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The increase in fat content in the warm-acclimated striped hamsters is associated with the down-regulated metabolic thermogenesis

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ABSTRACT

It has been well known that metabolic thermogenesis plays an important role in the thermoregulation of small mammals under different temperatures, while its role in fat accumulation is far from clear. In the present study, several physiological, hormonal, and biochemical measures indicative of metabolic thermogenesis were measured in the weaning striped hamsters after acclimated to a warm condition (30 °C) for 1, 3 and 4 months. The warm-acclimated groups significantly decreased energy intake, and simultaneously decreased nonshivering thermogenesis compared to those housed at 21 °C. Body fat content increased by 29.9%, 22.1% and 19.6% in the hamsters acclimated to 1, 3 or 4 months, respectively relative to their counterparts maintain at 21 °C ($P < 0.05$). The cytochrome *c* oxidase (COX) activity of brain, liver, heart and skeletal muscle, and the ratio of serum tri-iodothyronine to thyroxine significantly decreased in warm-acclimated groups compared with 21 °C group. COX activity and uncoupling protein 1 (UCP_1) mRNA expression of brown adipose tissue (BAT) were significantly down-regulated under the warm conditions. COX activity of BAT, liver, heart and muscle were significantly negatively correlated with body fat content, and the correlation between UCP_1 expression and body fat content tended to be negative. These findings suggest that the decrease in the energy spent on metabolic thermogenesis plays an important role in the fat accumulation. The attenuation of COX and UCP_1-based BAT activity may be involved in body fat accumulation in animals under warm conditions.

1. Introduction

Proper adjustments of both physiology and behavior are required for small mammals living in a temperate zone to cope with considerable changes in seasonal environment (Bartness and Wade, 1985; Mercer, 1998; Klingenspor et al., 2000; Concannon et al., 2001; Bartness et al., 2002; Jefimow et al., 2004; Zhou et al., 2015). The variations in body mass/or fat mass are important adaptive strategies for small mammals to cope with the changes of environment temperature, within which the changes in both energy intake and expenditure are involved (Concannon et al., 2001). Hyperphagia is reported to be an important factor inducing an increase body fat, within which the plasticity of digestive enzymes and digestibility are likely involved (Mercer, 1998; Zhao et al., 2014a; Zhang et al., 2015). It has been observed that metabolic rate and thermogenesis increase notably in many small mammals to cope with winter or winter-like conditions (Bartness et al., 2002; Wang et al., 2006; Zhu et al., 2010), but decrease significantly in response to summer or summer-like conditions (Heldmaier et al., 1982; Wang and Wang, 1996; Zhao et al., 2014a). The cold-exposed rodents, such as Brandt's voles (*Lasiopodomys brandtii*) (Li and Wang, 2005a), Mongolian gerbils (*Meriones unguiculatus*) (Li and Wang, 2005b) and Syrian hamsters (*Mesocricetus auratus*) (Bartness et al., 2002) markedly increase energy intake to meet the increase in metabolic thermogenesis, but exhibit significantly lower body mass or body fat. However, they usually consume less energy under summer or warm conditions, while show significant increases in either body mass or body fat reserves, or the both (Steinlechner et al., 1983; Ebling, 1994; Li and Wang, 2005a, 2005b). It may suggest that, in some situations, the energy expended for metabolic thermogenesis plays more important roles in regulations of body mass and body fat than energy intake (Steinlechner et al., 1983; Ebling, 1994).

Basal metabolic rate (BMR) is the minimum rate of energy expenditure for maintaining normal physiological function (AL-Mansour, 2004; Mckechnic and Wolf, 2004). Many factors affect the variations of BMR in animals, such as body size (White and Seymour, 2003), food habits (McNab, 1986), life history traits (Harvey et al., 1991) and climate (Lovegrove, 2003). BMR is also associated with the mass of metabolically active internal organs, including brain, liver, heart, *etc.* The variation of mass-specific BMR can be reflected by the differences in mitochondria density in these organs (Else and Hulbert, 1985; Porter and Brand, 1995), as well as in the activity of enzymes underlying metabolic

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pathways (Guderley et al., 2005; Vézina and Williams, 2005). Inconsistently, non-shivering thermogenesis (NST) belongs to facultative thermogenesis, and it is an adaptive thermogenic response to winter or winter-like conditions (Cai et al., 1998; Li et al., 2001). NST is primarily produced in BAT, which is the main organ for adaption of thermoregulation in rodents (Heldmaier, 1985; Cannon and Nedergaard, 2004). It has been well established that BMR and NST are physiologically regulated in animals to cope with variations of ambient temperature (Haim and Izhaki, 1993). Numerous studies have been performed to focus on the adaptive strategy of metabolic thermogenesis in small mammals in response to cold environment, whereas few studies work on its roles in regulation of body mass and body fat under warm-experience (Heldmaier et al., 1982; Rafael et al., 1985; Klaus et al., 1988; Jefimow et al., 2004).

BAT is known to be a main site of NST in small mammals (Nicholls and Locke, 1984). BAT mitochondrial protein content and mitochondrial cytochrome *c* oxidase (COX, complex IV of the respiratory chain) activity represent oxidizability at cellular level (Heldmaier et al., 1989; Wang et al., 1995). Cytochrome *c* oxidase (COX) is the terminal respiratory complex of the mitochondrial respiratory chain and is responsible for catalyzing the reduction of molecular oxygen (Cannon and Nedergaard, 2004; Zhang et al., 2009). Uncoupling protein 1 (UCP_1), located in the inner mitochondrial membrane of BAT (up to 10% of mitochondrial protein), uncouples energy substrate oxidation from mitochondrial ATP production and transforms electro-chemical energy into heat (Argyropoulos and Harper, 2002; Cannon and Nedergaard, 2004). It has been demonstrated that COX activity and UCP_1 expression of BAT are significantly up-regulated in response to cold temperatures, which is in parallel with the changes of NST, indicating that the UCP_1-based BAT system plays an important role in the regulation of body temperature (T_b) (Kozak et al., 2010). As a corollary to this conclusion, the UCP_1-based BAT system may be also involved in body mass and body fat regulation, *i.e.* BAT prevents body fat accumulation by burning off excess energy to maintain energy balance (Kozak et al., 2010; Nedergaard and Cannon, 2014). Temperature is one of the important factors influencing metabolic thermogenesis and body mass or body fat. There is no doubt that warm acclimation induce down regulation of BAT activity. Therefore, the warm-acclimated animals may be suitable for the examination of the possible role of BAT in body mass and/or body fat regulations.

The striped hamster is a principal rodent in northern China and is also distributed in Russia, Mongolia and Korea (Zhang and Wang, 1998; Song and Wang, 2003; Zhang and Zhao, 2015). The striped hamsters do not show significant changes in body mass after being maintained in an outside enclosure for over a year, but show significantly higher body fat mass in summer relative to those in winter (Zhao et al., 2014a). It has been previously found that the metabolic thermogenesis significantly increase in cold temperature, and notably decreased in warm temperature (Liu et al., 2003; Song and Wang, 2003; Zhao et al., 2010a, 2010b). UCP_1-based BAT thermogenesis has been demonstrated to play an important role in the regulation of T_b in the hamsters acclimated to seasonal environment and to cold or warm temperature. The aim of this work was to examine the effect of different warm experience on energy intake, metabolic thermogenesis, body mass and body fat in the striped hamsters. BAT COX activity and UCP_1 mRNA expression were examined. We hypothesized that the down-regulation of BAT activity might be involved in body fat accumulation in hamsters under different warm experience.

2. Material sand methods

2.1. Animals and experiment protocol

All experimental procedures were in compliance with guidelines of the Animal Care and Use Committee of Wenzhou University. Striped hamsters were obtained from our laboratory-breeding colony, maintained in the animal house at Wenzhou University. Animals were held at ambient temperature of 21 °C (±1 °C) and photoperiod 12L:12D (light: dark, lights on at 08:00 h). The colony was housed in clean plastic cages (29 × 15 × 18 cm^3) with sawdust beddings. Food (standard rodent chow; produced by Beijing KeAo Feed Co., Beijing, China) and water were provided *ad libitum*.

Forty-four hamsters were randomly assigned into one of four groups after weaning: 21 °C-4 M group ($n = 12$), hamsters were maintained at 21 °C for four months; 30 °C-1 M group ($n = 12$), hamsters were maintained at 21 °C for three months, and then transferred into a warm condition (30 ± 1 °C) for one month; 30 °C-3 M group ($n = 8$), hamsters were maintained 21 °C for one month, and then transferred into 30 °C for three months; 30 °C-4 M group ($n = 12$), hamsters were transferred into 30 °C for four months after weaning.

2.2. Gross energy intake (GEI) and digestibility

The measurements of GEI and digestible energy intake (DEI) were performed over 48 h at the end of the experiment. As described previously (Grodzinski and Wunder, 1975; Liu et al., 2003), food was provided quantitatively and the spillage of food mixed with bedding and feces were collected from each animal and separated manually after they were dried at 60 °C to constant mass. The water content of the diet (%) was calculated from the decrease in mass of the diet. The gross energy contents of the food and feces were determined by IKA C2000 oxygen bomb calorimeter (IKA, Germany). GEI, DEI and apparent digestibility of energy (hereafter referred to simply as digestibility) were calculated according to the following equations (Grodzinski and Wunder, 1975; Liu et al., 2003; Zhao and Wang, 2007):

$$\begin{aligned}\text{GEI (kJ/d)} = {}& \text{food take (g/d)} \times \text{dry matter content of food (\%)} \\ & - \text{dry spillage of food} \times \text{gross energy content of food (kJ/g)};\end{aligned}$$

$$\begin{aligned}\text{DEI (kJ/d)} = {}& \text{GEI} - [\text{dry feces mass (g/d)} \\ & \times \text{gross energy content of feces (kJ/g)}];\end{aligned}$$

$$\text{Digestibility (\%)} = (\text{DEI/GEI}) \times 100\%.$$

2.3. Basal metabolic rate (BMR) and maximal NST (NST_{max})

Both BMR and NST were measured following the GEI measurements, and qualified as the rate of oxygen consumption, using an open-flow respirometry system (TSE systems, PhenoMaster/LabMaster, Germany). In detail, hamsters were fasted for 4 h and were in a postprandial state before being transferred into a cylindrical sealed Perspex chamber. Air was pumped at a rate of 1000 ml/min through the chamber. Gases leaving the chamber were directed through the oxygen analyzer at a flow rate of 380 ml/min after they were dried using a special drier. The data were averaged and collected every 10 s by a computer connected analogue-to-digital converter (TSE system, Germany), and analyzed using a standard software (TSE system, Germany). BMR was measured for 3 h at 30 ± 0.5 °C (within the thermal neutral zone of this species, Song and Wang, 2003; Zhao et al., 2010b). BMR was calculated from the lowest rate of oxygen consumption over 10 min.

NST_{max} was induced by subcutaneous injection of norepinephrine (NE) (Shanghai Harvest Pharmaceutical Co. Ltd.) and measured at 25 ± 0.5 °C. The mass dependent dosage of NE was calculated according to the equation NE (mg/kg) = 6.6 $Mb^{-0.458}$ (g) (Mb, body mass) (Heldmaier, 1971). NST_{max} was calculated according to the same methods as BMR but used two continuous stable maximal recordings. NST was calculated as NST_{max} minus BMR. BMR, NST_{max} and NST were finally corrected to standard temperature and air pressure (STP) conditions. All measurements were performed between 09:00 and 17:00 to correct for a possible effect of the circadian rhythm.