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Chronological analysis of caloric restriction-induced alteration of fatty acid biosynthesis in white adipose tissue of rats

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ABSTRACT

The beneficial actions of caloric restriction (CR) could be mediated in part by metabolic remodeling of white adipose tissue (WAT). Recently, we suggested that CR for 6 months increased the expressions of proteins involved in *de novo* fatty acid (FA) biosynthesis in WAT of 9-month-old rats. Herein, we compared the CR-induced chronological alterations of the expression of mRNAs and/or proteins involved in FA biosynthesis in the WAT and liver of rats subjected to CR starting from 3 months of age and their age-matched controls fed *ad libitum*. The findings suggested that CR was more effective on FA biosynthesis in WAT than in liver. In WAT, CR markedly increased the expressions of mRNAs and/or proteins involved in FA biosynthesis, including sterol regulatory element-binding protein 1c (SREBP1c), a master transcriptional regulator of FA biosynthesis, throughout the experimental period. Interestingly, the CR-enhanced upregulation was temporally attenuated at 5 months of age. CR markedly increased the nuclear phosphorylated form of Akt only at 3.5 months of age. In contrast, CR significantly reduced the expression of leptin at 9 months of age. The CR-induced upregulation was not observed in obese fa/fa Zucker rats homozygous for nonfunctional leptin receptor. Collectively, these data indicate that the V-shaped chronological alterations in WAT are regulated *via* SREBP1c, which is probably activated by CR duration-dependent modulation of both insulin and leptin signaling.

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1. Introduction

Caloric restriction (CR) can extend both the median and maximum lifespans, and retard several age-related pathophysiological changes in laboratory rodents (Masoro, 2005; Sinclair, 2005). It has been reported that growth hormone (GH)/insulin-like growth factor (IGF)-1/insulin signaling, adenosine monophosphate-activated protein kinase (AMPK) signaling, mammalian target of rapamycin (mTOR) signaling, sirtuin activity, and oxidative and other stresses may mediate the effects of CR, but the exact underlying mechanisms are still under debate (Masoro, 2005; Sinclair, 2005; Speakman and Mitchell, 2011).

White adipose tissue (WAT) is a major tissue for energy storage in the form of triglycerides (TG). It consists predominantly of white adipocytes that store energy in TG-containing unilocular droplets. During the last two decades, several WAT-derived secretory molecules (adipokines) have been characterized, and their secretory profiles are altered according to the size of adipocytes. Large hypertrophic adipocytes, which possess more TG, secrete less adiponectin, an anti-inflammatory and anti-atherogenic cytokine, and more pro-inflammatory adipokines including leptin and monocyte chemotactic protein 1 (MCP1), while small adipocytes, which contain less TG, secrete more adiponectin and less pro-inflammatory adipokines (DeClercq et al., 2008; Torres-Leal et al., 2010; Ouchi et al., 2011). In addition, small adipocytes act as powerful buffers, by absorbing lipids in the postprandial period and releasing them prior to feeding. If this lipid-buffering action is impaired, non-adipose tissues accumulate lipids in the form of TG, resulting in insulin resistance (Frayn, 2002). Consequently, small adipocytes with higher lipid-buffering activity are considered more beneficial for a healthy lifespan than large adipocytes. A recent report demonstrated that visceral fat removal deteriorated insulin sensitivity, increased fat accumulation in skeletal muscle, and raised the body temperature and respiratory quotient in long-living GHR/BP knockout (KO) mice, but had opposite effects in wild-type mice (Masternak et al., 2012). It has been reported that fat-specific insulin receptor knockout (FIRKO) mice live longer than their controls. The mice show reduced adiposity and altered secretion of adipokines, including higher adiponectin and lower pro-inflammatory cytokine

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secretion (Blüher et al., 2002, 2003; Katic et al., 2007). The transcription factors C/EBPα, C/EBPβ, and peroxisome proliferator-activated receptor γ (PPARγ) are master regulators of adipocyte differentiation (Farmer, 2006). Mice in which C/EBPα was replaced with C/EBPβ (β/β mice) live longer and have reduced adiposity with an increased population of small adipocytes (Chiu et al., 2004). In contrast, hetero-deficient PPARγ KO mice have a shorter lifespan (Argmann et al., 2009). Transgenic mice expressing adiponectin in the liver live longer than controls and are resistant to high-calorie diet-induced obesity (Otabe et al., 2007). These observations show that the quality of WAT or adipocytes, and the adipokine secretory profile influence whole body metabolic homeostasis, including insulin sensitivity and ectopic fat accumulation in non-adipose tissues, probably resulting in a healthy and/or maximum lifespan.

CR reduces adiposity, downsizes adipocytes, increases plasma adiponectin, and lowers proinflammatory cytokines including leptin (Higami et al., 2004, 2006; Yamaza et al., 2007; Zhu et al., 2007). Recently, our proteomic analysis of WAT in 9-month-old Wistar male rats fed *ad libitum* and subjected to CR for 6 months showed that CR upregulated the expressions of proteins involved in fatty acid (FA) biosynthesis and the pyruvate/malate (P/M) cycle including ATP-citrate synthase (ACLY), NADP-dependent malic enzyme (ME1), and pyruvate dehydrogenase E1 component subunit beta, mitochondrial. Moreover, CR increased mitochondrial DNA contents, upregulated gene expressions involved in mitochondrial biogenesis, and enhanced the enzyme activities of citrate synthase and cytochrome c oxidase, suggesting that CR activates *de novo* FA biosynthesis, P/M cycle activity, and mitochondrial energy metabolism in WAT. In CR animals, it is likely that WAT functions as an energy transducer from glucose to energy-dense lipid to use energy effectively against the shortage of energy supply (Okita et al., 2012). Based on data derived from the DNA microarray analysis of WAT, we also reported that CR increased and decreased the expressions of genes involved in FA biosynthesis and inflammation in a GH/IGF-1-independent manner, respectively. Moreover, the CR-associated upregulation of genes involved in FA biosynthesis might be regulated in a sterol regulatory element-binding protein (SREBP) 1-dependent manner in WAT (Chujo et al., 2013). Therefore, we hypothesized that metabolic remodeling, including enhanced FA biosynthesis *via* SREBP1c and altered adipokine profile in WAT, plays a pivotal role for the beneficial actions of CR. In this study, to understand the metabolic remodeling over time after onset of CR, the time courses of the CR-induced changes in the expressions of mRNAs and/or proteins involved in FA biosynthesis were examined in the WAT and liver of rats. Moreover, to clarify the impact of leptin signaling on CR-activated FA biosynthesis in WAT, the effects of CR were compared between obese fa/fa Zucker rats homozygous for nonfunctional leptin receptor and control lean +/+ rats.

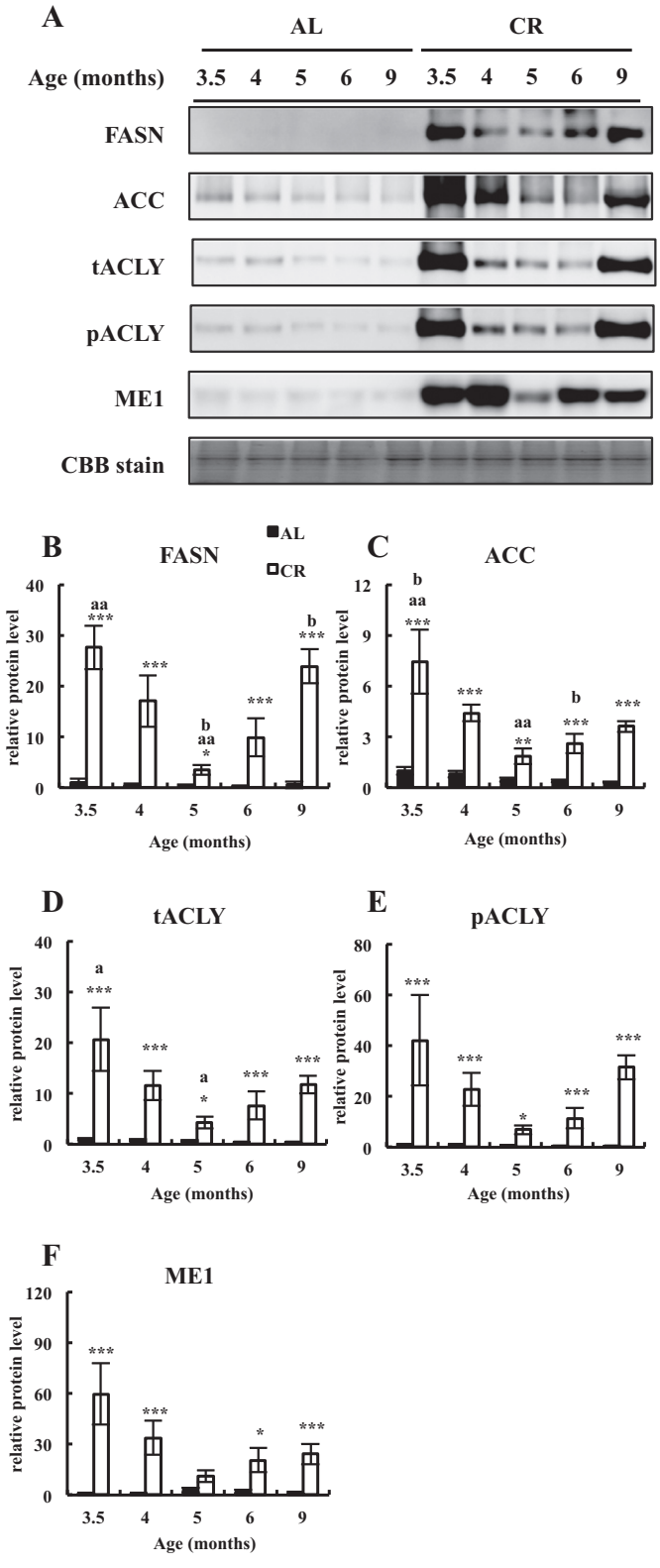

Fig. 1. CR-associated chronological alterations of protein expressions involved in *de novo* FA biosynthesis in WAT of Wistar rats. Protein samples were extracted from WAT of AL and CR rats at 3.5, 4, 5, 6, and 9 months of age. Western blot analyses of total FASN, ACC, tACLY, pACLY, and ME1 were performed using a chemiluminescence method. The antibody-bound proteins were visualized using an LAS3000 Image Analyzer. The intensity of Coomassie Brilliant Blue (CBB) staining was used as a normalization control. The western blot analyses were performed in duplicate or triplicate for each sample with biological repeats of $n = 4$ for each group. (A) Representative images of western blots and CBB staining. (B–F) Densitometry data for FASN (B), ACC (C), tACLY (D), pACLY (E), and ME1 (F). The values shown in the panels are means ± SEM for each group. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, *vs.* age-matched AL rats by Tukey's *t*-test. Values indicated by the same single and double superscripts differ significantly with age in the same dietary group at $p < 0.05$ and $p < 0.01$ by Tukey's test, respectively.

2. Materials and methods

2.1. Animals and diet

The present study was approved under the provisions of the Ethics Review Committee for Animal Experimentation at both Tokyo University of Science and Nagasaki University. Male 5–7-week-old Wistar rats were purchased from Clea Inc. (Tokyo, Japan) and maintained under specific pathogen-free (SPF) conditions in the Laboratory Animal Center at the Faculty of Pharmaceutical Sciences, Tokyo University of Science. The animals, and their husbandry care and diet were previously described in detail (Okita et al., 2012). All rats were provided with water and fed *ad libitum* with a Labo MR Stock diet (NOSAN, Yokohama, Japan). From 12 weeks of age, the rats were divided into two groups: one was fed *ad libitum* (AL group) and the other was calorie-restricted

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