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Resveratrol restores the circadian rhythmic disorder of lipid metabolism induced by high-fat diet in mice

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ABSTRACT

Circadian rhythmic disorders induced by high-fat diet are associated with metabolic diseases. Resveratrol could improve metabolic disorder, but few reports focused on its effects on circadian rhythm disorders in a variety of studies. The aim of the present study was to analyze the potential effects of resveratrol on high-fat diet-induced disorders about the rhythmic expression of clock genes and clock-controlled lipid metabolism. Male C57BL/6 mice were divided into three groups: a standard diet control group (CON), a high-fat diet (HFD) group and HFD supplemented with 0.1% (w/w) resveratrol (RES). The body weight, fasting blood glucose and insulin, plasma lipids and leptin, whole body metabolic status and the expression of clock genes and clock-controlled lipogenic genes were analyzed at four different time points throughout a 24-h cycle (8:00, 14:00, 20:00, 2:00). Resveratrol, being associated with rhythmic restoration of fasting blood glucose and plasma insulin, significantly decreased the body weight in HFD mice after 11 weeks of feeding, as well as ameliorated the rhythmities of plasma leptin, lipid profiles and whole body metabolic status (respiratory exchange ratio, locomotor activity, and heat production). Meanwhile, resveratrol modified the rhythmic expression of clock genes (*Clock*, *Bmal1* and *Per2*) and clock-controlled lipid metabolism related genes (*Sirt1*, *Pparα*, *Srebp-1c*, *Acc1* and *Fas*). The response pattern of mRNA expression for *Acc1* was similar to the plasma triglyceride. All these results indicated that resveratrol reduced lipogenesis and ultimately normalized rhythmic expression of plasma lipids, possibly via its action on clock machinery.

1. Introduction

Overweight and obesity have become a serious and growing public health problem in the twenty-first century [1]. Previous ways to combat against obesity have failed, and new approaches need to be taken. In mammals, the circadian clock is an endogenous oscillator with a period of approximately 24 h, and rhythmicity refers organisms to adapt with environmental changes. The central circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus in the brain, but circadian clock is also an intracellular mechanical sharing of the same molecular components in peripheral tissues as in the case of liver tissue [2,3]. Recent research has revealed the relationship between liver tissue clock gene desynchronization and the development of certain diseases, such as obesity [4,5].

The mammalian circadian clock could be reset by input signals, such as light (light/dark) changes or meal condition (intake/fast). Light is perceived by the retina, and then signal is transmitted via the retinohypothalamic tract (RHT) to the SCN. The SCN dictates the entrainment of peripheral oscillators via humoral factors or autonomic innervation. Meanwhile, food and feeding regimens affect either peripheral clocks or the central clock in the SCN. Hence, the modification of these signals leads to the clock gene metabolic disruption. It has been well reported that constant light or constant dark conditions cause a free-running period and reduce the rodent behavioral circadian rhythmic activity [6]. Similarly, restricted feeding strongly entrained the expression of circadian clock genes in the liver without the participation of an SCN clock function [7]. Different reports have also shown nocturnal mice fed only during

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the 12 h light phase gain significantly more weight than mice fed only during the 12 h dark phase [8].

As mentioned previously, high-fat diet, one of the characteristic unhealthy lifestyle choice in developed countries, is partially responsible for increasing obesity. Several articles have shown that introduction of a high-fat diet to mammalian leads to rapid changes in both cycling of hormones and nuclear hormone receptors involved in fuel utilization [4,9,10]. It has been demonstrated that high-fat diet delays the circadian expression of adiponectin signaling components in mice liver. Conversely, fasting has opposite effects, resulting in a phase advance [11]. Thus it could be proposed that fasting or caloric restriction could reverse the changes in temporal phase and daily rhythm of clock genes caused by high-fat diet.

Resveratrol (3,5,4′-trihydroxystilbene), a natural antioxidant polyphenol compound that is found in red wine and grapes, has shown activity to extend the lifespan of many organisms [12]. The effects of this molecule on circadian rhythmicity in liver tissue have not been previously studies; however, considering that many health benefits associated with resveratrol have been attributed to its ability to mimic the effects of a calorie-restrictive diet [13], resveratrol may be a useful tool in avoiding circadian disruption caused by high-fat diet. The evidence that resveratrol regulates the expression of clock genes period homolog (PER1), PER2, brain and muscle Arnt-like 1 (Bmal1) in Rat-1 fibroblast cells is in good accordance with this proposal [14].

Thus, the purpose of the present study was to analyze the potential effect of resveratrol on changes induced by high-fat diet in the expression of different clock genes and clock-controlled lipid metabolism in liver tissue.

2. Materials and methods

2.1. Animals

Male C57BL/6 mice were purchased from Shanghai Slac Laboratory Animal Center (Shanghai, China). All animal experiments were carried out in accordance with the guidelines of Institutional Animal Care and Use Committee of the Jiangnan University, Wuxi, China.

2.2. Feeding schedule and diets

Three-week-old mice were grouped in a house (5 mice/cage) at controlled temperature (22 ± 2 °C) and humidity (55 ± 5%) in a 12-h/12-h light–dark cycle with standard diet chow. Tap water ad libitum for 1 week to adapt the housing condition. Then they were randomly divided into 3 groups (32 mice per group): control diet (CON, 8.9% energy from fat) group; high-fat diet (HFD, 45% energy from fat) group; and HFD with 0.1% (w/w) resveratrol (RES) [13]. The diets contained a standard vitamin and mineral mix with all essential nutrients.

2.3. Whole body metabolic status

After 10-week period, whole body metabolic status (4 mice per group) were tested by indirect calorimetry in a Comprehensive Laboratory Animal Monitoring System (CLAMS, Columbus Instruments, Columbus, OH) for 24 h after 48 h of habituation following manufacturer's instructions. Lighting and feeding conditions were kept the same as in the home cages. The system was performed by indirect calorimetry and allowed to determine the respiratory exchange ratio (RER). An RER of 1.0 indicates high utilization of carbohydrates for energy, and an RER of 0.7 indicates increased fatty acid oxidation [15]. Ambulatory locomotor activity was measured by consecutive beam breaks in adjacent beams. Heat production was calculated by multiplying the calorific value (CV; $3.815 + 1.232 \times \text{RER}$) by the observed VO_2 (Heat = CV × VO_2).

2.4. Tissue, blood collection and plasma analysis

After 11-week period, mice were sacrificed at 6 h intervals across the LD cycle to obtain liver tissue and blood samples (8 mice per group for each time point). Plasma insulin and leptin levels were determined by ELISA kits(Huijia, Xiamen, China), and Plasma total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) contents were examined by the corresponding enzymatic colorimetric assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China) according to the manufacturer's instructions.

2.5. RNA extraction and quantitative real-time PCR

Total RNA was extracted from liver tissue (8 mice per group for each time point) using Trizol reagent (Biomiga, San Diego, USA) according to the manufacturer's instruction. Briefly, 1% agarose gel electrophoresis was used to evaluate the quality of the RNA. Total RNA was reverse-transcribed to cDNA according to the manufacturer's instructions (Promega, Madison, Wisconsin, USA). We used Platinum Taq polymerase and SYBR Green I dye (SYBR Green Master Mix, Bioneer, Korea) to measure in the exponential phase of amplification by the ABI prism 7500 Sequence Detection System. The reactions were incubated at 95 °C for 10 min for 1cycle and at 95 °C (30 s), 60 °C (45 s), and 72 °C (45 s) for 44 cycles. The final extension was for 5 min at 72 °C. The relative expression levels of the target genes were expressed as a ratio to the housekeeping gene β-actin. Meanwhile, melting curve analysis was applied to assess the specificity of the amplified PCR products. Supplemental Table 1 shows the sequences of the primer pairs.

2.6. Statistical analysis

All data were expressed as mean ± SD. Comparisons across groups were performed using one-way analysis of variance with the post hoc Duncan's test with $P < 0.05$ being considered statistically significant. The data were analyzed by SPSS 17 (SPSS, Chicago, IL, USA).

3. Results

3.1. Effect of resveratrol on body weight and circadian rhythmities of plasma parameters

Mice were fed for 11 weeks (Fig. 1A). After 5 weeks, mice of HFD group gained more body weight than the CON group ($P < 0.05$). Interestingly, RES caused significantly reduction in body weight since 5 weeks in HFD-fed mice ($P < 0.05$). As shown in Fig. 1B, fasting blood glucose levels of HFD group were much higher than that in control group in 8:00, 20:00, and 2:00 time points ($P < 0.05$), meanwhile markedly lower than that in control group in 14:00 time point ($P < 0.05$). Moreover, resveratrol supplementation to the high-fat diets succeeded in ameliorating the fasting blood glucose compared with HFD in different time points ($P < 0.05$). Plasma leptin and insulin levels under CON condition both expressed rhythmicly (Fig. 1C, D), whereas plasma leptin and insulin levels were significantly higher at all circadian time points in HFD than in CON mice, respectively ($P < 0.05$). While resveratrol remarkably decreased the plasma leptin of HFD mice at two circadian time points and restored the circadian rhythm of plasma leptin ($P < 0.05$). In conjunction with the changes in fasting blood glucose,

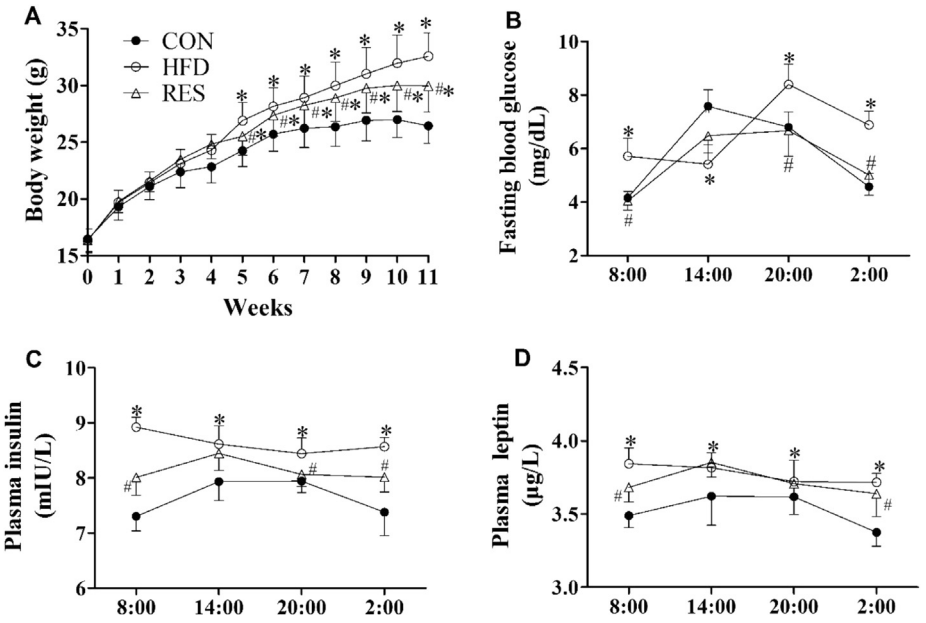

Fig. 1. Effects of resveratrol on body weight and circadian rhythmities of plasma parameters. (A) body weight, (B) fasting blood glucose, (C) plasma insulin, and (D) plasma leptin in mice fed on the experimental diets for 11 weeks (CON, group fed a standard diet, used as a control; HFD, group fed a high-fat diet; RES, group fed a high-fat diet supplemented with 0.1% (w/w) resveratrol). Values indicate the mean ± SD of n = 32 mice per group in (A). Values indicate the mean ± SD of n = 8 mice per group for each time point in (B, C and D). *Mean value was different from that of the CON group at the same time point ($P < 0.05$). #Mean value was different from the HFD group at the same time point ($P < 0.05$).

the plasma insulin levels of RES mice were significantly lower than those of the HFD mice at three circadian time points ($P < 0.05$).

3.2. Effects of resveratrol on plasma lipid status

As shown in Fig. 2, both CON and RES groups displayed obvious circadian rhythm in TC, TG, LDL and HDL. Compared with control group, the levels of plasma TG, TC, LDL of HFD group in different time points were significantly increased ($P < 0.05$), except TG in 14:00 and LDL in 2:00 of HFD group ($P > 0.05$). Meanwhile HDL levels of HFD were significantly decreased at each time point ($P < 0.05$). Thus, plasma lipid status of HFD group lost the rhythms.

3.3. Effect of resveratrol on whole body metabolic status in vivo

During the 24-h monitoring period, CON, HFD, and RES mice were placed in metabolic cages for measurement of diurnal variations of RER, locomotor activity and heat production (Fig. 3). Both CON and RES groups displayed obvious day–night variations in RER, locomotor activity and heat production. In contrast, HFD mice nearly lost the rhythms of these parameters. However, the variation

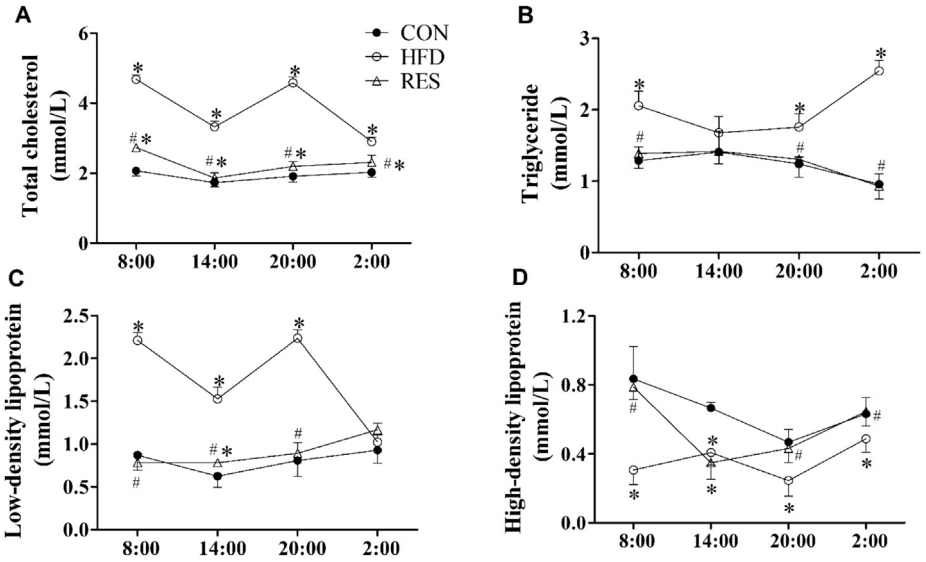

Fig. 2. Effects of resveratrol on plasma lipid status. (A) Plasma total cholesterol, (B) plasma triglyceride, (C) plasma low-density lipoprotein, and (D) plasma high-density lipoprotein contents in mice fed on the experimental diets for 11 weeks (CON, group fed a standard diet, used as a control; HFD, group fed a high-fat diet; RES, group fed a high-fat diet supplemented with 0.1% (w/w) resveratrol). Values indicate the mean ± SD of n = 8 mice per group for each time point. *Mean value was different from that of the CON group at the same time point ($P < 0.05$). #Mean value was different from the HFD group at the same time point ($P < 0.05$).

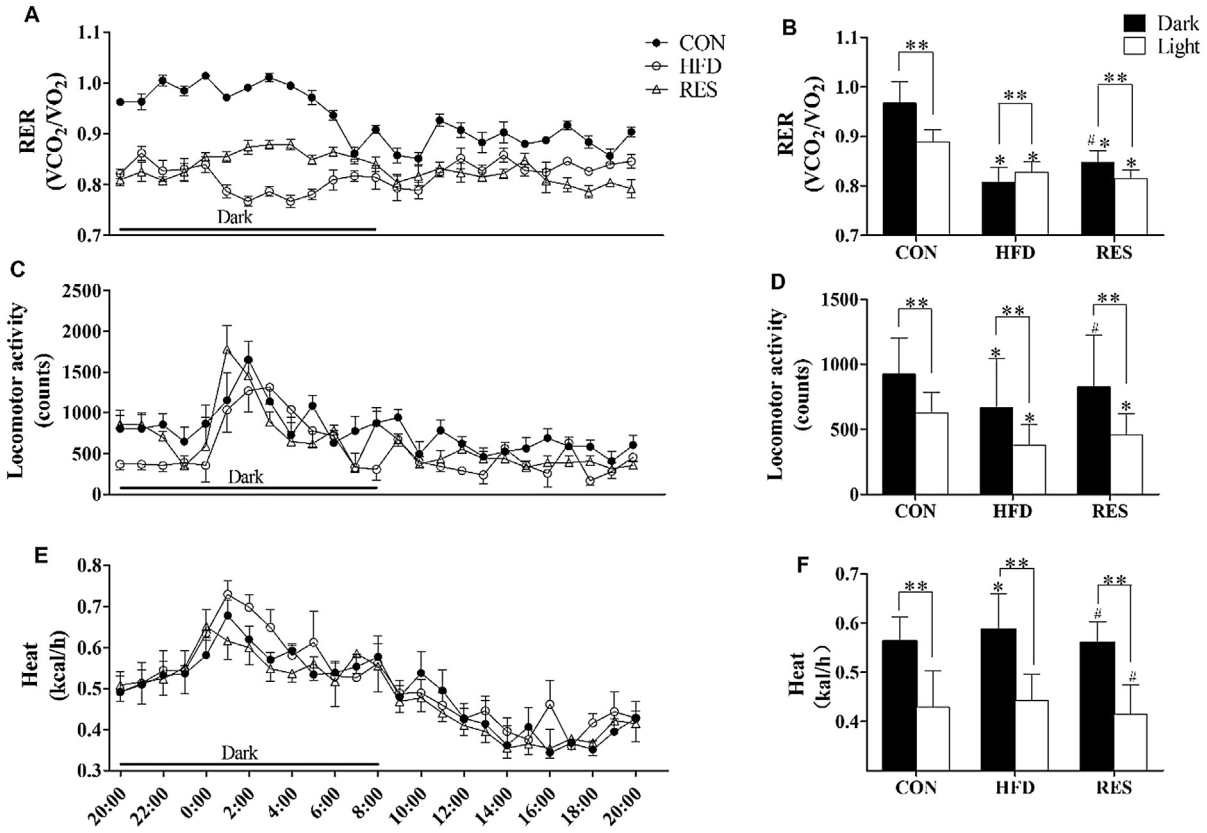

Fig. 3. Effects of resveratrol on whole body metabolic status. (A and B) respiratory exchange ratio (RER), (C and D) locomotor activity, and (E and F) heat production in mice fed on the experimental diets for 10 weeks (CON, group fed a standard diet, used as a control; HFD, group fed a high-fat diet; RES, group fed a high-fat diet supplemented with 0.1% (w/w) resveratrol). Bar graphs represent cumulative values during the light and dark cycles. Values indicate the mean ± SD of n = 4 mice per group for each time point. *Mean value was different from that of the CON group at the same illumination ($P < 0.05$). #Mean value was different from the HFD group at the same illumination ($P < 0.05$). **Mean value was different from the different illuminations at the same group ($P < 0.05$).

of locomotor activity was unaffected in the HFD mice, suggesting the compensatory mechanisms that might be operated under the light/dark cycle.

3.4. Effect of resveratrol on circadian regulation of lipid metabolic networks

A rhythmic expression was observed for all tested clock genes (*Clock*, *Bmal1*, *Per2*, and clock-controlled genes, *Sirt1*, *Pparα*, *Srebp-1c*, *Fas*, and *Acc1*) in the normally fed mice. The core components of clockwork consists of a transcriptional feedback loop in which *Clock* and *Bmal1* play the positive regulation role while *Per2* acts as the negative regulator. The mRNA expression of genes encoding positive regulators (*Clock* and *Bmal1*) was in bottom at the onset of daytime, 20:00. In contrast, the rhythm of genes encoding negative regulator was in the opposite phase to that of *Clock* and *Bmal1*, namely, a zenith at around 20:00 and a nadir at 8:00. In particular, the expression of the clock-controlled output gene PPARα and downstream lipid metabolism genes, *Srebp-1c*, *Fas*, and *Acc1* also showed an overt circadian rhythm.

As shown in Fig. 4, the expressions of core clock genes, *Clock*, *Bmal1*, and *Per2* were significantly altered at several circadian time points in mice fed HFD. Interestingly, rhythms of *Sirt1*, *Pparα*, *Srebp-1c*, *Fas*, and *Acc1* expressions in the liver were significantly altered in HFD mice.

In addition, to examine the hypothesis that RES restores hepatic expressions of core clock genes and downstream lipid metabolism genes, we analyzed the circadian expressions of corresponding transcripts in the livers of RES group. Interestingly, almost all the clock genes were expressed in a circadian manner, and downstream lipid metabolism genes were restored in the circadian rhythm.

4. Discussion

A lot of evidence from human and animal studies has demonstrated that high-fat diet could change both the circadian rhythm and energy metabolism [9,16]. Meanwhile, the circadian components and metabolism could interact with each other [17,18]. A better understanding of the molecular machinery of the relationship between the molecular clocks and metabolism may shed light on the therapies of metabolic diseases. In this study, we demonstrated the effects of resveratrol on ameliorating body weight and lipid status using several circadian time points. The results show that the high-fat diet could increase the body weight and disrupt the circadian rhythm of lipid status in mice as other studies reported, in addition resveratrol could restore those disorder.

The most novel finding of the present study was the robust alteration of circadian rhythms in a spectrum of metabolic and behavioral parameters of three groups mice fed different diets. Under regular light/dark cycles, HFD mice displayed a nearly complete loss of circadian rhythms of metabolism (RER, and heat production), and locomotor activity. The variations of most of these parameters in RES mice were restored under the same light/dark condition. The reason for the difference in the study is unclear but one confounding factor may come from the alterations of *Sirt1* and downstream clock genes regulating network. *Sirt1* functions as

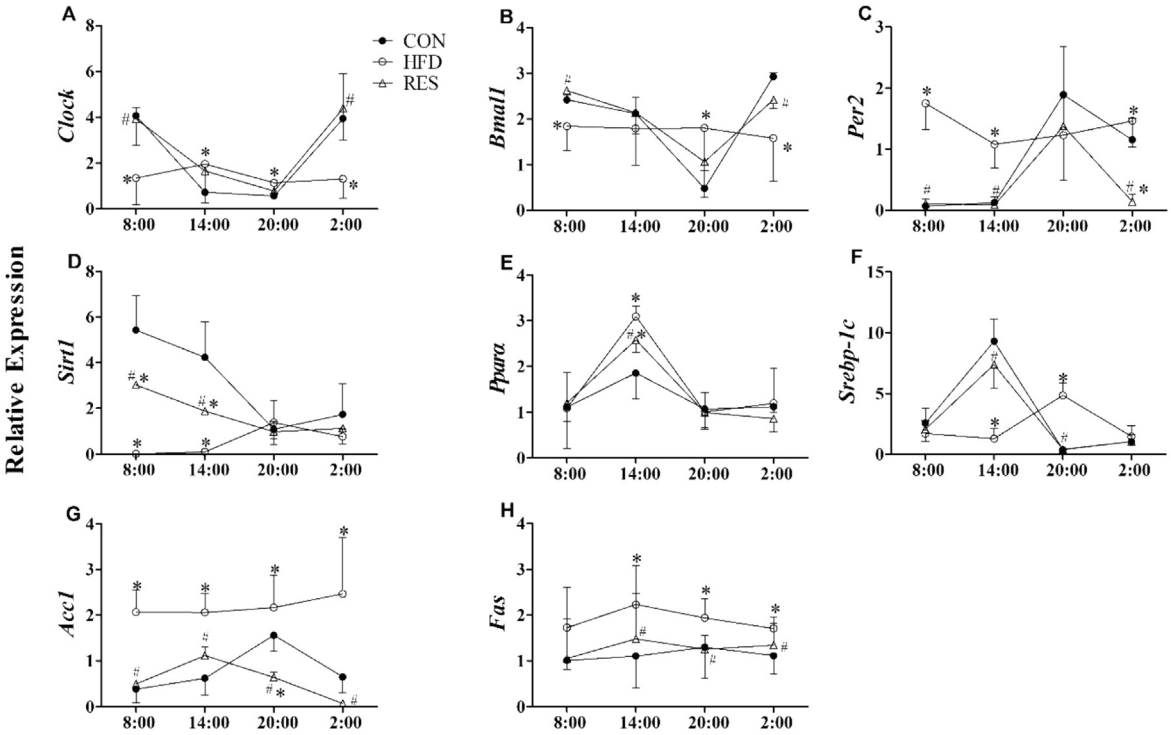

Fig. 4. Effects of resveratrol on circadian mRNA expression of liver tissue. (A) clock homolog (CLOCK), (B) brain and muscle Arnt-like 1 (BMAL1), (C) period homolog (PER2), (D and E) clock-controlled genes (SIRT1, and PPARα) and (F, G and H) lipogenesis genes (SREBP-1C, ACC1 and FAS) mRNA levels expressed as values relative to the contros (control group), in liver tissue of mice fed on the experimental diets for 11 weeks (CON, group fed a standard diet, used as a control; HFD, group fed a high-fat diet; RES, group fed a high-fat diet supplemented with 0.1% (w/w) resveratrol). Values indicate the mean ± SD of n = 8 mice per group for each time point. *Mean value was different from that of the CON group at the same time point ($P < 0.05$). #Mean value was different from the HFD group at the same time point ($P < 0.05$).

class III histone deacetylases, binding to NAD^+ and acetyllysine within protein targets and generating lysine, 2′-O-acetyl-ADP-ribose, and nicotinamide as enzymatic products [19]. *Sirt1* plays the role of the integration of circadian and metabolic transcription networks and has now been shown to interact directly with *Clock* and to deacetylate *Bmal1* and *Per2* [20,21]. Interestingly, we found dampening of *Sirt1* under high-fat diet, which could result in further deviation of the expression of core clock genes in the liver, suggesting that SIRT1 may be the link between high-fat diet and the loss of circadian rhythms of metabolism (RER, and heat production), and locomotor activity.

Resveratrol is a natural polyphenol phytoalexin existing in grapes, berries and peanuts [22]. It has been reported to activate SIRT1 and extends lifespan in multiple model organisms [23]. In addition, it has been suggested that resveratrol is a promising new therapeutic approach for longevity and metabolic abnormalities in high-fat diet-induced obese mice [19,24]. In this article, we showed that RES intervention resulted in increased level and rhythmic expression of *Sirt1*; and there was an improvement not only in the expression of *Sirt1* but also in the expressions of downstream core clock genes. The effect of RES on amelioration of rhythmic expressions of core clock genes is not unexpected, a dose of 100 μM resveratrol, which did not show cytotoxicity, regulated the expression of clock genes *Per2* and *Bmal1* [14]. Thus resveratrol, a *Sirt1* activation, can be used as a potential therapeutic approach to combat against disruption of circadian rhythm induced by high-fat diet.

Pparα was identified as a direct target gene of *Bmal1* and *Clock* via an E-box-dependent mechanism [25]. The expression level of *Pparα* in the liver was decreased and its circadian oscillation was abolished in *Bmal1* knockout mice or *Clock*-mutant mice [25,26]. Reciprocally, *Pparα*-null mice showed altered oscillation of *Bmal1* in the liver. In the present study, we found that *Pparα* loses its circadian expression rhythm resulting from the alteration of the expression of clock genes in HFD mice. Of note, resveratrol restored the expression of *Pparα* in the resveratrol-treated group; this phenomenon further indicated that resveratrol regulated *Pparα* via *Sirt1*-mediated core clock genes. More importantly, as a mediator of circadian regulation of lipid metabolism, *Pparα* also regulates the expression of numerous genes involved in lipid metabolism and energy homeostasis [27,28]. Many of these genes, such as *Srebp-1c*, *Fas*, and *Acc1*, display daily fluctuations in mouse liver; however, their amplitudes are attenuated or abolished in *Pparα* knockout mice [29,30]. *Serbp-1c* plays a central role in lipogenesis and enhances transcription of genes required for fatty acid synthesis, such as *Fas* and *Acc1* [31]. *Fas* is a key enzyme that controls the rate of fatty acid synthesis [32]. *Acc1* is the rate-limiting enzyme in the biogenesis of long-chain fatty acids, and regulating fatty acid synthesis [33]. In this present study, we found that rhythmic changes in the three genes varied significantly in CON mice. After administration of high-fat diet for 11 weeks, the rhythm of the *Serbp-1c* expression shifted and that of the *Fas* and *Acc1* expressions were substantially disrupted. By contrast, the three genes expressions were restored in RES mice. The temporal expression of *Acc1* over light/dark cycles was notably similar to the alteration in TG level and contrasted the alteration in HDL level. These results reveal that rhythm of lipid metabolism may be altered by the rhythmic expression of lipogenic genes under high-fat diet environmental condition, which could be restored by resveratrol intervention.

In summary, our results demonstrated that high-fat diet could change the liver circadian expressions of clock genes such as *Clock*, *Bmal1*, and *Per2*, via *Sirt1*, and subsequently alter the circadian expression of *Pparα*-mediated lipogenic genes, resulting in lipid metabolism disorder. In addition, resveratrol could affect the

circadian expression of *Sirt1* to restore the clock genes, and subsequently restore the circadian expression of *Pparα*-mediated downstream lipogenic genes, ameliorating circadian disorder of lipid metabolism induced by high-fat diet.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.01.072.

Transparency document

The transparency document associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrc.2015.01.072.

References

[1] S.B. Wyatt, K.P. Winters, P.M. Dubbert, Overweight and obesity: prevalence, consequences, and causes of a growing public health problem, Am. J. Med. Sci. 331 (2006) 166–174.
[2] K.L. Eckel-Mahan, V.R. Patel, R.P. Mohney, K.S. Vignola, P. Baldi, P. Sassone-Corsi, Coordination of the transcriptome and metabolome by the circadian clock, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 5541–5546.
[3] O. Froy, The circadian clock and metabolism, Clin. Sci. 120 (2011) 65–72.
[4] A. Kohsaka, A.D. Laposky, K.M. Ramsey, C. Estrada, C. Joshu, Y. Kobayashi, F.W. Turek, J. Bass, High-fat diet disrupts behavioral and molecular circadian rhythms in mice, Cell. Metab. 6 (2007) 414–421.
[5] I. Iurisci, E. Filipski, H. Sallam, F. Harper, C. Guettier, I. Maire, M. Hassan, S. Iacobelli, F. Levi, Liver circadian clock, a pharmacologic target of cyclin-dependent kinase inhibitor seliciclib, Chronobiol. Int. 26 (2009) 1169–1188.
[6] M. Sudo, K. Sasahara, T. Moriya, M. Akiyama, T. Hamada, S. Shibata, Constant light housing attenuates circadian rhythms of mPer2 mRNA and mPER2 protein expression in the suprachiasmatic nucleus of mice, Neuroscience 121 (2003) 493–499.
[7] R. Hara, K. Wan, H. Wakamatsu, R. Aida, T. Moriya, M. Akiyama, S. Shibata, Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus, Genes Cells 6 (2001) 269–278.
[8] D.M. Arble, J. Bass, A.D. Laposky, M.H. Vitaterna, F.W. Turek, Circadian timing of food intake contributes to weight gain, Obesity 17 (2009) 2100–2102.
[9] P.J. Havel, R. Townsend, L. Chaump, K. Teff, High-fat meals reduce 24-h circulating leptin concentrations in women, Diabetes 48 (1999) 334–341.
[10] P. Cano, V. Jimenez-Ortega, A. Larrad, C.F. Reyes Toso, D.P. Cardinali, A.I. Esquifino, Effect of a high-fat diet on 24-h pattern of circulating levels of prolactin, luteinizing hormone, testosterone, corticosterone, thyroid-stimulating hormone and glucose, and pineal melatonin content, in rats, Endocrine 33 (2008) 118–125.
[11] M. Barnea, Z. Madar, O. Froy, High-fat diet delays and fasting advances the circadian expression of adiponectin signaling components in mouse liver, Endocrinology 150 (2009) 161–168.
[12] F. Pifferi, A. Dal-Pan, M. Menaker, F. Aujard, Resveratrol dietary supplementation shortens the free-running circadian period and decreases body temperature in a prosimian primate, J. Biol. Rhythm. 26 (2011) 271–275.
[13] L.L. Chen, H.H. Zhang, J. Zheng, X. Hu, W. Kong, D. Hu, S.X. Wang, P. Zhang, Resveratrol attenuates high-fat diet-induced insulin resistance by influencing skeletal muscle lipid transport and subsarcolemmal mitochondrial beta-oxidation, Metabolism 60 (2011) 1598–1609.
[14] H. Oike, M. Kobori, Resveratrol regulates circadian clock genes in Rat-1 fibroblast cells, Biosci. Biotechnol. Biochem. 72 (2008) 3038–3040.
[15] L.E. Matarese, Indirect calorimetry: technical aspects, J. Am. Diet. Assoc. 97 (1997) S154–S160.
[16] M.C. Cha, C.J. Chou, C.N. Boozer, High-fat diet feeding reduces the diurnal variation of plasma leptin concentration in rats, Metabolism 49 (2000) 503–507.
[17] L.N. Fu, M.S. Patel, A. Bradley, E.F. Wagner, G. Karsenty, The molecular clock mediates leptin-regulated bone formation, Cell 122 (2005) 803–815.
[18] S. Shimba, N. Ishii, Y. Ohta, T. Ohno, Y. Watabe, M. Hayashi, T. Wada, T. Aoyagi, M. Tezuka, Brain and muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 12071–12076.
[19] M. Kitada, D. Koya, SIRT1 in type 2 diabetes: mechanisms and therapeutic potential, Diab. Metab. J. 37 (2013) 315–325.
[20] G. Asher, D. Gatfield, M. Stratmann, H. Reinke, C. Dibner, F. Kreppel, R. Mostoslavsky, F.W. Alt, U. Schibler, SIRT1 regulates circadian clock gene expression through PER2 deacetylation, Cell 134 (2008) 317–328.
[21] Y. Nakahata, M. Kaluzova, B. Grimaldi, S. Sahar, J. Hirayama, D. Chen, L.P. Guarente, P. Sassone-Corsi, The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control, Cell 134 (2008) 329–340.
[22] Z. Kiraly-Veghely, E. Tyihak, L. Albert, Z.I. Nemeth, G. Katay, Identification and measurement of resveratrol and formaldehyde in parts of white and blue grape berries, Acta Biol. Hung 49 (1998) 281–289.
[23] J.M. Yun, A. Chien, I. Jialal, S. Devaraj, Resveratrol up-regulates SIRT1 and inhibits cellular oxidative stress in the diabetic milieu: mechanistic insights, J. Nutr. Biochem. 23 (2012) 699–705.
[24] F. Picard, M. Kurtev, N. Chung, A. Topark-Ngarm, T. Senawong, R.M. De Oliveira, M. Leid, M.W. McBurney, L. Guarente, Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-γ, Nature 429 (2004) 771–776.
[25] K. Oishi, H. Shirai, N. Ishida, CLOCK is involved in the circadian transactivation of peroxisome-proliferator-activated receptor alpha (PPARalpha) in mice, Biochem. J. 386 (2005) 575–581.
[26] L. Canaple, J. Rambaud, O. Dkhissi-Benyahya, B. Rayet, N.S. Tan, L. Michalik, F. Delaunay, W. Wahli, V. Laudet, Reciprocal regulation of brain and muscle Arnt-like protein 1 and peroxisome proliferator-activated receptor alpha defines a novel positive feedback loop in the rodent liver circadian clock, Mol. Endocrinol. 20 (2006) 1715–1727.
[27] X. Wang, J. Xue, J. Yang, M. Xie, Timed high-fat diet in the evening affects the hepatic circadian clock and PPARalpha-mediated lipogenic gene expressions in mice, Genes Nutr. 8 (2013) 457–463.
[28] B.L. Knight, A. Hebbachi, D. Hauton, A.M. Brown, D. Wiggins, D.D. Patel, G.F. Gibbons, A role for PPARalpha in the control of SREBP activity and lipid synthesis in the liver, Biochem. J. 389 (2005) 413–421.
[29] G.F. Gibbons, D. Patel, D. Wiggins, B.L. Knight, The functional efficiency of lipogenic and cholesterogenic gene expression in normal mice and in mice lacking the peroxisomal proliferator-activated receptor-alpha (PPAR-alpha), Adv. Enzyme Regul. 42 (2002) 227–247.
[30] D.D. Patel, B.L. Knight, D. Wiggins, S.M. Humphreys, G.F. Gibbons, Disturbances in the normal regulation of SREBP-sensitive genes in PPAR alpha-deficient mice, J. Lipid Res. 42 (2001) 328–337.
[31] J.D. Horton, J.L. Goldstein, M.S. Brown, SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver, J. Clin. Invest. 109 (2002) 1125–1131.
[32] G.G. Hammes, Fatty acid synthase: elementary steps in catalysis and regulation, Curr. Top. Cell. Regul. 26 (1985) 311–324.
[33] K.H. Kim, Regulation of mammalian acetyl-coenzyme A carboxylase, Annu. Rev. Nutr. 17 (1997) 77–99.