & Cao 2014b) may reflect animals' adaptive changes in reducing energy expenditure (Gao *et al.* 2013, 2014). Finally, our data show that such morphological changes were similar in both L-MR and H-MR hamsters.

Hormonal and neuropeptide gene expression changes

Serum leptin is secreted by white adipose tissues and serves as a satiation signal in the brain to regulate food intake and energy balance (Zhang *et al.* 1994; Verhagen *et al.* 2011). Data from previous studies on striped hamsters (Zhao & Cao 2014; Wen *et al.* 2018), tree shrews (Gao *et al.* 2014) and mice (Kastin & Akerstrom 2000) have shown that fasting for more than 12 h results in significant decreases in the levels of serum leptin and leptin mRNA expression in white adipose tissues. In the present study, 36-h FD decreased leptin mRNA expression in subcutaneous fat in male striped hamsters. Decreased leptin may allow animals to increase their food intake and energy storage when food resources become abundant (Hardie *et al.* 1996; Cheng *et al.* 2002).

Decreased leptin expression has often been associated with neuroendocrine and neurochemical changes in response to fasting or FD (Ahima *et al.* 1996; Doring *et al.* 1998). For example, food restriction resulted in upregulation of AgRP and NPY in the arcuate nucleus of the hypothalamus associated with decreased leptin expression in striped hamsters (Zhao & Cao 2014), golden spiny mice (Gutman *et al.* 2008) and rats [*Rattus norvegicus* (Berkenhout, 1769)] (Brady *et al.* 1990; Schwartz *et al.* 1993; de Rijke *et al.* 2005; Johansson *et al.* 2008; Sucajtys-Szulc *et al.* 2008, 2009). In the present study, the hypothalamic AgRP showed a marginal increase ($P = 0.06$) in FD males compared to the control males, which is consistent with previous findings (Wen *et al.* 2018). However, FD did not affect the expression of hypothalamic NPY and other neuropeptides that were examined in the present study. Several caveats and possibilities should be noted. First, lack of significant FD effects on AgRP expression may be due to the limited sample sizes. Second, FD affects neuropeptide gene expression in a brain region-specific manner (Wen *et al.* 2018). In the present study, the neuropeptide gene expression was assessed in the entire hypothalamus, which might have led to a "floor effect," reducing the quantitative sensitivity (Wen *et al.* 2018). Third, regulation of AgRP and NPY gene expression in the brain of striped hamsters may be in a paradigm-specific and stimulus-specific manner. Food restriction was examined in a previous study (Zhao & Cao 2014), whereas a FD paradigm was used in the present study. It is also worth mentioning that in Syrian hamsters, hypothalamic NPY gene expression was not changed following 48-h FD (Mercer *et al.* 1996, 1998; Jones *et al.* 2004). Finally, the lack of differences in the neuropeptide gene expression between L-activity and H-activity hamsters may suggest that individual differences in physical activity are not involved in leptin and neuropeptide responses to FD.

Effects of fasting and re-feeding

Although the same fasting and re-feeding paradigm had been used in previous studies in rats, mice, Syrian hamsters, Djungarian hamsters [*Phodopus sungorus* (Pallas, 1773)] and yunnan red-backed voles (Bartness *et al.* 1994; Day *et al.* 1999; Day & Bartness 2003; Friedman & Halaas 1998; Woods *et al.* 1998; Schneider *et al.* 2000), this is the first study that examines fasting and re-feeding in striped hamsters. Our data have collectively illustrated several interesting phenomena. First, after 4 weeks of fasting and re-feeding, L-re and H-re groups still showed significantly persistent differences in their active MR. These data have provided further evidence to support the notion that individual differences in physical activity are persistent and enduring, and are likely regulated by intrinsic factors with little or no influences from fluctuations of food availability. Second, H-re males had a significantly lower level of body fat content than L-re males. Interestingly in Experiment 1, no group differences were found in body fat content between L-activity and H-activity males either with *ad libitum* feeding or under FD. It can be speculated that during the repeated fasting and re-feeding, more fat had been mobilized/utilized to meet the high energy demand for the H-re group, compared to the L-re group. This speculation is further supported by the trending decrease in leptin mRNA expression in H-re than in L-re groups, which is consistent with the data from other studies (Girard *et al.* 2007; Bouassida *et al.* 2010; Golbidi & Laher 2014).

In some rodent species, including rats and mice (Friedman & Halaas 1998; Woods *et al.* 1998), fasting is followed by hyperphagia and compensatory increases in body mass during re-feeding: a strategy that may allow animals to cope with scarcity of food resources (Gao *et al.* 2013). However, in other rodent species, such as Syrian hamsters (Bartness 1997; Schneider *et al.* 2000), Djungarian hamsters (Day *et al.* 1999; Day & Bartness 2003) and Yunnan red-backed voles (Gao *et al.* 2013), re-feeding following fasting did not induce compensatory body growth. In the present study of striped hamsters, hyperphagia, indeed, occurred during re-feeding after fasting in both L-re and H-re males with some fluctuations. However, no compensatory increases in body mass were found in striped hamsters. Although hypotha-

lamic neuropeptide and adipose tissue HSL and leptin mRNA expression did not differ significantly between L-re and H-re groups, we could not exclude their roles in food intake and fat storage in the animals recovering from FD. The neurochemical involvement of such adaptive changes needs to be further studied. These data provide additional evidence to further support the notion of species-specific adaptation to fluctuations in food availability (Zhao 2012).

CONCLUSION

In summary, data from the present study show that in response to 36-h FD, male striped hamsters displayed several metabolic, morphological and hormonal/ neurochemical changes. Interestingly, L-MR males displayed decreased MR during both the day and night phases of a circadian cycle, whereas H-MR males only showed a decrease in MR during the day (resting phase). These data indicate individual differences in metabolic responses to FD between males with different MR. This notion is further supported by the data from the second experiment in which H-re males showed a persistent high level of MR, with a decreased body fat content and a trending decrease in leptin mRNA expression compared to L-re males. Together, our data suggest that male striped hamsters with different levels of MR can display similar as well as different adaptive responses to variations in food availability. The specific roles of neurochemicals in the regulation of such responses need to be examined in further studies.

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SUPPLEMENTARY MATERIALS

Additional supporting information may be found in the online version of this article at the publisher's website.

Table S1 Gene-specific primer sequences used for RT-qPCR analysis

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