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Cyclophilin D deficiency prevents diet-induced obesity in mice

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ABSTRACT

Mitochondrial coupling efficiency is pivotal in thermogenesis and energy homeostasis. Here we show that deletion of cyclophilin D (CypD), a key modulator of the mitochondrial permeability transition pore, demonstrated resistance to diet-induced obesity (DIO) in both male and female mice, due to increased basal metabolic rate, heat production, total energy expenditure and expenditure of fat energy, despite increased food consumption. Absorption of fatty acids is not altered between CypD$^{-/-}$ and wild-type mice. Adult CypD$^{-/-}$ developed hyperglycemia, insulin resistance and glucose intolerance albeit resistant to DIO. These data demonstrate that inhibition of CypD function could protect from HFD-IO by increasing energy expenditure in both male and female mice. Inhibition of CypD may offer a novel target to modulate metabolism.

1. Introduction

When dietary energy is maintained at a constant level, weight gain or loss depends on the energy expenditure through exercise and other obligatory bodily functions and on the coupling efficiency. Coupling efficiency is defined as the proportion of the calories burned and oxygen consumed that is coupled to ATP synthesis. One of the mechanisms by which metabolic efficiency can be lowered is to activate futile cycles of ATP synthesis and hydrolysis. Proton leaks have been reported to account for 26% of resting energy expenditure in isolated hepatocytes and up to 50% in perfused rat skeletal muscle [1]. Although the mechanism for the proton leak is not defined, the adenine nucleotide translocase (ANT), involved in export of ATP from mitochondria, is implicated [2]. In addition, oxidative phosphorylation is uncoupled by inducible proton leak in specialized tissues such as brown fat by uncoupling proteins (UCPs) to cause adaptive thermogenesis.

Obesity is associated with diminished brown fat activity [3] and it was proposed that a malfunction of the brown-fat-specific uncoupling by UCP-1 may explain this phenomenon. Interestingly, UCP-1 gene deletion, although lacked the ability to respond to β-adrenergic stimulated thermogenesis during acclimation to cold [4], they failed to demonstrate an obese phenotype [5,6]. However, a recent report demonstrated that at thermoneutrality, the metabolic efficiency was increased in UCP-1 deficient mice and they had an obesogenic phenotype [7], rekindling the role for UCP1 in bioenergetics.

Another possible mechanism by which leakage of protons may occur is by the intermittent opening of mitochondrial permeability transition pore (MPTP). MPTP opening allows small molecules below the size of 1500 Da to pass through the inner mitochondrial membrane causing disruption of the transmembrane potential and proton gradient [8]. Cyclophilin D (CypD) is a critical component of the PTP that can modulate the permeability of the channel in response to various stress stimuli [9]. A role for MPTP in diet-induced obesity has not been investigated. We hypothesized that modulation of MPTP by CypD could be an alternate mechanism by which energy metabolism is uncoupled and adaptive thermogenesis could occur. To test, we fed HFD to CypD deficient mice and determined the effect of CypD deficiency on body weight, food intake, energy expenditure, body fat stores and glucose tolerance.

2. Results

2.1. CypD deficient mice are resistant to high fat diet-induced obesity

In order to determine the effect of CypD deficiency on energy homeostasis, we fed 6 week-old male and female cypD$^{-/-}$ mice along with age and genetically matched wild-type (WT) (B6129SF2/J) mice with either high fat (HF; 45% fat by calories,

Abbreviations: CypD, cyclophilin D; WT, wild-type; HF, high fat; RQ, respiratory quotient; MPTP, mitochondrial permeability transition pore

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4.76 kcal/g) or normal diet (ND; 10% fat by calories, 3.85 kcal/g) for a period of 19 weeks. The body weight of mice from different groups was similar at the beginning of the study. Mice from all groups were weighed weekly and quantitative data demonstrated that the rate at which body weight increased was significantly lower in HF fed CypD$^{-/-}$ male (Fig. 1A) and female (Fig. 1B) mice compared to their WT counterparts. CypD$^{-/-}$ mice appeared smaller in size compared to their WT counterparts at 17 weeks post-HF diet and a representative photograph of the male animals is shown (Supplementary Fig. S1A). These results demonstrate that both male and female cypD$^{-/-}$ mice are resistant to HF diet-induced obesity.

To understand the mechanism by which CypD deficiency protects against obesity, the body weight and fat mass, food intake, metabolic level and energy expenditure were measured in CypD$^{-/-}$ and WT mice. At 19 weeks post-HF feeding, the difference in body weight between cypD$^{-/-}$ and WT male mice was 34.6% ($n = 4$; $P < 0.01$) and female mice was 38.4% (Fig. 1C-top panel). No difference in body weight between control diet fed WT and CypD$^{-/-}$ mice was noted up to 19 weeks post-feeding. Analysis of the body composition of cypD$^{-/-}$ and WT male mice fed HF, using quantitative nuclear magnetic resonance (NMR) method, at the 19 week study's completion time point revealed that CypD$^{-/-}$ mice have significantly lower percentage of fat mass ($P < 0.01$; $n = 4$), increased water content ($P < 0.01$; $n = 4$) but no change in the percentage of lean mass compared to WT mice (Fig. 1C-bottom panel).

2.2. Food consumption is decreased in female but not in male cypD$^{-/-}$ mice

Measurement of food intake in HF-fed CypD$^{-/-}$ and WT male mice demonstrated that the cumulative food intake over a period of 17 weeks adjusted for body mass demonstrated a significant increase in both male and female CypD$^{-/-}$ mice (Fig. 2A and B, respectively). However, the average feed consumption in absolute mass and kilocalories are comparable during the HF feeding period in male CypD$^{-/-}$ and WT mice but significantly decreased in female CypD$^{-/-}$ mice on HF diet compared to their WT counterparts (Supplementary Fig. S2A and S2B). The cumulative feed efficiency (increase in body weight relative to energy intake), determined as previously described [10] was also significantly decreased in both male and female CypD$^{-/-}$ mice compared to their WT counterparts (Supplementary Fig. S2C). These data suggest that the decrease in body weight in CypD$^{-/-}$ male mice is independent of feed intake, and despite similar levels of feed consumption, CypD$^{-/-}$ male mice

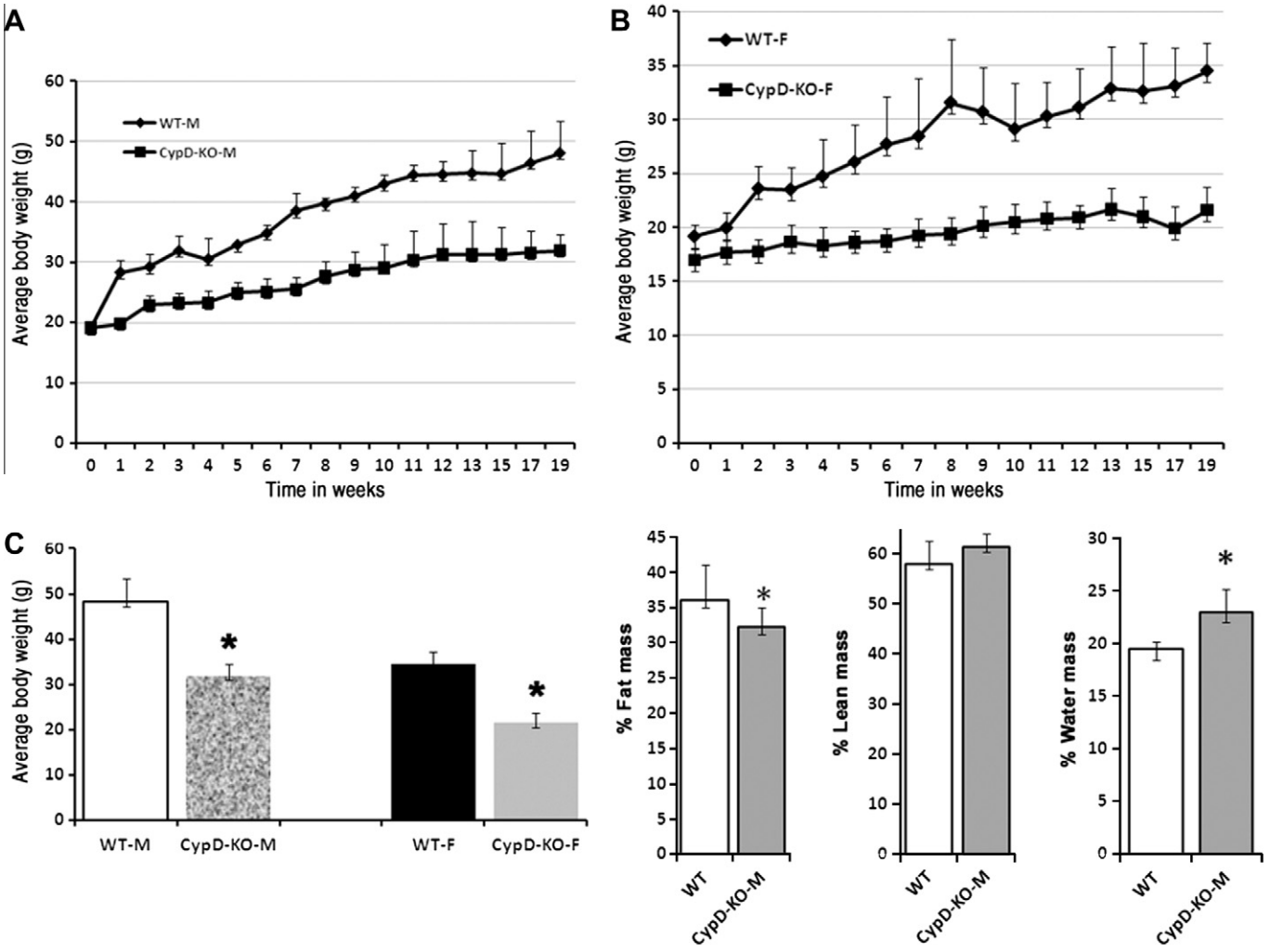

Fig. 1. (A) Average body weights of WT and CypD$^{-/-}$ male mice: ($^*P < 0.001$; $n = 6$–8) compared to WT high-fat diet fed male mice. (B) Average body weight of female mice: $^*P < 0.001$ ($n = 6$–8) compared to WT high-fat fed female mice. (C-top panel) The average body weight of WT and CypD$^{-/-}$ male mice fed HF-diet for 19 weeks. (C-bottom panel) The percentage of fat mass ($^*P < 0.01$), lean mass ($P > 0.05$) and water mass ($^*P < 0.01$) in WT and CypD$^{-/-}$ male mice fed HF-diet for 19 weeks were analyzed by the NMR method ($n = 4$ per group).